

# CINP 2018 VIENNA WORLD CONGRESS

Poster Abstract Book



# CINP 2018: Poster Abstracts



## Rafaelsen Award Winner Posters: RAF01 – RAF10

*Displayed for the duration of  
the Congress*

### RAF01

#### Value-Based Decision-Making of Cigarettes and Non-Drug Rewards in Dependent and Occasional smokers: An fMRI Study

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#### Background

Value-based decision-making is theoretically impaired in substance use disorders. However, very little is known about the neural functioning that underpins drug valuation and purchase, within addiction. In a sample of dependent and occasional cigarette smokers, using a neuroeconomics paradigm, we aimed to: (1) identify the brain's value signal for cigarettes and vouchers, (2) investigate neural and behavioural decision-making differences between the groups.

#### Methods

Twenty dependent smokers (smoked  $\geq 10$ /day; FTND  $\geq 5$ ) and 19 occasional smokers (smoked 0.5-5/week; FTND = 0), following *ad libitum* smoking, completed a decision-making task, in which cigarettes and vouchers could be purchased. In the first stage (outside of the MRI scanner), participants stated their willingness-to-pay (WTP) for a variety of cigarette 'bundles' (e.g. 5 Marlboro cigarettes) and voucher 'bundles' (e.g. 5 Amazon vouchers). In the second stage (inside the MRI scanner), participants made a series of purchase decisions about the cigarette and voucher 'bundles'. One decision, across both stages, for each reward type was selected at random and happened in reality. Scanning took place in a Philips 1.5T MRI scanner. Using whole brain and ROI analyses, and parametric modulation, we investigated which brain

regions encode cigarette and voucher value and examined group differences in this value processing. We also investigated behavioural group differences in WTP, choices and their relationships (using generalised estimating equations).

#### Results

In the first stage, dependent smokers had a higher WTP for cigarettes than occasional smokers ( $t_{37}=4.262$ ,  $p<0.001$ ). In the second stage, choices were positive affected by WTP ( $\beta=0.984$ ,  $p<0.001$ ). There was an interaction between group, reward type and WTP: dependent smokers were more sensitive to changes in WTP for cigarettes than vouchers ( $\beta=1.063$ ,  $p<0.001$ ), while the opposite was true of occasional smokers ( $\beta=-0.232$ ,  $p=0.015$ ). We identified a cigarette value signal within the ventromedial prefrontal cortex across both groups ( $p_{(FWE)}=0.022$ , [ $x=0$ ,  $y=53$ ,  $z=-10$ ]). We did not identify a voucher value signal and we did not find any group differences between the groups in cigarette or voucher value signals.

#### Conclusions

Behaviourally, dependent smokers valued cigarettes more than occasional cigarettes and, when making purchase decisions, were more sensitive to the value of the cigarettes on offer. In terms of neural correlates of value, we identified a value signal for cigarettes in the ventromedial prefrontal cortex, for the first time. However, we did not observe any group differences in the neural processing of value between dependent and occasional smokers. Further research into drug-related value-based decision-making in nicotine dependence is needed.

### RAF02

#### The development of dissociable and common aspects of psychopathology from childhood to adolescence and their brain structural correlates

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**Background:** On the one hand, psychiatric symptoms tend to aggregate into distinct clusters. On the other, symptoms across these clusters tend to co-occur. Here I will investigate the longitudinal development of dissociable and common aspects of psychopathology and their structural brain correlates in youth.

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**Methods:** The sample included 2,511 children and adolescents (6-14 years), of which 80% were followed after 3-years (9-17). Psychopathology was measured by four points in time using the Child Behavioral Checklist. A bifactor model with three dissociable symptomatic dimensions (fear, distress and externalizing) in combination with one common factor representing psychopathology shared across all symptomatic domains (the “p-factor”) was fitted to the data. Growth mixed effects models investigated longitudinal trajectories. Measures of cortical thickness, area and volume were measured using T1-weighted imaging in a subsample of 720 participants.

**Results:** The bifactor model with one common factor and three dissociable factors presented excellent fit to the data. Growth mixed models revealed inverted U quadratic trajectories with development for the distress factor (peaking at age 13) and for the fear factor (peaking at age 12) and non-significant mean changes for the externalizing factor. For the p-factor, a significant trend-level ( $p=0.055$ ) interaction emerged between age and sex, showing an inverted U quadratic trajectory for boys (peaking at 11) and a linear increasing predicted trajectory for girls. Brain structural analysis revealed higher p-factor was associated with higher thickness and lower area in several brain regions; whereas fear and distress were associated with higher volume of the left putamen and with higher thickness of the right cuneus.

**Conclusions:** These results demonstrate the potential of bifactor models to disentangle common and dissociable aspects of psychopathology in youth. They also reinforce the importance to start looking for shared mechanisms for psychiatric disorders, but also to account for p-factor when looking for specific mechanisms.

## RAF03

**Therapeutic Drug Monitoring in quantifying in vivo fetus/infant drug exposure to psychotropic agents**

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**Background:** Effects of psychotropic drugs on fetus/infant remain poorly understood, although the number of women treated with psychotropic drugs is continuously increasing. We aimed to quantify the ability of various agents to enter the fetal circulation.

**Materials and methods:** 47 samples of maternal serum (MS), amniotic fluid (AF), umbilical cord blood (UC) and mother milk (MM) were analyzed. To compute the so called ‘concentration by dose’ (C/D), we divided the drug concentrations by the applied daily dose. We also calculated penetration ratios (PR) as the ratios of drug concentrations in AF, UC and MM divided by the drug concentration in MS.

**Results:** AF concentrations as well as UC and MM concentrations varied in a wide range. The lowest median C/S ratio in AF was found for quetiapine, while the lowest median C/D ratio in UC and MM were found for lamotrigine. Venlafaxine showed the highest C/D in all different environments. Quetiapine showed the lowest penetration ratio into AF and UC but the highest ratio between MS and MM, while the lowest penetration ratio between MS and MM was found for lamotrigine. Venlafaxine showed the highest penetration ratio into AF and Venlafaxine showed the highest penetration ratio values in UC.

**Conclusions:** The preliminary data of this ongoing study highlight the penetration of different psychotropic drugs during pregnancy into the unborn child and into the AF as one way of fetal exposure. Understanding the current evidence and their limitations will help clinicians to guide their patients efficiently in choosing adequate psychopharmacological treatment options.

## RAF04

**Higher interleukin 17 is associated with greater severity of anhedonia in male, but not female, depressed outpatients: Findings from CO-MED trial**

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**Background:** Among individual depressive symptoms, anhedonia (loss of interest or pleasure) has been consistently shown to worsen with increased inflammatory markers in depressed patients. However, it is unclear whether gender differentially affects association of anhedonia with peripheral markers of inflammation.

**Methods:** Levels of inflammatory markers (IL-17, T-helper (Th) 1-, Th2- and non-T cell-markers) were measured with

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the Bioplex Pro™ human cytokine 27-plex kit in Combining Medications to Enhance Depression Outcomes (CO-MED) trial participants who provided plasma at baseline (n = 166). Anhedonia was measured with three items of the 30-item Inventory of Depressive Symptomatology clinician-rated version and depression severity was measured with Quick Inventory of Depression Severity. Separate general linear model for anhedonia and overall depression severity (minus anhedonia item), anxiety and irritability as dependent variables were used with gender-by-inflammatory (IL-17, Th1-, Th2-, and non-T cell-) marker interaction as primary outcome of interest. Subsequent analyses stratified by gender were conducted for those markers with a significant interaction.

**Results:** Based on gender, there was a differential association of anhedonia with IL-17 (p=0.05) but not with Th1- (p=0.20), Th2- (p=0.74) and non-T cell- (p=0.49) markers. Anhedonia severity increased with higher IL-17 in males (r=0.42, p=0.0025) but not in females (r=0.09, p=0.34). There was no significant gender-specific difference in association of the inflammatory markers and overall depression severity (minus anhedonia item), irritability, and anxiety.

**Conclusions:** Gender is an important biological factor which moderates association of IL-17 mediated immune response and anhedonia. Males but not females experience greater severity of anhedonia with higher levels of peripherally circulating IL-17.

## RAF05

### Altered fatty acid composition of phospholipids in the corpus callosum of patients with schizophrenia

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#### Objective

Schizophrenia is a severe mental disorder. Recent genetic and brain imaging studies have indicated the disturbance in myelination and the structural changes of the corpus callosum in schizophrenia. However, the underlying molecular mechanism remains unknown.

Lipids are major constituents of myelin sheath. Although lipids, especially fatty acids, have attracted attention in the schizophrenia etiology, previous postmortem studies have focused mainly on gray matter (e.g. Emanuel S. *et al.*, 2008; Matsumoto J. *et al.*, 2017).

In this study, to examine whether the fatty acid composition of phospholipids, and its biosynthesis and

remodeling in the corpus callosum are involved in the pathology of schizophrenia, we quantified the amounts of various phospholipid species and transcripts of genes for lipid-metabolizing enzymes in the postmortem corpus callosum samples from schizophrenia patients and control subjects.

#### Methods & Results

We evaluated the fatty acid composition of phospholipids of the corpus callosum from 15 schizophrenia patients and 15 unaffected controls by liquid chromatography-mass spectrometry (LC-MS). We found that subsets of phospholipids were significantly reduced in schizophrenia. Interestingly, many of them contain oleic acid, one of major fatty acids enriched in myelin, and  $\omega$ 6 polyunsaturated fatty acids (PUFAs), precursors to the eicosanoids. To explore the causes of these alterations, we performed real-time PCR analysis of potentially relevant genes using extended corpus callosum samples (95 schizophrenia patients and 92 unaffected controls). We found that the mRNA levels of specific acyltransferases and eicosanoid-producing enzymes were significantly decreased in schizophrenia.

#### Conclusions

The present data provide intriguing evidence for altered amounts of oleic acid-containing phospholipids and  $\omega$ 6 PUFA-containing phospholipids in the corpus callosum of patients with schizophrenia. Our findings suggest the possibility that abnormal lipid synthesis/remodeling and/or  $\omega$ 6 eicosanoid signaling may be molecular underpinnings for the myelin abnormalities reported in schizophrenia.

## RAF06

### Targeting microRNAs to screen new compounds to treat bipolar disorder.

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#### Objectives

MicroRNAs have the potential to be an effective way to explore the complex biological interactions involved in

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bipolar disorder (BD). Our previous findings showed that a cocktail of BD drugs (lithium, valproate, quetiapine, lamotrigine) increased the expression of miR-128 and miR-378 in NT2-N cells, both of which have been implicated in pathways involved in neurogenesis, neuron development and axonogenesis. Therefore, the aim of this pilot study was to conduct a screen in order to identify compounds that increase the expression of miR-128 and miR-378.

## **Methods**

NT2-N cells were treated with a series of compounds at a dose of 10  $\mu$ M for 24 h in 24-well plates. Vehicle (0.2% DMSO) treated wells serving as controls were included on each assay plate to obtain a confidence interval, and control for variation between plates. RNA was extracted from each well using RNeasy kits, reverse transcribed and the expression levels of miR-128 and miR-378 were measured using Taqman miRNA assays.

## **Results**

The pilot screening study identified several compounds that increased the expression of both miRNAs and are, therefore, potentially interesting for the treatment of BD. The compounds identified increased miR-128 and miR-378 expression and decreased the expression of key target genes of these miRNAs in a dose-dependent manner, and this was associated with increased neurite outgrowth from the cells. These compounds include tacrine, betulinic acid and dextromethorphan.

## **Conclusions**

Neuronal plasticity may be an important pathophysiological component of neuropsychiatric disorders such as BD, with this study proposing that at a transcriptional level, novel compounds have the potential to mediate neuronal plasticity and act as valid treatment options for the condition.

## **RAF07**

### **Elevation of p11 in Lateral Habenula Mediates Depression-Like Behavior**

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The lateral habenula (LHb) is a key brain region involved in the pathophysiology of depression. It is activated by stimuli associated with negative experiences and is involved in encoding aversive signals. Hyperactivity of LHb is found in both rodent models of depression and human patients with depression. However, little is known about the underlying molecular mechanisms. Here we show that,

in LHb neurons, p11, a multifunctional protein implicated in depression, is significantly upregulated by chronic restraint stress. Knockdown of p11 expression in LHb alleviates the stress-induced depression-like behaviors. Moreover, chronic restraint stress induces bursting action potentials in LHb neurons, which are abolished by p11 knockdown. Overexpression of p11 in dopamine D2 receptor (D2R)-containing LHb neurons of control mice induces depression-like behaviors. These results have identified p11 in LHb as a key molecular determinant regulating negative emotions, which may help to understand the molecular and cellular basis of depression.

Key words: stress, depression, p11, lateral habenula, hyperexcitability, dopamine D2 receptor, glutamatergic neurons.

## **RAF08**

### **The impact of stress during adolescence or adulthood is dependent on the state of the critical period**

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**Background:** Unregulated stress exposure occurring during sensitive periods of development leads to the emergence of circuit deficits consistent with schizophrenia in the adult. If accurate, one would predict that re-opening the sensitive period in the adult could make it susceptible to a similar disruption.

**Methods:** Male rats were submitted to a combination of footshock (FS) and restraint stress (RS) during adolescence (PD31-40) or adulthood (PD65-74). The activity of dopamine neurons in the ventral tegmental area (VTA) and the pyramidal in the ventral hippocampus (vHipp) were evaluated 1-2 or 5-6 weeks post-stress. Parvalbumin (PV) interneurons in the vHipp are proposed as a site of vulnerability. We therefore investigated the effects of adolescent and adult stress on the maturation of PV interneurons and the associated perineuronal nets (PNNs) expression in the vHipp. We also evaluate if the administration of the HDAC inhibitors valproic acid (VPA; 300 mg/kg) and SAHA (25 mg/kg), which are known to re-instate the critical period in adults, would recreate an adolescent phenotype of susceptibility to stress.

**Results:** The adolescent stress increased VTA dopamine population activity 1-2 and 5-6 weeks post-stress, these changes seem to be driven by an increased vHipp activity. In addition, adolescent stress produced decreases in number of PV+, PNN+, PV+/PNN+ cells in the ventral subiculum (vSub). FS+RS in adult rats decreased dopamine

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population activity 1-2 weeks post-stress, but not after 5-6 weeks. Also, adult stress did not induce changes in the vHipp activity, and PV and PNN expression in the vSub. Interestingly, VPA treatment altered the impact of adult stress. When rats were treated with VPA or SAHA, FS+RS increased VTA dopamine population activity 1-2 and 5-6 weeks post-stress, similar to that observed with adolescent stress. VPA treatment reduced the PV+ and PV+/PNN+ cell number in the vSub.

**Conclusion:** Timing of the stress is a critical determinant of the pathophysiology that is present in the adult. While adolescent stress could lead to changes that recapitulates the MAM model of schizophrenia, adult stress induced changes observed in animal models of depression. Re-opening the sensitive period in the adult restores vulnerability to stress-induced pathology resembling schizophrenia.

**Financial support:** MH57440

## RAF09

### Peripheral methylome analysis in bipolar disorder patients suggests brain-relevant alterations in the glutathione system

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Recent studies have implicated a role for DNA methylation in bipolar disorder (BD). However, previous reports have failed to identify robust brain-relevant alterations in periphery, which has limited functional and follow-up studies with genes of interest. In this study, we aimed to investigate blood methylome alterations in a large sample of BD patients and explore their relevance to brain tissue. Genome-wide methylation was assessed in DNA isolated from peripheral blood from 157 patients diagnosed with BD (136 BD-I, 21 BD-II) and 51 controls matched by age, sex, ethnicity, race, and body mass index. Assessments were made using the Infinium MethylationEPIC BeadChip (Illumina) and analyzed by the RnBeads R package. Groups were compared for individual CpGs and for region levels (genes and promoters) controlling for age, sex, sex, batch, and predicted blood cell count, with  $p$ -values adjusted for false discovery rate. Quality control and preprocessing steps led to the analysis of 838,529 sites. Groups showed a significant difference in the methylation of cg11141652 ( $p=0.027$ ), which is annotated to the glutathione S-transferase theta pseudogene 1 (*GSTTP1*). Exploratory bioinformatics analysis suggested a strong correlation of methylation at this probe between blood and different brain regions (prefrontal cortex -  $r=0.68$ , entorhinal cortex -  $r=0.816$ , superior temporal gyrus -

$r=0.818$ , and cerebellum -  $r=0.754$ ,  $p<0.05$  for all). Region-level analysis also identified between-group differences in three genes: mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 1 pseudogene 13 (*MTND1P13*;  $p=0.000658$ ), eukaryotic translation initiation factor 4E binding protein 1 pseudogene 2 (*EIF4EBP1P2*;  $p=0.000658$ ), and ENS0000023689 (unknown annotation,  $p=0.013883$ ). Finally, we also found significant differences in the promoter regions of the *GSTTP1* gene ( $p=0.000843$ ), *EIF4EBP1P2* ( $p=0.000843$ ), and the glutathione S-transferase theta 1 (*GSTT1*) gene ( $p=0.0167$ ). Although preliminary, these results suggest peripheral alterations with potential implications in brain tissue and in BD's pathophysiology, particularly in genes involved in the glutathione metabolism.

## RAF10

### Maternal prenatal psychological distress and the early infant gut microbiome in a South African birth cohort

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An aberrant gut microbiome has been identified as a mechanism linking maternal prenatal distress (pNDS) with negative neurodevelopmental and lifelong health trajectories in the offspring [1]. One study showed that self-reported pNDS was associated with a pathogenic gut microbiota profile in infant offspring [2]. However, the

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association of specific types of distress exposure during pregnancy on the infant gut microbiome is still unknown. The aim of this study was to investigate the association of multiple types of maternal pNDS with infant faecal microbiota profiles over time in a South African birth cohort study, the Drakenstein child health study.

Bacterial 16S rRNA gene sequences of the V4 hypervariable was used for identification and relative quantification of bacterial taxa in meconium and stool specimens from 90 mothers and 107 infants at birth, and longitudinally from a subset of 72 and 36 infants at 4–12 and 20–28 weeks of age. Maternal pNDS, symptoms of depression, psychological distress (SRQ-20), post-traumatic stress symptoms and intimate partner violence (IPV) were evaluated antenatally in the second trimester. The association between antenatal pNDS and changes in gut microbiota was determined.

IPV during pregnancy was significantly associated with higher proportions of unclassified genera in the family Enterobacteriaceae in the infants' meconium, and of the genus *Weissella* at 4-12 weeks of age. In addition, infants born to mothers with IPV had smaller increases of Actinobacteria (class Coriobacteriia) measured over time. Higher SRQ-20 scores were significantly associated with lower abundances in the family Veillonellaceae at 20–28 weeks of age. (All  $p < .05$ ). No significant changes in the infants' gut microbiome were found for symptoms of depression or post-traumatic stress.

IPV during pregnancy may have adverse effects on the infants' gut microbiome early in life, indicative of impaired maturation.

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Sunday 17<sup>th</sup> June 2018

Poster Number	Level 1 Topic	Sub Topic By Disorder
PS001-PS012	Clinical	Addictive Disorders
PS013-PS015	Clinical	Anxiety Disorders
PS016	Translational	Anxiety Disorders
PS017-PS018	Clinical	Attention Deficit Disorders
PS019-PS027	Clinical	Bipolar Disorders
PS028	Preclinical	Anxiety Disorders
PS029-PS041	Clinical	Bipolar Disorders
PS042-PS044	Clinical	Childhood & Adolescent Disorders
PS045-PS056	Clinical	Dementia
PS057-PS080	Clinical	Depression
PS081	Translational	Depression
PS082	Clinical	Bipolar Disorders
PS083-PS097	Clinical	Depression
PS098	Preclinical	Schizophrenia
PS099-PS100	Clinical	Depression
PS101	Clinical	Attention Deficit Disorders
PS102-PS110	Clinical	Depression
PS111	Clinical	Epilepsy
PS112-PS113	Clinical	Obsessive-Compulsive Disorders
PS114-PS128	Clinical	Others
PS129	Translational	Attention Deficit Disorders
PS130-PS131	Clinical	Panic Disorders
PS132-PS134	Clinical	Post Traumatic Stress Disorders

PS001

## Systematic evaluation of dose-escalation strategies after initial non-response to standard-dose antidepressant pharmacotherapy in unipolar depression

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**Objectives:** To examine if increasing the dose of an antidepressant drug (high-dose treatment, dose escalation) is beneficial for unipolar depressive patients with insufficient initial symptom improvement after standard-dose treatment with the same antidepressant.

**Methods:** In a systematic literature survey, all randomized controlled trials (RCTs) that compared a dose increase directly to the continuation of standard-dose medication in depressive patients with initial non-response to standard-dose pharmacotherapy with the same antidepressant were identified. Primary outcome was mean change in the Hamilton Rating Scale for Depression (HAM-D) total score. Secondary outcomes were dichotomous response and attrition rates. We estimated effect sizes (Hedges's *g*, risks ratios) applying the Mantel-Haenszel random-effects model. Unrestricted maximum-likelihood meta-regression analyses were used to measure the impact of the degree of the dose increase on the effect sizes.

**Results:** Altogether, 7 trials with 1208 patients investigating fluoxetine (*n*=2, *n*=448), sertraline (*N*=2, *n*=272), paroxetine (*N*=2, *n*=146), duloxetine (*N*=1, *n*=255), and maprotiline (*N*=1, *n*=87) could be included. We found no significant difference for the mean HAM-D total score change between the pooled dose-increase group and the standard-dose continuation group, even not when stratified according to the individual antidepressant drugs. Moreover, there were no between-group differences for response rates, drop-outs due to any reason, and due to inefficacy. On the other hand, significantly more patients in the dose-escalation group dropped out due to side effects. The non-significant meta-regressions indicate no influence of the different amounts of dose increments on effect sizes. Sensitivity analyses suggest robustness of the statistical results.



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**Conclusions:** This systematic review suggests no evidence for dose-escalation strategies in unipolar depression in case of initial non-response to standard-dose pharmacotherapy; at least for the five investigated antidepressants. Since the high-dose treatment was not accomplished by a significant increase of the overall attrition rates, appropriate tolerability and acceptability of this pharmacological strategy can be assumed.

**Key words:** unipolar depression, treatment resistance, non-response, high-dose treatment, antidepressants

## PS002

### Deep Transcranial Magnetic Stimulation for Smoking Cessation study: Sampling characteristics.

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**BACKGROUND:** Transcranial Magnetic Stimulation (TMS) is a technique to modulate neuronal activity over specific brain areas related to multiples neuropsychiatric diseases. TMS and Deep TMS are promising tools to treat nicotine addiction. This prospective, placebo-controlled, randomized, double-blind trial aims to evaluate the efficacy/safety of dTMS on smoking cessation, using H-ADD coil on activation parameters over the bilateral prefrontal cortex and insula.

**OBJECTIVE:** To describe sampling limitations.

#### METHODS:

The inclusion criteria are:

- > 10 cigarettes/day, ≥ 1 year, no interruption ≥ 3months
- ♂&♀
- 22-70 years.

The exclusion criteria are:

- Psychiatric disorders other than depression and/or anxiety (HAM-D<15, HAM-A<25)
- Minimental (MMSE)<24
- TMS security violation (ex.pacemakers)
- Motor Threshold>83

#### SAMPLE

From a sample of 59 patients, screened between feb and oct/2017, 84.75% (47) were excluded. The main reasons were:

- Tinnitus/Hearing loss 9
- Axis I mental disorder 6 (TAB, Cyclothymia, Other substances dependence)
- Schedule unavailability 5

- Taking not allowed medication 4
- Frequent headaches 2
- <10 cigarettes/day 2
- Age 2
- Previous seizure 2
- Active Depression 2
- Low MMSE 2
- Cardiac pacemaker 1
- Mixed causes 3

Twelve patients (15.25%) went through neuropsychological examination prior to treatment: 3 voluntarily dropped out. They were 20♂/39♀, with mean age 52.15 years (SD ±10.58),

#### CONCLUSION:

Since smoking is highly comorbid it has been extremely difficult to find an eligible sample for this type of controlled study.

Among the most frequent sample limitations are tinnitus/hearing loss + mental disorder, representing 34,03% individuals.

All other sample limitation causes added 50,72%.

Besides above cited sample limitations, attrition may be related to the high number of consecutive sessions. Literature shows that accelerated TMS is safe and effective; this could be a future alternative to the current design.

## PS003

### Altered Corticostriatal Functional Connectivity in Patients with Methamphetamine Psychosis

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**Objectives:** Methamphetamine (METH) can cause psychosis that closely resembles the symptoms observed in schizophrenia. Dysregulation of corticostriatal circuitry that has been implicated in the etiology of schizophrenia might mediate the risk of drug-related psychosis. However, most studies examining the functional connectivity (FC) related to METH-associated psychosis

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(MAP) typically enrolled a drug-naïve group for comparison. In this study, we used resting-state functional magnetic resonance imaging (rs-fMRI) to characterize the corticostriatal FC alterations in individuals with MAP, by comparing with age-, gender-, and education-matched METH abusers with no psychosis (MNP), schizophrenia patients and healthy controls.

**Methods:** Rs-fMRI was acquired in 11 participants with MAP, 11 MNP, 8 schizophrenia, and 8 controls. Whole-brain voxelwise statistical maps quantified the strength of functional connectivity between 6 striatal seed regions of interest (3 caudate and 3 putamen) per hemisphere and all other brain regions.

**Results:** MAP group exhibited abnormal patterns of aberrant corticostriatal FC when compared to healthy controls. A dorsal-to-ventral gradient of hypoconnectivity to hyperconnectivity between caudate and prefrontal regions was observed. The gradient was not noted for putamen, which overall showed decreased connectivity with other brain regions. When compared to MNP group, the above gradient is less remarkable in MAP group whereas decreased connectivity between putamen and inferior parietal/posterior cingulate gyrus became manifest. On the contrary, MAP group showed increased corticostriatal FC than schizophrenia group, in particular, between striatum and ventral tegmental area (VTA).

**Conclusions:** We suggest that MAP was characterized by the simultaneous presence of corticostriatal hypoconnectivity and hyperconnectivity, with a dysconnectivity pattern different from MNP and schizophrenia. The dysconnectivity was most extensive in schizophrenia group, followed by MAP, then MNP and control group. A decreased FC between putamen and inferior parietal/posterior cingulate gyrus might reflect a risk phenotype for psychosis in METH users. Furthermore, striatal-VTA hyperconnectivity might help differentiate MAP and schizophrenia.

**Keywords:** methamphetamine psychosis; schizophrenia; resting-state fMRI; corticostriatal circuitry; ventral tegmental area

## PS004

### Morphological abnormalities in the globus pallidum as a vulnerability marker for gambling disorder

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#### Introduction

Gambling disorder (GD) is a common and functionally impairing condition, recently classified in the category of substance-related and addictive disorders (DSM-5). Despite being implicated in disease models of behavioural addictions, relatively little is known about sub-cortical abnormalities in GD, and whether these extend to people at risk of future GD. In the current study, we examined subcortical structures and relationships with clinical measures among GD, at risk gamblers, and matched healthy controls (HC).

#### Method

18 GD patients, 14 at risk gamblers, and 22 matched HC were recruited in the study. Subcortical structural analyses were conducted using FIRST implemented in FMRIB Software Library (FSL). We specifically examined striatum and globus pallidus, based on existing models of disordered gambling, including in the context of Parkinson's Disease. Differences in sub-cortical volumes of interest among 3 groups were explored using ANOVA, and localized subcortical morphology in the combined group of GD and at risk gamblers was compared with that of HC group, using permutation testing. The participants were also examined with Eysenck Impulsivity Questionnaire (EIQ) to explore potential correlations with structural brain changes.

#### Result

Groups did not differ for age, gender or IQ. Participants with GD and at risk gamblers had elevated impulsiveness on the Eysenck questionnaire, versus controls ( $F=7.15$ ,  $p=0.002$ ). No significant volume differences among 3 groups were found for subcortical regions of interest. However, significant morphological abnormalities, common to GD and at risk gamblers, were identified in bilateral globus pallidum and left putamen. Localized contraction in right globus pallidus strongly correlated with the impulsivity score ( $r=0.51$ ,  $p<0.001$ ).

#### Conclusion

Structural abnormalities of subcortical structures, especially globus pallidum which is involved in inhibitory control, appear to play a key role in the pathophysiology of gambling disorder, and this feature was common between GD and at risk gamblers.

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## PS005

### Cognitive and neuroanatomical alterations associated with chronic exposure to levamisole-adulterated street cocaine

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Currently, levamisole is the most common cocaine adulterant worldwide and it is known to induce a variety of adverse immunological side effects. Animal studies and human case reports suggested potential neurotoxicity of the compound but neither neuroanatomical nor cognitive effects of levamisole have been investigated in humans so far. Therefore, we examined cognitive and cortical impairments in chronic cocaine users with low and high exposure to levamisole objectively determined by quantitative toxicological hair analyses. In Study 1, we compared 26 chronic cocaine users (CU) with low levamisole exposure in hair, 49 matched CU with high levamisole exposure in hair, and matched stimulant-naïve healthy controls (n=78) with regard to cognitive functioning using a comprehensive neuropsychological test battery. In Study 2, we investigated cortical thickness from structural magnet resonance imaging data of the frontal cortex and an occipital control region in a subgroup of 12 CU with low exposure to levamisole, 17 CU with high exposure to levamisole, and 38 stimulant-naïve healthy controls. In Study 1, both CU groups showed significant impairments in the cognitive domains of attention and working memory as well as in the global cognitive index. However, CU with high exposure to levamisole showed significantly worse executive functions compared to CU with low levamisole exposure although both groups did not differ in severity of cocaine consumption and other clinical dimensions. Study 2 revealed that high levamisole exposure CU showed reduced cortical thickness specifically in the middle frontal gyrus – a region well-known to be involved in executive functioning – compared to low levamisole exposure CU and controls. In conclusion, our results suggest that levamisole-exposure is associated with increased cognitive impairment and pronounced thinning of the lateral prefrontal cortex in cocaine users likely impacting their everyday functioning. Consequently, prevention and harm reduction approaches should aim to reduce levamisole contamination of street cocaine.

## PS006

### Increased Serum Levels of PVRL4 in Ketamine-Dependent Patients and the Correlation with Emotional Abuse

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**Background:** Ketamine has emerged as a major substance of abuse worldwide. The mechanisms underlying the development of addiction have been unclear yet. PVRL4 (nectin-4) is a 66 KD cell adhesion molecule that involves in cell migration, proliferation, and invasion. Though PVRL4 is known to be associated with tumor metastasis and ectodermal dysplasia-syndactyly syndrome, its role in brain disorders remains unclear. Previous study reported nectin family can serve as a serological marker for traits of neuroticism and stress-related behavior alterations. The pilot study was aimed to examine the differences of serum concentrations of PVRL4 between ketamine-dependent patients and healthy controls and the relationship with stress-related clinical characteristics.

**Methods:** We recruited 57 subjects that fulfilled the DSM-IV diagnostic criteria of ketamine dependence from inpatient and outpatient department of Taipei City Psychiatric Center and had their last dose of ketamine within 24 hours before enrollment. We also included 21 healthy controls without a history of systemic or psychiatric illnesses. Serum levels of PVRL4 were assessed by enzyme-linked immunosorbent assay. The ketamine-dependent patients were assessed using Visual Analogue Scale of craving (VAS), Severity of Dependence Scale (SDS), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). Childhood Trauma Questionnaire-Short Form (CTQ-SF) was used to measure a range of childhood trauma types.

**Results:** Compared to controls, ketamine-dependent patients had significantly higher serum level of PVRL4. Serum PVRL4 levels correlated inversely with emotional abuse (EA) scores ( $r=-0.292$ ,  $p=0.038$ ), but without significant correlations with VAS, SDS, BDI, BAI, or other types of childhood trauma. The PVRL4 levels were significantly lower in ketamine-dependent patients with EA than those without ( $p=0.039$ ).

**Conclusion:** We observed for the first time that chronic and heavy ketamine use was associated with an increased PVRL4 level. The increased levels of PVRL4 correlated inversely with EA severity. Our results suggest cell

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adhesion molecules might be upregulated in the neuroadaptive response to long-term ketamine use. In addition, those with EA might develop a less compensatory adaptation. A larger sample to replicate the preliminary finding and further mechanism exploration is required.

## PS007

### **Mesolimbic cue-reactivity predicts drinking outcome in OPRM1 A118G carriers: a functional imaging study in alcohol dependent subjects**

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#### **Specific objective of the study**

The development and maintenance of alcohol addiction is a complex interaction between environmental factors and a person's predisposition. The endogenous opioid system is involved in the pathophysiology of alcohol-use disorders. Genetic variants of the opioid system alter neural and behavioral responses to alcohol. In particular, a single nucleotide polymorphism rs1799971 (A118G) in the mu-opioid receptor gene (OPRM1) is suggested to modulate alcohol-related phenotypes and neural response in the mesocorticolimbic dopaminergic system. The mu-opioid receptor (MOR), encoded by the OPRM1 locus, mediates in part the reinforcing properties of alcohol. It is also the target for naltrexone that is clinically used since many years in relapse prevention. Little is known about the clinical implications of these changes.

#### **Methods used**

We investigated genotype effects on subjective and neural responses to alcohol cues (fMRI) and relapse in a sample of abstinent alcohol-dependent patients. In addition, we examined associations between brain activity and clinical variables and relapse risk.

#### **Summary of results**

Our results show that alcohol-dependent G-allele carriers' increased cue-reactivity is associated with an increased relapse risk. This suggests that genotype effects on cue-reactivity might link the *OPRM1* A118G risk allele with an increased relapse risk that was reported in earlier studies.

#### **Conclusions reached**

From a clinical perspective, risk-allele carriers might benefit from treatments, such as neuro-feedback or extinction-based therapy that are suggested to reduce mesolimbic reactivity.

## PS008

### **Sexual behaviour and satisfaction in ketamine abuser in Taiwan: a cross-sectional study**

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#### **BACKGROUND:**

Ketamine abuse in Taiwan is of concern because it is most popular drug and may be used in Raves for sexual excitement. However, it might be linked to urinary incontinence, sexual violence, unprotective sex and sexual dysfunction. Evidence about the sexual dysfunction or sex satisfaction in ketamine abuser is limited. We describe patterns of ketamine use and associations with sexual behaviours and satisfaction in Taiwan.

#### **METHODS:**

We conducted a cross-sectional survey among 578 Han Chinese people which include 453 men(78.4%) and 125 women(22.6%) who have used ketamine and were forced to come for abstinence course. We collected their basic demographic data, drug use history, Chinese health questionnaire and The Arizona Sexual Experience Scale Chinese version scale. Men(222, 49.7%) were more self-aware cognitive impairment than women(54, 43.5%) without statistic difference. People who complains urinary function impairment was not correlated with cognitive impairment (men(206, 26.4%), woman(76, 61.8%). The sexual dysfunction was reported by 100 people(17% of participants) but woman predominately(female, 55; male, 45). The ejaculation subscale of The Arizona Sexual Experience Scale Chinese version scale shows 9.7% men has premature ejaculation..

#### **Discussion:**

Our findings suggest ketamine abuser has sexual dysfunction especially premature ejaculation. Efforts made to provide ketamine side effect in sexual function as a way to reduce ketamine abuse.

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## PS009

### Disulfiram-induced seizures with convulsions in a young male patient: A case study

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**Background and Objectives:** Disulfiram has been used in the management of alcohol dependence as an aversive therapeutic agent for over 50 years, and it has been shown to be efficacious when taken under supervision. It inhibits the enzyme called aldehyde dehydrogenase, probably after conversion into the active metabolite. In addition to the physical symptoms associated with the concomitant use of alcohol, disulfiram may lead to adverse drug reactions when used alone, which are flushing, throbbing headache, perspiration, etc. The aim of this study is to report a case of disulfiram-induced seizures in a patient of alcohol dependence syndrome.

**Case Report:** A 40-year male patient diagnosed with alcohol dependence for the past 15 years presented with uncomplicated withdrawal symptoms. Detoxification was done using benzodiazepines in tapering dose, and vitamin supplementation was initiated. Interventions, including motivation enhancement therapy, were done for relapse-prevention. Complete blood count, blood sugar, liver, and renal function tests, Serum electrolytes, were within normal limits. After patient gave written informed consent, disulfiram was started at a dose of 250 mg twice daily for initial 7 days then once daily dose was continued. Patient after the discharge from hospital readmitted with history of one episode suggestive of generalised tonic-clonic seizures. There was no past history or family history or childhood history of seizures. Physical examination was normal. CT Scan of the brain revealed no abnormality and electroencephalography showed epileptiform discharges.

**Conclusions:** Apart from disulfiram ethanol reaction, evidences suggest that disulfiram when used alone can cause various effects and adverse effects including seizures, which are rare but needs to be considered. This needs further research on mechanisms by which disulfiram causes seizures with convulsions and about prevention.

## PS010

### Is the Glasgow Modified Alcohol Withdrawal Scale (GMAWS) a reliable tool for monitoring of alcohol withdrawal in an acute hospital setting? A Singapore-based study.

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#### Introduction

Alcohol Withdrawal Syndrome (AWS) is a common presentation to acute hospitals and if not managed adequately can lead to adverse outcomes. Adherence to the gold standard Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) in a busy general hospital setting is challenging to ensure.

The 5-item Glasgow Modified Alcohol Withdrawal Scale (GMAWS) (Figure 1) was found by a team in Glasgow to be a reliable and easier to use monitoring tool (McPherson, Benson, & Forrest, 2012). It also aimed to provide clinicians with a treatment algorithm based on the scores.

<b>Tremor</b> 0) No tremor 1) On movement 2) At rest
<b>Sweating</b> 0) No sweat visible 1) Moist 2) Drenching sweats
<b>Hallucination</b> 0) No present 1) Dissuadable 2) Not dissuadable
<b>Orientation</b> 0) Orientated 1) Vague, detached 2) Disorientated, no contact
<b>Agitation</b> 0) Calm 1) Anxious 2) Panicky

Figure 1

#### Objectives

To determine the clinical utility of GMAWS in the management of alcohol withdrawal in an acute hospital setting in Singapore.

#### Methods

Patients who were deemed by the primary clinician to be at risk for alcohol withdrawal were placed on the GMAWS as the intervention arm (IA). Clinical outcomes were compared to a retrospective arm of patients who were

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screened to be at risk for alcohol withdrawal prior to the implementation of GMAWS (treatment-as-usual arm, TA).

## Results

Clinical outcomes of 50 subjects in IA were compared with 54 subjects from TA. Subjects in IA were admitted for an average of 6.94 days compared to 6.41 days in TA. 25% of subjects in IA required restraints compared to 13% in TA. Both arms had 4% of subjects who became aggressive. 8% of subjects in IA compared to 4% in TA had a withdrawal seizure while in hospital. 4% in IA were diagnosed with delirium tremens compared to 7% in TA. No subjects in both arms required high dependency or intensive care unit as a result of AWS. There were no deaths in both arms due to AWS. Only 3 out of 54 subjects in TA were placed on an AWS monitoring tool.

Statistical analysis remains ongoing to determine if there are significant difference in the data.

## Conclusion

The usage of GMAWS hopes to improve identification of alcohol withdrawal specific symptoms by clinicians and nurses using a routine monitoring tool. We await the results from statistical analysis to determine if it is a reliable alternative for AWS monitoring and not inferior to TA in a busy inpatient hospital setting.

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## PS011

### A Decade Experience of Methadone Maintenance Treatment In Taiwan From 2006 To 2016

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Due to HIV prevalence increased significantly by intravenous drug users (IDU) in 2006, HIV spread by IDU is 72% of HIV case diagnosed in 2006. Center for disease control, Taiwan (CDC) started IDU harm reduction pilot program in 2005, and formally started IDU harm reduction program in 2006. HIV spread route by IDU had been significantly decreased to 5%. Methadone Maintenance Treatment Program (MMT) had been argued for years in Taiwan. The medical professionals have more better

methods to resolve the problems of heroin addicts after MMT started to be executed.

Collect related data by literatures review, website information and government document compared with the past related experience. The result of this study release, because of MMT program, the spread of HIV by IDU has been significantly controlled. The life quality, economic status also improves in heroin addicts. Data analysis from Ministry of Justice, the amount of first degree illicit drugs and prosecuted due to use first degree illicit drugs decrease gradually in recent years. In data analysis from CDC system, data extracted by two methods are different significantly in attendance rate of addicts on MMT program.

It is recommended that related authority should collect the correct data since MMT implemented from all institutions that executed MMT program. Data transformation from old Management Information System (MIS) to new MIS correctly is also suggested. Finally, adjusting new MIS gradually according to response to users is also should be done.

Keywords : HIV Harm Reduction Program, Heroin, Methadone Maintenance Treatment

## PS012

### APBB2 is associated with amphetamine use in a methadone maintenance treatment population

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**Objectives:** APBB2, amyloid beta (A4) precursor protein-binding family B member 2, has been reported to be associated with opioid dependence. In this study, we reported the first time that the genetic variants in the *APBB2* gene were associated with use of amphetamine in opioid dependent patients undergoing methadone maintenance treatment (MMT).

**Methods:** 344 heroin-dependent patients undergoing MMT were recruited and assessed for use of amphetamine and opioids by urine toxicology, withdrawal severity, and side effects. DNAs were genome-widely genotyped for all patients. Single nucleotide polymorphisms (SNPs) in

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*APBB2* were selected for association analyses for methadone treatment responses. Gene expression levels of *APBB2* were measured by real-time polymerase chain reaction (PCR) in the EBV-transformed lymphoblastoids from patients.

**Results:** MMT patients who used amphetamine showed a significantly higher percentage of positive results in the urine morphine test ( $P=0.005$ ), and insomnia ( $P=0.018$ ). In single locus association analyses, SNPs rs3935357 and rs4861075 located at intron 6 were significantly associated with amphetamine use in both genotype and allele type (general linear model (GLM),  $P=0.0003$ , and  $0.0002$  for genotype, and  $0.0003$ , and  $0.002$  for allele type, respectively). The major allele type carriers had twice risk of amphetamine use compared to the minor allele type carriers. Subjects with the TT genotype of rs4861075 showed significantly higher levels of *APBB2* gene expression in both total ( $P=0.02$ ) and long-form ( $P=0.037$ ) than those with CC genotype.

**Conclusion:** Genetic variants in the *APBB2* gene were associated with use of amphetamine in opioid dependent patients under MMT. In the functional SNP rs4861075, it showed that the levels of the total- and long-form *APBB2* gene expression were positively correlated to the severity of amphetamine use. Detailed mechanisms underlying the association of *APBB2* with amphetamine use and level of plasma amyloid beta in MMT patients require further investigation.

**Keywords:** APBB2; amphetamine; methadone

## PS013

### Social Anxiety Disorder patients exhibits reduced 5-HT<sub>1A</sub> receptor binding across the cerebral cortex – Improved cortical quantitative analysis of positron emission tomography data using Freesurfer

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#### Objectives

Social anxiety disorder (SAD) is associated with alterations in the serotonin neurotransmitter system [1] and previous findings suggest decreased availability of the serotonin-1A receptor subtype (5-HT<sub>1A</sub>) in several brain regions using

positron emission tomography (PET) and volumetric data processing approaches [2]. PET-dedicated extensions of the software Freesurfer have recently provide a major contribution to the field of molecular neuroimaging by enabling a detailed analysis of the cerebral cortex due to the reconstruction of its surface, including better statistical power and improved inter-subject co-registration of different cortical areas [3]. In the present study we applied this method to examine if these former findings can be verified and extended in more detail to cortical maps.

#### Methods

In a study sample of 12 SAD patients (age $\pm$ SD 32.08  $\pm$ 8.6) and 30 healthy subjects (26.7  $\pm$ 6.8) we quantified the 5-HT<sub>1A</sub> receptor binding potential (BP<sub>ND</sub>) using the radioligand [carbonyl-11C]WAY-100635. Surface reconstruction and co-registration to structural magnetic resonance images were done with Freesurfer 6.0. We quantified the cortical 5-HT<sub>1A</sub> receptor distribution by applying the multilinear reference tissue model [4]. To test for statistical differences in binding, we performed a linear mixed model including 33 regions, using group as fixed factor and *post-hoc* t-tests to examine the relevant areas.

#### Results

Linear mixed model analysis yielded a main effect of group ( $F(1, 31.09) = 4.5$ ,  $p=0.042$ ). *Post-hoc* t-tests revealed a significantly decreased binding of averagely more than 30% in 19 regions, including the frontal pole, parahippocampal gyrus, the parietal, inferiortemporal, entorhinal and insular cortices.

#### Conclusion

We could confirm the outcome of previous studies and were able to demonstrate a significantly decreased binding of 5-HT<sub>1A</sub> receptors in patients with SAD across the cerebral cortex. Using Freesurfer it enabled us to localize cortical 5-HT<sub>1A</sub> receptors binding in greater detail and a more robust outcome in the statistical analysis.

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## PS014

### “Anxious-Depressive Attack” among outpatients on first admission in an anxiety clinic

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**Background:** Anxious-depressive attack (ADA; Kaiya, 2016) is a proposed novel symptom complex associated with anxiety and mood disorders. ADA is, so to speak, a mental version of the panic disorder. The main features of the attack are composed of: (1) sudden intense distressing emotions with no direct psychological cause, (2) intrusive memories of various negative events, (3) worry and agitation regarding the details of the rumination and (4) various coping behaviors, including acting out. This syndrome is typically not recognized by patients themselves. The present study investigated the frequency and diagnostic confirmation rate of ADA in new outpatients.

**Methods:** New outpatients were randomly selected to undergo the Mini-International Neuropsychiatric Interview (MINI) and the Structured Clinical Interview for DSM Disorders (SCID). Patients were examined if they experienced ADA. We examined the nature of ADA—frequency of the attack, severity of distressing emotions, contents of intrusive memory, and varieties of coping behaviors, by a psychiatrist and a clinical psychologist, separately.

**Results:** Concordance for the presence of ADA between the psychiatrist and the psychologist was moderate ( $\kappa = 0.59$ ,  $p < .001$ ), and eight patients with ADA were confirmed among a sample of 106 patients. Patients with ADA exhibited more depressive symptoms ( $t = -4.52$ ,  $p < .01$ ), more anxious symptoms ( $t = -2.72$ ,  $p < .05$ ), greater sensitivity to rejection ( $t = -4.71$ ,  $p < .001$ ), and worse CGI scores ( $t = -3.04$ ,  $p < .05$ ) than those without ADA.

**Conclusion:** ADA was identified in approximately 8% of outpatients. Patients exhibiting ADA were more depressive and anxious, and more sensitive to interpersonal rejection.

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## PS015

### Mindfulness-based cognitive therapy for community-dwelling adults with anxiety symptoms: An exploration of efficacy and cognitive mechanism

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**Background:** Mindfulness, originally derived from the Buddhist tradition, is commonly defined as the awareness cultivated by paying attention to the present moment in a non-judgmental manner. The Mindfulness-based cognitive therapy (MBCT) combining mindfulness meditation practices with elements from cognitive-behavioral therapy was developed as a relapse prevention program for patients suffering from major depression. Clinical trials conducted in recent years suggested that MBCT could be effective in reducing acute anxiety symptoms. Positive effects of mindfulness meditation on executive functioning have also been reported, suggesting that improved executive control could be the mechanism underlying the clinical outcomes of MBCT.

**Objective:** The aim of this clinical trial is to investigate the efficacy of MBCT for anxiety symptoms in community-dwelling adults comparing with an active control, and to examine the impact of MBCT on executive functioning.

**Method:** A total of 43 participants were randomized to receive either MBCT or a psychoeducation and physical exercise program. Both interventions lasted for eight weeks and participants were assessed at baseline, end of treatment, and two months after treatment. Paper-based inventories were used to measure participants' psychological well-being, anxiety level, depressive symptoms, and mindful awareness in daily life. Computer-based neuropsychological tests were used to assess participants' executive functioning.

**Results:** Significant reductions in anxiety and other psychological symptoms were observed at the end of treatment in both groups. The MBCT group showed improved performance in specific executive functions such as inhibition and cognitive flexibility. Preliminary data from follow-up at two months after treatment suggested that MBCT might have more long-lasting impact on participants' psychological well-being.

**Conclusion:** MBCT could be an effective treatment for reducing anxiety and other psychological symptoms in community-dwelling adults. Such benefits could be accounted for by improved executive functioning following mindfulness meditation practices. Future directions include clinical trials with neuroimaging measures and combination with neuromodulation treatments.



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## PS016

### Combinatorial Pharmacogenomic Testing Decreases Benzodiazepine Use and Improves Antidepressant Response in Individuals with Generalized Anxiety Disorder

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**Background:** Controlled substance prescription use in US has become a public health epidemic. Benzodiazepine abuse in 2013, specifically, has increased 400% since 1996. Generalized anxiety disorder (GAD) was the most frequent reason benzodiazepines were prescribed (56% of prescriptions). Although antidepressants are the first-line pharmacological treatment for GAD, only 30-50% of patients respond to the first antidepressant. Thus, there is a strong need for improving GAD treatment. Previously, GeneSight®, a psychiatric pharmacogenomic decision support tool, was reported to significantly: a) improve depressive symptoms in treatment-resistant depression patients; b) reduce prescription costs; and c) decrease polypharmacy. Thus, our primary goal is to evaluate whether the combinatorial pharmacogenomics report leads to a reduction in benzodiazepine use and an improvement in antidepressant response in GAD patients.

**Methods:** We analyzed data from two separate studies: (1) Individualized Medicine: Pharmacogenetic Assessment and Clinical Treatment (IMPACT) study, a longitudinal pilot research program, where 315 participants with anxiety disorders (N=210 with GAD) and follow-up data on symptom severity using the GAD-7 questionnaire were identified; and (2) MEDCO dataset (Winner et al., 2015 Curr Med Res Opin.;31:1633-43) in which patients (N=660) who were prescribed at least one benzodiazepine six months pre-testing and were followed six months post-testing.

**Results:** The IMPACT analyses showed that medication decisions guided by (congruent) the combinatorial pharmacogenomics test results led to significantly greater improvement in anxiety symptom severity (congruent: -44.9±35.9% versus non-congruent: -25.5±31.8%; t=2.19; P=0.031). For MEDCO, 18% (N=116) of the patients originally taking at least one benzodiazepine pre-testing ceased their use of benzodiazepines, with a significant decrease in benzodiazepine drug counts and refills post-

testing (mean count 1.2 versus 0.9, P<0.001; mean refill 3.3 versus 2.9, P<0.001). **Conclusion:** These are the first large longitudinal GAD studies demonstrating the effectiveness of a combinatorial pharmacogenomics test, leading to improved symptoms and decreased benzodiazepine use.

## PS017

### Effects of methylation on the norepinephrine transporter expression measured by PET in ADHD.

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#### Objectives

Attention Deficit Hyperactivity Disorder (ADHD) is common neurodevelopmental disorder with a strong genetic influence [1]. As ADHD is a complex and a polygenetic disorder, the possible regulation by epigenetic processes has received increased attention [2]. Our objective was to examine possible differences in the DNA methylation levels of CpG sites in the norepinephrine transporter (NET) promoter between patients with ADHD and healthy controls. Furthermore, we tested whether differences are demonstrated in differential expression levels of the NET measured by PET.

#### Methods

25 adult non-medicated ADHD patients (age±SD: 30.5±9.6, 15 males) and 25 healthy controls (age±SD: 30.7±9.9, 15 males) were included in this study. Subjects underwent a (S,S)-[<sup>18</sup>F]FMeNER-D<sub>2</sub> PET scan using an advance full-ring scanner (General Electric Medical Systems, Milwaukee, WI, USA) in 3D acquisition mode. DNA was extracted and converted into bisulfite using the EZ-96 DNA methylation kit [3]. NET binding potential (BP<sub>ND</sub>) values were quantified using the caudate as a reference region. Average mean of methylation levels was calculated for two regions (high (region A) vs low methylation (region B)) of the NET promoter gene. Potential association with behavioural scales and NET BP<sub>ND</sub> were tested for.

#### Results

Across region A, patients with ADHD had higher methylation (0.47) in comparison to healthy controls (0.37)(p<0.01). In region B, patients had lower methylation

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(0.12) compared to controls (0.13)( $p < 0.02$ ). Negative correlation was detected between CpG site 4 with the NET BP<sub>ND</sub> of the thalamus ( $r = -0.59$ ) and locus coeruleus ( $r = -0.51$ ) in patients only. Several CpG sites were negatively associated with hyperactivity-impulsivity symptom scores.

## Conclusions

Our results support the idea of an epigenetic dysregulation in ADHD. We detected hypermethylation in ADHD patients in region A while this effect reversed for region B. Negative association between methylation levels and hyperactivity-impulsivity scores was detected as well as between a CpG site and in vivo NET expression in patients. Further studies are warranted.

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[3] Suchiman, H.E., Sliker, R.C., Kremer, D., Slagboom, P.E., Heijmans, B.T., Tobi, E.W. (2015) Design, measurement and processing of region-specific DNA methylation assays: the mass spectrometry-based method EpiTYPER. *Front Genet*, 6:287.

Keywords: methylation, epigenetics, ADHD, norepinephrine transporter, positron emission tomography

## PS018

### Omega-3 Fatty Acids in Youth with Attention Deficit Hyperactivity Disorder

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**Objectives:** Deficiency in omega-3 fatty acids, a type of essential fatty acids (EFA), has been associated with cognitive function and emotional regulation, and it has also been associated with the manifestation of attention deficit hyperactivity disorder (ADHD). This study

investigated the association of omega-3 fatty acids and clinical symptoms in youth with ADHD.

**Methods:** The first part of the study examined the relationship between omega-3 fatty acids intake (EFA deficiency, measured using Fatty Acid Deficiency Symptoms Questionnaire), and ADHD symptom severity, in 21 youth diagnosed with DSM-IV ADHD and 21 typically developing youth (TD). The second part of the study is a meta-analysis of 7 clinical trials of omega-3 fatty acids supplementation in youth with ADHD (n=534).

**Results:** The ADHD youth, when compared with TD, had a greater severity of EFA deficiency ( $7.24 \pm 4.56$ ,  $p = .02$ ). Moreover, the severity of ADHD symptoms was positively correlated with severity of EFA deficiency. Meta-analysis showed ADHD youth had lower levels of total omega-3 fatty acids ( $g = -0.58$ ,  $p = 0.0001$ ), and that omega-3 fatty acids supplementation, compared with placebo, improved ADHD clinical symptom scores ( $g = 0.38$ ,  $p < 0.0001$ ) in ADHD youth.

**Conclusion:** Youth with ADHD have EFA deficiency and lower levels of omega-3 fatty acids. Moreover, omega-3 fatty acid supplementation improves inattention and hyperactivity symptoms in ADHD youth. Our study further supports the role of omega-3 fatty acids in ADHD. Omega-3 fatty acids may serve as an alternative treatment option for youth with ADHD.

## PS019

### Efficacy and safety of treatments in bipolar depression in randomized controlled trials: Systematic review and meta-analysis

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#### Aims:

The aim of this research was testing whether treatments including antipsychotics, antidepressants, anticonvulsants, and lithium are associated with different clinical benefits and harms for the acute bipolar depression.

#### Methods:

We conducted systematic review and meta-analysis of randomized placebo-controlled trials (RCTs) assessing the clinical benefit and harm of treatments for bipolar depression, using number needed to treat (NNT), number

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needed to harm (NNH), and likelihood of being helped or harmed (LHH, NNH/NNT)

## **Results:**

We identified 42 RCTs (antipsychotics=22, antidepressants=6, anticonvulsants=13, and lithium=1).

Some antipsychotics (cariprazine, lurasidone, olanzapine, olanzapine+fluoxetine, and quetiapine) had significantly higher response rate compared with placebo and they had single digit NNT though aripiprazole and ziprasidone were not. Cariprazine, lurasidone, olanzapine, and olanzapine+fluoxetine appeared to be well tolerated as there was no significant difference between these antipsychotics and placebo in adverse effect-related discontinuation rates. Aripiprazole, quetiapine, and ziprasidone had significantly higher discontinuation rate due to adverse effect.

Antidepressants except for fluoxetine were not significantly different from placebo in treatment response though they were well tolerated. Anti-convulsants were effective, but significant difference from placebo was observed only with lamotrigine and valproate, and they were well tolerated. Lithium appeared to be poorly effective but well tolerated in only one trial.

## **Conclusions:**

Meta-analysis results suggest that there are significant differences in the clinical benefit and harm among treatments for bipolar depression. Some antipsychotics, anticonvulsants and fluoxetine seemed effective for acute bipolar depression, but most antidepressants were not. Lithium remain inadequately tested. New drug development needs to focus on trade-offs between clinical benefit and harm.

## **PS020**

### **Benefits and harms of atypical antipsychotics in the treatment of bipolar depression: A systematic review and meta-analysis**

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## **Aims:**

The aim of this systematic review and meta-analysis was testing whether atypical antipsychotics (AAPs) are

associated with different clinical benefits and harms for the acute treatment of bipolar depression.

## **Methods:**

We conducted systematic review and meta-analysis of randomized placebo-controlled trials (RCTs) assessing the efficacy and adverse effects of AAPs in acute bipolar depression to compare clinical benefits and harms. We assessed clinical benefit and harm of AAPs for major depressive episodes associated with bipolar disorder, using number needed to treat (NNT), number needed to harm (NNH), and likelihood of being helped or harmed (LHH, ratio of NNH to NNT).

## **Results:**

We identified 22 RCTs with a total sample size of 8,823 patients. Some antipsychotics (cariprazine, lurasidone, olanzapine, olanzapine+fluoxetine and quetiapine) had significantly higher response rate compared with placebo and they had single digit NNT. Aripiprazole and ziprasidone, however, were not significantly different from placebo in treatment response.

Cariprazine, lurasidone, olanzapine, and olanzapine+fluoxetine appeared to be well tolerated as there was no significant difference between these AAPs and placebo in adverse effect-related discontinuation rates. Aripiprazole, quetiapine, and ziprasidone had significantly higher discontinuation rate due to adverse effect. Lurasidone, Olanzapine and Quetiapine showed favorable profile for benefit and harm balance in the treatment of bipolar depression with lurasidone demonstrating most favorable LHH among all.

## **Conclusions:**

In conclusion, results from this meta-analysis suggest that there are some significant differences in the clinical benefit and harm among AAPs in the treatment of bipolar depression. New drug development needs to focus on trade-offs between clinical benefit and harm.

## **PS021**

### **Safety/tolerability of atypical antipsychotics in the treatment of bipolar depression: A systematic review and meta-analysis**

Katsuhiko Hagi, PhD<sup>1</sup>, Tadashi Nosaka<sup>1</sup>, Andrei Pikalov, MD, PhD<sup>2</sup>, Antony Loebel, MD<sup>2</sup>, Christoph Correll, MD<sup>3,4,5,6</sup>.

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## **Aims:**

The aim of this systematic review and meta-analysis was to meta-analytically compare atypical antipsychotics (AAPs) regarding clinical harms during the acute treatment of bipolar depression.

## **Methods:**

We conducted systematic review and meta-analysis of randomized, placebo-controlled trials (RCTs) assessing the adverse effects of AAPs in patients with acute bipolar depression to compare clinical harms. Clinical harm outcomes included adverse effect-related discontinuation rates, sedation/somnolence, dry mouth, body weight change and  $\geq 7\%$  body weight gain.

## **Results:**

We identified 22 RCTs with a total sample size of 8,823 patients. Cariprazine, lurasidone, olanzapine, and olanzapine+fluoxetine were generally well tolerated, as there was no significant difference between these AAPs and placebo in adverse effect-related discontinuation rates. Conversely, aripiprazole, quetiapine, and ziprasidone had significantly higher discontinuation rates due to adverse effects (risk ratios (RRs)=1.49-2.29).

Except for cariprazine and lurasidone, AAPs had significantly higher risk of sedation/somnolence than placebo (RRs=2.42-3.61). Olanzapine, olanzapine+fluoxetine, and quetiapine had significantly higher risk of dry mouth (RRs=2.02-3.80). Cariprazine, olanzapine, olanzapine+fluoxetine, and quetiapine had significantly higher body weight gain than placebo (effect size=0.42-1.19). Finally, lurasidone, olanzapine, olanzapine+fluoxetine, and quetiapine had significantly higher risk of  $\geq 7\%$  body weight gain (RRs=2.93-69.27), with olanzapine and olanzapine+fluoxetine having single digit numbers-needed-to-harm (NNHs=5-6), and with double digit NNHs for lurasidone (NNH=59) and quetiapine (NNH=20).

## **Conclusions:**

Results from this meta-analysis suggest that there are some significant differences in the clinical harm potential among AAPs in the treatment of bipolar depression. New drug development needs to focus on trade-offs between clinical benefit and harm.

## **PS022**

### **Efficacy of atypical antipsychotics in the treatment of bipolar depression: A systematic review and meta-analysis**

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## **Aims:**

The aim of this systematic review and meta-analysis was to compare the clinical benefits of atypical antipsychotics (AAPs) during the acute treatment of patients with bipolar depression.

## **Methods:**

We conducted systematic review and meta-analysis of randomized, placebo-controlled trials (RCTs) assessing the efficacy of AAPs in acute bipolar depression to compare clinical benefits. Clinical benefit outcomes included depressive symptom improvement using the Montgomery-Åsberg Depression Rating Scale (MADRS), global improvement using the Clinical Global Impressions scale for use in bipolar illness (CGI-BP), and treatment response and remission.

## **Results:**

We identified 22 RCTs (n=8,823) testing 7 different AAPs vs. placebo. Five of these AAPs, namely cariprazine, lurasidone, olanzapine, olanzapine+fluoxetine and quetiapine, demonstrated significant improvement in MADRS total scores (effect sizes=0.27-0.58) and the CGI-BP (effect sizes=0.25-0.53). These AAPs had significantly higher response rates compared with placebo (risk ratio=1.30-1.84), translating into single digit NNTs. These AAPs had significantly higher remission rate compared with placebo, and lurasidone, olanzapine+fluoxetine and quetiapine had single digit numbers-needed-to-treat (NNTs=4-9). Conversely, aripiprazole and ziprasidone, were not significantly different from placebo in depressive symptom improvement, treatment response, nor remission.

## **Conclusions:**

Results from this meta-analysis suggest that there are some significant differences in terms of symptoms improvement, treatment response and remission rates among AAPs in the treatment of bipolar depression. These

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data need to be integrated with adverse effect profiles of specific AAPs and individual patient characteristics (e.g., clinical urgency and adverse effect sensitivity) to optimize the management of acute bipolar depression.

## PS023

### **Five year course of bipolar disorder following treatment of first manic episode (FEM) with risperidone versus olanzapine: a retrospective review.**

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**Objective:** Contemporary treatment guidelines recommend use of second generation antipsychotics (SGAs) either as monotherapy or in combination with mood stabilizers as first line treatment. While these drugs have been established to have superior efficacy compared to placebo, there is meagre data comparing these antipsychotics with one another. We sought to study differences in the five year course of first episode of mania (FEM) treated with olanzapine or risperidone, either alone or in combination with mood stabilizer.

**Methods:** We conducted a retrospective chart review of patients diagnosed with FEM (ICD-10) in the year 2008 (n = 108) at our Centre. We selected the data of patients prescribed either olanzapine or risperidone for the purpose of this analysis. We examined time to recovery and recurrence after FEM, total number of episodes, drug compliance and response, and number of follow-up visits from 2008-2013. The study was approved by the Institute Ethics Committee.

**Results:** A total of 108 patients received diagnosis of FEM in the year 2008, out of which 62 (57.4%) received risperidone and 43 (39.8%) received olanzapine. The two groups were comparable in socio-demographic and clinical symptomatology of FEM (all p > 0.08). Complete recovery was significantly more in the olanzapine group than the risperidone group ( $\chi^2=4.84$ ,  $p<0.05$ ). Time to recovery and recurrence and mean number of episodes over five years was comparable between the groups (all p > 0.13).

**Conclusion:** Our study indicates that risperidone and olanzapine, either alone or in combination with mood stabilizers have a similar impact on the five year course of BD following a first manic episode. However, olanzapine is

associated with more complete recovery from FEM than risperidone.

## PS024

### **The development of a “ Web-Mobile” integrated system to improve the medication adherence in major mental illnesses**

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#### **Background**

Major mental illnesses are associated with serious consequences, such as suicide and accidental death, implying the need to implement effective preventive measures. One obstacle to make treatment effective is the poor adherence. Improving medication adherence is therefore one of the most cost-effective strategies for desirable outcomes. However, effective and easy-to-implement interventions to improve adherence are still needed. We thus aimed to develop a “Web+Mobile” integrated system for enhancing the medication adherence.

#### **Methods**

We recruited 30 subjects with major mental illnesses at outpatient clinics. The information regarding medication adherence and related factors, such as symptom severity and adverse effects, were collected from medical records and interview with patients or family members. All information gathered was integrated and depicted as a life chart to display the clinical course. The adherence status to drug therapy during a 6-month period was evaluated according to the life chart, including visiting frequency and duration of prescription.

#### **Results**

The “Web+Mobile” integrated system has been developed with a web-supported management operated by the health care provider and a Mobile APP for the patient. The system may remotely track down the revisit schedule and remind patients of the appointment by sending-out text messages. The intervention-relevant information can be shared between both sides and across in-charge health providers. For confidentiality, we use a multi-layered strategy across industry-best practices and state-of-the-art tools to ensure the data are safe (HIPPA Privacy Standards, 2016). In this combined e- and m-health system, we may provide patient management, input illness journey, and set up revisit notification. For example, the Clinical Global

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Impression scale may be inserted and care provider may evaluate symptom severity in the system.

## Conclusion

The contribution of this study is to give important implication for using an electronic system to improve adherence to long term treatment at the clinical practice.

## PS025

### Effectiveness and Safety of Long-term Treatment with Lurasidone in Children and Adolescents with Bipolar Depression: Interim Analysis at 1-year of a 2-year Open-label Extension Study

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**Objective:** To evaluate long-term effectiveness and safety of lurasidone in children and adolescents with bipolar depression.

**Method:** Patients ages 10-17 with bipolar I depression who completed 6 weeks of double-blind (DB) treatment with lurasidone were eligible to enroll in a 2-year, open-label (OL), flexible-dose (18.5-74 mg/d) extension study. These data are the results of an interim analysis. Effectiveness measures included the Children's Depression Rating Scale, Revised (CDRS-R).

**Results:** A total of 223 patients completed 6 weeks of DB treatment and entered the 2-year extension study. At the time of the interim analysis, 93 patients (41.7%) had completed 52 weeks of OL treatment, 36 patients were still ongoing and had not reached 52 weeks, and 94 patients had discontinued prior to week 52. For patients randomised to DB treatment, significant improvement was observed for lurasidone vs. placebo in the CDRS-R total score at week 6 (-21.0 vs. -15.3;  $P < 0.0001$ ). For patients who completed 6 weeks of DB treatment and entered the extension study, mean CDRS-R total scores at DB and OL baselines were 58.1 and 37.6, respectively. Mean change from OL baseline in the CDRS-R total scores at weeks 12, 28 and 52 were -6.5, -10.0, and -10.7, respectively. During OL lurasidone treatment, the most common adverse events were headache (19.7%), nausea (14.3%), anxiety (9.9%), somnolence (8.5%), and vomiting (8.1%). Small median changes from DB baseline to weeks 28/52 were noted for total cholesterol (-4.5/-5.0 mg/dL), triglycerides (-2.0/-2.0 mg/dL), and hemoglobin A1c (0.0/+0.1 mg/dL); and mean changes in weight at weeks 28/52 were

+3.0/+5.0 kg (vs. an expected weight gain of +2.3/+3.9 kg, based on gender-and-age specific CDC growth charts).

**Conclusion:** In children and adolescents with bipolar depression, up to 52 weeks of treatment with lurasidone was generally well-tolerated, with headache, nausea and anxiety being the most common adverse events.

**Clinicaltrials.gov identifier:** NCT01914393

**Sponsored by Sunovion Pharmaceuticals Inc.**

## PS026

### Efficacy and Safety of Lurasidone in Bipolar Depression: Treatment Review

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Sunovion Pharmaceuticals, Inc., Fort Lee, NJ and Marlborough, MA, USA

**Objective:** To review lurasidone safety and efficacy data in the treatment of adults with bipolar depression.

**Methods:** Lurasidone data are derived from three double-blind, placebo-controlled, 6-week trials of patients with bipolar I depression: monotherapy with lurasidone (fixed-flexible doses of 18.5-55.5 mg/d and 74-111 mg/d, 1 study (N=505); adjunctive therapy with lurasidone (flexible doses of 18.5-111 mg/d) and lithium or valproate, 2 studies (total combined N=1,193); a 6 month open-label continuation study (N=813; flexible doses of 18.5-111 mg/d); an 18-month open-label extension study (N=122; flexible doses of 18.5-111 mg/d); and a separate recurrence prevention study in stabilised bipolar patients who were randomised to 28 weeks of double-blind adjunctive treatment with lurasidone (flexible doses, 18.5-74 mg/d) or placebo (N=496).

**Results:** Treatment with lurasidone significantly reduced mean week 6 MADRS scores in both the monotherapy and adjunctive therapy studies. Continued improvement in mean MADRS score was observed during 6 months of extension treatment, and improvement was maintained during 18 months of continuation treatment. In the recurrence prevention study, among patients with an index episode of bipolar depression, treatment with lurasidone was significantly more effective than placebo in increasing time to recurrence of any mood episode, with a hazard ratio of 0.57 (95% CI=0.34-0.97; Cox model  $P=0.039$ ). In the 3 placebo-controlled short-term studies, adverse events more frequently reported with lurasidone vs. placebo included nausea, somnolence, akathisia, and extrapyramidal symptoms. Across both short-term and long-term studies, minimal changes were observed in weight, lipids, and measures of glycemic control during treatment with lurasidone.

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**Conclusions:** Treatment with lurasidone 18.5-111 mg/d, both as monotherapy and as adjunctive therapy with lithium or valproate, was a safe and efficacious treatment of bipolar depression with minimal effect on weight and metabolic parameters.

**Sponsored by Sunovion Pharmaceuticals Inc.**

## PS027

### Use of Asenapine in the complex chronic patient.

Laura Prats<sup>1</sup>, María Cecilia Navarro<sup>1</sup>, Carlos Alonso<sup>1</sup>

<sup>1</sup> Parc Sanitari Sant Joan de Déu

#### Introduction

Asenapine is an antagonist receptor (5-HT<sub>2</sub>, D<sub>2</sub>, NE alpha-2) focused on treatment of manic and depressive symptoms<sup>1,2</sup>. The evidence for the efficacy of asenapine in the treatment of bipolar disorder comes from a number of clinical studies that focus on patients with manic or mixed episodes<sup>2</sup>.

#### Objective

Evaluate the effectiveness (control of manic symptoms) and tolerability (extrapyramidal effects) of asenapine in bipolar disorder type 1 and schizoaffective disorder, both in the manic phase.

Material and methods

Prospective observational study of 10-week follow-up in a long-stay unit (average stay of 2 years) of complex chronic patients. We included 10 patients who had undergone change to asenapine due to clinical or tolerability issues. The scarce sample is explained by the low number of new admissions in the unit.

The patients were over 18 years of age, with a diagnosis of schizoaffective disorder and bipolar disorder type 1. Emphasize that these are refractory patients, with a history of multiple pharmacological trials and a torpid evolution of their underlying disorder, which has not allowed their reintegration in the community from other devices.

CGI-SI (severity of the disease) and Young mania scale prior to the introduction of asenapine are collected.

After 10 weeks of treatment with asenapine, the global improvement (CGI-GI), the Young mania scale and the extrapyramidal effect scale were collected (Simpson, Angus, 1970).

#### Results

10 patients were included (6 men and 4 women). 50% of them had a diagnosis of bipolar disorder type 1 and the rest a diagnosis of schizoaffective disorder bipolar type. In 40% of cases, the reason for the change of treatment was the poor tolerability to previous pharmacological trials.

In 7 cases, asenapine was administered together with other antipsychotics, and in all cases with mood stabilizers.

The average dose of asenapine was 20mg / day.

The following means were obtained from the baseline scores for the different evaluation scales:

. Severity of the disease (CGI-SI): 5.6

. Young mania scale: 32.12 (severe mania)

After ten weeks:

. Global improvement (CGI-GI): 2 (moderately better).

. Young's mania scale: 14.25

. Extrapyramidal effects scale (Simpson, Angus, 1970): 12.8 (9 in patients not associated with other drugs with extrapyramidal effects).

#### Conclusions

In our experience, Asenapine is effective for the clinical management of severe manic symptoms in patients with resistant bipolar and / or schizoaffective disorders. Patients have adequate tolerability at the level of extrapyramidal side effects.

Further research is needed to reach conclusive results. A study with a larger sample, which is limited by the low rate of admissions / discharge in our unit.

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## PS028

### Overexpression of sigma-1 receptor rescues (G4C<sub>2</sub>)RNA repeats-mediated defect in the nucleocytoplasmic transport of Ran GTPase: implication in ALS

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The GGGGCC (G<sub>4</sub>C<sub>2</sub>) hexanucleotide repeat expansions within *chromosome 9 open reading frame 72 (C9ORF72)* have been characterized as the most common genetic abnormality in amyotrophic lateral sclerosis (ALS). Expanded G<sub>4</sub>C<sub>2</sub> repeats led to the mislocalization of nuclear pore complex (NPC) component protein nucleoporins in *C9ORF72* motor cortex as well as the nucleocytoplasmic transport defect of Ran GTPase in patient-derived induced pluripotent stem cells (iPSCs) neurons. G<sub>4</sub>C<sub>2</sub> repeat expansions can directly interact with Ran GTPase-activating protein 1 (RanGAP1), leading to the nucleocytoplasmic transport disruption by impairing the nucleus/cytosol (N/C) gradient of Ran GTPase. Therefore,

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understanding how G<sub>4</sub>C<sub>2</sub> repeat expansions work in the NPC is important for treatment of ALS/FTD patients. Our results showed that sigma-1 receptors (Sig-1Rs) bind to FG-repeat NPC nucleoporins and increase their half-life. Immunoprecipitation assay and fluorescence confocal microscopy revealed that Sig-1Rs interact with RanGAP1 in the nuclear envelopes. The biotin labeled G<sub>4</sub>C<sub>2</sub> RNA repeats interacted with the recombinant glutathione S-transferase (GST)-tagged Sig-1Rs proteins in the GST pull-down assay. We also found here that by using the RNA fluorescence in situ hybridization (RNA-FISH) assay that Sig-1Rs partly colocalize with Cy3-labeled G<sub>4</sub>C<sub>2</sub> RNA repeats in the perinuclear region. Interestingly, the overexpression of Sig-1Rs can attenuate the defect of N/C ratio of RanGTPase caused by the G<sub>4</sub>C<sub>2</sub> repeats. Our results propose a novel mechanism whereby increasing the level of Sig-1Rs in the NPC by pharmacological or cellular biological means may represent a novel avenue for treating the C9ORF72 G4C2-repeats subtype of ALS (This work was supported by IRP/NIDA/NIH/DHHS)

## PS029

### Prediction of functional impairment in bipolar disorder with machine learning techniques

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**Background:** Early interventions may result in better clinical outcomes in bipolar disorder (BD). Therefore, accurate and objective tools with sufficient sensitivity and specificity are needed to predict which patients will have functional impairment. Differentiating these groups of patients will allow for front-loaded preventative interventions rather than post-hoc attempts to remediate functional impairment. Machine learning algorithms with a great potential for prediction and stratification of clinical outcomes that might be helpful in this scenario.

**Objective:** To create a predictive signature to identify single-individual risk for functional impairment in patients with BD. **Method:** 68 euthymic BD subjects were included. We used random forest with recursive feature elimination coupled with clinical variables that existed prior to the current state of euthymia to predict which patient would have functional impairment as assessed by the Functioning Assessment Short Test. We used leave-one-out cross validation and four sampling methods to circumvent overfitting and cross imbalance. **Results:** The best algorithm differentiated patients with functional impairment with AUC of 0.865, sensitivity of 95.2%, specificity of 74.5%, and balanced accuracy of 84.8%. The most relevant variables in the differentiation of the groups were age at onset, duration of untreated BD, family history of BD and depression as the first episode. We also created an algorithm able to identify late stage BD with an AUC of 0.789, sensitivity of 67.3%, specificity of 75.0%, and balanced accuracy of 71.1%. The most relevant predictors of late stage were lifetime anxiety disorders, lifetime use of benzodiazepines and age of onset. **Conclusion:** We reported a clinical tool using machine learning algorithm with high accuracy to differentiate BD patients with functional impairment from those without functional impairment. Future studies should examine the performance of these models in other populations of BD and investigate their utility in selecting interventions to prevent functional impairment.

## PS030

### Body Mass Index-related brain volume change in elder patients with bipolar disorder

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**Uploaded full poster, have emailed to request only the abstract 19.04.18**

**Followed up 08.05.18**



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## PS031

### Effects of Lithium Monotherapy on Serotonin Transporter and Serotonin-1A Receptor Binding in Bipolar Depression

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**Introduction:** Serotonergic abnormalities are thought to play a critical role in bipolar depression (BPD). Lithium is one of the few effective treatments for BPD, and has been hypothesized to work by enhancing serotonergic transmission<sup>1-3</sup>. Despite preclinical evidence<sup>1,4-7</sup>, in humans it is unknown whether this mechanism is mediated by the 5-HT<sub>1A</sub> receptor or 5-HTT uptake. Here we examined the effects of lithium on 5-HTT and 5-HT<sub>1A</sub> in BPD. Additionally, we characterized the relationship between lithium-induced 5-HTT or 5-HT<sub>1A</sub> alterations and clinical response. We hypothesized that: a) lithium would increase cortical 5-HTT and decrease 5-HT<sub>1A</sub> binding towards control levels (CITE)<sup>8-12</sup>, b) these lithium-induced alterations would associate with better response.

**Materials & Methods:** 21 medication-free patients with BPD were scanned with [<sup>11</sup>C]-CUMI-101 and 16 were scanned with [<sup>11</sup>C]DASB. Following eight-week lithium monotherapy patients were rescanned. Arterial sampling or a simultaneous estimation technique using a single blood sample<sup>13</sup> served as input to tracer specific modeling<sup>14-16</sup> to obtain binding potential outcomes. A-priori regions were: midbrain, amygdala, and anterior cingulate (5-HTT)<sup>8,9</sup>; raphe and 12 previously defined regions (5-HT<sub>1A</sub>)<sup>15</sup>. **Results:** No significant differences were found between pre-lithium and post-lithium scans in V<sub>T</sub>/f<sub>p</sub> (DASB only), BP<sub>F</sub>, or BP<sub>ND</sub>. No significant relationship was found between lithium-induced changes in binding and treatment response (24-item Hamilton Depression Rating Scale)<sup>17</sup>. **Discussion/Conclusion:** To our knowledge, this is the first investigation of lithium's effects on the serotonergic system. We find that lithium does not directly act upon 5-HTT or 5-HT<sub>1A</sub> to mediate treatment response. Future studies are necessary to determine lithium's mechanism of action.

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## PS032

### Prescription patterns in patients with bipolar disorder at a tertiary care center in Japan

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Little is known regarding the prescription patterns of antipsychotics and mood stabilizers in patients with bipolar disorder. In the present study, we examined the prescription patterns in patients with bipolar disorder treated on an outpatient basis at a tertiary care center in Japan. Subjects were patients who were diagnosed as bipolar disorder and received outpatient treatment during the period of April, 2017 to June, 2017 at the Department of Psychiatry, Shinshu University Hospital, Japan. A total of 90 patients (35 men and 55 women, mean age (standard deviation): 42.1 (11.6) years) were included in the study. Antipsychotics and mood stabilizers were prescribed to 31 and 26 patients, respectively. Among them, 12 patients were prescribed both antipsychotics and mood stabilizers. The mean daily chlorpromazine equivalent dose and the rate of antipsychotic polypharmacy in those prescribed antipsychotics were 250 mg/day and 19.3%, respectively. Second generation antipsychotics were more commonly prescribed compared to first generation antipsychotics. The most commonly prescribed mood stabilizer was sodium valproate, followed by lithium carbonate, lamotrigine and carbamazepine. Our findings revealed that current pharmacotherapy for bipolar disorder in Japan generally follows the treatment guidelines in Japan, which has recently been revised to incorporate the most current evidence-based recommendations. The main limitation is that our results from a single institution may not be generalized to other treatment settings such as nontertiary

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facilities or inpatient treatment. Further research is necessary to investigate the prescription pattern in the treatment of bipolar disorder and to enhance the appropriate prescription of mood stabilizers and antipsychotics.

## PS033

### Demographic and therapeutic characteristics of Japanese outpatients with bipolar disorder: a nationwide survey.

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**Objective:** The Japanese Society of Mood Disorders published guidelines for the treatment of bipolar disorder in 2011, with updates in 2012 and 2017. Since bipolar disorder is a severe, recurrent, and sometimes highly impairing psychiatric disorder, we often experience cases where the treatment on the basis of the guidelines is not successful. The aim of this study is to carry out the survey of patients with bipolar disorder including their pharmacological treatment in Japan.

**Methods:** We conducted a large-scale investigation of patient's characteristics such as age, gender, academic background, and employment, psychiatric symptoms and courses of the illness, and details of the pharmacological treatment using a questionnaire for psychiatrists in Japan. 3142 patients (1405 men; mean±standard deviation age: 50.4±13.8 years) with bipolar disorder were included in this study at 179 outpatient facilities of the Japanese Association of Neuro-Psychiatric Clinics between September and October 2016.

**Results:** Compared to the general population dynamics in Japan, the patients of this study were more educated but had a higher unemployment rate. Although nearly half of the patients were in remission, more than three quarters of the patients were judged to be inadequate or poor for social adaptation. While 1253 patients (39.9%) had received monotherapy of mood stabilizers or antipsychotics, 1175 patients (37.4%) were treated with mood stabilizers or antipsychotics in combination with antidepressants.

**Conclusions:** This announcement is the first report of bipolar disorder treatment on-site investigation in Japan.

This study revealed the actual situations of the patients with bipolar disorder in Japan. While analyzing the results even more, it is necessary to consider differences from the guidelines of bipolar disorder.

## PS034

### The Difference of Co-aggregation of major psychiatric disorders in individuals with first-degree relatives with Bipolar I or Bipolar II disorder: a nationwide population-based study

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Several genetic studies has suggested that schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) share common disease-associated genes. However, whether the difference between individuals with first-degree relatives (FDRs) with Bipolar I and Bipolar II have same higher risk of these major psychiatric disorders requires further investigation.

This study used Taiwan's National Health Insurance Research Database and identified 188,290 individuals with FDRs with Bipolar I and II disorder. The relative risks (RRs) of Bipolar I and II and other major psychiatric disorders were assessed in individuals with FDRs with Bipolar I and Bipolar II.

The individuals with FDRs with Bipolar I exhibited higher RRs of major psychiatric disorders, namely schizophrenia (3.4), bipolar disorder (7.82), major depressive disorder (2.99), ASD (2.14) and ADHD (2.05) than were found in the total population. The individuals with FDRs with Bipolar II exhibited higher RRs of major psychiatric disorders, namely schizophrenia (2.39), bipolar disorder (5.64), major depressive disorder (2.86), ASD (2.12) and ADHD (2.30) than were found in the total population. Several sensitivity analyses were conducted to confirm these results. The increased risks of major psychiatric disorders were consistent in different family relationships, namely among parents, offspring, siblings and twins.

Our study supports the familial co-aggregation of schizophrenia, bipolar disorder, major depressive disorder, ASD and ADHD, and our results may prompt governmental public health departments and psychiatrists

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to focus on the mental health of individuals with FDRs with Bipolar I and II.

## PS035

### Lifetime psychiatric comorbidity moderates the rate of accumulation of medical comorbidity associated with bipolar disorder

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**Background-Objectives:** Patients with bipolar disorder (BD) exhibit physical illness at a significantly higher percentage than the general population. However, prospective studies focusing on the accumulation of medical comorbidity in these patients are lacking. Available cross-sectional studies fail to adjust for the presence of medical comorbidity before the onset of BD. The present study aimed to identify demographic, clinical and pharmacological predictors of comorbid physical illness appearing along the course of BD.

**Methods:** The sample consisted of 148 BD (92 BD-I, 56 BD-II) patients (68.9% females, 24-78 years old) who had been hospitalized or followed-up in the Affective Disorders and Suicidal Behavior unit of our department. Cumulative Illness Rating Scale (CIRS, items 1-13) was used to record physical comorbidity on study entry and, retrospectively, before the onset of BD, on the basis of medical records and patients' or relatives' self-report. Patients' clinical characteristics were recorded with a MINI-5-based clinical interview. Lifetime classes of psychotropics (antipsychotics, antidepressants, lithium, mood-stabilizers) received were also recorded.

**Results:** In bivariate analyses, BD-II patients demonstrated higher rates of lifetime psychiatric comorbidity ( $p < 0.001$ ) and higher CIRS total scores ( $p = 0.004$ ) than BD-I patients. In multivariate analyses, identified risk factors for the severity of physical comorbidity were female gender, age, duration of illness, body mass index, smoking (packyears), lifetime psychiatric comorbidity and physical comorbidity before the onset of BD. A significant interaction of lifetime psychiatric comorbidity with BD duration was also detected ( $p = 0.003$ ), suggesting that physical comorbidity appearing after the onset of BD accumulates at a higher rate in those suffering from comorbid psychiatric disease than in those without.

**Conclusions:** The clinical profile of BD patients contributes significantly to the extent and rate of accumulation of BD-related comorbid physical disease. In specific, medical comorbidity after BD onset accrues faster

in those with lifetime psychiatric comorbidity than in those without.

## PS036

### Prevalence and correlates of bipolar disorder comorbid with substance use disorder.

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**Keywords:** Bipolar disorder, substance use disorder, early onset, suicide.

**Background:** Bipolar disorder (BD) presents its onset typically at early adult life and is commonly associated with comorbid psychiatric and substance use disorders (SUD). **Objective:** To evaluate clinical characteristics and outcomes associated with bipolar disorder comorbid with SUD when compared with those patients without comorbid SUD. **Methods:** A cross-sectional study with patients with bipolar I disorder according to DSM-IV and age between 18 and 70 years old. Patients were divided into a group with comorbid abuse or dependence of alcohol, cannabis, cocaine, benzodiazepines, or amphetamines and another group without any SUD. We assessed demographic data, lifetime clinical outcomes, and comorbid psychiatric disorders. Diagnostic and clinical assessment were carried out using SCID for DSM-IV. Mood symptoms were assessed with Young Mania Rating Scale and Hamilton Depression Rating Scale. Demographic and clinical characteristics were analyzed by using chi-squared test to categorical variables and Wilcoxon test to numeric variables. **Results:** A sample of 258 subjects were included and the prevalence of lifetime comorbid SUD was 91 (35.2%). Patient with BD and comorbid SUD presented earlier age at onset ( $p < 0.01$ ) and larger duration of untreated symptoms before correctly diagnosis ( $p < 0.01$ ) when compared to those without comorbid SUD. In addition, they presented a greater prevalence of rapid cycling ( $p = 0.01$ ), suicide attempts ( $p < 0.01$ ) and hospitalization ( $p = 0.02$ ), and were more likely to have comorbid post-traumatic stress disorder ( $p < 0.01$ ) and anorexia nervosa ( $p = 0.01$ ). Other clinical characteristics were not significantly different between groups. **Conclusions:** BD comorbid with SUD was associated with earlier age at onset, larger duration of untreated symptoms and rapid cycling, factors associated with accelerated illness progression. In addition, the

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comorbidity with SUD was associated with pernicious clinical outcomes, such as suicide, and was also associated with other comorbid psychiatric disorders.

## PS037

### Development and Preliminary Evaluation of Manual-Based Group Intensive Outpatient Program (M-IOP) for Patients with Bipolar Disorder in China

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#### Background:

Psychotherapy is now considered as part of the integrated treatment for bipolar disorder (BPD). However, there are few studies has been down in China. This study aimed to develop a comprehensive manual-based group intensive outpatient program (M-IOP) for patients with bipolar disorders in China, and evaluate the effectiveness and feasibility of it.

#### Methods:

1. The primary version of the M-IOP manual was developed on the base of literatures, clinical experiences and expert advises. The final version was formed after 2 rounds of revise.

2. Forty-eight paired patients with BPD, who remitted recently, from out-patient department were assigned to study group (M-IOP, 90 min each session, three times per week, total 10 sessions, n=25) or control group (treatment as usual, TAU, n=23). Total scores of HAMD-17 and YMRS were used to assess the effectiveness and be measured at before -and-after treatment and 3 months after the treatment. The attendance and compliance to M-IOP treatment were used to evaluate the feasibility of M-IOP.

#### Results:

Forty-one patients completed the study. Compared with baseline, symptoms of depression and mania decreased significantly by the end of treatment ( $P=0.008, P=0.022, P=0.010$ ) as well as compliance ( $P=0.009$ ), but no significant differences was found between study group and control group. The average time of attendance was 8.44 of 10 sessions.

#### Conclusions:

M-IOP is helpful to decrease symptoms of patients with BPD and improve their compliance to treatment. In the future, studies on long term follow-up and different population should be down to further evaluation of M-IOP.

## PS038

### Ginkgo Biloba Induced Mood Dysregulation: A Case Report

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**Background:** Ginkgo biloba is considered safe, as there are neither significant adverse effects, nor known drug interactions. However, it can potentially influence the serotonergic, adrenergic, and HPA axis system and thereby affect the formation of mood symptoms.

**Case presentation:** Ms. J was a schizophrenic patient maintained in remission with risperidone 2 mg. In November 2016, the patient reported chronic cognitive impairment and we used ginkgo biloba, 80 mg twice a day. In January 2017, Ms. J reported irritability, difficulty in controlling anger, and agitation after taking ginkgo biloba for one week. She said that these symptoms were the first experience of her illness. She stopped taking ginkgo biloba after these adverse events and the symptoms disappeared after about 2 or 3 days. Although she was instructed to discontinue the use of ginkgo biloba, the patient once again reported that she had tried ginkgo biloba against our instructions because of the subjective cognitive discomfort in February 2017. After about 5 days of resuming ginkgo biloba intake, she experienced the same symptom of mood dysregulation as earlier. She immediately stopped taking the drug and the symptoms disappeared within two days.

**Discussion:** The exact mechanism of EGb (extract Ginkgo biloba) 761, the main pharmacological component of Ginkgo biloba, is poorly understood, but it exerted an effect on the neuronal membranes to restore 5-HT<sub>1A</sub> receptors, and MAO-A and B types were also reversibly

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inhibited by EGb 761 in animal studies. Furthermore, ginkgo biloba increased cerebral noradrenalin in another animal study and interrupted HPA axis by reducing CRH expression. These results indicate the possible mechanism by which ginkgo biloba affects mood regulation.

**Conclusions:** The significance of this case suggests that ginkgo biloba, which is generally accepted as safe, may nevertheless have adverse effects that merit attention.

**Key Words:** Ginkgo biloba, Mood dysregulation, Schizophrenia.

## PS039

### Correlation of Pro-inflammatory Cytokine and Reduced Gray Matter Volume between Bipolar disorder and Unipolar depression

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**Objective:** Bipolar disorder (BD) and unipolar depression (UD) are both related to inflammatory dysregulation, and the pro-inflammatory cytokines could be the biomarkers of mood disorders. However, the study comparing the differences of pro-inflammatory cytokines and neuroimaging abnormality between patients with BD and UD are very limited.

**Methods:** The study enrolled the symptomatically stable patients with BD and UD from the psychiatric outpatient clinic. Magnetic resonance imaging Images were acquired using a 3.0-T GE Discovery MR750 whole-body high-speed MRI device. Pro-inflammatory cytokines, including soluble interleukin-6 receptor (sIL-6R), soluble interleukin-2 receptor (sIL-2R), C-reactive protein (CRP), soluble tumor necrosis factor receptor type 1 (sTNF-R1), were assessed in all subjects by enzyme-linked immunosorbent assays.

**Results:** In all, 72 patients with BD and 64 patients with UD were enrolled, with 33.8% males and an average age of  $39.25 \pm 12.8$  years. The BD patients had significantly higher levels of sIL-6R, and sTNF-R1 than the UD patients. The BD patients had significantly reduced gray matter volume over 12 areas (Right cerebellar lobule 8, Right putamen, Left putamen, Right superior frontal gyrus, Left lingual gyrus, Left precentral gyrus, Right fusiform gyrus, Left calcarine, Right precuneus, Left inferior temporal gyrus, Left hippocampus and Left superior frontal gyrus) than the UD patients after controlling age, gender, body mass index, duration of illness, and intracranial volume. Furthermore, there were significant correlations between sIL-6R, and sTNF-R1 and the 12 areas gray matter volume reduction.

**Conclusion:** Compared to patients with unipolar depression, the patient with bipolar disorder is with more

severe inflammation reaction and reduced gray matter volume; which negatively correlated with the levels of sIL-6R, and sTNF-R1. The results provided the further evidence for the inflammatory pathophysiology of mood disorder, and represent a new therapeutic target for the development of new treatments.

**Key words:** Bipolar disorder, depression, pro-inflammatory cytokine, grey matter, neuroimaging

## PS040

### The relationship of N-methyl-D-aspartate receptor antibody and psychiatric disorders

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#### Objective

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the autoimmune encephalitis that presents various psychiatric symptoms. Several studies investigated the relationship between schizophrenia and anti-NMDAR encephalitis, but there were little studies examined about the others and anti-NMDAR encephalitis. We investigated whether the patients with psychiatric disorders have anti-NMDAR antibody and the effectiveness of immunotherapy.

#### Methods

We investigated the existence of anti-NMDAR antibody in the serum and cerebrospinal fluid (CSF) of 112 patients (initial diagnosis: schizophrenia spectrum disorder 38 patients, depression 31 patients, bipolar disorder 13 patients, epilepsy 7 patients, autism spectrum disorder 4 patients, others 19 patients) with psychiatric disorders by the cell-based-assay (CBA). We used prospective study method. This study was approved by the Okayama University ethics committee and patients gave informed consent prior to the study.

#### Results

Three of 112 patients (2.2%) were identified to have anti-NMDAR antibody (one male and two females). One patient was initially diagnosed as schizophrenia and the other two were bipolar disorder. One of the patients had an ovarian teratoma. The other one patient had AQP4 antibody in the serum that co-existed with NMDAR antibody. Each patient was treated with first-line immunotherapy included steroid pulse, plasma exchange and intravenous immunoglobulin (IVIg). The effectiveness of immunotherapy was different among those three patients. We will also present the clinical details of three cases.

#### Conclusion

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Our data suggested that NMDAR antibody exists in the patients initially diagnosed as mood disorder. Immunotherapy was effective to mood disorder like symptoms of anti-NMDAR encephalitis. The improvement of psychiatric symptoms depended on the diminish of anti-NMDAR antibody. Further studies by examining large cases are necessary to assure our findings.

## PS041

### Comparison of YKL-40 levels in manic-depressed-euthymic patients with bipolar disorder and healthy controls

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<sup>1</sup>Bakirkoy Ruh ve Sinir Hastaliklari Hastanesi

**OBJECTIVE:** There has been a noteworthy increase in the understanding the pathophysiology of Bipolar Disorder (BD). The underlying biological mechanisms of several stages still remain unidentified although new studies support growing evidence on the role of the inflammatory systems in BD. Several immune and inflammatory alterations, such as increased acute phase reactants, abnormal levels of inflammatory cytokines, and activated lymphocyte cell subsets, have been observed in different stages of patients with BD (1). In this study, we aimed to compare YKL-40 levels, which is considered as one of the pro-inflammatory markers, between BD patients and healthy subjects.

**METHODS:** Male patients with bipolar-1 disorder according to DSM-5, who were hospitalized or admitted to out-patient units between June 2016 and June 2017 were included in this study. 44 patients with manic episode, 35 patients with depressive episode and 42 euthymic patients were included randomly and these patients underwent a psychiatric interview by using socio-demographic data form, Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HAM-D). 41 volunteers who were matched for age and smoking included in the study as healthy controls. Serum samples were drawn from patients and healthy subjects to analyze YKL-40 levels.

**RESULTS:** The major finding of our study is, statistically significantly increased levels of YKL-40 in all states (manic, depressive or euthymic) of BD when compared to healthy subjects. There were no statistically significant difference for YKL-40 levels in pairwise comparisons between patient groups. When we evaluated the relationship between YKL-40 levels and clinical features, we found a positive correlation between YKL-40 levels and

white blood cell counts, neutrophil counts, and HAM-D scores in euthymic state.

**CONCLUSION:** Higher levels of YKL-40 in manic, depressive and euthymic states of BD when compared with healthy controls suggest that there is an inflammatory process independent from the disease state and YKL-40 can be considered as a trait marker. Previous studies also indicate a relationship between YKL-40 and BPD (2-4). But to understand the role of YKL-40 in bipolar etiology, studies with large number of participants are needed.

## References

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## PS042

### Comparative Study on the Effect of Risperidone and its Combination with Naltrexone in Pediatric Patients with Autistic Spectrum Disorders: A Clinical Trial Study

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**Background:** Autistic spectrum disorder (ASD) refers to a syndrome associated with persistent impairments in communication skills, social interactions, and so forth. Given the approval of risperidone and naltrexone by U.S. Food and Drug Administration (FDA) for ASD cases and extant controversy concerning their pertained side effects, this double-blind, placebo-controlled, crossover clinical

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trial with 2-treatment, 2-sequence, 2-period design was intended to evaluate the behavioral effectiveness of individual risperidone and its combination with naltrexone in autistic children aged 4-12 years old.

**Materials and Methods :** A total of 30 autistic children were recruited in this study, and then equally assigned into groups A and B. The first group underwent co-treatment with risperidone and naltrexone, while group B was instructed to use placebo and risperidone for 8 weeks. After a washout period of two weeks, treatments were crossed over for another 8 weeks. The behavioral changes were assessed applying the childhood autism rating scale (CARS).

**Results:** There were five out of 30 cases at the risk of drop-out due to side effect in group A, while only three failed to complete the trial in group B. The effect size of the combined treatment was greater than the individual which was manifest in the total score of CARS, improved 4-week listening response(0.539), and 8-week general impressions (0.050).

**Conclusion:** According to the results, naltrexone can be a promising candidate for the management of behavioral symptoms in autism children.

## PS043

### **Screening with the Korean version of the Mood Disorder Questionnaire for Bipolar Disorders in Adolescents: Korean validity and reliability study**

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#### **Aims**

This study aimed to evaluate the validity and reliability of a Korean version of the Mood Disorder Questionnaire-Adolescent Version (K-MDQ-A) as a screening instrument for bipolar disorders in adolescents.

#### **Methods**

102 adolescents with bipolar disorders and their parents were recruited from November 2014 to November 2016 at the outpatient and inpatient facilities of 7 training hospitals. 106 controls were recruited from each middle school in 2 cities of south Korea. The parent version of the original MDQ-A was translated into Korean. The parents of all participants completed the K-MDQ-A. The diagnoses of bipolar disorders were determined based on the Korean version of K-SADS-PL. The test-retest reliability with a 10-month interval was investigated in 33 bipolar adolescents.

#### **Results**

K-MDQ-A yielded a sensitivity of 0.90 and a specificity of 0.92 when using a cut-off score of endorsement of 5 items, indicating that symptoms occurred in the same time

period and caused moderate or serious problems. The internal consistency of the K-MDQ-A was good. The correlations between each item and the total score ranged from 0.40 to 0.76 and were all statistically significant. Factor analysis revealed 3 factors that explained 61.25% of the total variance. The mean total score was significantly higher in bipolar adolescents (7.29) than in controls (1.32). The Pearson correlation coefficient for the total test-retest score was 0.59( $P < .001$ ).

#### **Conclusions**

The present study developed and validated the K-MDQ-A, a Korean translated Mood Disorder Questionnaire-Adolescent version for parents. The K-MDQ-A Korean showed good internal consistency. Each questionnaire and the total K-MDQ-A score were significantly correlated. The frequency of each questionnaire and the total score were significantly higher in the adolescents with bipolar disorder than in the controls. In accordance with the original MDQ-A, the sensitivity and specificity were excellent when using a cut-off score of 5 for the total K-MDQ-A score with co-occurrence of endorsed symptoms and functional problems caused by symptoms. These results propose that the K-MDQ-A is an adequate screening instrument for Korean adolescents with bipolar disorders.

The K-MDQ-A completed by parents showed the excellent validity and reliability and may be a useful screening tool for adolescents with bipolar disorders attending in- and outpatient psychiatric clinics.

## PS044

### **Cortisol and cytokine/chemokine profiles associated with behavioral difficulties in children**

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Evidence suggests that psychological distress can influence the neuroendocrine-immune system. Measurement of salivary cortisol and cytokines has been proposed as a noninvasive way of monitoring neuroendocrine-immune interactions. However, the large number of interrelated cytokines necessitates multivariate statistical techniques incorporating the complex interactions between cytokines. Here, we used the principal component analysis (PCA) to examine the associations of salivary cortisol and cytokines/chemokines with behavioral difficulties in children, as assessed by the Strengths and Difficulties Questionnaire (SDQ). Subjects were 15 children (8 boys and 7 girls) with mean (standard deviation) age of 9.9 (2.7) years. The diagnoses of the subjects were as follows: 6 with comorbid autism spectrum disorder (ASD) and attention-



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deficit hyperactivity disorder (ADHD), 1 with ASD only, 5 with ADHD only, and 3 unaffected. Cortisol and cytokines/chemokines in morning saliva were measured using an enzyme immunoassay kit and a human 27-plex cytokine/chemokine kit, respectively. Salivary levels of cortisol and 20 cytokines/chemokines with detection rate  $\geq 80\%$  were used for PCA. PCA extracted 5 principal components (PCs) with eigenvalues  $> 1.0$ . The first PC (PC1) included all cytokines/chemokines except for interferon- $\gamma$ -inducible protein-10 and represented 62% of the variance. Cortisol was included only in PC4, which also included interleukin-6 (IL-6) and macrophage inflammatory protein-1a (MIP-1a) and explained 5.5% of the variance. Cortisol, IL-6, and MIP-1a all had high positive loadings on PC4 (0.43-0.68), and PC4 score was significantly correlated with the SDQ score (Pearson's  $r = 0.80$ ,  $p < 0.001$ ). The results suggest that PC including cortisol, MIP-1a, and IL-6 are associated with behavior difficulties in children. The results are in line with previous evidence that cortisol and IL-6 are implicated in stress-related psychiatric disorders. Although limited by the small sample size, our findings suggest that salivary cortisol and cytokine/chemokine patterns revealed by the PCA may be associated with mental health status in children.

## PS046

### **Mortality risk associated with antipsychotics in Patients with Dementia in Hong Kong**

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Previous studies have shown that use of antipsychotics in patients with dementia was associated with greater mortality and greater risk of stroke. However, there may be cross-cultural difference in this finding, as one study in Hong Kong found that antipsychotic use was not associated with an increased mortality risk in patients with dementia (Chan et al., 2011).

#### **Objectives**

To compare the incidence and relative risk of mortality between patients with dementia receiving antipsychotics and non-users in a psychiatric clinic in Hong Kong.

#### **Methods**

This is a retrospective cohort study of Chinese patients aged 65 years or above, diagnosed with dementia who first attended the psychiatric clinic in 1 catchment area of Hong Kong in the study period from 1<sup>st</sup> January 2008 to 31<sup>st</sup> December, 2012.

The observation period was till the end of December 2014. Medical records of all eligible patients were retrieved and

their sociodemographic data and relevant clinical data were recorded.

Mortality rate among these patients were calculated, and risk of mortality compared among patients treated with antipsychotics and control patients with no antipsychotic exposure.

#### **Results**

716 subjects were included. In both the unadjusted and the multivariate Cox's regression model, the mortality risk did not differ in typical or atypical antipsychotic groups compared with non-user group statistically. The adjusted hazard ratio (HR) of typical and atypical antipsychotic users were 1.031 (95% Confidence Interval [CI]: 0.696-1.528) and 0.96 (95% CI: 0.638-1.445). Kaplan-Meier survival curves showed no significant difference between antipsychotic non-users and antipsychotic users ( $P=0.452$ ).

#### **Conclusions**

Our study did not find increased mortality in Chinese patients with dementia in Hong Kong treated with antipsychotics compared with a control group of non-users. Limitations of this study include the retrospective design and the sample size is too small to conclusively rule out the increased risk for mortality.

#### **Reference**

Chan, T.C., et al (2011). Continuous use of antipsychotics and its association with mortality and hospitalization in institutionalized Chinese older adults: an 18-month prospective cohort study. *Int Psychogeriatr*, 23(10), 1640-1648.

## PS047

### **Mortality risk in older adults with dementia treated with atypical antipsychotics: a systematic review and network meta-analysis of randomized controlled trials**

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The UK Committee for Safety of Medicines and the US Food and Drug Administration have issued a strong warning that the use of atypical antipsychotic medications (AAPs) increases the risk of mortality in individuals with dementia. In recent years, several national cohort studies have indicated that quetiapine carries the lowest risk of mortality for the treatment of behavioral and psychological symptoms of dementia (BPSD). For BPSD treatment, only a few head-to-head RCTs with AAPs have been conducted, precluding conclusions based on comparisons of all pairwise meta-analysis. This study used network meta-analysis (NMA) to assess the relative mortality risk and rank individual AAPs based on all RCTs with placebo and head-to-head RCTs. Major electronic databases were searched from inception up to December 2017 for RCTs with AAPs for BPSD treatment. A total of 19 RCTs were included (n = 5386, mean age 81.3 years), and the analyzed AAPs were amisulpride, aripiprazole, olanzapine, quetiapine, and risperidone. The mean chlorpromazine equivalent dose of the five AAPs was 119.7 mg/d, and the mean study duration was 10.4 weeks. We determined that quetiapine carried the highest risk of mortality, while amisulpride and risperidone had superior safety. Only slight risk differences existed for quetiapine, olanzapine, and aripiprazole. The mortality risk of amisulpride is controversial, as the only trial was subject to high risk of bias. The NMA did not identify a dose-response relationship between AAPs and risk of mortality. In conclusion, the hierarchy of treatment options for BPSD should be guided by both efficacy and adverse-effect profiles of AAPs, and the risk of mortality warrants the strongest safety concern. The use of quetiapine, olanzapine, and aripiprazole for BPSD treatment requires more deliberate consideration. Risperidone shows superior safety over the other four AAPs for the short-term treatment of elderly patients with BPSD.

## PS048

### Suvorexant decreases risk for nighttime falls in the inpatient with dementia

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**Objective:** Hypnotic treatment has been associated with increased risk for falls in cognitive impairment patients. Suvorexant, a novel dual orexin receptor antagonist was created as a drug for promoting physiological sleep.

Unlike existent hypnotic agents, it does not have antiepileptic and antianxiety function. These characteristics reduce the side effects like muscular atonia, stagger, dependence on and tolerance for medicines. The authors examined the association between hypnotic treatment and falls in cognitive impairment hospitalized patients, focusing on the suvorexant.

**Methods:** This retrospective case-control study was conducted in an acute geriatric ward in Saitama Neuropsychiatric Institute. Medical records, including demographic, clinical, biochemical, and pharmacological variables, of cognitive impairment patients with falls (n = 41), admitted during a 24-Month period, were reviewed and compared with a control group (n = 89) of patients matched for age and gender and without falls.

**Results:** The usage rates of antipsychotics, antidepressants, mood stabilizers, and various nonpsychiatric medications were similar in the two groups, except for suvorexant (higher rates in patients without nighttime falls). There were no significant differences in the anticholinergic burden values, clinical dementia ratings, and comorbidity burden between the two groups. There was a significant difference in the nighttime falls between the two groups.

**Conclusion:** There were few accidents of nighttime falls in cognitive impairment inpatients with the use of suvorexant, admitted during a 24-Month period. It suggests that suvorexant may provide protection against nighttime falls in hospitalized patients with dementia. In addition, suvorexant significantly improved patients' sleep experience. Further studies are needed in the future.

## PS049

### Role of genetics and functional imaging in the differential diagnosis of pseudodementia: two case reports

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**Objective:** The aim of this work is to present and discuss two clinical cases of pseudodementia with psychotic symptoms in which the diagnostic investigation showed biological markers of neurodegenerative disease.

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**Methods:** In addition to the information from the patients' clinical files, we conducted a conventional literature review in PubMed.

**Results and Discussion/Conclusions:** Case 1: 63-year-old-woman with a diagnosis of bipolar disorder at 59, with three psychiatric hospitalizations in the last 4 years due to recurrent psychotic depression associated with marked cognitive decline. During the second hospitalization we conducted a genetic study for degenerative dementias, prompted by a family history of dementia in her mother and her sister. The study revealed heterozygosity for two mutations (c.388T > C in the ApoE gene, which predisposes to Alzheimer's disease, and c.1993G > A of the APP gene, which is not reported in the literature). Case 2: 63-year-old-man with a diagnosis of recurrent depressive disorder with psychotic symptoms and three psychiatric hospitalizations in the last 5 years, with severe cognitive decline since last admission. MRI scan was unremarkable. Fludeoxyglucose PET scan revealed hypometabolism in the posterior temporal, posterior parietal and anterior occipital regions. Both patients fully recovered psychopathologically, despite a discrete but progressive functional decline. The findings support recent studies suggesting that psychiatric conditions with pseudodementia features may be early manifestations of a neurodegenerative process. A more in-depth investigation with functional imaging exams or genetic tests may be indicated in patients age > 50 and < 65, with new-onset psychotic depression and acute cognitive decline, and may have ethical relevance in patients with offspring. Where genetic and or functional imaging is impossible or not consented, patients should be followed-up, with careful monitorization of cognitive function.

## PS050

### **Effect of education on Alzheimer's disease-related neuroimaging biomarkers in healthy controls, and participants with mild cognitive impairment and Alzheimer's disease - a cross-sectional study**

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**Running title: Educational effect on brain volume in MCI**

**Background:** Cognitive reserve is the acquired capacity reflecting a functional brain adaptability/flexibility in the

context of aging. Educational attainment is thought to be among the most important factors that contribute to cognitive reserve.

**Objective:** The aim of this study is to investigate the relationships among duration of education and Alzheimer's Disease (AD) related neuroimaging biomarkers such as amyloid- $\beta$  deposition, glucose metabolism, and brain volumes in each stage of AD.

**Methods:** We reanalyzed a part of the datasets of the Alzheimer's Disease Neuroimaging Initiative. Participants were between 55 and 90 years of age and diagnosed with one of the follows: healthy controls (HC), mild cognitive impairment (MCI), or AD. Multiple regression analyses were conducted to examine the relationships among duration of education and amyloid- $\beta$  deposition (n=825), brain metabolism (n=1304), and brain volumes (n=1606) among three groups using data for 18F-Florbetapir (AV-45) imaging, Fludeoxyglucose (FDG) Positron Emission Tomography, and T1-weighted magnetic resonance imaging.

**Results:** Duration of education had no correlations with amyloid- $\beta$  deposition or brain metabolism in any groups. However, duration of education was positively associated with the total brain volume only in participants with MCI.

**Conclusions:** Our findings suggest that education may exert a protective effect on total brain volume in the MCI stage but not in HC or AD. Thus, education may play an important role in preventing the onset of dementia through brain reserve in MCI.

## PS051

### **A Meta-Analysis of the Effect of Apolipoprotein E $\epsilon$ 4 Carrier Status on the Cognitive Response to Acetylcholinesterase Inhibitors in Patients with Alzheimer's dementia**

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**Objectives :** The apolipoprotein E-  $\epsilon$ 4 (*APOE*- $\epsilon$ 4) genotype is the major genetic risk factor for Alzheimer's disease (AD). The effect of *APOE*- $\epsilon$ 4 on an individual's response to

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treatment is less well understood. Many publications have reported that the presence or absence of *APOE-ε4* may contribute to therapeutic response for a range of AD drugs, but the results have been inconsistent. The aim of the study was performed the systematic review and meta-analysis to evaluate the link between treatment response of acetylcholinesterase inhibitors (ChEIs) and the *APOE-ε4* carrier status. **Methods:** We conducted a systematic review and meta-analysis for published articles from inception to January 30, 2018. Clinical studies with AD patients reporting *APOE ε 4* genotype were included. Cognitive outcome was measured by the change in Mini-Mental State Examination (MMSE) or Alzheimer's Disease Assessment Scale, cognition subscale scores (ADAS-cog). **Results :** 37 studies were identified, 29 studies were included for meta-analysis. Continuous data for the comparison between differential *APOE ε4* allele expression were available from 18 studies. The cognitive outcomes were not significantly different among *APOE-ε4* carrier or *APOE-ε4* non carrier (SMD= -0.016, 95% CI [-0.107 to 0.075],  $p=0.735$ ). 11 studies with binary data were included, there were also no significant difference between the two groups (OR 1.100, 95% CI [-0.688 to 1.758],  $p=0.692$ ). Subgroup analysis indicated ChEIs were significantly effective than placebo in both two groups. **Conclusions :** We found that the *APOE ε4* carrier status showed no different effect to the treatment response of ChEIs in patients with AD. ChEIs had positive effect than placebo regardless of *APOE* genotype.

## PS052

### Expression of Intestinal endotoxemia (IETM) on APP, PS1 and BACE in Alzheimer's disease

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**Objective:** Early our animal experiments study showed that AD rats occurs intestinal endotoxemia (IETM), and with the increasing of endotoxin, the APP, PS1, BACE mRNA increased and promote the generation of Aβ. The aim of this study was to observe the occurrence of IETM in AD patients and to investigate the effect of intestinal endotoxemia in AD, provide evidence for the prevention and treatment of AD.

**Methods:** According to the inclusion and the exclusion criteria, choose AD patients and healthy elderly, evaluate cognition by the Mini mental state examination (MMSE) and Alzheimer's disease assessment scale cognitive subscale (ADAS-cog), detect the serum LPS, TNF-α and Aβ level by ELISA, detect APP, PS1 and BACE mRNA

expression by real-time PCR. All the data were analyzed by SPSS 17.0.

**Results:** 1. The AD group and the control group showed no significant differences in sex ( $\chi^2=0.312$ ,  $P=0.576$ ), age ( $t=0.243$ ,  $P=0.809$ ) and education level ( $u=735.000$ ,  $P=0.682$ ).

2. The MMSE score of AD group was significantly lower than the control group ( $u=0.000$ ,  $P<0.001$ ), the ADAS-cog score was significantly higher than that in control group ( $u=0.000$ ,  $P<0.001$ ), the differences were statistically significant.

3. The LPS ( $u=0.000$ ,  $P<0.001$ ), TNF-α ( $t=6.175$ ,  $P<0.001$ ), Aβ ( $u=13.000$ ,  $P<0.001$ ) levels were significantly higher than the control group, the differences were statistically significant.

4. The APP ( $u=16.000$ ,  $P<0.001$ ), PS1 ( $u=24.000$ ,  $P<0.001$ ) and BACE ( $u=60.000$ ,  $P<0.001$ ) mRNA expression levels in AD group were significantly higher than the control group, the differences were statistically significant.

5. The LPS level was highly related to the Aβ level ( $r=0.894$ ), The LPS level was moderately related to the APP ( $r=0.563$ ), BACE ( $r=0.486$ ) mRNA expression. The correlation between LPS level and PS1 mRNA expression was not significant.

**Conclusions:** This study preliminary confirmed that AD patients occurs IETM, and IETM could upregulate the expression of APP, the key enzyme BACE by induce inflammatory cytokines, and then promote Aβ generation, lead to the development of AD.

## PS053

### Ritalin for Apathy in Dementia

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#### Introduction

Psychostimulants have been employed in the treatment for cognitive and behavioural symptoms in dementia for some years but when used as a treatment for cognitive deficits in older persons, results have been varied with most studies employing Ritalin having produced little or no effect on cognition. Being a stimulant drug used mainly to treat attention deficit hyperactivity disorder in children, it acts by augmenting the activity of dopamine in the brain which influences many cognitive processes, including executive function.

Ritalin has also been tried in older persons with advanced physical disease and as a form of palliative care to treat fatigue, depressive symptoms and apathy. It has also been reported to have helped people with 'vascular depression'

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not responding to regular antidepressants, where emotional blunting frequently occurs as a sign of depression and should not be mistaken for apathy.

The limited literature available have consistently reported improvements in apathy with Ritalin and that it helps that aspect of dementia.<sup>1</sup> Supporting this are related findings of reduced activity in parts of the brain responsible for the dopaminergic reward system.<sup>2</sup> Furthermore, recent results on the use of Ritalin have been more promising and it has even been shown to improve mobility and gait stability, in addition to executive function.<sup>3</sup> The benefits of its use seem to outweigh its drawbacks.<sup>4</sup>

## Method

We describe two cases of different forms of vascular dementia, one Binswanger's Disease and the other Multi-infarct Dementia. Cognitive impairment was first confirmed using the Mini Mental State Examination (MMSE), with them scoring 19/30 and 13/30 respectively, and the Clinical Dementia Rating (CDR) Scale was then used to determine the severity of dementia, both obtaining CDR-2 scores indicating moderate stage of disease. Apathy Evaluation Scale<sup>5</sup> (AES) scores were evaluated before introduction of Ritalin therapy, 13 and eight months respectively after treatment and finally four weeks after reducing the dose of Ritalin.

## Results

We ascertained that executive function in both subjects benefitted from Ritalin as add-on therapy by improving apathy.

## Conclusion

Methylphenidate may help improve apathy in dementia and appears to be dose-related.

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## PS054

### Tardive dyskinesia induced by donepezil; a paradox

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**Background.** Tardive dyskinesias (TD) are repetitive, involuntary, purposeless movements of the tongue, lips, face, trunk, and extremities that occur usually in patients treated with long-term dopaminergic antagonist medications. It is considered that central dopamine blockade plays a role in the pathogenesis of TD. Besides typical neuroleptics several other drugs have been linked to the development of TD, but cholinesterase inhibitors may improve it. We present a case in which donepezil seems to provoke TD.

**Case report.** A 70 years old female patient received donepezil for 18 months because of dementia (MMSE 23/30). Twelve months after receiving the medication she started experiencing annoying and persistent orofacial hyperkinesias that progressively spread to other parts of the body, mainly on the trunk. Tongue protrusion and facial grimacing made her speech almost incomprehensible and she felt very embarrassed. She was receiving citalopram, too. Although no previous reference has been made linking donepezil to TD, we tried to stop this medication (instead of citalopram). Three months after stopping donepezil, dyskinesias were considerably eliminated and the patient felt relieved. Quetiapine was administered (25 mg BID) and further but not total improvement was achieved.

**Discussion.** Donepezil has been tested as a possible agent to treat TD on the basis that cholinesterase inhibitors, may improve TD by directly increasing cholinergic synaptic transmission and decreasing dopaminergic activity. Upregulation or supersensitivity of the dopaminergic receptors in the nigrostriatum has been considered a likely mechanism, as well as the imbalance of the dopaminergic/cholinergic systems and dysfunction of GABAergic neurons in the nigrostriatum. In our case donepezil had the opposite effect. On the other hand, atypical antipsychotics, like quetiapine have also been implicated as both producing and alleviating TD. Further randomized trials are needed to explore the role of

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cholinesterase inhibitors in the occurrence and managing of TD.

## PS055

### Systemic Inflammation and long term outcome of Alzheimer disease

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**Objectives:** Inflammatory mechanisms have been hypothesized to play a role in the pathogenesis of age-associated diseases such as dementia. Several inflammatory markers as tumor necrosis factor ( TNF- $\alpha$  ), C-Reactive Protein ( CRP ), homocysteine has been implicated in the pathogenesis of Alzheimer's disease ( AD ). Our study aimed to evaluate the association between inflammatory cytokine and cognitive function, neuropsychiatric symptoms in patient with Alzheimer disease in a longitudinal study. **Methods :** Participants diagnosed with AD were recruited. They were administered neurological examination including Mini-Mental State Examination ( MMSE ), Cognitive Ability Screening test Instrument ( CASI ), Neuropsychological index( NPI ), and Alzheimer's Disease Assessment Scale-cognitive subscale ( ADAS-Cog ), and tested for serum level of CRP, TNF- $\alpha$  and homocysteine. We followed patients' neurological examination and inflammatory parameters in an interval of 6 months. We evaluated the the association between inflammatory parameter and the result of neuropsychological test by using nonparametric Chi-square test and linear regression. **Results :** A total of 46 subjects with AD were cognitively assessed at baseline and a blood sample taken for inflammatory markers. Our results found that the MMSE scores were negatively associated with serum CRP and TNF- $\alpha$ , the CDR total box score were correlated with the serum CRP. Regarding the neuropsychiatric behaviors, affect subcategory of NPI was significantly correlated with serum CRP. Moreover, the inflammatory parameters showed strong correlations between each other. **Conclusions:** Raised serum TNF- $\alpha$  and CRP were associated with cognitive decline in AD patients. The finding indicated a relationship between neuroinflammation and neuropsychiatric symptoms in patients with AD the serum.

## PS056

### Effects of Rivastigmine Transdermal Patch on Cognitive Function and Body Weight: An Observational, Retrospective Study in Japanese Patients with Alzheimer Disease

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**Objective:** Data on the treatment by rivastigmine transdermal patch (rivastigmine patch) in Japan are still limited [1,2]. This study evaluated the effects of rivastigmine patch particularly on cognitive function in Japanese patients with Alzheimer disease. There are some reports in clinical-settings that patients with Alzheimer disease treated with rivastigmine patch showed the improvement of appetite loss, and thus gained or maintained body weight [3,4]. This study also evaluated the effects of rivastigmine patch on body weight in the patients.

**Methods:** The study patients were 87 administered rivastigmine patch. Patients fulfilled the diagnosis of Alzheimer disease (DSM-IV), with FAST scores 4 or 5 (mild-to-moderate), and had been treated with rivastigmine patch as the first option or switched to rivastigmine patch from any other oral cholinesterase inhibitor, and not in combination with memantine. Neurocognitive function was assessed using the Revised Hasegawa's Dementia Scale (HDS-R). This study was exempt from requiring informed consent from individual patients because the data investigated were retrieved from databases and de-identified before data analyses.

**Results:** Forty-four out of 87 patients had been treated with rivastigmine patch for 6 months or more. Neurocognitive function was assessed in 31 out of 44 patients. After 6 months of the treatment, HDS-R total scores did not show significant increase nor decrease. Among 9 items, "delayed recall" scores showed significant increase ( $p < 0.05$ ). Regarding body weight, there was no significant change between the two assessments. After 12 months of the treatment, HDS-R total scores did not show significant increase nor decrease. Among 9 items, "calculation" scores showed significant decrease ( $p < 0.05$ ). Regarding body weight, there was no significant change between the two assessments.

**Conclusions:** As suggested, rivastigmine patch has been indicated to improve "delayed recall," and also prevent weight loss in Japanese patients with mild-to-moderate Alzheimer disease.

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## PS057

### **An approach to clinical dose escalation in a Phase 1 study for TAK-653, a novel AMPA positive allosteric modulator**

#### Authors

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Recent findings support the role of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), L-glutamate type 1 receptor subunit (GluR1) as a potential target for rapid onset of antidepressant activity. However, excessive AMPA receptor stimulation can lead to high levels of neuronal excitation, and seizures in preclinical studies have been reported with AMPA potentiators [1, 2]. TAK-653 is a novel, potent, and selective potentiator of AMPA receptors currently in development for treatment-resistant depression.

The traditional approach to initial human studies with compounds having seizure liability has been to identify a no observed adverse effect level (NOAEL) of the compound, apply a safety factor (generally 10x below), and limit the maximal human dose to exposures 10x below the NOAEL. However, this approach provides no information regarding the threshold exposure for eliciting the adverse effect, only what exposure is not associated with the adverse effect. Thus, exposure cutoffs in humans may be lower than necessary. Conducting a toxicity study in non-human primates (NHPs) with continuous video monitoring, EEG monitoring using subcutaneous electrodes, and comprehensive toxicokinetic data allowed escalation to a dose, close to the NOAEL exposure, that may otherwise not have been possible using the standard approach.

One traditional dose-escalation strategy in single- and multiple- rising dose studies has been to rapidly increase the dose at lower dose levels and reduce the dose escalation interval as exposure approaches the NOAEL, relying primarily on safety data. This may not be appropriate for AMPA receptor potentiators, given the absence of a useful biomarker predictive of seizures and good clinical tolerability profiles. Utilising exposures at which seizures occurred in the toxicity study in NHPs, the clinical exposure could be escalated to <2x of the NOAEL

threshold (9 mg QD) rather than stopping at an exposure 1/10<sup>th</sup> the NOAEL, as is more typically done when seizures occur in animal studies.

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## PS058

### **The clinical impact of post-traumatic stress disorder as comorbidity on patients with unipolar depression as primary diagnosis – results from a cross-sectional European multicenter study**

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**Key words:** depression, post-traumatic stress disorder, comorbidity

#### **Specific objective of the study:**

The aim of the present study was to investigate clinical features, pharmacotherapeutic prescription trends and treatment outcomes in patients suffering from major depressive disorder (MDD) as primary diagnosis and post-traumatic stress disorder (PTSD) as comorbidity.

#### **Methods used:**

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1346 adult in- and outpatients with MDD were enrolled in this international, multicenter and cross-sectional study. We applied the Mini International Neuropsychiatric Interview (MINI) to assess the presence of comorbid PTSD. Furthermore, we evaluated clinical and socio-demographic data as well as information on psychopharmacotherapy and treatment response. Descriptive statistics, analyses of covariance (ANCOVA) and binary logistic regression were employed to compare clinical characteristics of MDD patients with and without comorbid PTSD.

## **Summary of results:**

In the sample of 1346 MDD patients 1.49% exhibited comorbid PTSD. Significantly more patients with primary MDD and comorbid PTSD suffered from atypical clinical features (odds ratio, OR = 4.49, 95%CI:1.01–20.12;  $p \leq .05$ ), anxiety disorders (any comorbid anxiety disorder: OR = 3.89, 95%CI:1.60–9.44;  $p = .003$ , comorbid panic disorder: OR = 6.45, 95% CI:2.52–16.51;  $p = .001$ , comorbid agoraphobia: OR = 6.51, 95%CI:2.54–16.68;  $p \leq .001$ , comorbid social phobia: OR = 6.16, 95%CI:1.71–22.17;  $p \leq .001$ ) and bulimia nervosa (OR = 10.39, 95%CI:1.21–88.64;  $p = .03$ ) as comorbidities, current suicide risk (OR = 3.58, 95%CI:1.30–9.91;  $p = .01$ ) as well as augmentation with low-dose antipsychotics (OR = 6.66, 95%CI:2.50–17.77;  $p < .001$ ).

## **Conclusions reached:**

While significantly lower prevalence rate of comorbid PTSD in patients suffering from primary MDD was detected, reverse prevalence rate was found in patients with primary PTSD and concurrent MDD. Furthermore, comorbid anxiety disorders and an increased suicide risk were highly present in patients with primary MDD and comorbid PTSD.

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## **PS059**

### **Substance use disorders are risk factors for treatment resistant depression**

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## **Background**

Treatment resistant depression (TRD), defined as non-response to at least two treatment attempts, is common among patients with major depressive disorder (MDD). Substance use disorders (SUD) can co-occur in MDD and may lead to worse treatment outcomes. However, in previous clinical studies, SUD have not been identified as risk factors for TRD.

## **Objective**

To investigate whether SUD are risk factors for TRD, using national health-care register data in a nested case-control study comparing TRD with non-TRD MDD patients.

## **Methods**

Nationwide Swedish register data on pharmacological prescriptions, diagnoses from specialized psychiatric care, and various sociodemographic variables were used to establish a prospectively followed antidepressant-treated MDD cohort (n=121,669) in the years 2006–2014. 15,631 patients (13%) were defined as TRD cases, having at least



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three registered antidepressant treatment attempts within a single MDD episode. Each case was closely matched on sociodemographic data with five non-TRD MDD controls using incidence density sampling. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the risk of having a SUD diagnosis, or treatment, for alcohol, opioids, cannabis, central stimulants, cocaine, hallucinogens, volatile solvents, or multiple drug use before entering the MDD cohort. Analyses were adjusted for education level, anxiety disorders and personality disorders.

## Results

Adjusted OR for history of any SUD was 1.16 for TRD cases compared to non-TRD controls (95%CI 1.10-1.22). When investigating specific SUD diagnoses, OR were significantly elevated for opioids (1.53, 1.01-2.30), central stimulants (1.44, 1.31-1.58) and alcohol (1.36, 1.22-1.53).

## Conclusion

A history of SUD increases the risk for TRD among MDD patients in specialized psychiatric care. The impact of comorbid substance use should be considered when planning antidepressant treatment.

## PS060

### Enuresis induced by SSRI à case report

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#### Objective:

Although there is a relationship between selective serotonin reuptake inhibitor (SSRI) in the treatment of enuresis. Their use for the treatment of enuresis is well established. We present a case of a married woman aged fifty years who presented a secondary enuresis induced by the use of an SSRI. These selective serotonin reuptake inhibitor to the extent that they are still commonly prescribed in the treatment of enuresis, the monitoring the possibility of occurrence of enuresis precipitated by these drugs is increasingly important.

#### Method:

Mrs B, 50 years old, married, three children, without a profession, the eldest in a family of five brothers and sisters, was addressed by a general practitioner for major depression with psychosomatic complaints evolving over the past month. The diagnosis of Major Depressive Disorder (MDD) was according to the DSM-IV criteria (Diagnostic and Statistical Manual fourth edition) of Mental Disorders. All laboratory tests, including blood and biochemical tests, liver and renal function was normal. Serotonin-Selective Reuptake Inhibitor has been prescribed. Sertraline 50 mg/day

#### Results:

Symptoms of depression are resolved within two months under medical treatment after twelve weeks of treatment,

the patient develops a nocturnal secondary enuresis every night. Fifteen days after stopping the drug enuresis has disappeared in a progressive manner. The pathophysiological mechanisms of these drugs that induce enuresis are not specified at the moment.

#### Conclusion:

This case illustrates the importance of being alert for a possible enuresis induced by the SSRI drugs early in the diagnostic process. To our knowledge only 5 enuresis (4 adults and 1 adolescent) induced by SSRIs were reported. We describe a case adult (woman) who develops a bed-wetting during treatment with serotonin-selective reuptake inhibitor.

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## PS061

### Drug-induced hyponatremia in the treatment of depression

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**BACKGROUND AND OBJECTIVE(S):** Hyponatremia is defined as a serum sodium concentration of less than 130 mEq/L by some sources or less than 135 mEq/L by others. Its clinical spectrum ranges from asymptomatic or aspecific general symptoms such as nausea, fatigue, muscle cramps and headache, to serious neuropsychiatric symptoms of cerebral oedema, causing confusion, restlessness, gait abnormality, lethargy, seizures and coma. Multiple published case reports implicate antidepressant use as a cause of hyponatremia, often related to secretion of antidiuretic hormone (SIADH). The risk for developing hyponatremia seems to increase with age, female sex, previous history of hyponatremia and concomitant use of other medications known to cause hyponatremia. Our aim is to conduct a review of the literature on this topic, trying to identify which antidepressant drugs are more associated with this electrolyte imbalance and identify potential alternative options.

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**METHODS:** The review of the literature was made with research terms “hyponatremia”; “SIADH”; “inappropriate ADH”; “antidepressants”; different antidepressant classes and generic drug names in scientific databases – pubmed, medscape and google scholar – and relevant scientific literature concerning the issue addressed.

**RESULTS:** Antidepressant-induced hyponatremia in patients is a fairly common complication. Current evidence suggests a relatively higher risk of hyponatremia with selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors (mainly venlafaxine). The association for tricyclic antidepressants and mirtazapine is small to moderate. And smaller for bupropion, trazodone and mianserin.

**CONCLUSIONS:** Hyponatremia is a potentially dangerous side effect of antidepressant treatments, not exclusive to SSRIs. The risk is different between drug classes and between drugs of the same class. When starting a treatment in a person with high risk to develop hyponatremia, this should be considered.

## PS062

### Efficacy of Fufangcongrongyizhi Capsule on cognitive function of senile depression patients

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**Objective:** To investigate the efficacy of Fufangcongrongyizhi Capsule on cognitive function of depressed patients over 60 years old.

**Methods:** The 126 patients with depression were randomly divided into 2 groups, and the group of patients in the study group (n=72) was combined with Sertraline hydrochloride by compound Fufangcongrongyizhi Capsule, and the control group (n=54) was treated with Sertraline hydrochloride for 8 weeks.

Hamilton Depression Scale -17 item (HAMD-17) was used to assess the effect of depression before and after treatment 2, 4, 6, 8 weeks. The clinical efficacy, HAMD score and adverse reactions of the two groups were compared. Using the Wechsler Adult Memory Scale (WMS) test memory quotient. The clinical efficacy, HAMD score, memory quotient and adverse reactions were compared between the two groups.

**Results:** There was no statistically significant difference between the study group and the control group in the 2, 4, 6 weeks HAMD score and the WMS. Compared with the control group in 8 weeks, the HAMD score of the group was lower (t=3.21, P<0.01), and the total effective rate of the study group was higher than that of the control group ( $\chi^2=4.87$ , P<0.05).

In the treatment process, there was no statistically significant difference in the incidence of adverse reactions

between the study group and the control group ( $\chi^2=0.12$ , P>0.05). Increased memory quotient (t=6.43, P<0.001).

**Conclusions:** The treatment efficiency of the compound Fufangcongrongyizhi Capsule combined with Sertraline hydrochloride was effective in the treatment of elderly patients with depression, and the cognitive function of the elderly patients with depression was improved, and the adverse reactions were mild.

**Key words:** Fufangcongrongyizhi Capsule; Depression; The curative effect

## PS063

### How did psychiatrists of the Karasuyama Hospital prescribe antidepressants for psychiatric symptoms?

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#### **Purpose:**

Japanese psychiatrists can use various kinds of antidepressants after 1997, when first SSRI in Japan, fluvoxamin was released.

The medicine for depression was tricyclic antidepressant primarily in Japan 30 years ago.

However, SSRI and SNRI is a first-line drug now.

We investigated the pharmacotherapy for depressive symptoms to clarify that whether depressive symptoms influenced the prescription in outpatient department of Showa University Karasuyama Hospital.

#### **Method:**

This study was a retrospective analysis of information abstracted from the medical records of 501(238 males, 268 females) outpatients, who took any antidepressant and had visited in August and October 2012 at the Department of Psychiatry.

We checked the following items age, diagnosis, sex, presence or absence of work, marital history, psychiatric symptoms, and prescription.

#### **Results:**

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The most common depressive symptom was anxiety. There were 239 Mood (affective) disorders, 109 Neurotic, stress-related and somatoform disorders, and 43 Disorders of psychological development.

Especially, SNRIs were used significantly for amotivation (AOR:3.77(95%CI:2.15-6.63)), pain(AOR: 3.79(95%CI:1.15-12.5)).

Trazodon was significantly used for insomnia (AOR:9.12(95%CI:1.15-72.4)).

The SSRIs were mainly used for anxiety and depressed mood, but not significantly.

Conversely, psychiatrists significantly avoided SSRI prescription from hypochondria (AOR:0.44(95%CI:0.23-0.86)).

About half of the outpatients with depressive symptoms were prescribed psychotropics such as sleeping drugs, anxiolytics, antipsychotics, and mood stabilizers.

Approximately 20% patients took another antidepressants.

## Conclusions:

The results of this study suggest that there are differences in pharmacotherapy of depressive symptoms by the characteristic of antidepressant.

Japanese psychiatrists may consider monotherapy is not effective for recovery because of the prescription of various kinds of psychotropic drugs with antidepressant in the real world.

It will be necessary to examine relations between symptoms, prescription motive and medicational effect in future.

Key words: Mood disorder, antidepressants, anxiety, depressive symptoms

## PS064

### Early effects on depressed mood, suicidality and anxiety of duloxetine in depression

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**Background:** Recent patient-level post-hoc analyses show that SSRIs, already after one week of treatment, cause i) a reduction in depressed mood<sup>1</sup>, ii) a reduction in suicidality<sup>2</sup> and iii) a reduction in psychic anxiety, but also that they iv) elicit a transient increase in somatic anxiety during the first week<sup>3</sup>. The aim of the present study was to explore if these findings could be extended to a serotonin and noradrenaline reuptake inhibitor, duloxetine.

**Methods:** We had access to patient-level data for 11 company-sponsored, acute-phase, placebo-controlled trials of duloxetine in adult depression using the Hamilton Depression Rating Scale (HDRS-17). A pooled analysis comprising in total 2521 subjects was undertaken using MRMM (Mixed-Effect Model Repeated Measures, SAS 9.4). All patients with  $\geq 15$  points on the HDRS-17 at baseline were included. Doses ranged between 40-120 mg. *Total HDRS-17-sum*, as well as the individual items *depressed mood*, *suicidality*, *psychic anxiety* and *somatic anxiety* were analyzed.

**Results:** The duloxetine-induced reduction in depressed mood, suicidality and psychic anxiety, but not that in HDRS17-sum, was significant already at week 1. In contrast, somatic anxiety was rated higher in patients on duloxetine at week 1.

**Conclusions:** In line with our previous observations regarding the SSRIs, duloxetine also displayed a significant superiority over placebo already after one week of treatment with respect to depressed mood, suicidality and psychic anxiety, but not with respect to the conventional effect parameter, i.e. total HDRS-17-sum. Also in line with previous data regarding the SSRIs, psychic anxiety was rated lower but somatic anxiety rated higher at week 1 in patients given active drug. The results support the notion that a small but significant antidepressant effect, that cannot be detected using HDRS17, is at hand earlier than previously assumed, and also that reuptake inhibitors may cause an initial aggravation of somatic anxiety but not psychic anxiety.

**References:** 1. Hieronymus et al., *Molecular Psychiatry* 2016; 21, 523–530  
2. Näslund et al., *Br J Psychiatry* 2018; *in press*  
3. Näslund et al., *Acta Psychiatr Scand* 2017; 136, 343–351

## PS065

### Discrepancies between nomenclature and indications of psychotropics

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## Objective:

While the current nomenclature of psychotropic drugs is disease-based, their approved indications do not always match their classifications. For example, "antipsychotics" are used not only for schizophrenia but also for other psychiatric disorders including depression. Such

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discrepancies between the nomenclature and approved clinical indications often confuse patients and their families. This confusion may be detrimental for maintaining adherence to pharmacotherapy. The aim of this study was to examine approved indications of “atypical antipsychotics” and “newer antidepressants” in a systematic manner.

## Method:

In this study, information on approved indications of “atypical antipsychotics” and “newer antidepressants” that are available in the United States (US), the United Kingdom (UK), France, Germany, and Japan, were extracted from their packet inserts in September, 2017.

## Results:

A significant proportion of “atypical antipsychotics” was approved for psychiatric conditions other than schizophrenia and schizoaffective disorder (i.e. bipolar disorder, major depressive disorder, autistic disorder) as follows: 76.9% in the US, 66.7% in the UK, 66.7% in France, 60.0% in Germany, and 44.4% in Japan. Likewise, more than half of “newer antidepressants” had approved indications for psychiatric conditions other than depression (i.e. panic disorder, obsessive compulsive disorder, social anxiety disorder, general anxiety disorder, post-traumatic stress disorder, bulimia nervosa, chronic pain, and nicotine-dependence): 56.3% in the US, 69.2% in the UK, 69.2% in France, 50.0% in Germany, and 62.5% in Japan.

## Conclusion:

Our results cast serious concern regarding generic terminologies of “antipsychotics” and “antidepressants” since the conventional indication-based nomenclature of psychotropic drugs does not fit well with the official indication, let alone with their efficacy (i.e. off label use). A pharmacologically-driven nomenclature such as Neuroscience-based Nomenclature (NbN) may be more appropriate.

## PS066

### **Efficacy and safety of intranasal esketamine plus an oral antidepressant in elderly patients with treatment-resistant depression**

Rachel Ochs-Ross<sup>1\*</sup>, Ella Daly<sup>1</sup>, Yun Zhang<sup>2</sup>, Rosanne Lane<sup>1</sup>, Pilar Lim<sup>1</sup>, Karen Foster<sup>3</sup>, David Hough<sup>1</sup>, Hussein Manji<sup>1</sup>, Wayne Drevets<sup>4</sup>, Gerard Sanacora<sup>5</sup>, Caleb Adler<sup>6</sup>, Rupert McShane<sup>7</sup>, Raphaël Gaillard<sup>8</sup>, Jaskaran Singh<sup>4</sup>

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**Objective:** This double-blind phase 3 study (NCT02422186) evaluated the efficacy and safety of intranasal esketamine (ESK) in elderly patients with treatment-resistant depression.

**Methods:** Patients  $\geq 65$  years (N=138) were randomized (1:1) to either ESK + oral antidepressant (AD) or AD + placebo (PBO). The primary efficacy endpoint – change from baseline to day 28 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score – was assessed by mixed-effects model at a one-sided 0.025 significance level. Pre-specified subgroup analyses were performed for 65-74 years (n=116) and  $\geq 75$  years (n=21). Remote raters, blinded to the treatment arm, conducted the MADRS assessments by telephone.

**Results:** The mean (SD) change in MADRS total scores from baseline to day 28 was -10.0 (12.74) for ESK+AD and -6.3 (8.86) for AD+PBO. The median-unbiased estimate of the difference between ESK+AD and AD+PBO was -3.6 (95% CI: -7.20, 0.07; one-sided p=0.029). A treatment difference favoring ESK+AD was seen for the 65-74 years subgroup. The difference in LS mean (SE) change at day 28 was -4.9 (2.04) for 65-74 years (one-sided p=0.009) and -0.4 (5.02) for  $\geq 75$  years (one-sided p=0.465). The most common treatment-emergent adverse events (TEAEs) in the ESK+AD group were dizziness (20.8%), nausea (18.1%), headache (12.5%), fatigue (12.5%), increased blood pressure (12.5%), vertigo (11.1%) and dissociation (11.1%). The most common TEAEs in the AD+PBO group were anxiety, dizziness and fatigue (7.7% each).

**Conclusion:** While treatment with ESK+AD did not demonstrate a statistically significant difference vs AD+PBO on the primary outcome, a statistically significant and clinically meaningful treatment effect was observed for patients aged 65-74 years.

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## PS067

### Genes involved in neurodevelopment, neuroplasticity and Major Depression: No association for CACNA1C, CHRNA7 and MAPK1

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**Objective:** Genetics factors are likely to play a role in the risk, clinical presentation and treatment outcome in Major depressive disorder (MDD). In this study, we investigated the role of three candidate genes for MDD: Calcium voltage-gated channel subunit alpha1 C (CACNA1C), Cholinergic receptor nicotinic alpha 7 subunit (CHRNA7) and Mitogen-activated protein kinase 1 (MAPK1).

**Methods:** Two-hundred forty-two (242) MDD patients and 326 healthy controls of Korean ancestry served as samples for the analyses. Thirty-nine (39) single nucleotide polymorphisms (SNPs) within CACNA1C, CHRNA1 and MAPK1 genes were genotyped and subsequently tested for association with MDD (primary analysis) and other clinical features (symptoms' severity, age of onset, history of suicide attempt, treatment outcome) (secondary analyses). Single SNPs, haplotypes and epistatic analyses were performed.

**Results:** Single SNPs were not associated with disease risk and clinical features. However, a combination of alleles (haplotype) within MAPK1 was found associated with MDD-status. Secondary analyses detected a possible involvement of CACNA1C haplotype in resistance to antidepressant treatment.

**Conclusion:** These data suggest a role for MAPK1 and CACNA1C in MDD risk and treatment resistance, respectively. However, the results must be considered with great caution and needed to be replicated due to many limitations including under-power of samples.

Keywords: MAPK1, CACNA1C, CHRNA7, Major Depressive disorder

## PS068

### Randomized, Double-Blind Study of Flexibly-Dosed Intranasal Esketamine Plus Oral Drug for Depression vs. Active Control in Treatment-Resistant Depression

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**Background:** About 30% of patients with depression fail to achieve remission despite adequate treatment with multiple drugs for depression, and are considered to have treatment-resistant depression (TRD).

**Methods:** This Phase 3, double-blind, active-controlled, multicenter study (NCT02418585), using blinded raters, was conducted at 39 sites in Spain, Germany, the Czech Republic, Poland, and United States from August 2015 to June 2017. The study enrolled adults with moderate-to-severe, non-psychotic, recurrent or persistent depression, and history of non-response to  $\geq 2$  drugs for depression in the current episode, with 1 of them assessed prospectively. Non-responders were randomized (1:1) to flexibly-dosed intranasal esketamine (56 or 84 mg twice weekly) and a new oral drug for depression (serotonin-norepinephrine reuptake inhibitor [SNRI] or selective serotonin reuptake inhibitor [SSRI]) or intranasal placebo and a new oral drug for depression (SNRI or SSRI; active control). The primary efficacy endpoint – change from baseline to endpoint (day 28) in Montgomery-Asberg Depression Rating Scale (MADRS) total score – was assessed by mixed-effects model using repeated measures.

**Results:** 435 patients were screened, 227 randomized, and 197 completed the 4-week double-blind period. Change (LS mean [SE] difference vs. placebo) in MADRS total score with intranasal esketamine/oral drug for depression was superior to oral drug for depression/intranasal placebo at day 28 (-4.0 [1.69], 95% CI: -7.31, -0.64; one-sided  $p=0.010$ ), as well as at earlier timepoints (one-sided  $p \leq 0.009$  at 24 hours postdose and days 8 and 22). The most common adverse events reported for esketamine/oral drug for depression were dysgeusia, nausea, vertigo, and dizziness; the incidence of each (20.9-26.1%) was  $>2$ -fold higher than for oral drug for depression/intranasal placebo.

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**Conclusions:** Study findings indicate a positive risk-benefit profile of intranasal esketamine, an investigational drug, for treating TRD.

## PS069

### Effects of gap in perception of subjective vs objective illness severity on subjective cognitive impairments in depression?

Kyosuke Sawada<sup>1</sup>, Kazunari Yoshida<sup>2</sup>, Chisa Ozawa<sup>1</sup>, Takefumi Suzuki<sup>3</sup>, Masaru Mimura<sup>1</sup>, Hiroyuki Uchida<sup>1</sup>

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#### Objectives:

The objectives of this study were to explore factors associated with cognitive impairment and investigate differences in the impact of subjective versus objective illness severity on subjective cognitive impairment in outpatients with depression.

#### Methods:

This study is a post-hoc analysis of a cross-sectional study in which Japanese outpatients with depressive disorder (ICD-10) were recruited (Ozawa 2017). The participants received assessments with the Japanese version of the Perceived Deficits Questionnaire (J-PDQ), the Quick Inventory of Depressive Symptomatology (QIDS), and the Montgomery-Asberg Depression Rating Scale (MADRS). First, multiple regression analysis was conducted to examine effects of PDQ total score, and demographic and clinical characteristics including medications used (e.g. antidepressants and benzodiazepines) on QIDS or MADRS total score. Next, we categorized the participants into 4 groups based on the presence/absence of subjective symptom remission (i.e. a QIDS total score of  $\leq 5$ ) and objective symptom remission (i.e. a MADRS total score of  $\leq 9$ ), and compared the differences in PDQ total scores between the QIDS- and MADRS-remitted group and the QIDS-non-remitted but MADRS-remitted group, using an independent t-test.

#### Results:

102 participants were included: 45 men; mean $\pm$ SD age, 50.5 $\pm$ 14.7 years; duration of illness, 6.5 $\pm$ 6.1 years. Higher QIDS or MADRS total score was significantly associated with a greater PDQ total score ( $p < 0.001$ , respectively) whereas the other factors including medications did not exhibit any significant associations. The QIDS-non-remitted but MADRS-remitted group showed a significantly higher PDQ total score than that of the QIDS- and MADRS-remitted group ( $p < 0.001$ ).

#### Conclusions:

Greater illness severity seems to affect subjective cognitive impairment in depression. Objective remission in the absence of subjective remission may not represent favorable outcome in terms of cognitive function.

## PS070

### Repeated two doses of ketamine followed by a randomized double-blind placebo controlled add-on trial of D-Cycloserine in treatment resistant bipolar and major depression

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**Objectives:** Controversial results were found in efficacy of D-Cycloserine (DCS) on treatment resistant depression (TRD). Our aims are to 1) investigate the effect of two repeated doses of ketamine on TRD; 2) test the maintaining antidepressant effect of DCS vs. Placebo.

**Methods:** 49 subjects with bipolar depression (N=19), and major depression (N=30) collected for **phase 1 open-trial study**. They received I.V. ketamine infusion 0.5mg/kg twice on day 1 and day 4, each. Responder was defined by  $\geq 50\%$  reduction of HAMD or MADRS score from baseline at any two days of the experimental week. The responders were enrolled into the **phase 2 DCS trial** in a randomized double-blind, placebo controlled study, using HAMD<sub>17</sub> and MADRS mood rating at each investigating time point.

**Results: In phase 1 study:** 1) No difference of responder rate between major depression (N=19, 63.3%) or bipolar depression (N=13, 65.4%) were identified, yielding overall response rate 65.3%; 2) decreasing rate of depression on day 2 may predict the efficacy on day 7 with sensitivity 75-78% and specificity 100%; 3) the reduction of suicidal rate was greater in responder than non-responder (81% vs, 29.5%,  $p < 0.001$ ); **In phase 2 study:** 1) repeated ANOVA with adjusting baseline mood ratings revealed no time (day 1 to 42), group (DCS, vs. placebo) and time X group effect, indicating no differences of maintaining efficacy between DCS (500-1,000mg) and placebo for 6-week trial. Reduction of depression from baseline in phase 1 was

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around 50% on day 1 through 42 in phase 2; 2) Similar findings was noted in suicidal rate, which showed either DCS or placebo may maintain reduction of suicidal rate around 55-63% in phase 2. **Conclusions:** The results showed efficacy of ketamine can be maintained for 6 weeks by both D-Cycloserine and placebo. DCS did not show significant therapeutic advantages than placebo adjunct treatment.

**Key words: ketamine, D-Cycloserine, depression**

## PS071

### **Down regulation of serotonin transporter binding in raphe nuclei with long term pharmacological treatment for major depressive disorder**

Authors: Mikael Tiger, Lars Farde, Johan Lundberg, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Major Depressive Disorder (MDD) is the world leading cause of disability. Selective Serotonin Reuptake Inhibitors (SSRI) constitute first line pharmacological treatment. The serotonin transporter is a common target for both SSRI and some Tricyclic Antidepressants (TCA). In most in vivo occupancy studies antidepressant binding to serotonin transporters (5-HTT) in striatum is reported, representing 5-HTT occupancy in projection areas. 5-HTT occupancy in the raphe nuclei is less well explored. Moreover, 5-HTT occupancy with SSRI has mainly been studied after short term (less than two months) treatment. Applying positron emission tomography (PET) and the 5-HTT selective radioligand [<sup>11</sup>C]MADAM we examined 5-HTT occupancy in MDD treatment responders on monotherapy with one of six antidepressants (amitriptyline, clomipramine, and four SSRIs), to examine long term effects of 5-HTT occupancy in putamen and the raphe nuclei. All but two patients were in remission with current treatment. The patients had been on antidepressant treatment for at least two months, and most patients had been treated for more than a year. In all patients 5-HTT occupancy was higher in raphe nuclei than in putamen (83 % vs 67 %,  $p < 0,001$ ). In a previous study we found no significant

difference in 5-HTT occupancy in putamen compared to raphe nuclei after a single dose of escitalopram given to healthy volunteers. Since [<sup>11</sup>C]MADAM 5-HTT affinity is expected to be the same throughout the brain, the higher 5-HTT occupancy likely reflects decreased 5-HTT density in raphe nuclei with long term antidepressant treatment in MDD treatment responders. This finding has potential bearing on chronic antidepressant mechanism of action.

## PS072

### **The effects of personality on the association between paroxetine plasma concentration and response**

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#### **Background**

We studied the differences between groups that were divided according to the characteristics of their personalities with respect to the relationship between drug concentration and symptom improvement.

#### **Methods**

In this study, 120 patients with major depressive disorder (MDD) were treated with 10-40 mg/day of paroxetine for 6 weeks; 89 patients completed the protocol. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to evaluate the patients at 0, 1, 2, 4, and 6 weeks. The patients' paroxetine plasma concentrations at week 6 were measured using high-performance liquid chromatography. Their personalities were evaluated by the Temperament and Character Inventory (TCI) at the first visit. We divided the patients into two groups according to the median of each TCI dimension. We compared the responder rate between High and Low groups in each TCI dimension and analyzed the Pearson's correlation coefficients of paroxetine plasma concentration and MADRS improvement rate for all groups.

#### **Results**

A total of 62 patients completed the TCI. The low novelty seeking, high harm avoidance, low reward dependence and low self-directedness groups exhibited significant negative correlations between paroxetine plasma concentration and MADRS improvement. Among the groups with combined personality traits, the high harm avoidance and low self-directedness group showed a markedly significant negative correlation.

#### **Conclusions**

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Patients with depression exhibiting specific personality traits, especially those with high harm avoidance and low self-directedness scores, exhibited a significant negative association between paroxetine plasma concentration and MADRS improvement rate. Thus, a lower dose might be suitable for patients with specific personality traits.

## PS073

### Increased levels of CREB and pCREB in major depressive patients with antidepressant treatment

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**[Objective]** Cyclic AMP response element-binding protein (CREB) is considered key mediator of antidepressant drug effect. We investigated whether CREB (inactive form), pCREB (active form), and the pCREB/CREB ratio in peripheral T lymphocytes as a potential predictor of response to selective serotonin reuptake inhibitor (SSRI), differed between patients with depression treated with antidepressants and healthy controls.

**[Methods]** We recruited 23 outpatients undergoing antidepressant treatment for major depressive disorder and 47 healthy volunteers. Psychopathology was evaluated with the Hamilton Depression Rating Scale (HAM-D), Clinical Global Impression - Severity scale (CGI-S), and the Global Assessment of Functioning (GAF) scale. CREB and pCREB levels were determined via an enzyme-linked immunosorbent assay (ELISA). The protocol was approved by the ethics committee of Hirosaki University, and signed informed consent was obtained from all participants.

**[Results]** The comparison between patients with depression and controls showed significant differences in CREB levels ( $p = 0.002$ ) and in pCREB levels ( $p = 0.022$ ), although there were no group differences in the pCREB/CREB ratio ( $p = 0.429$ ). Neither the age or sex of the patients and controls nor the HAM-D scores, GAF scores, CGI-S scores, imipramine equivalent doses, number of episodes, duration of illness, or duration of treatment were correlated with the CREB or pCREB levels or the pCREB/CREB ratio ( $p > 0.05$ ).

**[Conclusion]** The findings of this research suggest that CREB and pCREB levels in T lymphocytes are increased by antidepressant treatment in major depressed patients. Further studies with larger sample size are needed to investigate whether CREB and pCREB are biomarkers for

depression and to facilitate the prediction of antidepressant response.

## PS074

### Long-Term Safety of Intranasal Esketamine plus Oral Antidepressant in Patients with Treatment-Resistant Depression: Phase 3, Open-label, Safety and Efficacy Study (SUSTAIN-2)

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**Funding:** This study was funded by Janssen Research & Development, LLC.

#### \*Presenting Author

#### Objective:

This long-term safety study evaluated intranasal esketamine (ESK, 28, 56 or 84 mg) plus a newly initiated oral antidepressant (AD) in patients with treatment-resistant depression (TRD).

#### Methods:

In this phase 3, open-label, 52-week safety study, patients ( $\geq 18$  years) were directly enrolled or transferred from another phase 3 study of elderly ( $\geq 65$  years) patients. Eligible patients entered a 4-week induction (IND) followed by a 48-week optimization/maintenance (OP/MAINT) phase and a 4-week follow-up. Safety evaluations (primary outcome) included treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory tests, physical examination, nasal tolerability and cognitive tests. Efficacy evaluations (secondary outcome) included mean Montgomery-Åsberg Depression



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Rating Scale (MADRS) total score, response rate and remission rate over time.

## Results:

Of the total 802 enrolled patients, 691 (86.2%) were direct-entry and 111 (13.8%) were transfer-entry. Discontinuation rates due to AEs were 6.7% during IND and 4.1% during OP/MAINT phases. The most common TEAEs ( $\geq 10\%$  patients) were: dizziness (33.0%), nausea (25.1%), headache (24.9%), dissociation (22.4%), somnolence (16.7%), dysgeusia and hypoaesthesia (11.8% each), vertigo and vomiting (10.8% each), and viral upper respiratory tract infection (10.2%). No clinically meaningful changes in cognition were noted. Fifty-five (6.9%) patients experienced 68 serious TEAEs and 2 deaths were reported in the treatment phase. Laboratory tests, physical examination, and nasal tolerability revealed no trends of clinical concern. The mean (SD) change in MADRS total score from IND baseline to endpoint was  $-16.4$  (8.76) and from OP/MAINT baseline to endpoint was  $0.3$  (8.12). At IND endpoint, the response rate was 78.4% and remission rate was 47.2%; of the responders proceeding to the OPT/MAINT phase, 76.5% were responders and 58.2% were remitters at endpoint.

## Conclusion:

Long-term treatment with intranasal ESK plus oral AD was tolerable and no new safety concerns emerged; improvement in depressive symptoms appeared to be sustained in TRD patients.

## PS075

### Obesity and Its Potential Effects on Antidepressant Treatment Outcomes in Patients with Depressive Disorders: A Literature Review.

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Accumulating evidence regarding clinical, neurobiological, genetic, and environmental factors suggests a bidirectional link between obesity and depressive disorders. Although a few studies have investigated the link between obesity/excess body weight and the response to antidepressants in depressive disorders, the effect of

weight on treatment response remains poorly understood. In this review, we summarized recent data regarding the relationship between the response to antidepressants and obesity/excess body weight in clinical studies of patients with depressive disorders. Although several studies indicated an association between obesity/excess body weight and poor antidepressant responses, it is difficult to draw definitive conclusions due to the variability of subject composition and methodological differences among studies. Especially, differences in sex, age and menopausal status, depressive symptom subtypes, and antidepressants administered may have caused inconsistencies in the results among studies. The relationship between obesity/excess body weight and antidepressant responses should be investigated further in high-powered studies addressing the differential effects on subject characteristics and treatment. Moreover, future research should focus on the roles of mediating factors, such as inflammatory markers and neurocognitive performance, which may alter the antidepressant treatment outcome in patients with comorbid obesity and depressive disorder.

**KEYWORDS:** antidepressant; depressive disorder; obesity; response; treatment outcome

## PS076

### Attitudes toward placebo-controlled clinical trials of depressed patients in Japan

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**Background:** Placebo-controlled clinical trials are the standard in the design of clinical studies for the licensing of new drugs. However, medical and ethical concerns for placebo use, still exist in clinical trials of depressed patients.

**Aims:** The aim of this study is to investigate the attitudes toward placebo-controlled clinical trials and to assess factors related to the willingness to participate in such trials among depressed patients in Japan.

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**Method:** A total of 206 depressed patients aged  $49.5 \pm 15.7$  (mean  $\pm$  SD) who were admitted to three psychiatric hospitals, was recruited in a cross-sectional design from June 2015 to March 2016. After a thorough explanation of the placebo, the study participants completed a brief 14-item questionnaire developed to survey patients' attitudes regarding possible participation in placebo-controlled clinical trials. The Quick Inventory of Depressive Symptomatology was also administered to assess depressive symptoms.

**Results:** The results indicated that 47% of the patients would be willing to participate in a placebo-controlled clinical trial. Expectations for improvement of disease, desire to receive more medical care, encouragement by family or friends, and wish to support the development of new drugs, were associated with the willingness to participate in such trials, whereas a belief of additional time required for medical examinations, and fear for exacerbation of symptoms due to placebo, were associated with non-participation.

**Conclusions:** Less than half of the respondents agreed to possible participate in placebo-controlled clinical trials. Attitudes to participation in placebo-controlled clinical trial need to be considered when deciding whether to conduct such a trial.

## PS077

### **Clinical characteristics associated with therapeutic adherence of the patients with major depressive disorder: a report from the National Survey on Symptomatology of Depression in China.**

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Key Words: National Survey on Symptomatology of Depression, adherence, clinical characteristics

#### **Objective**

The high level of disability associated with depression is mainly caused by relapse and recurrence, yet a large percent of patients discontinue the use of antidepressant prematurely, increasing the relapse and recurrence rates. Few studies have systematically analyzed the relationship

between clinical characteristics, especially symptoms, of depressive patients and their adherence over a relatively large sample. The present study aimed to assess adherence with antidepressant treatment in a Nation-wide survey in China during 2014-2015, and investigate factors of non-adherence.

#### **Method**

Major depressive disorder (MDD) participants met DSM-IV criteria were recruited from 16 sites in 22 cities of 15 provinces. The institutional review boards at each site approved the study and all participants provided written informed consent prior to study entry. Patients were all over 18 years old. A doctor-rating assessment questionnaire with 58 symptoms based on DSM framework was constructed to evaluate depression related feeling and behavior. 889 patients of poor adherence and 850 patients of good adherence were used in the final analysis. Single factor logistic regression was utilized to screen variables and multi-factor logistic regression analysis was used to identify which factors were risk or protective factors for non-adherence. Significance levels were two-sided, with statistical significance set at  $p < 0.05$  for all tests.

#### **Results**

Recurrence, untreated first episode, TCA-treated first episode, antidepressants-only treated current episode, decrease or loss of interest, more somatic symptoms and symptoms that are more "atypical" were risk factors for non-adherence in MDD individuals. While better economic condition and SNRI-treated first episode were protecting factors.

#### **Conclusion**

Clinical characteristics may play an important role in predicting non-adherence. Doctors may have to pay more attention on patients with these factors and should keep on discussing them with patients.

## PS078

### **Effect of aripiprazole augmentation on plasma levels of homovanillic acid in major depressive disorder**

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**[Background]** Aripiprazole (APZ) has unique pharmacological profile as a partial agonist for dopamine D2 receptors. Plasma levels of homovanillic acid (pHVA), a metabolite of dopamine, may reflect dopamine turnover in brain. The aim of presented study was to elucidate whether pHVA is useful biomarker in major depressive

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disorder (MDD) with insufficient response to antidepressant therapy. In this study, we longitudinally measured plasma levels of pHVA in MDD with APZ augmentation therapy.

**[Method]** Twenty-six patients with inadequate response to antidepressant therapy were treated with APZ (3-12mg/day) for 6 weeks. We measured Montgomery-Åsberg Depression Rating Scale (MADRS) and pHVA at baseline, weeks 2, and endpoint. Patients with a 50% or greater decrease from baseline in the MADRS total score were defined as responders. This study was approved by the ethics committee of Fukushima Medical University, and the patients consented to participate after having been informed of the purpose of the study.

## **[Results]**

In the whole sample, APZ decreased MADRS score after 6 weeks. At weeks 2, pHVA in responders (n=8) were significantly lower than those in non-responders (n=18) (p=0.028). Furthermore, there was a significant negative correlation between pHVA at weeks 2 and changes in MADRS score at endpoint in responders (p=0.033, r=-0.72).

**[Discussion]** Our results suggest that the changes of pHVA at weeks 2 might be useful clinical marker of aripiprazole augmentation with antidepressants, indicating lower pHVA at weeks 2 are associated with favorable response to APZ. Further studies with larger sample size are needed to confirm and extend our preliminary results.

## **PS079**

### **Efficacy of Lurasidone in Major Depressive Disorder with Mixed Features: Treatment Review**

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Marlborough, MA, USA*

**Objective:** This review summarises a priori and post-hoc analysis results of a study designed to evaluate the efficacy and safety of lurasidone in patients with major depressive disorder with mixed features.

**Methods:** Patients meeting DSM-IV-TR criteria for major depressive disorder who presented with 2 or 3 protocol-defined manic symptoms were randomly assigned to 6 weeks of double-blind treatment with either lurasidone at 18.5-56 mg/day (N=109) or placebo (N=100). The primary endpoint was week 6 change from baseline in the Montgomery-Åsberg Depression Rating Scale score (MADRS) total score. We also analysed efficacy in clinical subgroups based on depression severity at baseline (moderate: MADRS≤30; marked: MADRS 31-35; high

severity: MADRS≥36), and anxiety severity at baseline (mild: HAM-A≤14) and moderate-to-severe: HAM-A≥15).

**Results:** Lurasidone significantly improved week 6 MADRS score vs. placebo (-20.5 vs. -13.0; P<0.0001; effect size 0.8). Significant improvement in the Young Mania Rating Scale (YMRS) was also observed. Effect sizes increased as baseline depression severity increased from moderate to marked to high severity (effect size, 0.6, 0.7, and 1.2, respectively); MADRS effect sizes also increased as baseline anxiety increased from mild (effect size, 0.6) to moderate-to-severe (effect size, 0.95). In patients who presented with irritable features, treatment with lurasidone was associated with significant week 6 change vs. placebo in mean MADRS (effect size, 1.4). In the anxious and irritable subgroups, treatment with lurasidone was also associated with significant improvement in symptoms of anxiety and irritability.

**Conclusions:** These results found that treatment with lurasidone significantly improved depressive symptoms in patients with major depressive disorder with mixed features. Response to lurasidone in this difficult to treat population was found to be robust, and was not reduced in patients presenting with high baseline depression severity, or with concurrent symptoms of anxiety or irritability.

**Clinicaltrials.gov:** NCT01421134.

**Sponsored by Sunovion Pharmaceuticals Inc.**

## **PS080**

### **The influence of benzodiazepine medication on the antidepressant effect of ketamine.**

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**Introduction:** rapid antidepressant effect of ketamine became a breakthrough in the research on depression. Nevertheless, nearly 30% of patients do not respond to ketamine infusion<sup>1</sup>. Concerning our empirical impression of mitigated response to ketamine in patients medicated with benzodiazepines, and GABA being a shared target for both ketamine and benzodiazepines, we aimed to study this interference as a possible modulating factor for nonresponse.

**The objective of the study** was to assess the influence of BZD on the antidepressant effect of single ketamine infusion in depressed patients and to study eventual dose-dependence of this interaction.

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**Methods:** we have analyzed the data from 47 depressed patients (MADRS  $\geq 20$ ,  $\geq 1$  prior non-response to antidepressant treatment in current episode, on a stable dose of antidepressants min. 4 weeks prior to admission) from two consecutive randomized, placebo-controlled, cross-over trials in our clinic. All subjects were given racemic ketamine intravenous infusion (0.54 mg/kg) as an add-on medication to previous depression treatment.

**Summary of results:** the sample was divided into responders ( $\geq 50\%$  MADRS reduction,  $n=13$ ) and non-responders ( $<50\%$  MADRS reduction,  $n=34$ ). Logistic regression has revealed that concomitant benzodiazepine medication (daily dose 10 mg and more in diazepam equivalent) predicted nonresponse anytime during one-week follow-up after ketamine infusion (Odds ratio=1.5;  $p=0.0445$ ).

**Conclusions:** benzodiazepine medication ( $\geq 10$  mg diazepam equivalent pro die) predicted nonresponse to ketamine's antidepressant effect. Our findings are consistent with a previous study on a small sample<sup>2</sup> suggesting dose-dependent benzodiazepine influence on ketamine response in a group of 10 patients. The results should be considered in future research on concomitant medication and clinical aspects of individualized ketamine application.

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## PS081

### Decreased brain pH in patients with depression and in a social defeat mouse model

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Decreased pH in the postmortem brain has been observed in particular psychiatric disorders, but it remains controversial whether this phenomenon is a primary feature of these diseases or is a result of confounding factors. We recently showed that the pH of the postmortem brain is significantly decreased in patients with schizophrenia and bipolar disorder based on a meta-analysis of existing datasets, even when a few potential confounding factors were considered. We also showed that brain pH is decreased and lactate levels are increased in five strains of mouse models of schizophrenia, bipolar disorder, and autism spectrum disorders. The mouse models can be studied without concern for the confounders inherent in human studies. These results support the idea that a decrease in brain pH is the underlying pathophysiology of these psychiatric disorders, rather than a mere artifact. In the present study, we have extended a similar analysis to a stress mouse model of depression and patients with major depression.

We examined pH and lactate levels in the brain of a social defeat mouse model of depression. Mice were exposed to chronic social defeat stress, and then behaviorally tested (social avoidance test, open field test, light/dark transition test, and sucrose preference test, in this order). One day after the final behavioral test, the whole brain was harvested from each mouse and immediately frozen. All mice were drug-naive with equivalent agonal states, postmortem intervals, and ages. Data from the stressed mice were divided into susceptible and resilient group data based on a measure of social avoidance (susceptible: social interaction ratio, SIR  $< 1$ ; resilient: SIR  $\geq 1$ ). We found a significant decrease in pH and a trend toward increases in lactate levels in the susceptible mice compared to the non-stressed controls. There was a highly significant negative correlation between pH and lactate levels. The pH values or lactate levels also showed correlations with several measures of behaviors. We also confirmed a decrease in the brain pH of the stressed mice as well as a negative correlation between pH and lactate levels in the whole brain samples obtained from another laboratory. We then evaluated pH in the postmortem brains of patients with major depression by conducting a meta-analysis of publically available datasets. The meta-analytic approach revealed that the brain pH was significantly decreased in the patients with depression compared to the control subjects, even when the postmortem interval and age at the time of death were considered to be potential confounding factors.

Together with our previous findings in schizophrenia and bipolar disorder, the current depression-related results suggest that a decrease in brain pH associated with potential increase of lactate levels is a shared endophenotype in the brains of at least a subgroup of patients with these mental disorders.

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## PS082

### Management of Treatment Resistant Bipolar Depression with rTMS

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#### Background

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive FDA-approved treatment for unipolar treatment resistant depression (TRD). rTMS has been utilized clinically to treat bipolar TRD; however, there remains a lack of evidence and support of how to most effectively utilize this intervention for bipolar TRD. We retrospectively analyzed a group of patients who were treated with rTMS for unipolar or bipolar TRD.

#### Methods

Records of 71 patients treated with rTMS for unipolar (N=54) or bipolar (N=17) TRD from 2008 to 2017 were reviewed. The primary outcome of depression severity was the Quick Inventory of Depressive Symptomatology (QIDS) at baseline and after every 5 sessions throughout the course of 30 treatments.

#### Results

In the total sample, patients' depression improved significantly over the course of treatment. Bipolar TRD patients showed greater response and remission rates over the course of treatment as compared with unipolar TRD patients, but this difference was not statistically significant. Both groups showed a similar depression response pattern over treatment time. No manic episodes occurred during treatment, and one bipolar patient developed hypomania. A case example is provided discussing the timing of rTMS in a bipolar patient to decrease the likelihood of treatment-induced hypomania.

#### Limitations

Limitations include the smaller sample size of the bipolar TRD patient group compared with unipolar patients and the naturalistic setting of this study.

#### Conclusions

Our analyses show that both bipolar and unipolar TRD patients respond well to rTMS. Bipolar TRD patients have a similar response profile over treatment time to unipolar patients with TRD. We found one instance of a switch to hypomania. Our data suggest that rTMS may be equally as effective and safe for both unipolar and bipolar patients. Further research is needed to clarify the best rTMS protocol for bipolar TRD and how to monitor for treatment-induced mania.

**Key words:** (3-6) Transcranial Magnetic Stimulation, Bipolar, depression, neuromodulation, mania

Conflicts of interest: Dr. David Dunner owns a NeuroStar TMS device, has received payment for clinical services from Cyberonics for a former research patient, has served on advisory boards for Janssen and Otsuka/Lundbeck, has served as a McKesson consultant and provides forensic consultations, IME evaluations and legal testimony. Ms. Angela Phillips and Dr. Robert Burr hold no conflicts of interest with this project.

## PS083

### Repetitive Transcranial Magnetic Stimulation Effects in Patients with Co-Morbid Somatic Pain and Depressive Mood Disorders

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#### Background

Pain is a common co-morbidity among clinically depressed individuals [1]. Greater pain severity within the depressed population often results in greater treatment resistance [2].

#### Objective

The objective of this study was to assess levels of somatic pain in rTMS patients with TRD and the longitudinal impact of rTMS on pain and depression outcomes over the course of 30 rTMS treatment sessions.

#### Methods

Records of 71 patients treated for TRD with rTMS from January 2008 to June 2017 were reviewed. Primary outcome measures, which included depression severity using the Quick Inventory of Depressive Symptomatology (QIDS-16) and a 0-10 numeric pain rating scale, were assessed at baseline and after every 5 sessions throughout the course of 30 treatments. Within and across patient relationships of pain with respect to treatment session, depression with respect to treatment session, and pain with respect to depression over treatment were assessed using linear mixed models and GEE modeling.

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## Results

When dichotomizing patients into median split pain groups, the low baseline pain group (scores of 0-2) had a nonsignificant correlation with depression scores ( $r=0.153$ ,  $p=.372$ ), while the high baseline pain group (scores of 3-8) had a significant correlation with depression scores ( $r=0.501$ ,  $p=.003$ ). In the total sample, changes within subjects of QIDS are associated with the changes of pain ( $b=.057$ ,  $P=.011$ ). Within and across subjects pooled data showed significant differences in the relationships between pain and depression by group, over the course of rTMS treatment ( $p=0.016$ ;  $p=0.001$ ).

## Conclusion

Our data suggest that correlations between pain and depression at baseline may be a predicting factor in rTMS treatment response. Pain and depression severity in rTMS patients may be associated over the course of rTMS treatment in individuals with higher levels of baseline pain.

David Dunner, M.D. owns a NeuroStar TMS device (significant pertinent conflict of interest). Angela Phillips and Robert Burr hold no conflicts of interest with this project.

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## PS084

### Plasma metabolites are potential biomarker of antidepressant treatment response in patients with major depression.

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**Introduction:** There has been an ongoing search for putative biomarkers that can predict or assess response to psychiatric treatment. Recently, the metabolomics

approach has been receiving attention for new possibilities of biomarker. A previous study has revealed that several metabolites are associated with depressive symptoms (Setoyama et al., 2016, PLoS One). The aim of present study was to examine the relationship between baseline plasma metabolites and antidepressant response in depressed patients.

**Methods:** Plasma samples were obtained from 79 drug-free patients with major depressive disorder. Patients were treated with selective serotonin reuptake inhibitors. Depressive severity was recorded using 17-item Hamilton Rating Scale for Depression (HRSD) at baseline and 6 weeks of treatment. Response was defined as a reduction of 50% or more of the HRSD. The metabolome analysis of blood plasma at baseline were performed using liquid chromatography mass spectrometry, and 75 metabolites were detected.

**Results:** After 6 weeks, 38 patients had an improved response to antidepressant treatment, response rate 48.1%. Seven metabolites (Glu amide, Kynurenic acid, Kynurenine, Nicotinate, Serine, Tau, and Uridine) showed lower levels in responder group relative to non-responder group, and one metabolite (Methylnicotinamide) showed higher level. These metabolites were mainly involved in tryptophan metabolism. Calculating each the diagnostic accuracies for treatment response, as quantified by the area under the curve (AUC), the maximum AUC those of 8 metabolites was 0.687 (95% confidence interval (CI), 0.570-0.804, Uridine). The combination of these 8 metabolites improved the AUC to 0.843 (95% confidence interval, 0.751-0.934).

**Conclusion:** These results indicate that the combined biomarker pattern showed better performance than single metabolite in evaluating the efficacy of antidepressant treatment. Larger cohort studies including multi-center setting are needed to clarify these findings. (278/300 words)

**Acknowledgements:** This research is supported by the SRPBS from AMED.

## PS085

### The effect of Electroconvulsive therapy on Serum Brain-Derived Neurotrophic Factor

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**Objectives** Electroconvulsive therapy (ECT) has been in use for eighty years and is known to be the most effective treatment for major depressive disorder (MDD), being superior to psychopharmacological treatment (1). Although different mechanisms have been proposed, the neurophysiological effects of ECT remain unknown (2). Within the last decade investigations have suggested alterations of brain-derived neurotrophic factor (BDNF) in MDD (3). Therefore, we evaluated the effect ECT on serum levels of BDNF in patients with MDD.

**Methods** In a preliminary analysis, we included 29 patients (20f/10m) with a baseline Hamilton depression score (HAMD) of  $27 \pm 4$  (mean  $\pm$  SD). Serum BDNF levels and HAMD scores were assessed before (test-retest, time point TP1 and TP2), 1-2 hours after the first ECT (TP3), the day after the first ECT (TP4), the day after the fifth ECT (TP5), the day after the last of a series of 5-13 ECT treatments (TP6 = determination timepoint for response) as well as a week, a month and 6 month after the last ECT treatment (TP7, TP8, TP9). Linear mixed models using time as repeated fixed factor, subjects as random factor and BDNF levels and HAMD values as dependent variables, respectively, was applied for statistical analysis with post-hoc comparisons corrected using the Bonferroni procedure.

**Results** As expected, HAMD values declined significantly over the course of ECT treatment ( $F=26.0$ ,  $p<0.001$ ; TP1:  $27 \pm 1.6$ , TP5:  $15.6 \pm 1.4$  and TP6:  $12.3 \pm 1.4$ ). At baseline, no significant differences in BDNF levels between TP1 and TP2 were observed. Thereafter, we found a significant increase in BDNF levels over time ( $F=8.5$ ,  $p<0.001$ ), with post-hoc comparisons revealing significant differences between TP1 and TP4, TP5, TP6, TP7 and TP8, respectively. BDNF levels are increasing steadily between TP4 and TP8.

**Conclusions** In this study, linear mixed models analysis revealed that ECT treatment was associated with an increase in serum BDNF levels. Our results are in line with previous findings demonstrating an increase BDNF among patients with MDD after ECT (4).

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## PS086

### Meta-analysis of hippocampal volume change following electroconvulsive therapy in major depression

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Electroconvulsive therapy (ECT) is widely used and effective therapeutic option in major depression. However, its underlying neurobiological mechanisms remain to be fully understood. Apart from a well-documented involvement of the serotonergic system [1, 2], ECT was shown to promote neurogenesis in rodents, especially in the hippocampus [3], in line with the neurogenesis hypothesis of depression. To estimate the effect size of this influence, the aim of this study was to investigate the effect of ECT on hippocampal volume change by combining previously published studies using magnetic resonance imaging (MRI) using a meta-analytic approach.

Following a PUBMED search, we identified twenty studies investigating brain volumetric measures using MRI before and after ECT in depressed patients. After having contacted authors for incomplete data, only eight studies

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(see figure) providing absolute volumetric data and standard deviations for the hippocampus at two time-points could be included in our analysis. Statistical analyses were computed using the software package R 3.0.1 and the metafor package version 1.9-1. After computing standardized mean change scores for every single publication, the overall effect size was calculated using a random-effects model.

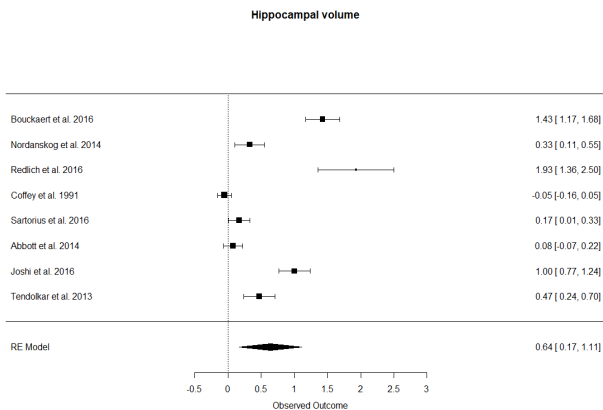
Out of the eight included studies, only one showed a negative outcome regarding the effect of ECT on hippocampal volume. In this very heterogeneous sample of studies ( $I^2=98\%$ ), the overall model showed a strong positive effect of ECT on hippocampal volume with a summary effect estimate of 0.64 [0.17–1.1] (see figure).

This meta-analysis shows a clear and strong positive effect of ECT on hippocampal volume, which is in line with the assumed promotion of neurogenesis by ECT as one of its main mechanisms of actions in treating major depression. Still, the interpretation of these findings must be done carefully when considering the possible publication bias on this topic and the fact that more than half of the available studies could not be included due to incomplete data.

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## PS087

### The why and how of cross-validation in clinical, predictive fMRI studies: The case of major depressive disorder

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**Objective:** Few neuroimaging studies have attempted to validate explored markers' predictive performance assessing clinical relevance beyond descriptives. Pretest probability for successful SSRI treatment of major depressive disorder (MDD) is at roughly 50%. Prediction identifies SSRI non-responders allowing clinicians to move to the next line of treatment immediately thereby reducing prolonged disease burden and suicidality. We offer a robust, methodological framework for the validation of potential fMRI predictors illustrated by data from a neuroimaging study assessing SSRI response in MDD patients.

**Methods:** Treatment outcome as percentage change in Montgomery-Åsberg Depression Rating Scale (MADRS) score between first and last time-point serves as independent, continuous variable. As associated binary measure, a median-split of MADRS scores allows for a clinically relevant classification into remitters and non-remitters. As dependent variables, activation in neural regions are found via exploring treatment outcome main effect across scan sessions. Leave-one-out cross-validation (CV) is applied to linear models to predict continuous outcomes, and on Receiver Operating Characteristic (ROC) to evaluate the binary predictor's performance aiming for improved generalizability and reduced overfitting.

**Results:** Identified imaging predictors revealed large statistically and clinically significant effect size prior and after clinical response. Leave-one-out cross-validation of prognostic predictors revealed large out-of-sample errors mainly after clinical response and after incorporating multiple brain regions/scans. Still, at least one predictor per time-point remained clinically significant in terms of large effect sizes ranging from 23% and 67% after cross-validation at treatment initiation. A significant reduction in effect size was observed passing from the full sample to the cross-validated model. These data suggest that involving repeated measures and multiple predictors result in more robust predictive models even prior clinical response.

**Discussion:** We highlighted the importance of CV in predictive neuroimaging studies by showcasing how overfitting and accordingly inflated effect sizes may be better controlled for leading to clinically applicable predictors.



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## PS088

### Elevated tumor necrosis factor-alpha receptor subtype 1 and the association with abnormal brain function in treatment-resistant depression

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#### Objective

Major depressive disorder (MDD) patients have shown elevated plasma levels of pro-inflammatory biomarkers compared to healthy controls. We hypothesized increased tumor necrosis factor-alpha receptor subtype 1 (TNF- $\alpha$  R1) is more associated with impaired brain function in Treatment-resistant depression (TRD) patients than non-TRD patients.

#### Methods

34 MDD patients and 34 healthy subjects were recruited and we separated MDD patients to TRD group (n=20) and non-TRD (n=14) group. Pro-inflammatory cytokines were assessed by enzyme-linked immunosorbent assays. A standardized uptake values (SUV) of glucose metabolism measured by <sup>18</sup>F-FDG positron-emission-tomography (PET) was applied to all subjects for subsequent region-of-interest analyses and whole-brain voxel-wise analyses. <sup>18</sup>F-FDG-PET measures the glucose uptake into astrocytes in response to glutamate release from neuronal cells [Magistretti and Pellerin, 1999]. The <sup>18</sup>F-FDG signals were thus used as a proxy measure for the quantification of glutamatergic neurotransmission in the human brain.

#### Results

Post-hoc analysis revealed that TRD group had higher serum concentrations of TNF- $\alpha$  R1 compared to healthy control or non-TRD group. In the MDD group, higher serum concentrations of TNF- $\alpha$  R1 significantly correlated with decreased SUV in anterior cingulate cortex (ACC) and bilateral caudate nucleus (corrected p<0.005). The ROI analysis further supported the negative correlations of

plasma TNF- $\alpha$  R1 and SUV in the ACC (r=-0.329, p=0.021) and caudate nucleus (r=-0.457, p=0.019). Such correlation is more consistent in TRD group (for ACC: r=-0.443, p=0.016; for caudate nucleus: r=-0.671, p=0.002) than in non-TRD and HC groups.

#### Conclusions

Increased TNF- $\alpha$  R1 was associated with impaired glutamatergic neurotransmission of caudate nucleus and ACC in MDD patients, particularly in the TRD. Our findings provided direct evidence to support that inflammation plays an important role in the development of TRD.

## PS089

### PCLO rs2522833-mediated gray matter volume reduction in patients with drug-naïve, first-episode major depressive disorder

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**Objective of the study:** Major depressive disorder (MDD) has been linked to differences in volume of certain areas of the brain and to variants in the piccolo presynaptic cytomatrix protein (PCLO), but the relationship of PCLO to brain morphology has not been studied. A single-nucleotide polymorphism (SNP) in PCLO, rs2522833, is thought to affect protein stability and the activity of the hypothalamic-pituitary-adrenal (HPA) axis. We investigated the relationship between cortical volume and this SNP in first-episode, drug-naïve MDD patients or healthy control subjects.

**Methods:** Seventy-eight, 30 patients with MDD and 48 healthy control participants were recruited via interview. PCLO rs2522833 genotyping and plasma cortisol assays were performed, and gray matter volume was estimated from structural magnetic resonance images.

**Results:** Among individuals carrying the C allele of PCLO rs2522833, the volume of the left temporal pole was significantly smaller in those with MDD than in healthy controls (FWE-corrected p = 0.003). Any other brain regions were however not different. In addition, the C-carrier individuals demonstrated a larger volume reduction than in the left temporal pole than in A/A individuals (p = 0.0099). Plasma cortisol levels were significantly higher in the MDD patient C-carriers than in the healthy control C-carriers (12.76 $\pm$ 6.10 nM, vs 9.31 $\pm$ 3.60 nM, p=0.045).

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**Conclusion:** PCLO SNP rs2522833 is associated with gray matter volume reduction in the left temporal pole in drug-naïve, first-episode MDD patients who are C-carriers.

## PS090

### Neurofeedback-based treatment of major depression using functional magnetic resonance imaging

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**Objective:** Neurofeedback (NF) using functional magnetic resonance imaging (fMRI) constitutes a novel treatment approach for major depressive disorder (MDD). Being still in its infancy, it is important to summarize present achievements and challenges of this method in order to ensure an evolution with maximal benefit for future patients.

**Methods:** A PubMed search for fMRI-NF studies including MDD patients was conducted (“fMRI neurofeedback (depression OR mdd)”). General as well as NF-specific methodology of the included studies were compared together with the respective validation criteria and outcomes.

**Results:** Five [1-5] out of the seven relevant publications present different aspects of the same study targeting the left amygdala (2 sessions, 3 runs each). The other two [6-7] used positive and negative images to identify feedback regions within the whole brain (4 sessions, 3 runs each) and salience network (1 session, 3 runs), respectively. Outcome criteria span a wide range of psychometric scores and functional image analyses. All studies were controlled (sham or no-feedback group) and showed significant impact of NF. Two papers explicitly state remission/response rates: [5] NF: 6/12 of 19, sham: 1/2 of 17; [6] NF: 2/5 of 8, no-feedback: 0/1 of 8. In [7], significant reductions in emotional and self-relevance scores for negative images were shown for the NF compared to the sham group (10 subjects each).

**Conclusion:** Despite varying substantially in methodology, all studies indicate positive effects of NF on MDD. Still, a publication bias cannot be excluded since NF performance is known to be highly individual and investigations without significant effects were possibly not released. Furthermore, setup and reporting of NF protocols need more standardization in order to make results comparable and avoid missing or contradictory information, especially when splitting results up into several publications.

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## PS091

### Behavioral activation for subthreshold depression changes neural activation during intrinsic motivational task

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**Title:** Behavioral activation for subthreshold depression changes neural activation during intrinsic motivational task

**Objectives:** Behavioral activation (BA) is an efficient psychological treatment for subthreshold depression, which increases response-contingent positive reinforcement based on personal value. BA seems to improve not only extrinsic, but also intrinsic motivation because individuals have more opportunities to feel a sense of accomplishment by doing things they hesitated to do because of depression [1]. However, how BA affects the neural underpinnings of intrinsic motivation remains unclear. We hypothesized that BA affects the fronto-striatal circuit, which underlies intrinsic motivation.

**Methods:** Subjects with subthreshold depression (Beck's Depression Inventory- II  $\geq 10$  [2]) were randomly allocated to either the intervention or non-intervention group. Functional magnetic resonance images were acquired from the participants on two separate occasions while performing the intrinsic motivation task [3]. The intervention group received five, weekly BA sessions between the two scanning sessions. We performed a two-sample t-test using the subtraction images of the first level

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contrasts (Time 2 –Time 1), reflecting the difference between Time 2 and Time 1 scans to determine whether the BA intervention resulted in brain activity changes. The imaging analysis statistical threshold was set at multiple comparisons with a cluster extent family-wise error rate (FWE) -corrected  $p < 0.05$ .

Results: Data from 25 subjects in the intervention group (16 males; mean [SD] age, 18.2 [0.4] years) and 26 subjects in the non-intervention group (18 males; mean [SD] age, 18.2 [0.4] years) were analyzed. Following BA, the intervention group had increased activation during the intrinsic motivation task in regions of the fronto-striatal circuit, including left putamen, right middle frontal gyrus, right superior frontal gyrus, and anterior cingulate gyrus (FWE-corrected  $P < .05$ ), compared with the non-intervention group.

Conclusion: These results suggest that BA increases activation of the fronto-striatal circuit, which underlies intrinsic motivation. This mechanism may underlie the clinical effectiveness of BA for subthreshold depression.

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## PS092

### Baseline functional connectivity between right amygdala and cingulate gyrus predict ketamine

### mood response in patients with treatment-resistant depression.

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#### Background and Aims

Ketamine is a novel antidepressant, effective to treatment-resistant depression (TRD). Despite its rapid antidepressant action, 30-50% of patients show insufficient response. Several clinical and physiological predictors of Ketamine response have been reported, however, neural substrate of the response is largely unknown and predictors have not been established. To investigate neural predictor of ketamine mood response, we conducted a resting-state fMRI study.

The present study was conducted as part of the study UMIN-CTR No. UMIN000017529. The ethical committee of Kurume University School of medicine approved the present study.

#### Methods

We treated TRD patients ( $n=13$ , age  $46.5 \pm 13.3$ , five male, all right handed, HAM-D $>18$ , acquired a written informed consent) with repeated intravenous ketamine infusion (bolus, 0.5mg/kg/40min, four times in two weeks) following discontinuation of previous antidepressant medication. Demographic data and resting-state fMRI scans were obtained before the treatment (baseline). Whole brain echo-planner images (TE=25ms, TR=3s, a total of 200 scans) and a SPGR T1-weighted structural image were acquired on a GE discovery 3T scanner. Data were analyzed using via FSL version 5.0.6 employing General linear modeling (GLM) method. Response was defined as a 50% MADRS-improvement after the treatment, resulting in 8 responders and 5 non-responders.

#### Results

In the right hemisphere, seed-based analysis using a priori amygdala seed at baseline demonstrated that more relevant functional connectivity to posterior cingulate cortex (PCC) and less relevant functional connectivity to subgenual anterior cingulate cortex (sgACC) engaged to ketamine mood response respectively ( $p=0.01$ ,  $p=0.009$ ,  $t$ -test). Employing GLM contrast parameter estimate of  $-0.03$  for the threshold, functional connectivity between amygdala and PCC predicted ketamine mood response with sensitivity and specificity of 87.5% and 80%, respectively.

#### Conclusions

The present study suggested that pre-treatment evaluation via resting-state fMRI could be a useful tool to

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predict ketamine mood response and to probe its neural bases.

## PS093

### The Normalization of Brain 18F-fluorodeoxy-D-glucose Positron Emission Tomography Hypometabolism following Electroconvulsive Therapy in a 55-year-old

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#### Aims

Major depressive disorder, especially in later life, has heterogeneous clinical characteristics and treatment responses. Symptomatically, psychomotor retardation, lack of energy, and apathy tends to be more common in people with late-onset depression (LOD). Despite recent advances in psychopharmacologic treatments, 20% to 30% of patients with mood disorders experience inadequate responses to medication, often resulting in a trial of electroconvulsive therapy (ECT). However, the therapeutic mechanism of ECT is still unclear. By using 18F-fluorodeoxy-D-glucose positron emission tomography-computed tomography (18F-FDG PET/CT), we can obtain the status of brain metabolism in patients with neuropsychiatric disorders and changes during psychiatric treatment course. The object of this case report is evaluating the effect of ECT on brain metabolism in treatment-refractory LOD by PET/CT and understanding the mode of action of ECT.

#### Case report

We presented a 55-year-old female patient who suffered psychotic depression that was resistant to pharmacological treatment. Several antidepressants and atypical antipsychotics were applied but there was no improvement in her symptoms. The patient presented not only depressed mood and behaviors but also deficit in cognitive functions. We found decreased diffuse cerebral metabolism in her brain 18F-FDG PET/CT image. ECT resulted in amelioration of the patients' symptoms and another brain PET imaging 7 weeks after the last ECT course showed that her brain metabolism was normalized.

#### Conclusions

We found decreased diffuse cerebral metabolism in her brain 18F-FDG PET/CT image. ECT resulted in amelioration of the patients' symptoms and another brain PET imaging 7 weeks after the last ECT course showed that her brain metabolism was normalized.

FDG-PET represents a promising marker of neuronal cell functions and reflects an epiphenomenon of a complex and dynamic interaction of different neurobiochemical processes.

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## PS094

### Comparison of serotonin transporter occupancy obtained at PET and PET/MR imaging systems

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#### OBJECTIVE:

The demonstration of reduced brainstem serotonin transporter (SERT) binding in major depressive disorder (MDD) is considered a milestone in molecular imaging [1]. However, clinically relevant neuroimaging markers in neuropsychiatric disorders are still awaiting. The aim of this investigation is to translate and further develop established SERT imaging procedures to recently introduced hybrid PET/MR scanners.

#### METHODS:

8 healthy subjects underwent two PET (GE advance) and two PET/MR (SIEMENS mMR) scans after double blind application of 7.5 mg citalopram or saline solution. Established standard protocols comprising 90 minutes scan time were used for PET scans. During PET/MR measurements [<sup>11</sup>C]DASB was applied as bolus plus constant infusion and data was acquired during the last 20 minutes of scanning. For PET scans the nondisplaceable binding potential (BP<sub>ND</sub>) was calculated using the multi-linear reference tissue model (MRTM2) [2]. For PET/MR bolus plus constant infusion scans BP<sub>ND</sub> was calculated as follows:  $BP_{ND} = (V_T - V_{ND})/V_{ND}$  using average activity at tracer equilibrium [3]. Occupancies were calculated as the relative decrease in BP<sub>ND</sub> between saline and citalopram scans.

#### RESULTS:

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Occupancies calculated from striatal  $BP_{ND}$  were highly correlated between PET and PET/MR scans ( $r = 0.94$ ,  $ICC = 0.82$ ). Compared to SERT occupancy derived from PET scans, occupancy obtained from PET/MR scans was underestimated by an average of 12%.

## CONCLUSION:

Striatal occupancy of SERT can be obtained with as little as 20 minutes of scan time and simple quantification models using bolus plus constant infusion of [ $^{11}C$ ]DASB. Resulting data are in high agreement with measures obtained from standard PET procedures which entail kinetic modeling of dynamic data acquired over a minimum of 90 minutes. Given the high correlation of occupancy between methods, reliable measurement of occupancy applying the bolus plus constant infusion method is possible. The reported methodological bias of 12% is corrigible by a linear factor.

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## PS095

### Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-resistant depression: a randomized, double-blind control study

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## Background

Increasing evidence supports the rapid antidepressant effect of a low-dose ketamine infusion in treatment-resistant depression (TRD). Proinflammatory cytokines play a crucial role in the pathophysiology of TRD. However, it is unknown whether the rapid antidepressant effect of ketamine is related to the rapid suppression of proinflammatory cytokines.

## Methods

Seventy-one patients with TRD were randomized into three groups according to the treatment received: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, and normal saline infusion. Proinflammatory cytokines, including C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)- $\alpha$  were examined at baseline and at 40 min, 240 min, Day 3, and Day 7 postinfusion. Montgomery-Åsberg Depression Rating Scale (MADRS) was assessed for depressive symptoms across time.

## Results

Log-transformed IL-6 ( $p = 0.002$ ) and TNF- $\alpha$  ( $p = 0.001$ ) levels differed significantly over time. The decrease in TNF- $\alpha$  between baseline and 40 min postinfusion was positively correlated with a decrease in MADRS scores across time in the 0.5 mg/kg ketamine group. Low CRP (odds ratio [OR]: 10.30, 95% confidence interval [CI]: 1.23–86.49) and high IL-6 (OR: 8.93, 95% CI: 1.16–68.86) levels at baseline were significantly associated with the likelihood of treatment response in the 0.5 mg/kg infusion group.

## Discussion

This is the first clinical study to support a positive correlation between changes in cytokine levels after ketamine infusion and improvements in depressive symptoms with TRD. The rapid suppression of proinflammatory cytokines contributes to the rapid antidepressant effect of the ketamine infusion.

## PS096

### Catecholaminergic Activity and Brain-Derived Neurotrophic Factor in Patients with Drug-Naïve Major Depressive Disorder

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**Background:** There are complicated interactions between catecholaminergic neurons and brain-derived neurotrophic factor (BDNF) in the brain. However, no reports have addressed the relationship among 3-methoxy-4-hydroxyphenylglycol (MHPG), homovanillic acid (HVA), and BDNF in the blood.

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**Objective:** This paper sought to investigate correlations between serum BDNF and plasma levels of MHPG and HVA in major depressive disorder (MDD) patients.

**Materials and methods:** A total of 148 patients (male/female 65/73, age 49.5±12.1 yr) who satisfied criteria for MDD based on the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) were enrolled in the present study. Plasma levels of MHPG and HVA were analyzed using high-performance liquid chromatography, and serum BDNF was measured using ELISA.

**Statistical analysis:** The Shapiro–Wilk test indicated that BDNF levels were normally distributed. We performed a multiple linear regression analysis of BDNF, HVA and MHPG levels, using potentially confounding variables (age, gender and HAMD-17 scores at baseline) as covariates, and regarded the adjusted results as the study outcomes.

**Results:** For the examined MDD patients, no associations between plasma MHPG levels and age, sex, HAMD scores, or serum BDNF levels were identified. In addition, no associations were detected between plasma HVA levels and age, sex, HAMD scores, or serum BDNF levels. Serum BDNF levels were negatively associated with HAMD17 scores for the MDD patients.

**Discussion:** The main finding of the present study was that plasma levels of catecholamine metabolites were not associated with serum BDNF levels, even though catecholamine might influence BDNF synthesis and secretion in the brain and BDNF might play an important role in the synthesis and/or secretion of catecholamine. We have previously reported a negative correlation between plasma MHPG and serum BDNF in healthy workers. In this study, no correlation between serum BDNF and plasma MHPG or HVA was observed in MDD patients. Given the aforementioned findings, it is plausible that individuals' sympathetic nerves are activated by stress, with potential imbalances when the MDD state is reached. Most BDNF in serum is derived from platelets because platelets are abundant in serum. However, plasma BDNF might be derived from the brain because there are few platelets in plasma. Based on the aforementioned findings, the transmission of catecholamine appears to be complicated and to involve many interactions. Levels of catecholamine metabolites are regulated by many genes. With respect to BDNF, we have previously reported that the BDNF Val66Met polymorphism is not correlated with serum BDNF levels.

**Conclusion:** The results suggest that there are no significant correlations between catecholamine metabolites and BDNF in the blood for MDD patients.

## PS097

### Factors of associated with delirium following electroconvulsive therapy: a systematic review

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**Objectives:** Delirium is one of the serious complications following electroconvulsive therapy (ECT). Factors associated with post-ECT delirium, including medications, have sporadically been reported. The objective of this study was to examine factors associated with post-ECT delirium through a systematic literature review.

**Methods:** We conducted a systematic literature search for original investigations that reported risk factors of post-ECT delirium, using PubMed (last search, July 2017) with the following search terms: (“electroconvulsive” or “electroshock” or ECT) and ((delirium or confusion or agitation) or lithium). Case reports or series were excluded.

**Results:** The literature search identified 33 relevant articles. Presence of cerebrovascular disease, dementia, or Parkinson's disease was related to higher incidence rates of post-ECT delirium in three studies. One study showed that long seizure length significantly associated with post-ECT delirium. Three studies examined the effects of electrode placement; two of them showed that bitemporal stimulation more frequently induced post-ECT delirium. Four studies evaluated the impact of prescribed lithium on post-ECT delirium; two of them found an increased risk whereas the other two studies did not. Pretreatment with ketamine was evaluated in four studies; it increased the incidence of post-ECT delirium in two studies and did not in the other two studies. On the other hand, pretreatment with dexmedetomidine decreased the incidence of post-ECT delirium in four studies. According to the study examining biomolecules, higher plasma lactate levels after stimulation were related to more frequent post-ECT delirium. One study showed catatonic feature as a predictor of post-ECT delirium.

**Conclusions:** While the findings are not always consistent in the literature, presence of cerebrovascular disease, dementia, and Parkinson's disease, bitemporal electrode placement, long seizure length, use of lithium and ketamine, high plasma lactate levels after stimulation, and catatonic feature seem to increase the risk of post-ECT delirium. Pretreatment with dexmedetomidine appears to reduce post-ECT delirium.

## PS098

### Isolation rearing produced DNA methylation changes in GABAergic and glutamergic systems in rat brain

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GABAergic and glutamatergic systems play an important role in the neurobiology of schizophrenia, and changes in their markers are reported in both postmortem human brain and in animal models. Isolation rearing from weaning in rats results in a spectrum of behavioral and neuropathological changes in adulthood, which resembles some of the characteristics of schizophrenia. Hence, this paradigm provides a non-pharmacological model relevant to the neurodevelopmental origins of schizophrenia. Recent studies have demonstrated that abnormalities in DNA methylation may underlie the alterations in various indicators of GABAergic and glutamatergic functions in schizophrenia. As we found altered gene expression in parvalbumin (Pvalb) and Grin2b, respectively GABAergic and glutamatergic indicators, we hypothesised that changes in DNA methylation may be responsible for these deficits in rats reared in isolation. We investigated DNA methylation in brain tissue (prefrontal cortex (PFC) and hippocampus) of rats reared in groups or isolated (n=10 each) from weaning over 10 weeks. After this period the animals were behaviourally tested following which hippocampus and PFC were dissected for DNA extraction. Bisulfite conversion and pyrosequencing were used to determine methylation levels in promoter sequences of Pvalb and Grin2b. Isolation rearing resulted in hyperlocomotion in the open field test and produced greater methylation at CpG2 of Pvalb in PFC of isolated rats, also hypermethylation at CpG4 of Grin2B in hippocampus. Our data reinforce the validity of the model in mimicking some aspects of schizophrenia and indicate that the alterations in methylation seen in this animal model may underlie changes in gene expression caused by isolation rearing.

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## PS099

### The effect of DLPFC regulation training using fMRI neurofeedback in healthy individuals

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**Introduction:** fMRI neurofeedback (NF) is a flexible, non-invasive technique for changing neural activity, and is viewed as a novel candidate for treating mood disorders. The left dorsolateral prefrontal cortex (DLPFC) is a potential target region of NF treatment for major depressive disorder (MDD). The DLPFC is thought to involve suppression of maladaptive cognitive processes such as depressive rumination. We investigated neural and psychological effect of DLPFC-NF training in healthy individuals to demonstrate the feasibility of the training.

**Methods:** Twelve volunteers (healthy adults, mean age 31.1) completed 5 sessions of left DLPFC fMRI-NF. In each NF session, participants were told to up- or down-regulate brain activity, visually presented in the figure as a yellow line. The feedback value was averaged BOLD signal within the left DLPFC. Participants also completed a resting state fMRI scan and psychological tests before and after NF sessions (pre / post training session). We compared resting state functional connectivity (FC) between pre- and post session.

**Results:** The comparison test revealed significant decrease of FC between the left DLPFC and the precuneus ( $p = .04$ ). The amount of FC reduction showed a moderate correlation with reduction of depression score ( $r = .58$ ,  $p = .08$ ).

**Conclusion:** Administration of the DLPFC fMRI-NF strengthened a negative FC between the left DLPFC and the precuneus in healthy individuals. Previous studies [1, 2] have indicated that MDD patients show weakened negative relationship between the left DLPFC and precuneus. The alteration of DLPFC-precuneus FC pattern induced by the DLPFC NF would have therapeutic effect for patients with MDD.

**Acknowledgements:** This research is supported by the SRPBS from AMED.

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[1] Takamura M et al. (2016). *Neuropsychobiology*, 74: 69-77.

[2] Ichikawa N et al. (2017). arXiv: 1704.01039.

## PS100

### Sensing Depression: Using Smartphone Sensors to Predict Changes in Depression Severity

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**Objective:** There is substantial evidence to suggest that episodes of major depressive disorder (MDD) are characterized by behavioral changes not easily captured with traditional measurement methods; however, many of these changes can be continuously and unobtrusively measured using the GPS and accelerometer sensors and phone display logs within commercial smartphones. Furthermore, these data can be acquired on a 24/7 basis over long periods with no effort on patients' part. We report on a collaboration between the Canadian Biomarker Integration Network in Depression (CAN-BIND) and HealthRhythms, Inc. to explore the utility of the smartphone as a means of acquiring clinically-relevant behavioral data and of understanding the relationship between such data and changes in depression status.

**Methods:** We used the smartphone app, Measure, to monitor adult outpatients with a lifetime diagnosis of MDD over an 8-week period. The PHQ-8 was administered at baseline and every two weeks. We examined the relationship of smartphone-derived variables to PHQ scores at both the group (using a generalized estimating equation) and the person-specific (using supervised machine learning and the Random Forest (RF) regression method) level.

**Results:** Eleven study participants provided 11,317 hours of data, constituting a median of 86.65% of the time enrolled in the study. At the group level, sensed measures associated with motor activity, sleep interruptions, and inferred social interaction level were significantly associated with PHQ score ( $p = 0.025, 0.023$  and  $0.017$ , respectively). At the individual patient level, we were able to build models predictive of PHQ score with an average error margin of 15%.

**Conclusions:** These preliminary findings suggest informative relationships between sensed inferences and self-reported depression levels. Both at the group and individual patient level, smartphone sensor data appear to be a feasible means of quantifying depression severity, independent of biases introduced by either clinician evaluation or patient self-report.

## PS101

### **Methylphenidate-induced Raynaud's phenomenon developed after increasing methylphenidate in an adult with attention deficit hyperactivity disorder**

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**Background:** Raynaud's phenomenon, a syndrome of peripheral vasoconstriction presented with pallor at hands and feet, has been rarely reported in children and adolescents with attention deficit hyperactivity disorder (ADHD), but has never been reported in adults. To our knowledge, this is the first adult patient with ADHD who developed Raynaud's phenomenon after increasing the dose of methylphenidate.

**Case:** A 35-year-old female was diagnosed with ADHD at the age of 24 and had been taking methylphenidate 10 mg daily for 10 years.

Three months ago, to achieve better clinical outcome, methylphenidate was slowly titrated to 7.5 mg 3 times a day (22.5 mg daily) which was well-tolerated and effective in controlling the ADHD symptoms.

A month ago, for convenience in taking the medication, methylphenidate was increased to 10 mg 3 times a day (30 mg/day). A week later, she developed a brief episode of peripheral vasoconstriction at both hands and feet resulting in pale and cold extremities. The patient was immediately examined by an orthopedic surgeon who confirmed that the symptoms and signs were compatible with Raynaud's phenomenon. After all extremities were warmed, the symptoms were ameliorated. Methylphenidate was therefore reduced to the previous dose at 22.5 mg daily and Raynaud's phenomenon disappeared completely.

Investigations including antinuclear antibodies (ANA), anti-dsDNA, erythrocyte sedimentation rate (ESR) and thyroid function test were unremarkable.

**Conclusion:** This is the first case report of Methylphenidate-induced Raynaud's phenomenon in an adult with ADHD. The resolution of Raynaud's phenomenon after methylphenidate dose reduction suggests dose-related association. Clinicians should be aware of this rare possible side-effect of methylphenidate in adults with ADHD.

## PS102

### **Longitudinal associations between glucocorticoid receptor methylation and late-life depression**

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**Running head:** NR3C1 methylation in late-life depression

It has been suggested that hypothalamus–pituitary–adrenal (HPA) axis dysregulation plays a role in the etiology of depression. HPA axis function is mediated by glucocorticoid receptors (GRs), which are influenced by epigenetic mechanisms (DNA methylation). The association between the DNA methylation of the GR gene (nuclear receptor subfamily 3, group C, member 1; *NR3C1*) and late-life depression as well as the role of *NR3C1* methylation in the prediction of the incidence of depression have not yet been investigated. Therefore, we examined the independent and longitudinal effects of the methylation of three CpG sites in exon 1<sub>F</sub> of *NR3C1* on late-life depression using peripheral blood. In total, 732 Korean community residents aged ≥65 years were assessed; 521 individuals in this group without depression at baseline were followed 2 years later. The Geriatric Mental State Schedule was used to identify depression, and demographic and clinical covariates were evaluated. The effects of *NR3C1* methylation (the individual methylation status of three CpG sites and their average values) on current and follow-up depression were calculated using a multivariate logistic regression model. Higher *NR3C1* methylation at CpG 2 and 3 and the average methylation value were independently associated with the prevalence of depression at baseline, and higher *NR3C1* methylation at CpG 2 was associated with depression incidence 2 years later in this population. Our findings suggested an association between the methylation of *NR3C1* exon 1<sub>F</sub>, especially CpG 2, and depression later in life.

**Keywords:** depression, NR3C1, DNA methylation, epigenetics, aged

## PS103

### **Geriatric Depression Scale (GDS) for classifying late-life depression as normal, minor depressive disorder and major depressive disorder**

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**Objective:** Assessing the severity of depression is important because it can affect treatment planning decisions. Therefore, various scales for objectively evaluating depression have been developed. However, the

scales used so far are lacking in categorizing such multiple stages of depressive disorders. Geriatric depression scale (GDS) is a useful tool for screening, diagnosing and evaluating depression in the elderly. However, previous studies have only identified dichotomous cutoff point (depressive vs. non-depressive) of GDS. The aim of this study is to investigate multi-stage discriminating ability of GDS on geriatric depression and derive the optimal cutoff points of GDS according to severity of geriatric depression. **Methods:** Depression was diagnosed according to DSM-IV-TR in 774 participants (650 normal, 94 with minor depressive disorder and 30 with major depressive disorder) of the Ansan Geriatric Cohort Study. Multi-category ROC surfaces were evaluated to classify three stages of geriatric depression. Optimal cut-off points were selected based on both the ROC surface and the Youden index.

**Results:** The volume under the surface statistic (VUS) was 0.66. Multi-category classification analyses derived the cutoff points of KGDS to multiple stages of depression as 10 (between normal and minor depressive disorder) and 22 (between minor and major depressive disorder). The Youden index for the GDS was calculated as 0.51 and the derived optimal cut-off points were 12 and 19.

**Conclusion:** GDS is useful to classify multi-category stages of geriatric depression.

## PS104

### **Association between depressive symptoms and metabolic syndrome in Korean Employees**

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[Running head: depressive symptoms and metabolic syndrome]

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Association between depressive symptoms and metabolic syndrome in Korean Employees

**Objective:** The purpose of this study was to investigate the bidirectional relationship depressive symptoms and metabolic syndrome in a cohort of Korean Employees

**Methods:** We retrospectively studied 24,216 employees, who receive regular checkups in the Health Screening Center of a one hospital from May, 2012 to April, 2016 (mean follow-up = 3.2 years). Metabolic syndrome and its components (abdominal obesity, low level of high-density lipoprotein [HDL] cholesterol, high level of triglycerides, hypertension, and elevated fasting glucose or diabetes). Depressive symptoms were assessed using Center for Epidemiologic Studies Depression scale.

**Results:** Presence of the metabolic syndrome was associated with an increased risk of future depressive symptoms, odds ratio 1.38 (95% CI 1.02–1.96) after adjustment for potential confounders. Of the five components, only central obesity, high triglyceride levels, and low HDL cholesterol levels predicted depressive symptoms. These components explained most of the association between the metabolic syndrome and the onset of depressive symptoms.

**Conclusion:** Our results indicate a bidirectional association between depression and Metabolic syndrome. These results support early detection and management of depression among patients with metabolic syndrome and vice versa.

## PS105

### Psilocybin impairs fear recognition in emotional morphing paradigm

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**OBJECTIVES:** Some studies have shown that classic serotonergic psychedelics/hallucinogens such as psilocybin or LSD altered emotional processing. Specifically it has been reported that classic psychedelics impair mainly emotional processing of negative emotions which could prove useful in treatment of depression or in broader context psychotherapy. Our aim was to further explore psilocybin effects on processing of facial expressions using paradigm that was previously used in social cognition research.

**METHODS:** Twenty healthy volunteers were given 0.26 mg/kg of psilocybin (average dose 18.7 mg) orally in a placebo-controlled, double-blind, cross-over design in a comfortable living-room-like setting. Four hours after psilocybin administration (after visual hallucination receded) they underwent emotional morphing paradigm based on facial expression recognition task including six basic emotions (happiness, surprise, sadness, fear, anger and disgust). Each emotional expression had been morphed from neutral expression (0%) to full expressed emotion (100%) in successive 5 % steps. The 48 morphed facial stimuli were presented on a computer screen for as long as the volunteer took to respond by pressing the keyboard. Each participant was asked to respond as soon as they recognized the facial expression and then to identify it from a forced-choice list of six options. The accuracy of the emotion recognition and reaction times were measured in this task.

**RESULTS:** Psilocybin compared to placebo has been found to impair recognition accuracy of fear in morphed facial expressions. It did not impair recognition of other emotions and we also did not find significant differences in reaction times on psilocybin compared to placebo.

**CONCLUSION:** In accordance with previous research our results describe impairment of fear processing during psilocybin intoxication. Given the higher sensitivity to negative emotional stimuli in depressed patients, this finding supports possible usefulness of psilocybin in treatment of depression.

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## PS106

### Associations of polymorphic variants of protein kinases genes with depression and response to antidepressant therapy

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**Introduction:** Protein kinases involved in neurobiological processes are believed to be a new targets for pharmacotherapy, prognosis and diagnostics of mood disorders. However, the role of genetic variations of neuronal protein kinases PIP5K2A and AKT1 are inconclusive. The authors aim to determine possible

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associations between polymorphisms of *PIP5K2A* and *AKT1* genes and response to antidepressant therapy in patients with depressive disorder.

**Methods:** After obtaining protocol approval of the Institutes Ethical Committee and informed consent of participants, 222 patients with depressive disorder (ICD-10: F32 or F33) were recruited. State severity and efficacy of treatment was assessed by applying Hamilton's depression scale (HDRS-17) and Clinical global impression scale (CGI-S, CGI-I) before initiation of treatment and 14 and 28 days later. The control group consisted of 103 mentally and physically healthy donors.

After DNA extraction according to standard procedure, single nucleotide polymorphisms (SNP) in *PIP5K2A* gene (rs10430590, rs10828317) and in *AKT1* gene (rs1130214, rs3730358) were genotyped by polymerase chain reaction using "StepOne Plus" (Applied Biosystems).

**Results:** Genotype distribution of *PIP5K2A* and *AKT1* gene polymorphisms was in consistency with Hardy-Weinberg equilibrium. A comparison between genotypes and allele frequencies of investigated SNPs in healthy donors and patients showed significant differences in two polymorphisms of *PIP5K2A* gene. No difference between HDRS-17 scores at baseline and after 14 and 28 days of treatment in patients with different genotypes was found. However, individuals with genotype CC of SNP rs1130214 in *AKT1* gene have higher CGI-I score after 28 of antidepressant treatment, which could indicate lower response to therapy. Polymorphisms rs10828317 and rs10430590 in the *PIP5K2A* gene were associated with the CGI-S total score at day 28 of therapy.

**Conclusion:** SNP rs1130214, rs10828317 and rs10430590 are relevant for antidepressant treatment response in patients with depressive disorders and can be potential biomarkers of the efficacy of psychopharmacotherapy.

This study was funded by RFBR 17-29-02205

## PS107

### CYP2D6 and CYP2C19 genotyping in routine psychiatric care

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**Introduction:** Variation in CYP2D6 and CYP2C19 activity has been linked to variable drug response or increased side effects of various drugs. Recently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) established guidelines for tricyclic antidepressant use

based on CYP2D6 and CYP2C19 genotype. Only limited knowledge is available concerning the applicability of these guidelines in routine psychiatric care.

**Methods:** We investigated the use of CYP2C19 and CYP2D6 genotyping at a tertiary care psychiatric unit in a retrospective observational cohort study. Frequencies for the combined phenotypes were connected to the recommendations of the CPIC guidelines.

**Results:** For 615 patients, we found 25.6% CYP2C19 intermediate metabolizers, 48.6% normal metabolizers, 2.9 % poor metabolizers, 21 % ultrarapid metabolizers, in 1.9 % no phenotype could be determined. For CYP2D6, 36 % intermediate metabolizers, 47 % normal metabolizers, 6.5 % poor metabolizers, 2.3 % ultrarapid metabolizers, and 8.4 % of patients with equivocal phenotype were found. Concerning CPIC guidelines, the recommendation was considered of moderate evidence for 18.1 % and optional for 33 % of patients, while 8.9 % of patients could not be matched due to unequivocal phenotype. The best rating ("Strong") was given in the largest group (40 %) but was only in 4.7 % of patients linked to a dosing recommendation departing from standard practice.

**Conclusions:** Only a minor fraction of patients exhibited a CYP2C19 and CYP2D6 phenotype that suggested a departing from standard care at the highest level of evidence. These results indicate that given the infrequent use of tricyclic antidepressants today prospective genotyping in all patients needs to be questioned at the current state of the evidence. Targeted genotyping of patients before use of tricyclics could be useful but needs to be tested against alternative strategies such as careful dosing and close monitoring of side effects in an inpatient setting.

## PS108

### Impact of comorbid thyroid disease in patients with major depressive disorder

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**Objective:** In the context of a multicenter study of the European group for the study of resistant depression (GSRD) (1) the association between major depressive disorder (MDD) and comorbid thyroid disease was explored. Existing evidence regarding a connection between thyroid disease and MDD revealed conflicting results (2).

**Methods:** Demographic characteristics and clinical information of all together 1410 patients were gathered in terms of cross-sectional data acquisition. Consecutively, descriptive statistics, analyses of covariance (ANCOVA) and binary logistic regression analyses were applied for a comparison of demographic and clinical information between MDD subjects with and without concurrent thyroid disease.

**Results:** The point prevalence rate for comorbid hypothyroidism was 13.2%, for comorbid hyperthyroidism 1.6% respectively. Individuals with both MDD + hypothyroidism and hyperthyroidism as comorbid conditions were significantly older and suffering from additional comorbid chronic somatic conditions. Patients diagnosed with MDD + comorbid hypothyroidism showed a significantly higher MADRS score at onset of the current depressive episode, furthermore, psychotic features of depression were rather expressed. Strategies for augmentation or combination were in favour of antipsychotic drugs, mood stabilizers and pregabalin. Overall, polypharmacy was common in the MDD + hypothyroidism group. As far as only the MDD + comorbid hyperthyroidism group of patients is concerned, Caucasian origin was significantly more likely.

**Conclusion:** Abnormal thyroid function, especially hypothyroidism, is linked to depression severity as well as distinct psychopathologic features of depression. However, comorbid thyroid disease has no influence on treatment response. The usefulness of thyroid hormones as augmenting strategy in non-hypothyroid patients has been questioned in a recent meta-analysis due to a lack of significant efficacy (3). Critical appraisal of thyroid hormones as treatment option for MDD might be supported by our results.

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## PS109

### Kynurenine pathway in Major Depressive Disorder: A Systematic Review and Meta-analysis

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#### Background

Evidence suggests that abnormalities of the kynurenine (KYN) pathway may be implicated in the pathophysiology of major depressive disorder (MDD). However, the details of the abnormality of the KYN pathway in MDD have not been systematically evaluated.

#### Methods

A literature search was conducted using PubMed and Embase with the search terms: (kynuren\* or KYNA or quinolinic or QUIN or QA) AND depressi\* NOT bipolar. English language studies measuring the levels of kynurenic acid (KYNA), KYN, and quinolinic acid (QUIN) using any method in patients with MDD and healthy controls (HCs) were identified. Standardized mean differences (SMDs) were calculated to determine differences in levels of the metabolites between the groups. Subgroup analyses were separately performed for antidepressant-free status. The influences of patients' age, male ratio, and proportion of those medicated on study SMDs were assessed through a meta-regression.

#### Results

Out of 899 initial records, 22 articles were identified to form the empirical basis of this analysis. Seventeen (77.2%), 10 (45.5%), and 18 (81.8%) studies examined levels of KYNA, QUIN, and KYN, respectively. Nineteen (86.3%) studies measured metabolites of the KYN pathway in serum. KYNA and KYN levels were lower in patients with MDD in comparison to HCs while QUIN levels did not

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differ between the two groups. Subgroup analyses showed that KYNA levels were decreased and QUIN levels were increased in antidepressant-free patients. A meta-regression noted that male ratios of the samples were negatively associated with study SMDs of KYNA.

## Conclusion

This meta-analysis has revealed decreases in KYNA and KYN levels and increases in QUIN levels in patients with MDD. However, given a small number of the included studies and heterogeneity of their sample characteristics, further research, including prospective examination of the metabolites, over the course of illness as well as treatment, is clearly needed.

## PS110

### Phospholipase A2 gene expressions related to omega-3 fatty acids treatment in acute depressed patients

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Omega-3 polyunsaturated fatty acids (PUFAs) have been proven critical in the development and management of major depressive disorder (MDD) by a number of epidemiological, clinical and preclinical studies. Eicosapentaenoic acid (EPA) seems to be more effective than docosahexaenoic acid (DHA) as an antidepressant agent, the biological effects about their difference of specific genetic regulations is still lacking in human subjects. We conducted a 12-week randomized-controlled trial comparing the effects of EPA and DHA on gene expressions of phospholipase A2 (cPLA2) and cyclooxygenase-2 (COX2), serotonin transporter (5HTT), and Tryptophan hydroxylase 2 (TPH-2) in 27 MDD patients, and compared the measures to 22 healthy controls. EPA was associated with a significant decrease in HAM-D scores and significant increases in erythrocyte levels of EPA and DHA. DHA was also associated with a significant decrease in HAM-D scores and a significant increase in DHA levels, but not of EPA levels. The cPLA2 gene expression levels were significantly increased in patients received EPA, but not DHA. There was a tendency for both EPA and DHA groups to decrease COX-2 gene expressions. The gene expressions of COX-2, cPLA2, TPH-2 and 5-HTT did not differ between MDD cases and healthy controls. EPA differentiates from DHA in clinical antidepressant efficacy and in upregulating cPLA2 gene regulations, which supports the clinical observation showing the superiority of EPA's antidepressant effects.

## PS111

### Improvement of hyponatremia in patients with epilepsy after switching from carbamazepine to lacosamide; a retrospective cases report

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**Objective:** Carbamazepine (CBZ) has been still one of the first choice drug for treatment of focal epilepsy, although some adverse effects of CBZ have been reported. Hyponatremia is sometimes observed during CBZ treatment, which has been regarded as adverse effect of CBZ. Lacosamide (LCM) is one of the new generation antiepileptic drugs. It is thought that LCM shows antiepileptic effect by sodium channel inhibition as same as CBZ in the broad sense. Hyponatremia caused by LCM is not observed commonly.

**Method:** We investigated the cases treated with LCM instead of CBZ because of hyponatremia (serum sodium level < 135 mEq/L) in our cases retrospectively. Every patient provided informed consent and the identity of the patients has been protected in this report.

**Result:** Five cases were found which was satisfied the above conditions. It was found that all cases were diagnosed with focal epilepsy. They were treated with antiepileptic drugs over ten years. In addition, every case had been seizure-free for at least 2 years at the beginning of LCM treatment. In every case, the serum level of sodium was normalized, and seizure freedom was maintained after a switch from CBZ to LCM with cross-taper switch method.

**Conclusion:** Replacement of CBZ by LCM might be useful to improvement of hyponatremia caused by CBZ.

## PS112

### Relationship Between Obsessive Compulsive Disorder and Retinal Nerve Fiber Layer

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**Aim:** Although several studies have examined retinal structural changes in various neuropsychiatric disorders<sup>1,2</sup>, the relationship between obsessive compulsive disorder (OCD) and retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) has not yet been investigated. In this study, we aimed to investigate the relationship between OCD and RNFL and GCL thickness.

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**Method:** 30 OCD patients, who applied to Psychiatry Outpatient Clinic of Şişli Hamidiye Etfal Education and Research Hospital, Sağlık Bilimleri University, and 29 healthy volunteers were included in the study. Sociodemographic data form was given to the control group. Sociodemographic and clinical data form was given to OCD group and Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Hamilton Depression Rating Scale (Ham-D) and Hamilton Anxiety Rating Scale (Ham-A) were administered to OCD patients. Spectral Domain Optical Coherence Tomography (SD-OCT) was used to measure RNFL and GCL thickness of all participants.

**Results:** Left and right nasal quadrants, left and right mean RNFL and left GCL thickness were higher in OCD patients, compared to control group. The age of onset was negatively correlated with left nasal quadrant, right RNFL and mean RNFL thickness, while no significant relationship was found between disease duration, disease severity, medications used and treatment duration and OCT parameters.

**Conclusion:** The thicker RNFL in OCD patients compared to control group may be related to the inflammatory process thought to play a role in OCD pathophysiology<sup>3</sup>. A more comprehensive study involving inflammatory markers and neuroimaging techniques will help to better understand the relationship between OCD and the retina.

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## PS113

### **N-acetylcysteine therapy for the treatment of obsessive-compulsive disorder: a systematic review & meta-analysis**

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**OBJECTIVES:** Dysfunctional glutaminergic signalling has been implicated in the pathogenesis of obsessive-compulsive disorder (OCD), and may represent a novel therapeutic target for the treatment of OCD. N-acetylcysteine (NAC) has diverse psychopharmacological effects, including modulation of glutamatergic activity. Given this, we undertook a systematic review and meta-analysis examining the efficacy of oral NAC therapy in OCD patients.

**METHODS:** EMBASE, MEDLINE, PsycINFO and Web of Science were systematically searched for randomised placebo-controlled trials (RCTs) examining oral NAC treatment in adult and paediatric patients with a DSM diagnosis of OCD. Using pre- and post-treatment Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores, effect sizes (standardised mean differences using Hedges' g) were calculated and, using STATA 11.0, Der Simonian-Laird random-effects models were used to compute a pooled effect size. Monte-Carlo permutation tests for meta-regression were performed using the following covariates, selected *a priori*: age, male gender, OCD duration and baseline Y-BOCS score.

**RESULTS:** Six studies satisfied inclusion criteria, with a total of 199 participants (mean age 32 years, mean pre-treatment Y-BOCS score 25.7 – within the 'severe' range – and mean daily NAC maintenance dose 2.6g). Reported effect sizes ranged from -0.02 to 1.65, with a pooled effect size of 0.56 calculated (95% confidence intervals: 0.06 – 1.07; p=0.03), indicative of an 'intermediate' effect. In meta-regression models, there was a significant negative correlation between effect size and proportion of male participants (p=0.02).

**CONCLUSIONS:** NAC treatment had a significant beneficial effect upon overall OCD symptomatology, which is all the more striking given the generally severe baseline OCD symptoms in included studies. Interestingly, female sex was seen to be a significant predictor of treatment response. Given these findings, larger and longer duration RCTs are warranted to examine the efficacy of NAC – especially in the context of severe and refractory illness – and the specific mechanisms underlying its action in OCD.

## PS114

### **An open trial of aripiprazole for the treatment of delirium**

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## Object

The object of this study was to assess the efficacy and safety of aripiprazole for the treatment of delirium.

## Method

We conducted an analysis of 22 hospitalized patients treated for delirium with aripiprazole at Tokyo Women's University Hospital from April 2015 to March 2016. Initial doses of aripiprazole were under 12 mg/day and the doses were adjusted based on clinical response with maximum dose of 24 mg/day. We evaluated the severity of delirium using Delirium Rating Scale-Revised-98 (DRS-R-98) at baseline (T1), 3 days (T2) and 7day (T3), and examined the efficacy of aripiprazole. For assessing the side effects, we checked electrocardiogram, blood test and evaluated some extra-pyramidal symptoms using Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS).

## Results

Among the 18 patients, except for 4 patients who could not be evaluated the endpoints, delirium resolved (based on DRS-R-98 < 10) in 9 patients at endpoint; the efficacy rate of aripiprazole was 50%. The DRS-R-98 scores were significantly decreased at both T2 ( $p < 0.01$ ) and T3 ( $p < 0.01$ ). 4 patients were discontinued of aripiprazole by side effects (2 cases of akathisia and 2 cases of oversedation), however, they were reversible after the discontinuations.

The mean doses of aripiprazole at T1 in effective, ineffective and discontinuation group were  $10.0 \pm 3.0$ mg,  $9.0 \pm 3.0$ mg and  $10.5 \pm 3.0$ mg, and the maximum doses were  $13.3 \pm 7.2$ mg,  $15.0 \pm 6.7$ mg and  $12.0 \pm 4.9$ mg, respectively.

## Conclusion

This study suggests that aripiprazole is available in the management of delirium, with caution for side effects of akathisia and oversedation.

## PS115

### The role of melatonin and melatonin agonists in counteracting antipsychotic-induced metabolic side effects: a systematic review

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**Aims and hypothesis:** This systematic review aims to investigate whether melatonin or melatonin agonists significantly attenuate metabolic side effects among psychiatric populations treated with atypical antipsychotics.

**Background:** Melatonin administration to high cholesterol-treated and high fat-treated rats has been shown to suppress body weight and visceral adiposity. In addition, in various animal models related to obesity, metabolic syndrome, and diabetes, melatonin has beneficial efficacy in ameliorating various metabolic symptoms, including attenuating weight gain, lowering blood pressure (BP), and improving insulin resistance.

**Methods:** Four randomized controlled trials were identified through a comprehensive literature search using MEDLINE, EMBASE, and the Cochrane Library on 22 October 2015. These four trials (including three melatonin studies and one ramelteon study) included 138 patients, of whom 71 were treated with melatonin or ramelteon and 67 were treated with a placebo. Because of high heterogeneity, we did not carry out a meta analysis.

**Results:** Melatonin was beneficial in lowering blood pressure among bipolar disorder patients; this blood pressure-lowering effect was not prominent among schizophrenic patients. Melatonin appeared to improve lipid profiles and body composition and attenuated weight gain among both schizophrenic and bipolar disorder patients. Ramelteon showed a significant efficacy in lowering total cholesterol level.

**Conclusion:** Despite the few studies included, this systematic review provided promising evidence of the potential benefits of melatonin and its agonists in attenuating one or more components of metabolic syndrome among psychiatric patients using atypical antipsychotics.

**Key words:** Melatonin, Antipsychotics, Metabolic syndrome

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## PS116

### Prevalence of Insomnia and Its Related Problems in Clinical Practice According To Primary Physician

# CINP 2018: Poster Abstracts

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**Introduction** : Insomnia become one of the problem in clinical practice that need attention from primary physician. In Indonesia one of the competency required by the Standard Competencies of Indonesian Medical Doctor is to treat patients with primary insomnia.

**Method** : We gather information from the medical doctors who attend insomnia seminar in Omni Hospital in November 2015. We asked them to fill the survey form about insomnia and its related problem in clinical practice. We concluded the results directly from the answer filled in the survey.

**Result** : There were 83 medical doctors conducted the survey. They worked in the hospital (32.5%), clinic (24.09%), private practice (15,67%) and in primary care health care (24.09%). Most of the doctors said that human needed 8 hours sleep (57.83%). There were 54 doctors (65.06%) said that they met insomnia cases about 1-3 cases per week and 19 doctors (22.89%) about 4-6 cases per week. There were 58 doctors (69.87%) that thought psychological problems was the underlying problem of insomnia that the patients had. Most of the doctors said that their insomnia patients were between 31 years to 50 years old. Alprazolam (48.19%) had became the most prescribed drug for insomnia followed by diazepam (34.93%). Most of the respondents suggested sleep hygiene (73.49) for insomnia patient. They also suggested relaxing music (46.98%) and aroma therapy (28.91%) for helping insomnia. Most of the respondents (61.44%) never heard about cognitive behavior therapy for insomnia (CBTI).

**Conclusion** : Most of the doctors still thought that people need 8 hours sleep at night to be consider as a good sleep. Psychological problems were the most underlying problem of insomnia. Alprazolam was the most prescribed drug for insomnia.

## PS117

### **Transcranial direct-current stimulation may reduce the expired carbon monoxide levels among cigarette smokers with heroin dependence**

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**Background**: Transcranial direct-current stimulation (tDCS) could be a promising intervention for smoking cessation.

Little is known on the effect of tDCS on expired carbon monoxide level, which is a reliable index of smoking.

**Method**: 26 smokers with heroin use were recruited whose methadone dosage was no change during the tDCS intervention period. We probed the effect of a 5 days, 20 minutes session of 2.0mA anodal stimulation on left dorsolateral prefrontal cortex (DLPFC, N = 10), orbital frontal cortex (OFC, N = 8), or sham control (N = 8), on the expired CO level, amount of cigarette consumed, and self-reported craving among heavy smokers. Five days of follow-up visit was also conducted.

**Result**: Active tDCS stimulation reduced the expired CO level after second day to fifth day ( $p < 0.01$ ). This effect was not found among sham controls. The effect remains at three days in the follow up period. No effect was found on other index. Supplemental analysis suggest that the effect of reducing expired CO level between DLPFC and OFC are similar.

**Conclusion**: While the amount of cigarette consumed is similar, tDCS might influence the intake dosage. The efficacy of tDCS on smoking is supported. Other supportive treatment may be needed to enhance the effect of tDCS.

## S118

### **Comparing spray vs nebulized oxytocin modulation of brainwide resting-state functional connectivity: a peripherally controlled pharmac-MRI study**

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#### **Introduction:**

We investigated changes in whole-brain resting-state functional connectivity comparing two methods of intranasal oxytocin administration (standard spray vs PARI



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*SINUS* nebulizer, expected to maximize oxytocin deposition in the olfactory region - putatively involved in direct nose-to-brain transportation) to intravenous administration. We aimed to understand the extent to which intranasal effects are explained by peripheral signalling or result from a privileged route of transport to the brain.

## **Methods:**

We recruited 17 healthy males who received 40 IU of oxytocin intranasally (through a spray or a nebulizer), 10 IU of oxytocin intravenously, or placebo, in 4 visits. Resting-state fMRI was acquired 60 min after last drug administration using a multi-echo EPI sequence in a 3T scanner. Blood samples for plasma oxytocin quantification were collected before and at several time-points after drug administration. After denoising our data using the ME-ICA approach and regressing out white-matter and CSF signals, we explored ROI-ROI functional connectivity across 132 anatomical regions using the CONN toolbox. Connectivity matrices were compared between sessions using T-contrasts ( $p < 0.05$ , FDR-corrected).

## **Results:**

Oxytocin spray resulted in widespread changes across the connectome, involving mostly decreases in the connectivity of the medial temporal gyrus, the lingual gyrus and the temporal and frontal poles. Increased connectivity could be observed between the supramarginal gyrus and the superior frontal gyrus. Despite identical pharmacokinetic profiles, nebulized oxytocin only produced increases in connectivity, involving mostly the precuneus and the paracingulate cortex. Importantly, intravenous oxytocin did not explain the pattern of changes in connectivity observed for the spray or the nebulizer.

## **Conclusion:**

We showed that two different methods of intranasal administration result in distinct changes in connectivity despite producing similar changes in plasmatic oxytocin. This observation raises the hypothesis these two intranasal methods may differ in the achieved bioavailability of oxytocin in the brain.

## **PS119**

### **Dopamine release is enhanced in healthy subjects after repeated amphetamine exposure: A [<sup>11</sup>C]-(+)-PHNO PET study**

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**Objective:** When repeated exposure to a certain stimulus leads to increased response to the same stimulus then we speak of sensitization. Sensitization of the dopamine system after repeated exposure to substances that increase extracellular dopamine such as cocaine or amphetamine is associated with an increased dopamine release and stronger behavioral effects such as feeling energetic or outgoing. Since patients with schizophrenia show increased neurochemical and behavioral response to stimulants, schizophrenia has been conceptualized as a state of "natural sensitization". Hence, amphetamine sensitization in healthy subjects serves as a useful tool to study neurobiological mechanisms underlying schizophrenia.

**Methods:** Twenty healthy stimulant-naive subjects (10 female, 10 male) underwent two positron emission tomographies using the dopamine  $D_{2/3}$  receptor agonist radioligand [<sup>11</sup>C]-(+)-PHNO, the current gold standard for measuring changes of extracellular dopamine. Subjects received one baseline scan and another scan 90-120 min. after an oral amphetamine challenge before and after two amphetamine sensitization visits. [<sup>11</sup>C]-(+)-PHNO binding potential was extracted from putamen, caudate, ventral striatum, globus pallidus and substantia nigra/ventral tegmental area using the simplified reference tissue model with the cerebellum as reference region. Furthermore, subjective effects of amphetamine were recorded.

**Results:** As expected enhanced dopamine release after amphetamine sensitization was observed in the ventral striatum and in the putamen ( $p < 0.05$ ), which was paralleled by a significantly increased behavioral response. We further observed an inverse relationship between amphetamine-induced dopamine release after the first dose and after sensitization in all of the chosen ROIs.

**Discussion:** Next to sensitization of the dopamine system after repeated amphetamine exposure we also observed a negative relationship of the response to the first compared to the fourth dose. This might suggest that the healthy brain is able to regulate increasing dopamine release, which might fail in patients with schizophrenia.

## **PS120**

### **ALKS-7119, a novel 5-HT transporter antagonist and NMDA receptor antagonist caused dose-dependent increases of cortisol and prolactin in a**

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## first-in-human, randomized, controlled trial with healthy volunteers

### Running title

Neuroendocrine effects of ALKS7119

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### Key words

NMDA, SSRI, neuropsychological disorder, cortisol, prolactin, drug development, biomarker

### Background

ALKS 7119 is a 5-HT transporter antagonist ( $K_i=0.035 \mu\text{M}$ ) and NMDA receptor antagonist ( $K_i=7.44 \mu\text{M}$ ), and could therefore be useful for the treatment of neuropsychological disorders. Safety, tolerability and pharmacokinetics (PK) of ALKS 7119 were investigated. Central nervous system (CNS) effects were assessed by a validated battery of drug sensitive CNS tests, the NeuroCart<sup>®</sup>, and serum cortisol and prolactin levels were measured. The profile of ALKS 7119 was compared to profiles of known CNS active drugs.

### Methods

This first-in-human, double-blind, placebo-controlled, randomized, single ascending dose study consisted of 10 cohorts of 10 healthy male volunteers. Subjects received ALKS 7119 or placebo (8:2). Dose levels were 3, 10, 25, 50, 75, 100, 125, 150, 175 and 200 mg. Safety was assessed by adverse events (AEs), vital signs, laboratory parameters, 12-lead ECG and continuous ECG monitoring. Plasma samples and neuro-endocrine hormone samples were collected predose until 36 hours post-dose. The NeuroCart<sup>®</sup> was repeatedly performed from predose until 12 hours post-dose.

### Results

PK was linear with a  $t_{\text{max}}$  between 0.5 - 4 hours and  $t_{1/2}$  approximately 7 - 9 hours. Common AEs were presyncope (20%), nausea (23.8%) and somnolence (10%). Mild blood pressure decreases were observed in the treatment groups. Increases in mean QTcF and QTcB of  $>30$  to  $\leq 60$  were observed in the treatment groups, without corresponding AEs. A significant dose-related increase in pupil/iris ratio was observed, left ( $p<0.001$ ), right

( $p=0.002$ ). A significant dose-dependent increase of serum cortisol ( $p=0.003$ ) and prolactin ( $p=0.001$ ) levels was observed at 1 and 2 hours post dose.

### Conclusion

ALKS 7119 was well tolerated and had a linear PK profile. Comparison of the CNS profile of ALKS 7119 to profiles of known CNS active drugs indicates that ALKS 7119 is most compatible with inhibition of SERT receptors.

## PS121

### No acute tolerance to the effects of LSD in healthy subjects

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**Objective** Repeated use of LSD leads to tolerance that could be due to 5-HT<sub>2A</sub> receptor downregulation. In rats, daily administration of LSD over 4 days decreased frontal cortex 5-HT<sub>2A</sub> receptor binding. However, there are no human data on the effects of LSD on similar changes in gene expression. Therefore, we investigated effects of single dose administration of LSD on the expression of the 5-HT<sub>2A</sub> receptor gene (*HTR2A*) and *EGR1-3* genes and also evaluated the presence of acute tolerance to the subjective effects of LSD in humans.

**Methods** mRNA expression levels were analyzed in peripheral blood cells in 15 healthy subjects (8 women, 7 men) before, 1.5 and 24 h after administration of LSD (100 $\mu\text{g}$ ) and placebo in a randomized, double-blind, placebo-controlled, cross-over study. Acute subjective effects of LSD were plotted against plasma concentrations to assess hysteresis (reduced response at corresponding concentrations over time) and thereby a marker of acute tolerance.

**Results** The expression patterns of the *HTR2A* ( $p = 0.39$  and  $p = 0.90$ ), *EGR1* ( $p = 0.83$  and  $p = 0.10$ ), *EGR2* ( $p = 0.86$  and  $p = 0.22$ ), and *EGR3* ( $p = 0.24$  and  $p = 0.16$ ) mRNA were unchanged 1.5 h and 24 h after administration of LSD compared with placebo, respectively. The effect-time curve reflected the plasma concentration-time curve of LSD with some delay due to the drug distribution to the effect site.

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There was no evidence of acute pharmacological tolerance after acute LSD administration.

**Conclusions** There was no change in gene expression of LSD's primary target receptor gene or genes implicated its downstream effects. In line with unaltered gene expressions there were no signs of acute tolerance. Our findings are consistent with observations in animals. However, since the mRNA expression was measured in periphery, in contrast to the CNS in animal studies, further analysis is needed.

## PS121B

### Effect of physical exercise intervention on mood and frontal alpha asymmetry in Internet gaming disorder

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**Objectives:** The purpose of this study was to evaluate the effect of physical exercise (PE) intervention combined with cognitive behavioral therapy (CBT) on mood and frontal alpha asymmetry (FAA) in the treatment of Internet gaming disorder (IGD).

**Methods:** Twenty-nine male adolescents with IGD were randomly assigned to one of two groups: a group with participants undergoing eight sessions of CBT and six sessions of PE intervention (CBT+PE group, n=15), or a group with participants undergoing eight sessions of CBT and six sessions of supportive counseling (CBT only group, n=14). Resting quantitative electroencephalogram, Young Internet Addiction Scale (YIAS), The Korean Attention Deficit-Hyperactivity Disorder Rating Scale (K-ARS), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were measured before and after the intervention.

**Results:** During the intervention period, BDI ( $F=5.21$ ,  $p<.05$ ) and BAI ( $F=5.91$ ,  $p<.05$ ) scores in the CBT+PE group were greatly reduced compared with those of the CBT only group. During the intervention period, the F4-F3 FAA ( $F=4.98$ ,  $p<.05$ ) and F8-F7 FAA values ( $F=4.76$ ,  $p<.05$ ) in the CBT+PE group was greatly decreased compared with those in the CBT only group. In the CBT+PE group, the change in F8-F7 FAA value was negatively correlated with the change in the BDI ( $r=-.63$ ,  $p<.05$ ).

**Conclusion:** PE intervention in combination with CBT for individuals with IGD seems to improve depressive mood and anxiety through enhancing left prefrontal activation.

## PS122

### Anxiety, depressed mood, and insomnia experienced by newly diagnosed patients with breast cancer and thyroid cancer in initial stage of cancer treatment in Korea

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**Objective:** In Korea, breast cancer and thyroid cancer are the most prevalent cancers in women. The purpose of this study was to evaluate the severity of anxiety, depressed mood, and insomnia and the degree of interference with daily life by each symptoms in first diagnosed breast cancer patients and thyroid cancer patients.

**Methods:** The subjects of this study were 1,794 women patients who visited the Ewha Womans University Cancer Center for Women. They included 1,119 newly diagnosed primary breast cancer patients and 675 newly diagnosed primary thyroid cancer patients. The patients completed the National Cancer Center Psychological Symptom Inventory (NCC-PSI) during their first follow-up visit after surgery, before starting chemotherapy or radiotherapy. The NCC-PSI is composed of the Modified Distress Thermometer (MDT) and the Modified Impact Thermometer (MIT) for insomnia, anxiety, and depressed mood.

**Results:** Anxiety severity was found to be greater in breast cancer patients than in thyroid cancer patients. A significant level of anxiety, depressed mood and insomnia was present in 28%, 24.5% and 20.7% of all the subjects, respectively. Moreover, anxiety symptoms, depressed mood and insomnia interfered in the daily lives of 20%, 18.4% and 14.2% of all the subjects, respectively. Dealing with anxiety (18.8%) was found to need the most help, followed by dealing with insomnia (8.9%) and depressed mood (8.7%).

**Conclusions:** A significant level of distress was found in about 40% of the total subjects. Nearly 30% of newly diagnosed breast cancer patients reported significant anxiety symptoms and interferences in daily living caused by anxiety, which most commonly needed special care. Early assessment and management of psychological distress, especially anxiety, in breast and thyroid cancer treatment are very important to establish integrated cancer care.

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## PS123

### A Study on the Initial Distress Assessment of the First Diagnosed Gynecologic Cancer Patients in Korea

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**Objective:** The purpose of this study is the early evaluation of distress and the comparisons of severity of insomnia, anxiety and depressed mood and degree of interference with daily life in first diagnosed gynecologic cancer patients.

**Methods:** We evaluated distress in 223 patients who underwent surgery for the first time after newly diagnosed gynecologic cancer; 112 cervical, 59 ovarian, and 59 endometrial cancer patients. National Cancer Center Psychological Symptom inventory (NCC-PSI) is a self-administered distress screening tool for patients to rate their severity of each symptom for the three categories of insomnia, anxiety, and depressed mood. It is composed of the Modified Distress Thermometer (MDT) and the Modified Impact Thermometer (MIT).

**Results:** In this study, 15.7% of first diagnosed gynecologic cancer patients were reported to have significant distress, the clinically significant distress was highest in the insomnia (10.8%), and distress that interference with daily life was highest in the anxiety (9.0%).

According to sociodemographic and clinical variables affecting distress, the distress is higher in highly educated, employed, married, without medical history, with family history of cancer and ovarian cancer types. Ovarian cancer patients group were more likely to be distressed than the other two groups (cervical vs endometrial vs ovarian cancer patients group: 10.5% vs 13.6% vs 27.1%), especially, in item of insomnia.

Ovarian cancer was an independent risk factor for distress (OR = 3.180, 95% CI 1.361 – 7.426, p = 0.008) when adjusted for education, job, marital status, and cancer type by multivariate logistic analysis.

**Conclusions:** Early assessment and management of distress from the beginning of gynecological cancer treatment, especially in ovarian cancer, is necessary to reducing the suffering of patients and enhancing the compliance of cancer treatment and positively affecting to improve quality of life.

## PS124

### Comparison of electroencephalographic parameters during electroconvulsive therapy under thiopental and propofol

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**Introduction:** Electroconvulsive therapy (ECT) is an important option for various psychiatric disorders, especially for patients resistant to or intolerable to pharmacotherapy. Because anesthetic agents have anticonvulsant property, the choice and dosing of anesthetic agents are important factors that influence seizure patterns. Propofol and thiopental are two of the most commonly used intravenous anesthetics for ECT. The aim of this study was to evaluate the difference in seizure duration and electroencephalographic (EEG) morphology during ECT between thiopental and propofol.

**Methods:** Subjects were 13 patients whose ECT anesthetic agent was changed from thiopental to propofol during the course of treatment. A total of 368 ECT sessions were analyzed. EEG parameters were collected and scored by trained psychiatrists. Wilcoxon rank sum test was used to compare the EEG parameters during ECT sessions under thiopental and propofol anesthesia, and p < 0.05 was considered significant.

**Results:** Thiopental sessions showed significantly longer duration of seizure (p = 0.033), polyspike phase (p = 0.005) and slow wave phase (p = 0.006). The maximum amplitudes of polyspike and slow wave phase were significantly larger in thiopental sessions than in propofol sessions (p = 0.007 and p = 0.015, respectively). The scores of stereotypy and postictal suppression were significantly higher in thiopental sessions than in propofol sessions (p = 0.033 and p = 0.046, respectively).

**Conclusions:** A more favorable seizure outcome in ECT sessions, as assessed by seizure duration EEG morphologic indices, was achieved with thiopental anesthesia than with propofol anesthesia. Although propofol has several advantages over thiopental, such as rapid recovery and reduced post-ECT hypertension, thiopental may be a choice of anesthetic agent for ECT in seizure-resistant patients.

## PS125

### Psychotic features of DiGeorge Syndrome

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**Goals:** To report a case of DiGeorge Syndrome, as hypoparathyroidism and calcifications of the basal ganglia, and briefly review the current literature about these pathologies.

**Methodology:** We summarize the clinical history and diagnostic investigation. We have carried out research in "PubMed" with the terms "hypoparathyroidism"; "DiGeorge Syndrome"; "Psychosis"; "Hypocalcaemia" and "basal ganglia calcification" and we selected review articles in English in the last decade.

**Results:** We found 6 articles that met the selection criteria. We reported the case of a man of 54 years, hospitalized for behavioral changes with 1 month of evolution, persecutory delusions and auditory-verbal hallucinations. Personal history of Noonan Syndrome, epilepsy and hypoparathyroidism (diagnosed with DiGeorge syndrome in the internment, because of doubts raised with the clinical picture). Analytically, with diminished iPTH, calcium and Vit.D; Ac. Anti-thyroglobulin positive. EEG with increased theta activity. TC-EC with bilateral calcification of the lenticular nuclei. It was observed improvement of the patient, under antipsychotic therapy and calcium supplementation.

**Discussion:** DiGeorge syndrome is a genetic disorder caused by the deletion of a portion of chromosome 22, q11.20 location, and is characterized by abnormalities of the face, hypoparathyroidism, heart defects, mental retardation, epilepsy and cognitive and behavioral changes. Hypoparathyroidism is a disease caused by decreased parathyroid hormone. The most frequent cause is the surgical trauma, with others less common. Can cause calcifications of the basal ganglia, with psychotic symptoms. The diagnosis is based on the clinical history, physical examination and laboratory and imaging studies, particularly serum levels of PTH and calcium. Treatment consists in maintaining calcium levels within normal limits, by administering regular doses of calcium and vitamin D. This case demonstrates the close link between calcification of the basal ganglia and psychosis.

## PS126

### Lasting subjective effects of Lysergic acid diethylamide (LSD) in healthy subjects

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**Objective** Serotonergic hallucinogenic drugs including psilocybin and LSD similarly induce profound alterations of consciousness. In several recent studies, psilocybin has been shown to produce long-term effects on subjective well-being and personality traits in healthy subjects and patients, possibly linked to the ability to produce profound insights and mystical-type experiences [1-5]. The aim was to similarly assess persisting effects of LSD in healthy participants.

**Methods** LSD (200 µg) was administered in a laboratory setting to 16 healthy participants. Acute alterations in consciousness were assessed with the Five-Dimensions of Altered States of Consciousness (5D-ASC) questionnaire. Subjective effects, including attitudes about life, mood, behavioral, and social changes were retrospectively rated 1 and 12 months after LSD using the Persisting Effects Questionnaire (PEQ). Changes in personality measures were assessed with the NEO-Five Factor Inventory (NEO-FFI), and State-Trait Anxiety Inventory (STAI).

**Results** On the PEQ, positive attitudes about life and/or self, positive mood changes, positive social effects, positive behavioral changes, and well-being/life satisfaction significantly increased at 1 and 12 months, with changes subjectively attributed to the LSD experience. In contrast, no negative changes could be observed on the PEQ. The 5D-ASC total score, reflecting acutely induced overall peak alterations in consciousness, correlated with changes in well-being/life satisfaction 12 months after LSD. 10 of 14 participants rated their LSD experience as among the top 10 most meaningful experiences in their lives, and five participants rated the LSD experience among the five most spiritually meaningful experiences in their lives after 12 months. LSD did not produce relevant changes in the NEO-FFI or STAI.

**Conclusions** In healthy volunteers, a single dose of LSD (200 µg) was subjectively considered a personally meaningful experience with lasting subjective positive effects, which could be beneficial in the use of LSD in a therapeutic setting.

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**Keywords:** LSD, lasting effects, personality

## PS127

### The prediction of the occurrence of postoperative nausea and vomiting using pharmacokinetic/pharmacodynamic factors in Japanese patients administered fentanyl

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**Background:** Postoperative nausea and vomiting (PONV) reduces the quality of life and prolongs treatment periods. Considering the use of opioids is one of risk factors for PONV, the pharmacological/pharmacogenomic differences of mu-opioid receptors deemed to be important. However, the relationship between pharmacokinetic (PK) profiles of opioids and PONV was not fully identified. Here, we investigated the relationship between pharmacological/pharmacogenomics/PK profiles of fentanyl (FEN) and PONV in patients administered FEN was investigated.

**Methods:** Overall, 102 patients who underwent laparoscopic colon resection were enrolled. Patients were administered FEN (1 µg/kg, IV) just before surgery. Ten min after FEN administration, FEN-induced symptoms were monitored. Over the next 48 h, the continuous infusion of epidural FEN (15 µg/h) was continued. Plasma samples at steady state were collected between 15 and 22 h post surgery. Plasma concentration of FEN were measured by LC-MS/MS. Polymorphisms of *OPRM1*, *CYPs* and *MDRs* were genotyped by PCR-RFLP or direct sequencing using DNA extracted from whole blood samples. Additionally, the PONV prediction formula was

constructed, and its predictive probability was evaluated using statistically significant risk factors found by univariate and multivariate analysis.

**Results:** PONV occurred in 47 patients (46.7%). The statistically significant risk factors of PONV were female gender and FEN-induced symptoms, but not PK-related factors, such as *MDR1* polymorphisms. The possession of the *OPRM1* 118A allele (wild type) was associated with severe nausea and the occurrence of vomiting. Based on the multivariate analysis, we established the formula to predict the occurrence of PONV, that could predict PONV with a probability of >70%.

**Conclusion:** Our present results suggest that pharmacological/pharmacogenomic-related factors, such as FEN-induced symptoms and the *OPRM1* 118A allele, are associated with PONV. The established formula that predicts the occurrence of PONV in every patient with a high probability would enable clinicians to treat PONV more appropriately.

## PS128

### Effects of oxytocin receptor gene variations on socio-emotional effects of 3,4-methylenedioxymethamphetamine in humans

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**Rationale:** 3,4-Methylenedioxymethamphetamine (MDMA) increases oxytocin, empathy, and prosociality [1]. Oxytocin plays a critical role in emotion processing and social behaviors and has been shown to mediate the prosocial effects of MDMA in animals [2]. Thus, genetic variants such as single-nucleotide polymorphisms (SNPs) of the oxytocin receptor (OXTR) may influence the emotional and social effects of MDMA in humans [3].

**Methods:** The effects of common genetic variants of the OXTR (rs53576, rs1042778, and rs2254298 SNPs) on the emotional, empathogenic, and prosocial effects of MDMA were characterized in 132 healthy subjects in a pooled analysis of eight similar double-blind, placebo-controlled studies. Plasma concentrations of MDMA and oxytocin were included in the analysis as covariates. Outcome values were analyzed as differences from the placebo condition ( $\Delta$ ).

**Results:** MDMA produced greater self-rated feelings of "trust" and "wanting to be with others" in rs1042778 TT genotypes compared with G allele carriers ( $\Delta$ AUEC<sub>6</sub>: 46±64 vs. 153±65 %×h;  $F_{1,51}=13$ ,  $p<0.001$  and 43±77 vs. 140±120 %×h;  $F_{1,51}=6.5$ ,  $p<0.05$ , respectively). The rs53576 and rs225498 SNPs did not moderate the subjective effects of

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MDMA. In contrast, in a Social Value Orientation test, MDMA lowered the inequality-aversion index, indicating an increased preference for fairness in rs1042778 GG and rs53576 AA genotypes but not in T or G allele carriers, respectively ( $F_{1,31}=6.5$ ,  $p<0.05$  and  $F_{1,31}=9.4$ ,  $p<0.01$ , respectively). MDMA and oxytocin concentrations did not differ between OXTR gene variants and did not confound the moderation of the MDMA effect by OXT genotype.

**Conclusion:** The present results provide preliminary evidence that OXTR gene variations may modulate aspects of the subjective and social-behavioral effects of MDMA in humans.

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## PS129

### The certain role of SOD/CAT imbalance and mitochondrial dysfunction in development of autism spectrum disorders

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The real impact of reactive oxygen species, antioxidant enzymes, mitochondrial dysfunction and chronic inflammation on the development of autism spectrum disorders (ASD) remains unclear, and even controversial. In this study we compared the plasma levels of antioxidant enzymes and their cofactors, markers of oxidative damage, and the respiratory burst in peripheral blood polymorphonuclear leukocytes (PMNL) as a surrogate marker of chronic inflammation obtained from 10 children (4-10 year old) who met DSM-5 criteria and their siblings. We clearly demonstrated diminished superoxide dismutase (SOD) and enhanced catalase (CAT) activities resulting in a markedly decreased SOD/CAT ratio and enhanced carbonyl content in the plasma of ASD patients. A clear correlation was present between SOD and CAT activities in the control group, which was not noted in ASD patients. Moreover, in autistic patients, we observed negative correlation between SOD activity on one side,

and carbonyl content in plasma, 8-Hydroxy-2-deoxyguanosin content in urine, and respiratory burst intensity in PMNL on the other side. At the same time, low SOD level in autistic children was positively correlated with the magnesium content in the packed RBCs, which might indicate the involvement of the mitochondrial MnSOD in ASD pathogenesis, and therefore the consequent partaking of mitochondrial dysfunction in the development of ASD. Altogether, these results indicate that decreased antioxidant capacity and increased oxidative stress in ASD patients may have functional consequence in terms of increased superoxide leakage, oxidative protein damage, chronic inflammatory response, and, finally, neuronal cell abnormal functioning or death.

## PS130

### Seed-based resting-state functional connectivity in patients with Persistent Somatoform Pain Disorder(PSPD)

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**Objectives:** Persistent somatoform pain disorder(PSPD)was characterized by the predominant complaint of persistent and distressing pain, which cannot be explained adequately by a physiological process or a physical disorder.PSPD patients have excessive thoughts, feelings or behaviors associated with pain symptom or excessive fear associated with health, to cause the patients to feel suffering or cause a significant disruption in their daily life. This study aimed to explore the whole-brain resting- state functional connectivity (rsFC) in patients with PSPD.

**Methods:** 13 PSPD patients and 23 matched healthy controls (HCs) were enrolled in this study. We assessed their pain, anxiety and depression symptoms with several scales including Visual Analogue Scale (VAS), The Zung Self-Rating Anxiety Scale (SAS) and the Zung Self-Rating Depression Scale (SDS) , and scanned the Functional Magnetic Resonance Imaging (fMRI). The FC intensity and degree centrality was utilized to evaluate the significance of a seed region in the whole-brain FC network. Then, the difference of the above parameters between the PSPD patients and HCs was analyzed by general linear model. Finally, the relationship between the identified aberrant fMRI parameters and the clinical assessments results was investigated. **Results:** Results showed that there was

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increased FC between the left Thalamus(THA.L) and bilateral Calcarine fissure and surrounding cortex(CAL.R), bilateral Lingual gyrus(LING), bilateral Fusiform gyrus(FFG), left Inferior occipital gyrus(IOG.L), right Amygdala(AMYG.R), right Hippocampus(HIP.R) in PSPD patients, and there was decreased FC between left Amygdala(AMYG.L) and right Putamen(PUT.R). Correlation analysis revealed that augmented THA.L - AMYG.R FC was negatively associated with the Zung Self-Rating Anxiety Scale(SAS) total scores in PSPD patients.

**Conclusion:** These findings demonstrated that the left Thalamus is the central seed region in the abnormal FC pattern in PSPD patients.

## PS131

### **Panic disorder with or without agoraphobia: changes in symptoms of 500 patients over 20 years in Japan**

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**[Introduction]** The authors have been working with panic disorder patients from 1993 to the present time. The current study compares clinical variables of panic disorder over this 20 year period.

**[Subjects and Methods]** The first phase of the survey was conducted between April 1993 and December 1998 with a total of 511 patients, while the second phase of the survey was conducted between September 2012 and November 2014 with another 500 patients (339 females). Clinical examination was performed using a self-reported questionnaire.

**[Results]** The mean age of illness onset (first vs second)  $\pm$  was  $29.3 \pm 9.0$  vs  $28.3 \pm 9.9$  years old,  $30.4 \pm 9.6$  vs  $28.0 \pm 9.7$  years in females, and  $28.5 \pm 8.3$  vs  $28.8 \pm 10.3$  years. The most frequent symptoms of panic in the first and second survey phases were palpitations, sensation of shortness of breath, and dizziness. However, the frequencies of all panic symptoms other than feelings of chopping, nausea, dizziness, chills or heat sensation, and paresthesias were decreased significantly in the second survey. The number of symptoms involved in the first panic attack and the frequencies of panic attacks during the month before first admission also decreased (6.1 vs 5.0).

**[Conclusion]** The results showed a reduction in the age at first onset of panic disorder, especially in female

patients, as well as a reduction in the severity of panic symptoms over this 20 year period in Japan.

## PS132

### **Prevalence and Clinical Correlates of Dissociative Subtype of Posttraumatic Stress Disorder at an Outpatient Trauma Clinic in South Korea**

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**Background:** Inclusion of the dissociative subtype of posttraumatic stress disorder (d-PTSD) in DSM-5 has opened enormous research opportunity for probing underlying mechanism and its clinical implications. However, there is no consensus about how the diagnoses of d-PTSD should be made because previous studies exclusively used latent profile or class analyses and unavailability of rating scales optimized for diagnostic criteria. This study investigated prevalence and covariates of d-PTSD in a cohort of outpatients with DSM-IV PTSD in a specialized trauma clinic in South Korea.

**Methods:** Data from 243 patients with civilian PTSD were examined for this study including demographics, clinical variables, the Clinical Global Index, and the Clinician-administered PTSD scale (CAPS). We defined d-PTSD as presence of either depersonalization or derealization in additional items of the CAPS. Accordingly, about one third ( $n = 79$ , 32.5%) were designated as having d-PTSD.

**Results:** Compared to non d-PTSD patients, they were younger and had more severe PTSD symptoms, frequent interpersonal trauma, and higher number of comorbid disorders. When these variables and their interactions were entered in logistic regression analysis, severe PTSD symptoms and younger age with two more comorbid conditions remained for the final model.

**Conclusions:** This study demonstrated high prevalence of d-PTSD in real-world clinical population. Associated features of d-PTSD were similar to findings in the literature and cross-cultural universality was supported from our findings. In fact, actual rate of d-PTSD may be higher using clinical rating than estimation from latent profile or class analyses.

Key words: PTSD; dissociative subtype; prevalence; comorbidity

## PS133



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## **New drug treatment and mechanism of the central anticholinergic drug trihexyphenidyl in reducing posttraumatic nightmares in patients with PTSD**

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**Objective:** The central anticholinergic drug trihexyphenidyl (TP) has previously been reported to show remarkable effectiveness against posttraumatic stress disorder (PTSD) flashbacks at WFSBP, 2015, Athens, and CINP, 2016, Seoul. The objective of this study was to assess its efficacy in reducing nightmares associated with PTSD and to elucidate the underlying mechanism for this.

**Methods:** An open-label trial was conducted between 2009 and 2017 in 29 outpatients diagnosed with PTSD in accordance with DSM-5. All were refractory patients who had experienced no therapeutic benefits from any psychotropic drug over a number of years. TP (2 mg 1T to 3T) was administered depending on the patient's condition. The primary outcome measures were the change from baseline to endpoint in the patients' global Clinician-Administered PTSD Scale scores and using the items related in this psychological test—B2 (nightmares) and B3 (flashbacks)—for PTSD memory-related assessment. The secondary efficacy measure was the Impact of Event Scale-Revised scores, which presents an overall clinical profile of patients.

Informed consent was obtained from all patients. This study was approved by the Ethical Committee of Warakukai.

**Results:** The therapeutic outcome in the 27 patients who experienced nightmares demonstrated an extremely high efficacy rate, with 19 (70%) achieving complete remission and the remaining 8 (30%) achieving partial remission. In addition, 18 (67%) achieved complete remission of flashbacks.

**Conclusion:** This is the first pharmacological report on the novel use of TP against nightmares in PTSD. TP was remarkably effective in the treatment of both nightmares and flashbacks.

Posttraumatic nightmares are flashbacks in dreams. The nightmare onset mechanism is closely associated with acetylcholine (ACh) transmission, and the resulting nightmares are different to regular dreaming caused by Ch5 pedunculo-pontine tegmental nucleus and Ch6 lateral tegmental nucleus in the brain stem. It is hypothesized that posttraumatic nightmares result during regular REM sleep because of the superimposition of the mechanism that generates PTSD flashbacks, i.e., neurotransmission in the ACh-memory-related-circuit, which comprises the nucleus basalis of Meynert (Ch4)-amygdala, medial septal

nucleus (Ch1)-hippocampus, and Broca's diagonal band (Ch2)-hippocampus circuits.

**Disclosure:** There are no financial conflicts of interest.

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Poster Number	Level 1 Topic	Sub Topic By Disorder
PM135-PM190	Clinical	Schizophrenia
PM191	Preclinical	Others
PM192-PM194	Clinical	Sleep Disorders
PM195-PM199	Clinical	Suicide
PM200	Others	Anxiety Disorders
PM201	Others	Bipolar Disorders
PM203	Others	Childhood & Adolescent Disorders
PM204	Others	Dementia
PM205-PM206	Others	Depression
PM207	Others	Epilepsy
PM208-PM211	Others	Others
PM212	Others	Personality Disorders
PM213-PM218	Others	Schizophrenia
PM219	Others	Suicide
PM220-PM228	Preclinical	Addictive Disorders
PM229-PM232	Preclinical	Anxiety Disorders
PM233	Preclinical	Schizophrenia
PM234	Preclinical	Anxiety Disorders
PM235	Preclinical	Attention Deficit Disorders
PM236-PM238	Preclinical	Bipolar Disorders
PM239	Preclinical	Childhood & Adolescent Disorders
PM240	Preclinical	Others
PM241-PM243	Preclinical	Childhood & Adolescent Disorders
PM244-PM248	Preclinical	Dementia
PM249-PM272	Preclinical	Depression

### PM135

**Addition of Evenamide (NW-3509), a Selective Voltage Gated Sodium Channel (VGSC) Antagonist, to Atypical Antipsychotics is Efficacious in Patients Worsening on their Current Medication.**

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#### Specific objective

This study was designed to demonstrate whether patients stabilized on risperidone (RIS) or aripiprazole (ARI), but

showing signs of worsening, could be improved by adding evenamide.

#### Methods

Double-blind, placebo-controlled, randomized, 4-week study evaluating safety, dose-titration, and preliminary evidence of efficacy of evenamide in previously responding schizophrenia (SCZ) patients on stable doses of RIS ( $\geq 2$ mg/day) or ARI ( $\geq 10$ mg/day) at 2 US (n=61) and 3 Indian (n=28) centres. Safety assessments included evaluation of adverse events, drop-outs, laboratory tests, ECG, vital signs, and physical examinations.

#### Results

A total of 89 patients with SCZ (mean baseline PANSS total:  $62.9 \pm 7.4$ ; CGI-S:  $3.5 \pm 0.5$ ), experiencing break-through psychotic symptoms on previously effective and stable doses of RIS (mean dose:  $4.2 \pm 2.0$  mg/day; n=70) or ARI (mean dose:  $19.7 \pm 7.0$  mg/day; n=19) were randomized (1.3:1 ratio) to treatment with evenamide (n=50) or placebo (n=39). The study treatments were very well tolerated; 2 patients on evenamide discontinued treatment due to AEs (atrial fibrillation and seizure). The most common AEs (evenamide vs placebo [%]), were somnolence (16 vs 12.8%), insomnia (10 vs 6%) and headache (6 vs 0%). The addition of evenamide to RIS or ARI was associated with statistically significant efficacy, compared to placebo at endpoint, based on the PANSS Positive Symptoms sub-scale [change from baseline, LS mean difference (SE): -1.28 (0.632), p=0.046; responders: 74.5% vs. 43.6%, p=0.0043], and CGI-C responders (55.3% vs. 35.9%, p=0.0855).

#### Conclusions

Evenamide, a VGSC antagonist that has been shown to normalize aberrant neuronal firing, and modulate glutamate release in preclinical models, without affecting dopaminergic and serotonergic pathways, demonstrated preliminary clinical evidence of antipsychotic efficacy as an add-on to RIS or ARI. Benefits of evenamide were greater in younger patients. Additional larger, longer studies are planned to conclusively demonstrate its efficacy as adjunctive treatment in patients with schizophrenia.

### PM136

**Patterns of antipsychotic prescription in patients with schizophrenia at a tertiary care center in Japan**

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Despite the limited evidence of efficacy, antipsychotic polypharmacy has become a common clinical practice for schizophrenia. Previous studies have shown that

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antipsychotic polypharmacy rate is especially high in Japan. In the present study, we examined the prescription pattern of antipsychotics in patients with schizophrenia treated on an outpatient basis at a tertiary care center in Japan. Subjects were patients who were diagnosed as schizophrenia or schizoaffective disorder and received outpatient treatment during the period of April, 2017 to June, 2017 at the Department of Psychiatry, Shinshu University Hospital, Japan. A total of 429 patients (151 men and 278 women, mean age (standard deviation): 40.6 (12.1) years) were included in the study. Antipsychotics were prescribed to 316 patients. The mean daily chlorpromazine equivalent dose and the rate of antipsychotic polypharmacy in those prescribed antipsychotics were 258.3 mg/day and 16.6%, respectively. No significant difference in mean age or sex distribution was observed between patients on single and multiple antipsychotics. The rate of antipsychotic polypharmacy and the daily chlorpromazine equivalent dose were both lower in the present study than previously reported in Japan. Recent studies have reported increased rate of monotherapy in Japan. Our findings suggest that antipsychotic polypharmacy has further decreased in Japan. Because the present study was conducted in a single institution, our findings may not be generalized to other treatment settings such as nontertiary facilities or inpatient treatment. Further research is warranted to better understand the prescription pattern in schizophrenia treatment and to enhance the widespread use of appropriate prescription strategies.

## PM137

### Prescription patterns in patients with schizophrenia who discontinued long-acting injectable antipsychotics: a chart-review

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**Objectives:** The primary objective of this study was to investigate patients with schizophrenia who discontinued long-acting injectable (LAI) antipsychotics.

**Methods:** A systematic chart review was conducted for patients with schizophrenia (ICD-10) who started to receive an LAI antipsychotic from January 2005 to December 2014 at Inokashira Hospital in Tokyo, Japan. Among them, those who discontinued LAI at least once were identified. The following information was collected: age, sex, duration of illness, duration of treatment, reasons

of discontinuation of LAIs, and prescription details until December 2016.

**Result:** Initial screening yielded 202 patients; of these, 49 patients were examined for this preliminary analysis. Among them, 22 patients fulfilled the selection criteria (mean±SD age 53.6±11.8 years; male, 36.4% [n=8]; duration of illness, 28.9±9.3 years; duration of treatment, 25.6±10.2 years). Fluphenazine decanoate, haloperidol decanoate, LAI risperidone, paliperidone palmitate, and fluphenazine decanoate plus haloperidol decanoate were used as their first LAIs in 9 (40.9%), 6 (27.3%), 5 (22.7%), 1 (4.5%), and 1 patients (4.5%), respectively. Reasons for discontinuation were as follows: insufficient response (n=6, 27.2%), side effects (n=4, 18.2%), symptom improvement (n=1, 4.5%), patient's request (n=2, 9.1%), unknown reasons (n=4, 18.2%), and other reasons (n=6, 27.2%). Nine patients (40.9%) resumed LAI antipsychotics later during the course of the treatment. At the time of final follow-up, 6 patients (27.2%) used LAI antipsychotics (LAI risperidone, n=4; fluphenazine decanoate, n=2), and 54.5% (n=12) of the patients were receiving antipsychotic polypharmacy (mean±SD number of antipsychotics, 1.7±1.0). The most frequently used oral antipsychotics were chlorpromazine and risperidone (n=8, 36.3% for both).

**Conclusion:** Relatively high rates of antipsychotic polypharmacy and re-introduction of LAI antipsychotics after discontinuation of the first LAI treatment represent a challenging clinical situation in this population, although the findings in this preliminary analysis need to be confirmed in the whole sample.

## PM138

### Idiopathic or Antipsychotic induced Thrombocytopenia? A treatment Dilemma

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**Background/Objective:** Thrombocytopenia is a very rare complication of antipsychotic treatment. It has never been reported with multiple antipsychotics trials in the same patient. We wish to share this report of a very rare occurrence which was ultimately resolved with splenectomy (39)

**Case Report:** A 21-year-old patient was psychiatrically hospitalized with persecutory and grandiose delusions, formal thought disorder, auditory hallucinations, and

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psychomotor agitation disorder. He met criteria for a diagnosis of Schizophrenia. Initial admission Complete Blood Count showed platelet count of 151 (normal 150 – 400). He failed trials of aripiprazole, ziprasidone, olanzapine and was eventually started on clozapine. Pre-treatment platelets were normal at 142. Subsequent weekly tests revealed falling platelet counts, reaching a nadir of 30. Despite its efficacy with his psychosis, clozapine was discontinued. He was restarted on olanzapine, yet platelets continued to fall. Trials of steroid therapy would transiently normalize platelet levels. Over the course of several months he was tried on trials of perphenazine, risperidone, paliperidone, quetiapine, with Lithium augmentation. Thrombocytopenia worsened every time an antipsychotic was initiated and would spontaneously improve upon its discontinuation. Hematology was consulted several times, recommending steroid therapy. While trials of steroids amended the thrombocytopenia, they exacerbated his psychosis. Antiplatelet antibodies were absent. Due to the temporal relation, antipsychotic induced thrombocytopenia was considered. Since he continued to experience severe psychosis and could not be treated with antipsychotics, hematology was re-consulted, diagnosed idiopathic thrombocytopenic purpura and recommended a splenectomy. Platelet counts returned to normal in a week, following splenectomy. The patient was restarted on clozapine and has since shown significant improvement. (217)

**Conclusion:** We could not find a case of thrombocytopenia occurring as a class effect with multiple antipsychotic trials. Though this appeared to be antipsychotic-induced, splenectomy provided resolution, corroborating the hematologic diagnosis. (30)

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## PM139

### Association between thioridazine use and cancer risk among patients with schizophrenia- a population-based study

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**Objective:** Several cell line studies have demonstrated thioridazine's anticancer, multidrug resistance-reversing and apoptosis-inducing properties in various tumors. We conducted this nationwide population-based study to investigate the association between thioridazine use and cancer risk among patients with schizophrenia.

**Methods:** Based on the Psychiatric Inpatient Medical Claim of the National Health Insurance Research Database of Taiwan, a total of 185,689 insured psychiatric patients during 2000 to 2005 were identified. After excluding patients with prior history of schizophrenia, only 42,273 newly diagnosed patients were included. Results: 1,631 patients ever receiving thioridazine for more than 30 days within 6 months were selected and paired with 6,256 randomly selected non-thioridazine controls. These patients were traced till 2012/12/31 to see if they have any malignancy. The incidence rates of hypertension and cerebrovascular disease were higher among cases than among matched controls ( $p=0.005$  and  $0.004$ , respectively). The incidence of hyperlipidemia, coronary artery disease and chronic pulmonary disease did not differ between the two groups. The time to event (cancer) in patient and control groups was 5.4 and 5.5 years ( $p=0.784$ ). Follow-up duration was 9.7 (SD 3.2) and 10.0 (SD 3.0) years ( $p<0.001$ ), respectively. By using Cox proportional hazard model for cancer incidence, the crude HR was significantly higher in age, hypertension, hyperlipidemia, cerebrovascular disease, coronary artery disease and chronic pulmonary disease. However, after adjusting for other covariates, age and hypertension remained significant in aHR (1.05, 95% CI 1.05-1.06; 1.41, 95% CI 1.03-1.93).

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**Conclusions:** Despite our negative finding, based on the biological activity of thioridazine, such as interference with membrane function, DNA repair, signaling pathways, and apoptosis induction, renders thioridazine a potential anticancer drug and further investigation concerning thioridazine use in human with cancer is warranted.

Key words: thioridazine, schizophrenia, cancer

## PM140

### Clozapine-induced procalcitonin elevation

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**Topics:** Antipsychotics: Basic / Clinical

**Objectives:**

To challenge the utility of procalcitonin as an indicator of infection in a febrile patient under clozapine treatment.

**Methods:**

A clinical case of a patient with clozapine-induced procalcitonin elevation is presented. PubMed database was searched for similar cases using the words: "procalcitonin", "clozapine", "hyperthermia", "fever" and/or "c-reactive protein" were included.

**Results:**

Clozapine is the only antipsychotic approved for treatment-resistant schizophrenia. Despite this, it is used with caution due to potentially life-threatening side-effects. Serious conditions (such as neutropenic sepsis), and milder conditions (such as clozapine-induced fever and flu-like symptoms), make the differential diagnosis of fever in clozapine treatment a clinical challenge. Situations of fever and C-reactive Protein (CRP) elevation with or without myocarditis have also been described. To distinguish between bacterial or viral infection the use of procalcitonin (PCT) is well established, being the best diagnostic predictor of bacterial infection in febrile patients.

We report the case of a 46-year-old patient with treatment-resistant paranoid schizophrenia (ICD-10) who started clozapine in July 2016 with a conservative titration schedule after the failure of his psychotic symptoms to respond to a number of different antipsychotic treatments and augmentation strategies. Despite having a normal physical exam, the patient developed intermittent pyrexia with PCT and CRP elevation. The blood count was normal, except for lymphopenia. Troponin and CK values were

within the normal range. However, after a comprehensive evaluation, albeit having high levels of PCT and CRP, this patient showed no focus of infection. We decided to interrupt the clozapine treatment with resolution of clinical symptoms and laboratory changes shortly after cessation and without use of antibiotic therapy. As of then, no changes in laboratory results were observed.

**Conclusions:**

We postulate that clozapine induced an increase in both PCT and CRP levels, making this the first reported case of clozapine-induced PCT elevation.

Whatever the definitive diagnosis, the usefulness of PCT in clozapine-induced fever might be considered unclear, as PCT levels can rise in the absence of bacterial infection. Given our findings, it is important that both PCT and CRP levels be interpreted together with all clinical and laboratory information.

## PM141

### Antipsychotic treatment in patients with catatonic schizophrenia

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Previous studies have shown that catatonia in patients with schizophrenia is less responsive to benzodiazepines. The use of antipsychotics, although controversial, has been reported to be effective in some patients with catatonic schizophrenia. We retrospectively examined the efficacy of antipsychotic treatment in patients with chronic schizophrenia who had developed catatonia at age 50 years or older. Subjects were 7 men (mean age (standard deviation): 57.3 (3.3) years) and 8 women (mean age: 57.6 (8.3) years) who received inpatient treatment and whose duration of illness exceeded 10 years. Catatonic symptoms were assessed using Bush-Francis Catatonia Rating Scale (BFCRS) and treatment efficacy was assessed by Clinical Global Impression (CGI) scale. Antipsychotic treatment was fully effective in 6 patients, partially effective in 2 patients, and ineffective in 7 patients. Serious adverse reactions included 1 case of neuroleptic malignant syndrome and 2 cases in which stupor and muscular rigidity worsened. Catatonic symptoms completely disappeared in the 9 patients who were administered electroconvulsive therapy (ECT); however, the catatonic symptoms relapsed promptly in 1 of the patients. Improvement of catatonia required several sessions of ECT, and the symptoms waxed and waned during the recovery process. The present findings showed that the efficacy rate of antipsychotic treatment in schizophrenic catatonia was relatively low and that

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repeated ECT sessions were necessary for the amelioration of schizophrenic catatonia. Although antipsychotics may be a choice of treatment for catatonia in patients with chronic schizophrenia, our data suggest a considerable incidence of serious adverse events due to antipsychotic treatment.

## PM142

### Early response to aripiprazole and plasma levels of monoamine metabolites in patients with acute schizophrenia

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**Background:** Although recent studies suggested that early response to antipsychotics is clinical marker of subsequent favorable response in the treatment of schizophrenia, its underlying biological basis remains unclear. We investigated the associations between early response to aripiprazole, subsequent clinical outcome, and plasma levels of homovanillic acid (HVA) and 3-methoxy-4hydroxyphenylglycol (MHPG) in antipsychotic-free acute schizophrenic patients.

**Methods:** Subjects were 40 Japanese patients with schizophrenia, and were treated with aripiprazole for 6 weeks. The Positive and Negative Syndrome Scale (PANSS) was used for assessment of clinical symptoms, and early response was defined as 20% or greater decrease from baseline in the PANSS total score at 2 weeks. Plasma levels of HVA and MHPG were measured using high-performance liquid chromatography at baseline and at week 6. This study was approved by the ethics committee of Fukushima Medical University, and the patients consented to participate after having been informed of the purpose of the study.

**Results:** Among the 40 patients, 12 patients (30%) were early responders to aripiprazole and 28 (70%) were early non-responders. Early responders to aripiprazole showed significantly greater improvement in PANSS total score than early non-responders ( $p=0.003$ ). Although plasma HVA levels of early responders ( $20.5\pm 9.5$  ng/ml) were higher than those of early non-responders ( $16.0\pm 5.7$  ng/ml) at baseline, there was no significant difference between the two groups ( $p=0.15$ ). There was a trend for time x early response interaction on the changes in plasma MHPG levels after the aripiprazole treatment ( $p=0.075$ ).

**Discussion:** Our results are consistent with previous studies which demonstrated that early response to

antipsychotics was useful clinical marker to predict favorable outcome. Furthermore, our results suggest that early response may be associated with subsequent decrease in monoamine turnover. Because of the small sample size, further studies are needed to confirm these results.

## PM143

### Risk factors for low bone mineral density in patients taking antipsychotics for psychosis

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**Objective:** Osteoporosis is a major yet covert, comorbidity in patients with schizophrenia that has recently attracted much clinical attention. This study examined clinical and gender-specific risk factors for low bone mineral density (BMD) in adult patients with psychotic disorders.

**Methods:** The study included 285 community-dwelling patients with psychotic disorders. Dual-energy x-ray absorptiometry was used to measure BMD. Laboratory examinations included vitamin D and prolactin levels. Low BMD was defined as  $<1$  standard deviation below the mean for young adults. Clinical characteristics associated with low BMD were identified with logistic regression analysis in total population and each gender.

**Results:** Fifty-eight (20.4%) subjects had low BMD. Low BMD was more common in men and in patients with low body mass indices (BMIs), as well as in those with shorter treatment durations, those on Medicaid, and patients using serotonergic antidepressants. Logistic regression analysis revealed that low BMD was negatively associated with BMI and treatment duration and positively with gender (male) and serotonergic antidepressants use in the overall population. In men, low BMD was associated with treatment duration and BMI; in women, low BMD was associated with BMI, prolactin level, vitamin D, and serotonergic antidepressant use.

**Conclusion:** Low BMI was risk factor for reduced BMD in both genders. Shorter treatment duration was associated with low BMD in men, whereas higher prolactin levels, lower vitamin D, and the use of serotonergic antidepressants were associated with low BMD in women. Managing the risk factors associated with low BMD among patients with psychotic disorder should be done gender-specifically. Psychotropic agents should be prescribed mindful of their effects on bone, as use of these

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medications is a modifiable risk factor for osteoporosis in women with psychotic disorders.

## PM144

### Relationship between Polydipsia and Antipsychotics: A Systematic Review of Clinical Studies and Case Reports

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**Background:** Polydipsia is not rarely observed in psychiatric patients during antipsychotic treatment; however, the relationship between polydipsia and antipsychotics still remains unclear. To elucidate this issue, we conducted a systematic review of literature on polydipsia and antipsychotics.

**Methods:** We systematically searched MEDLINE, Embase, and PsycINFO, and included clinical studies and case reports on polydipsia induced or improved by antipsychotics. We extracted information on psychiatric disorders, antipsychotic and other psychotropic treatment, and course of polydipsia including laboratory data from the articles.

**Results:** We identified 60 articles: 1 double-blind randomized trial, 4 single-arm trials, 3 cross-sectional studies, 3 case series, and 51 case reports. The double-blind randomized trial demonstrated no significant difference in improvement in polydipsia between patients treated with olanzapine and haloperidol. Two single-arm trials showed that polydipsia improved during clozapine treatment. One cross-sectional study reported a lower rate of hyponatremia in patients receiving second-generation antipsychotics (SGAs) than those receiving first-generation antipsychotics (FGAs). Among 89 cases from the case reports, 66 (75.0%) were diagnosed with schizophrenia; 47 (52.8%), 41 (46.1%), 18 (20.2%), and 12 (13.4%) developed psychiatric symptoms, convulsion, digestive symptoms, and rhabdomyolysis or neuroleptic malignant syndrome along with polydipsia, respectively; and 76 (85.3%) reported serum sodium levels. In 82 cases providing antipsychotic types before onset of polydipsia, 75 (91.5%) and 11 (13.4%) received FGAs, in particular haloperidol (24, 29.3%), and risperidone, respectively. In 40 cases providing antipsychotic types when polydipsia improved, 36 (90.0%) received SGAs, in particular clozapine (14, 35.0%). On average, psychopathology significantly improved after treatment of polydipsia.

**Conclusion:** FGAs and antipsychotics with high affinity to dopamine D2 receptors such as haloperidol and risperidone may be associated with risk for polydipsia,

while some SGAs, especially clozapine, may be a treatment option for polydipsia. Because of the paucity of high quality studies, further evidence is warranted to confirm the findings.

## PM145

### Placebo Effects in Trials for Schizophrenia: Combined Analysis of Nine RCTs

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**Objective:** The aims of this study were to examine whether early placebo improvement would be associated with later placebo response at the endpoint, to characterize characteristics of placebo responders, and to search optimal criteria of early placebo improvement for prediction of subsequent response in patients with schizophrenia.

**Method:** Data from patients with schizophrenia of nine double-blind randomized controlled trials of antipsychotics obtained through the YODA project were analyzed. Multiple logistic regression analyses were conducted to examine associations between placebo response at week 6 and the following variables: gender, age groups (<18 years and ≥18 years), locations of the studies conducted (Asia, North America, Europe, and Africa), Positive and Negative Syndrome Scale (PANSS) total score at baseline, and percent score reduction in the PANSS total score from baseline to week 1. Another regression analysis was performed by replacing the PANSS total score with PANSS Marder 5-Factor scores. The predictive power of improvement at week 1 for response at week 6 was investigated; sensitivity and specificity of incremental 5% cut-off points between 5% and 25% reduction in the PANSS total score at week 1 were calculated.

**Results:** The nine studies included a total of 735 placebo recipients. Percent reduction in the PANSS total score at week 1, the region of Asia, and a lower PANSS Marder disorganized thought score at baseline were significantly associated with placebo response at week 6. Cut-offs of 10-15% reduction in the PANSS total score at week 1 showed the highest accuracy in the prediction performance.

**Conclusions:** A 10-15% PANSS total score reduction at week 1 robustly predicted subsequent placebo response at

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week 6 in patients with schizophrenia. Moreover, placebo response seems to be influenced by study locations and severity of disorganization. These findings may provide critical insights to better design of international placebo-controlled trials for schizophrenia.

## PM146

### Placebo Effects in Long-Acting Injection Trials for Schizophrenia: Combined Analysis of Four RCTs

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**Objective:** Placebo effects remain largely unexplored in clinical trials of long-acting injectable (LAI) antipsychotics for schizophrenia. This study aims to characterize patients showing improvements after placebo injections and to search for criteria for the prediction of subsequent response based on the magnitude of score changes after the first week of treatment.

**Method:** Data from 1810 patients with schizophrenia of four double-blind randomized controlled trials evaluating efficacy of LAI paliperidone palmitate obtained through the YODA project (<http://yoda.yale.edu>) were analyzed.

Multiple logistic regression analyses were conducted to examine associations between placebo response and demographic and clinical characteristics. The predictive power of improvement at week 1 for response at week 9 was investigated; sensitivity and specificity of incremental 5% cut-off points between a 5% and 25% reduction in Positive and Negative Syndrome Scale (PANSS) total score at week 1 were calculated.

**Results:** Percent reduction in the PANSS total score at week 1 and a lower PANSS G-12 score (i.e. better in judgment and insight) at baseline were significantly associated with placebo response at week 9. Cut-offs of a 10% (per-protocol analysis) and 15% (last-observation-carried-forward analysis) reduction in the PANSS total score at week 1 showed the highest predictive power.

**Conclusions:** The appreciation that longer-term response following placebo injections can be predicted by a 10-15% score reduction in the PANSS at week 1 could guide the design of future clinical trials of LAI antipsychotics in schizophrenia in order to identify and exclude potential placebo responders early during the course of the study.

## PM147

### Time Courses of Central Dopamine D2 Receptor Occupancy and Peripheral Blood Concentrations of Antipsychotics: A Systematic Review

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**Objective:** It has remained unclear as to whether dopamine D<sub>2</sub> receptor occupancy with an antipsychotic in the brain changes with time in parallel to its concentration in peripheral blood. To elucidate this issue, we conducted a systematic review of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies.

**Methods:** We systematically searched MEDLINE and Embase, and included studies that met the following criteria: (1) including patients with schizophrenia spectrum disorders and/or healthy subjects; (2) using PET or SPECT; and (3) examining the time courses of D<sub>2</sub> occupancy and blood concentrations of risperidone, olanzapine, or quetiapine (i.e. simultaneous measurements of both at multiple time points). We extracted data on D<sub>2</sub> occupancy and blood concentrations of antipsychotics at each time point and calculated the ratio of % D<sub>2</sub> occupancy reduction from peak to % blood concentration reduction rate from peak.

**Results:** A total of 8 studies from 7 articles were identified (3, 2, 4, 2, and 1 studies for risperidone, olanzapine, quetiapine immediate release (IR), quetiapine extended release (XR), and long-acting injectable risperidone, respectively). Seven and one studies used [<sup>11</sup>C]raclopride PET and [<sup>123</sup>I]iodobenzamide SPECT for striatum, respectively. Six and two studies targeted patients with schizophrenia spectrum disorder and healthy subjects, respectively. All ratios were less than 1 across time points, except for quetiapine IR 300/450 mg/day and quetiapine XR 300 mg/day. The ratios at the time of 1±0.2 biological half-life (T<sub>1/2</sub>) were 0.28/0.43 for risperidone 3/6 mg/day, 0.10 for olanzapine 15-20 mg/day, and 1.39/0.99/0.84 for quetiapine XR 300/600/800 mg/day, respectively.

**Conclusion:** The findings indicate that the reduction rate of D<sub>2</sub> occupancy is lower than that of blood concentrations regardless of antipsychotic type in general and the dissociation may increase in a dose-dependent fashion. Further analyses are needed to examine potential causes of this kinetic discrepancy.



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## PM148

### Serum IL-1ra, a novel biomarker predicting olanzapine-induced dyslipidemia and hyperleptinemia in Schizophrenia

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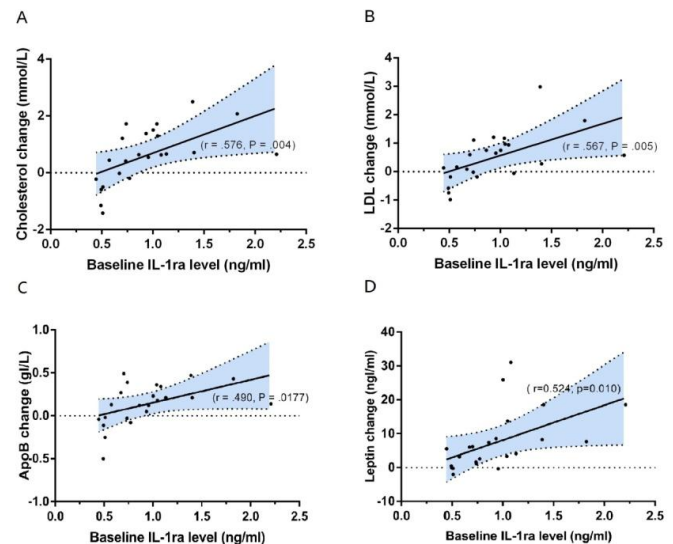
Olanzapine (OLZ) is highly efficacious whereas leads to adverse metabolic effects thus increases risk of cardiovascular diseases (CVD) on schizophrenia. Cytokines have been found associated with metabolic disorders. Therefore, pretreatment prediction of OLZ-induced adverse metabolic effects is urgently needed.

To investigate if baseline cytokine levels could become biomarkers for pathogenesis of schizophrenia or prediction for OLZ-induced adverse metabolic effects, we recruited 75 participants, including 23 schizophrenia inpatients, who were antipsychotic-free over the past 6 months or first episode and drug-naïve and 52 matched health controls, in our prospective cohort study and cross-sectional study. We simultaneously examined 7 serum cytokine levels (IFN- $\gamma$ , IL-1ra, IL-1 $\beta$ , IL-8, TNF- $\alpha$ , MCP-1, VEGF) before OLZ treatment by using liquid suspension array technique and obtained clinical correlates at 4-week intervals in total 8 weeks. The psychopathology was assessed with the Positive and Negative Symptom Scale (PANSS). The metabolic parameters were BMI, TG, total cholesterol, LDL, HDL, ApoA1, ApoB, lipoprotein a, fasting glucose, HbA1c, insulin, and leptin.

At baseline, IL-1ra and MCP-1 levels in schizophrenia were significantly higher than health controls ( $t=4.55$ ,  $P=0.0001$ ,

$t=3.08$   $P=0.003$ ). BMI, fasting insulin, cholesterol, triglyceride, LDL, ApoB and leptin were significantly increased in patients with schizophrenia after 8 weeks of olanzapine treatment. Correlation analysis showed that the baseline IL-1ra level were significantly correlated with the increased levels of cholesterol ( $P=0.004$ ), LDL ( $P=0.005$ ), ApoB ( $P=0.018$ ) and leptin ( $P=0.010$ ). Further stepwise multiple linear regression analysis indicated that IL-1ra levels prior to treatment remained significantly associated with increased levels of cholesterol, LDL, ApoB and leptin. Above all, higher IL-1ra and MCP-1 levels may be biomarkers indicating pathogenesis of schizophrenia. Higher serum levels of IL-1ra may predict subsequent higher possibility of dyslipidemia and hyperleptinemia following OLZ treatment in schizophrenia patients.

**Key words: schizophrenia; IL-1ra; adverse metabolic effect; biomarker**



## PM149

### Frequency of Tardive Dyskinesia in Research on Asian Psychotropic Prescription Pattern (REAP) survey (2001-2016)

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#### Objective

Tardive dyskinesia (TD) is a disabling and suffering side effect of long-term use of antipsychotics. The aim of this study was to survey the frequency of TD in patients with schizophrenia across 15 countries including China, Hong Kong, Japan, South Korea, Singapore, Taiwan, India, Thailand, Malaysia, Bangladesh, Indonesia, Myanmar,

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Pakistan, Sri Lanka, and Vietnam in year 2016 and compare with previous surveys.

## Methods

A total of 3744 patients with schizophrenia were examined according to the clinical judgment of experienced psychiatrists on the presence or absence of TD during the REAP survey. The patients' prescriptions of psychotropic drugs and demographics were recorded using a standard protocol and data collection system.

## Results

The frequency of TD in the whole sample was 6.8% (n=253) with wide variations between countries (0 – 22.6%, Taiwan). The frequency is significantly higher than previous 3 surveys in total (5.0%, n=8,711,  $P < 0.001$ ). The TD patients were older ( $42.3 \pm 12.5$  vs  $39.2 \pm 13.0$  years,  $P < 0.01$ ), more female (8.2 vs 6.1%,  $p = 0.02$ ). There was no difference between use of first generation and second generation antipsychotics, or polypharmacy (8.2, 7.3, and 6.2%, respectively), neither the use of antiparkinsonian drugs or not (50.6 vs 49.4 %).

## Conclusion

There frequency of TD in Asian patients with schizophrenia was lower than Western data, with a remarkable variation between these 15 countries. The frequency might be underestimated due to no case reported in some countries. We suggest that training for recognition and management of TD is warranted in Asian countries.

## PM150

### Sodium Benzoate, a D-amino Acid Oxidase Inhibitor, Added to Clozapine for the Treatment of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial

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**Background:** Clozapine is the last-line antipsychotic agent for refractory schizophrenia. To date, there is no convincing augmentation strategy for clozapine. Activation of NMDA receptors, including inhibition of D-amino acid oxidase (DAAO), has been reported to be beneficial for patients receiving antipsychotics other than clozapine. This study aimed to examine the efficacy and safety of a DAAO inhibitor, sodium benzoate, for schizophrenia patients who had poor response to clozapine.

**Methods:** In this 6-week, double-blind, placebo-controlled trial, 60 schizophrenia inpatients that had been stabilized with clozapine were randomized to receive add-on treatment of 1-g/d sodium benzoate, 2-g/d sodium benzoate, or placebo. The primary outcome measures were Positive and Negative Syndrome Scale (PANSS) total score, Scales for the Assessment of Negative symptoms (SANS), Quality of Life Scale (QOL), and Global Assessment of Function. Side-effect and cognitive functions were also measured.

**Results:** Both doses of sodium benzoate produced better improvement than placebo in SANS ( $p = 0.024$  and  $0.027$  at endpoint, respectively). 2-g/d sodium benzoate also produced better improvement than placebo in PANSS total score, PANSS-positive score, and QOL ( $p = 0.005$ ,  $0.005$  and  $0.008$ , respectively). Two-gram benzoate decreased more DAAO serum levels than placebo ( $p = 0.029$ ). Sodium benzoate was well tolerated.

**Conclusion:** Sodium benzoate adjuvant therapy, at 2-g/d, significantly improved overall symptomatology, positive and negative symptoms, and QOL of patients with clozapine-resistant schizophrenia and decreased blood DAAO levels, while 1-g/d benzoate decreased merely the negative symptoms. Further studies are warranted to elucidate the optimal dose and treatment duration of sodium benzoate for clozapine-resistant schizophrenia.

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## PM151

### **Variation in response to clozapine vs. all other antipsychotics in patients with schizophrenia: A systematic review and meta-analysis**

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#### **Objectives:**

Clozapine has established efficacy in treatment resistant schizophrenia (TRS). If clozapine's unique effects are related to the neurobiology of TRS, one would expect a different variation in symptom change following treatment with clozapine compared to other antipsychotics. We tested this hypothesis by performing a meta-analysis of variance across studies. In addition, we addressed whether clozapine's superior efficacy extends to patients without operationally-defined TRS by undertaking a meta-analysis of mean difference.

#### **Methods:**

This meta-analysis adhered to the PRISMA Statement. EMBASE, Medline, and PsycINFO were searched. Double-blind randomised controlled trials comparing clozapine with other antipsychotics in patients with schizophrenia were included. The primary outcome measure was change

in total BPRS/PANSS scores from baseline to endpoint. Standard deviations of change in symptom scores were pooled across studies to calculate the variability ratio (VR) and coefficient of variation ratio (CVR). Standardised mean differences (SMD) across TRS and non-TRS studies were calculated and compared using a Wald-type test.

#### **Results:**

Forty-two studies representing 48 comparisons between clozapine and other antipsychotics were identified (n=3467, TRS: 22, duration: 4-52 weeks). Twelve TRS studies (n=1303) were included in the meta-analysis of variance. Pooled variation of change in total symptoms was numerically greater in the clozapine group, but insignificant (VR=1.11, 95%CI: 0.89-1.38, p=0.447). Similar results were obtained for CVR, which adjusts for group-wise difference in mean change. Greater reduction in total symptoms was observed with clozapine treatment across 21 TRS studies (SMD=0.23, 95%CI: 0.10-0.37, p<0.001) and 18 non-TRS studies (SMD=0.24, 95%CI: 0.10-0.38, p<0.001), with no significant difference between these categories (p=0.951).

#### **Conclusions:**

The finding that clozapine is associated with greater symptom reduction compared to other antipsychotics regardless of operational-definitions of treatment resistance, and the lack of difference in variation of symptom change suggests that clozapine's mechanism of action is not necessarily specific to the underlying neurobiology of TRS.

#### **Keywords:**

Clozapine, treatment resistance, variation

#### **Conflict of Interest / Disclosure:**

None

## PM152

### **Clinical characteristics of patients with schizophrenia who were maintained without antipsychotics: A cross-sectional survey and a literature review**

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#### **[Objectives]**

While some patients with schizophrenia remain clinically well without continuous antipsychotic treatment, data on the features of such patients are still scarce and previous

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reports have not evaluated key elements such as physical comorbidities and functioning. We aimed to comprehensively explore the clinical characteristics of the patients who were maintained without antipsychotics.

## **[Methods]**

Six patients with schizophrenia who were withdrawn from antipsychotics after a 12-year follow-up survey underwent assessments including Positive and Negative Syndrome Scale (PANSS), WHOQOL-BREF, and Barthel Index of Activities of Daily Living (Barthel Index). A systematic literature review was also conducted to identify predictive factors for successful antipsychotic discontinuation in schizophrenia using PubMed (last search; July 2017) with the following search terms: (antipsychotic\* or neuroleptic) AND (withdraw\* or cessat\* or terminat\* or discontinu\*) AND (schizophreni\* or psychosis).

## **[Results]**

Four inpatients were old (mean±SD, 77.8±4.8 years) and chronically ill (duration of illness, 49.3±12.5 years) with a high PANSS total score (118.0±1.8), physical comorbidities, and low functioning (Barthel Index, 8.8±11.1). By contrast, two outpatients were relatively young (45.0±12.0 years) and clinically in good condition (PANSS total score, 44.5±0.5; Barthel Index, 100 for both). One patient discontinued antipsychotics after having achieved remission, while the other five stopped them due to physical comorbidities. Systematic literature search identified 37 relevant articles. Factors associated with a lower risk of relapse were lower symptom severity, better functioning, maintenance on a lower antipsychotic dose before discontinuation, older age, later onset, shorter duration of untreated psychosis, and a lower blink rate.

## **[Conclusions]**

There is a subgroup of patients with schizophrenia who may not need antipsychotics for relapse prevention. Although this literature review suggests some predictors for successful antipsychotic withdrawal in patients with schizophrenia, the very limited evidence base and unequivocally high relapse rates following discontinuation must remain a matter of serious debate for risk/benefit considerations.

## **PM153**

### **Safety switching from daily to once-monthly long-acting injectable antipsychotics associated with prolactin levels in schizophrenia patients**

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**Background:** The use of long-acting injectable antipsychotics (LAI) has shown to increase adherence,

reduce risks of relapse, and support recovery for schizophrenia patients. Paliperidone palmitate (PP) and Aripiprazole once-monthly (AOM) provide constant medication delivery offering low peak-to-trough fluctuations, however, there is a lack of clinical marker indicating dopamine (D) 2 receptor blockade in LAI-maintenance treatment.

**Aim:** To investigate the efficacy and tolerability of PP and AOM switched from daily antipsychotics and their relationships to prolactin levels.

**Methods:** Schizophrenia patients switched to PP or AOM were enrolled under the inclusion criteria: treated with oral preparations for at least previous 2 months, ongoing LAI-treatment for more than 12 months, and fulfilled recommended dose switching method. A total of 13 and 25 subjects with a mean age of 49.3 and 41.1 years for PP and AOM, respectively entered. Brief Psychiatric Rating Scale (BPRS) scores and Drug-induced Extrapyramidal Symptoms Scale (DIEPSS) scores, and fasting serum prolactin levels divided by gender were assessed at baseline, and 1, 3, 6, and 12 months. Multiple comparisons were performed with repeated measured ANOVA, followed by post-hoc analysis. The ethics committee of Kusatsu Hospital approved this study, and informed consent was obtained from all subjects.

**Results:** The total BPRS scores were significantly decreased at 6 and 12 months in AOM female subjects, while no statistical changes were found in AOM male subjects and PP subjects. There were no differences in the total DIEPSS scores in PP and AOM subjects. The prolactin levels decreased at 12 months in PP and AOM female subjects and consistently decreased in AOM male subjects, although not significantly.

**Conclusion:** Though non-double-blind method, small sample size were limitations in this 12-months prospective-designed study, the stabilization of psychotic symptoms and prolactin levels may suggest that LAI-maintenance treatment achieved an optimal D2 receptor occupancy in a psychiatric setting.

## **PM154**

### **Lurasidone and Risk for Metabolic Syndrome in Patients with Schizophrenia: A Comprehensive Database Analysis**

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**Objective:** The aim of this analysis was to assess the effect of treatment with lurasidone on risk of developing metabolic syndrome in patients with schizophrenia.

**Methods:** Changes in rates of metabolic syndrome during treatment with lurasidone (37-148 mg/d; N=xx) versus active comparators (olanzapine, N=xx; quetiapine, N=xx; risperidone, N=xx) were analysed using pooled short-term data from 3 randomised, double-blind, placebo-controlled studies. Also analysed were long-term data from 2 active-controlled studies (total N=xx); and data from 2 open-label switch studies (total N=xx). Metabolic syndrome was defined based on National Cholesterol Education Program criteria (NCEP ATP III; 2005 revision).

**Results:** In short-term studies, risk of developing metabolic syndrome was similar for patients in the lurasidone and placebo groups (odds ratio [OR]=0.97; week 6-LOCF); and was significantly greater for patients in the olanzapine (OR=2.68;  $P<0.001$ ) and quetiapine (OR=3.70;  $P<0.001$ ) groups vs. placebo. In long-term studies, risk of developing metabolic syndrome after 12 months was significantly lower for lurasidone vs. risperidone (OR=0.374; 95% CI, 0.180–0.774;  $P<0.01$ ), and non-significantly lower for lurasidone vs. quetiapine XR (OR=0.267; 95% CI, 0.040–1.806). In open-label switch studies, the rate of metabolic syndrome decreased in patients switched to lurasidone after 6 weeks of treatment with olanzapine or 12 months of treatment with risperidone.

**Discussion:** In this clinical trial database analysis, treatment with lurasidone (37-148 mg/d) was not associated with an increased risk of developing metabolic syndrome in patients with schizophrenia in short-term studies (vs. placebo). In the long-term studies reported here, patients were statistically significantly less likely to develop metabolic syndrome during treatment with lurasidone vs. risperidone, and numerically less likely vs. quetiapine XR. Switching from olanzapine or risperidone to lurasidone resulted in a decrease in the percent of patients meeting criteria for metabolic syndrome during the subsequent six months of lurasidone treatment.

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## PM155

### Prediction of Relapse with Residual Symptoms in Schizophrenia: A Reanalysis of the PROACTIVE trial data

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**Introduction:** Little is known about the contribution of each individual symptom to subsequent outcomes in patients with schizophrenia. The primary objective of this study was to examine which symptoms at baseline would be associated with subsequent relapse. The secondary objective was to evaluate the timing and degree of individual symptom worsening before relapse.

**Method:** This post-hoc investigation used the data from the Preventing Relapse Oral Antipsychotics Compared to Injectables - Evaluating Efficacy (PROACTIVE) study. In the original study, 305 outpatients with schizophrenia or schizoaffective disorder were randomly allocated to either long-acting injectable risperidone administered every two weeks (n=153) or daily oral second-generation antipsychotics (n=152), and assessed biweekly with key symptoms from the Brief Psychiatric Rating Scale (BPRS) for up to 30 months. Individual symptoms at the baseline that could predict relapse, which was defined as a score of 6 or 7 in the Clinical Global Impressions Scale – Improvement scale, were identified, using a Cox proportional hazards model. Moreover, scores in the individual symptom items were compared between baseline and 8, 6, 4 and 2 weeks before relapse, using t-test, among those who relapsed (n=73) during the course of the study.

**Result:** A greater score of grandiosity at baseline was significantly associated with subsequent relapse (HR=1.271,  $p=0.006$ ). On the other hand, no significant differences in any individual symptoms were observed between baseline and 8, 6, 4 or 2 weeks before relapse.

**Discussion:** Grandiosity may serve as a risk factor of subsequent relapse in patients with schizophrenia. On the other hand, it seems difficult to detect an early sign of relapse based on individual symptom changes before relapse. Further research is clearly needed to confirm these preliminary findings.

## PM156

### Typical and Atypical Long acting injectable antipsychotics in schizophrenia: a 2-year prospective cohort study

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**Background:** Schizophrenia is a severe and debilitating psychiatric disorder. The use of long acting injectable (LAI) antipsychotics **is expected to have greater relapse prevention**. Atypical antipsychotics have been associated with lower risk of extrapyramidal symptoms but are associated with a higher risk of metabolic adverse effects and higher cost. A clear difference in efficacy remains unestablished, making real-life setting decisions controversial.

**Aims:** Compare the efficacy of typical (T-LAI) and atypical long acting injectable antipsychotics (aT-LAI) in schizophrenia.

**Methods:** We conducted a two-year prospective cohort study in a community mental health team (*Oeiras* council). Patients with schizophrenia diagnosis, aged 18 years and above, followed during 2015 were selected. The clinical outcomes were number and days of psychiatric admissions and emergency department visits (ED). Non-parametric tests were used for statistical analysis.

**Results:** We have screened 145 patients with schizophrenia. Fifteen patients were lost during the follow-up period. At the baseline assessment the differences between group were: T-LAI 67% males, mean age of 48 years, mainly unemployed (45%), with 8.9 years of illness duration, mean of 1.3 psychiatric admissions and 29 days, a mean of 1.6 visits to the ED. aT-LAI 62% males, mean age of 46 years, 31% unemployed and 21% retired, with 8.2 years of illness duration, mean of 1.2 psychiatric admissions and 35 days, a mean of 1.9 visits to the ED. There were no statistical differences between samples. After a 2-year follow-up, there was a statistical difference between T-LAI and aT-LAI favouring T-LAI mean admission T-LAI 0.15 vs aT-LAI 0.33 ( $P=0.05$ ); mean admission days T-LAI 3.6 days vs aT-LAI 11.3 days ( $P=0.05$ ); mean ED visits T-LAI 0.18 vs aT-LAI 0.95 ( $P=0.003$ ).

**Conclusions:** Our data suggest that T-LAI could be more effective reducing admissions and ED visits, but further studies are needed to understand these results.

## PM157

### **Needs to psychopharmacological treatment in patients with schizophrenia and their psychiatrists' oversight: a cross-sectional study**

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### **Background]**

Data on needs, preferences, and complaints to psychopharmacological treatment in patients with schizophrenia are limited. Moreover, there has been no study to assess the degree of awareness of their psychiatrists regarding these issues.

### **[Methods]**

In- and outpatients with schizophrenia (ICD-10) were asked to fill in the questionnaire consisting of multiple-choice questions regarding (1) their needs (16 items) and complaints (24 items) to psychopharmacological treatment that they were receiving and (2) their preference of dosage form (9 items), dosing frequency (5 items), and timing of dosing (5 items). Additionally, their psychiatrists were asked to predict their patients' response to the above questions.

### **[Results]**

Fifty subjects have participated in this study so far; data 38 subjects were analyzed for this preliminary report. Their characteristics were as follows: 19 males (50.0%), 24 inpatients (63.2%), mean±SD age: 47.1±13.6 years, duration of illness: 18.8±13.4 years, and Positive and Negative Syndrome Scale total score: 73.7±19.2.

The most frequently endorsed need for psychopharmacological treatment was "poor sleep" (n=8, 19.5%), followed by "anxiety" (n=6, 14.6%), and "nothing in particular" (n=6, 14.6%); 27.9% (n=10) of their psychiatrists correctly predicted these responses. With regard to complaints to the current psychopharmacological treatment, "nothing in particular" was the most frequent response (n=8, 19.5%), followed by "medications do not reduce symptoms" (n=5, 12.2%); only 13.5% of their psychiatrists accurately estimated these responses. The most popular dosage form was "tablet" (n=22, 53.7%), which was correctly predicted by 64.9% (n=24) of their psychiatrists. "Once a day" (n=26, 63.4%) and "at bedtime" (n=24, 58.5%) were the subjects' most favorite dosing frequency and timing, respectively; 70.3% (n=26) and 54.1% (n=20) of their psychiatrists predicted them.

### **[Conclusions]**

The findings from this preliminary study suggest that there is substantial room for improvement on the side of psychiatrists to capture their patients' needs and complaints of psychopharmacological treatment.

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## PM158

### Changes of Body Weight, LDL and HDL Cholesterol Level in Schizophrenia Patients Treated with Atypical Antipsychotics

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Schizophrenia is a severe psychiatric disorder with mortality 2-3 times greater than the general population. The use of atypical antipsychotics in patients with schizophrenia may lead to an increased risk of cardiovascular events such as weight gain, central obesity, hyperglycemia and hyperlipidemia. Objective of this study is to determine changes in body weight, LDL and HDL cholesterol levels in schizophrenia patients receiving atypical antipsychotic therapy. This study uses an observational analytic design with a prospective cohort approach. In this study we measured body weight, body mass index, waist circumference, LDL and HDL cholesterol in 30 samples of schizophrenic patients using Risperidon and Clozapin. Measurements were performed before therapy, after 4 weeks of therapy and after 8 weeks of therapy. LDL cholesterol and HDL cholesterol testing using Cobas C111 with GPO-PAP method - Enzymatic reactions of colorimetry. Blood sampling is performed after 10 hours of fasting. The results showed a significant increase of body weight by  $1.43 \pm 0.66$  kg (2.96%) after therapy for 4 weeks and  $2.2 \pm 0.74$  g (4.43%) after therapy For 8 weeks ( $p < 0.05$ ). There was a significant reduction of HDL Cholesterol at  $4.37$  mg / dL (9.78%) after therapy for 4 weeks and  $3.84$  mg / dL (9.5%) after therapy for 8 weeks ( $p < 0.05$ ). There is an increase in LDL cholesterol but not significant. The use of atypical antipsychotics (risperidone and clozapine) can cause changes of body weight, HDL and LDL cholesterol level that require special attention. Preliminary and periodic checks on body weight, HDL and LDL cholesterol levels in schizophrenic patients receiving antipsychotics, especially atypical antipsychotics, need to be performed.

Keywords: Schizophrenia, Atypical Antipsychotic, Body Weight, LDL Cholesterol, HDL Cholesterol

## PM159

### Effect of Lurasidone on Cognition in Adolescents with Schizophrenia: Interim Analysis of a 2-year Open-label Extension Study

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**Objective:** To evaluate the short and long-term effects of lurasidone on cognitive performance in adolescents with schizophrenia.

**Methods:** Patients aged 13-17 years with schizophrenia who completed 6 weeks of double-blind (DB), treatment with lurasidone were enrolled in a 2-year, open-label (OL) study in which patients were continued on lurasidone or switched from placebo to lurasidone. Cognitive function was assessed with the Brief CogState battery, which evaluates 4 cognitive domains: processing speed, attention/vigilance, visual learning, and working memory. Based on normative data, an overall cognitive composite Z-score was calculated as the average of the Z-scores for the 4 cognitive domains.

**Results:** After 6 weeks of DB treatment, mean change in cognitive composite Z-score was -0.09 and +0.11 for lurasidone 37 mg and 74 mg, respectively. A total of 271 patients who completed 6 weeks of DB treatment entered the 2-year OL study. At the time of the interim analysis, 132 patients had completed 52 weeks of treatment (24 patients were 2-year study completers; 96 patients were still ongoing; and 12 patients had discontinued after 52 weeks); 57 patients were still ongoing in the first 1-year of treatment; and 82 patients terminated prior to week 52. The following mean changes in Z-scores, from DB baseline to weeks 28, 52, and 104, respectively, were observed for the cognitive composite score (+0.16, +0.30, +0.57), and for the CogState domains processing speed (-0.02, +0.16, +0.68), attention/vigilance (0.00, +0.05, +0.38), visual learning (+0.45, +0.75, +1.07), working memory accuracy (+0.24, +0.73, +0.30), and working memory speed (+0.23, +0.28, +0.15).

**Discussion:** Over the course of this 2-year study of adolescents with schizophrenia, lurasidone treatment was not associated with deleterious effects on cognitive function. Larger sample sizes are needed to confirm the robustness of the improvement observed in selected cognitive domain scores, most notably visual learning and processing speed.

**Clinicaltrials.gov identifier:** NCT01914393

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## PM160

### **Efficacy and Safety of Lurasidone in Adolescents with Schizophrenia: Interim Analysis of a 2-year, Open-label Extension Study**

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**Objective:** To obtain long-term data on the safety and effectiveness of lurasidone in adolescents with schizophrenia.

**Methods:** Patients ages 13-17 with schizophrenia who completed 6 weeks of double-blind (DB) fixed-dose treatment with lurasidone were eligible to enroll in a 2-year, open-label (OL), flexible-dose (18.5-74 mg/d) extension study. In this interim analysis, efficacy measures included the Positive and Negative Syndrome Scale (PANSS) total score.

**Results:** In the initial 6-week, DB study, mean improvement in PANSS total score at week 6 was significantly greater for lurasidone (37 mg and 74 mg) vs. placebo (-18.6 and -18.3 vs. -10.5;  $P < 0.001$  for both comparisons). 271 patients completed DB treatment and entered the 2-year OL study. At the time of interim analysis, 132 patients (48.7%) had completed 52 weeks of treatment; 57 patients (21.0%) were still ongoing in the first year of treatment; and 82 patients (30.3%) had terminated prior to week 52. Mean change from DB baseline in PANSS total score at weeks 28 (n=215), 52 (n=133), 76 (n=86), and 104 (n=24) was -29.2, -34.0, -35.0, and

-34.1, respectively. During OL lurasidone treatment, the most common adverse events were headache (21.8%), nausea (11.8%), anxiety (11.8%), and somnolence (11.4%). Median change in laboratory parameters from DB baseline to weeks 52 and 104, respectively, were: total cholesterol, -2.0 and -5.0 mg/dL; triglycerides, +3.5 and +3.0 mg/dL; and hemoglobin A1c, 0.0 and 0.1%; and mean change from DB baseline in weight at weeks 52 and 104 were 3.8 and 7.2 kg, vs. an expected weight gain of 3.3 and 5.1 kg, based on the gender-and-age specific CDC growth chart.

**Conclusion:** In adolescents with schizophrenia, long-term treatment with lurasidone was associated with continued improvement in symptoms of schizophrenia. After up to 2 years of lurasidone treatment, minimal effects were observed on weight, lipids, and glycemic indices.

**ClinicalTrials.gov identifier: NCT01914393**

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## PM161

### **Favorable Clinical Safety Profile for Lumateperone (ITI-007) - Switching from Standard-of-Care (SOC) Antipsychotic Therapy in Patients with Schizophrenia**

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#### **Objective**

Lumateperone is a first-in-class investigational agent that provides selective and simultaneous modulation of serotonin, dopamine and glutamate and represents a new approach to the treatment of schizophrenia and other neuropsychiatric disorders.

Lumateperone demonstrated antipsychotic efficacy in two well-controlled clinical trials and demonstrated consistent improvements from baseline on the PANSS total score across three clinical trials in patients with acute schizophrenia. In these trials, lumateperone was found to be well tolerated with a safety profile similar to placebo. The purpose of the present study was to evaluate the safety and tolerability of lumateperone administered to patients with stable schizophrenia switched from SOC antipsychotic therapy.

#### **Methods**

In an open-label safety study, 302 patients with stable schizophrenia were enrolled and treated for 6 weeks with lumateperone (ITI-007 60 mg). Following treatment with lumateperone, patients were switched back to SOC therapy and reassessed approximately 2 weeks thereafter. The primary objective was to determine the safety of lumateperone, assessed by adverse events, body weight, 12-lead electrocardiograms, vital signs, clinical laboratory tests, motor assessments, and the Columbia-Suicide Severity Rating Scale (C-SSRS). The secondary objectives were to determine the effectiveness of lumateperone to improve psychopathology.

#### **Results**

Lumateperone was well tolerated with a favorable safety profile. The most frequent treatment-emergent adverse event was somnolence. Statistically significant improvements from SOC were observed in body weight, cardiometabolic and endocrine parameters which worsened again when switched back to SOC. Symptoms of schizophrenia generally remained stable or improved. Greater improvements were observed in subgroups of patients with elevated symptomatology such as those with



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comorbid symptoms of depression and those with prominent negative symptoms.

## **Conclusions**

Lumateperone represents a novel approach to the treatment of schizophrenia with a favorable safety profile in clinical trials. The lack of metabolic, motor and cardiovascular safety issues presents a safety profile differentiated from SOC antipsychotic therapy.

## **PM162**

### **A preliminary multi-genic prediction model for antipsychotic-induced weight gain**

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## **Background**

Antipsychotic-induced weight gain (AIWG) is a common and serious side effects induced by many antipsychotic medications. We have reported on several replicated genetic associations with AIWG. The aim of this study was to develop a preliminary multi-genetic risk model for AIWG.

## **Methods**

We selected top, replicated variants from our previous genetic association studies to develop a preliminary, genetic risk model: CNR1 (rs806378), NPY (rs16147), GCG (rs13429709), MC4R (rs489693), HCRTR2 (rs3134701 and rs4142972), TSPO (rs6971), and NDUFS1 (rs6435326). We determined the mode of inheritance (dominant vs recessive) for each of selected SNPs using a *post hoc* pairwise comparison of mean AIWG among the genotypic groups: Genotypes were re-coded as '0' = no risk or as '1' = at-risk for AIWG. We determined the total risk score for each individual as a sum of risk genotypes in selected SNPs. The composite score ranged from 0 (no-risk) to 8 (highest risk). Finally, we assessed the impact of genetic burden on AIWG with ANCOVA model adjusted for baseline weight and duration of treatment as covariates, where the score was entered as a factor.

## **Results**

We found statistically significant between-group variation in AIWG ( $p=1.46 \times 10^{-7}$ ). Individuals who carried zero or one risk variant gained the least amount of weight ( $-1.80 \pm 3.9$  kg) compared to individuals with two or more risk genotypes explaining more than 60% of the variance.

## **Conclusions**

We developed a preliminary genetic risk model for AIWG. However, further validation studies are required to develop a prediction model for AIWG for clinical purposes.

## **PM163**

### **Effectiveness of continuation and maintenance ECT and combination of ECT and clozapine for treatment resistance schizophrenia ; A retrospective study for 1-year relapse rate after initial ECT**

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**Introduction;** Electroconvulsive therapy (ECT) is an effective treatment for mood disorders and acute schizophrenia. However, insufficient evidence exists as to whether this early advantage of ECT can be maintained over the medium to long term because of high rate of relapse. Therefore, in some cases, continuation and maintenance ECT or combination of ECT and clozapine are considered.

**Method;** We retrospectively investigated the efficacy of 36 patients with treatment resistance schizophrenia who received ECT. We also analyzed whether continuation and maintenance ECT or combination of ECT and clozapine could reduce non-relapse rate at 1 year after ECT course in those who responded to an initially ECT course. Efficacy was defined as a Clinical Global Impressions Improvement (CGI-I), which responder as very much improved and much improved and recurrence as much worse and very much worse.

**Result;** The response rate of initial ECT course of treatment resistance schizophrenia was 77.8% ( $n=28/36$ ) and 1-year non-relapse rate after ECT was 50% ( $n=14/28$ ). There was a significant difference of 1 year non-relapse rate between continuation and maintenance ECT group and clozapine group (80%,  $n=8/10$  vs 40%,  $n=4/10$ ,  $p<0.05$ , Log Rank test).

**Conclusion:** Combination of ECT and clozapine might be more effective than continuation and maintenance ECT at patients with treatment resistance schizophrenia over the medium and long term.

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## PM164

### Relation between psychotropic drugs and seizure threshold in electroconvulsive therapy

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**Objectives:** Electroconvulsive therapy (ECT) is a popular way to stimulate brain for achieving therapeutic effects. The minimal amount of electrical energy needed to induce seizure is known as the seizure threshold (ST). It is commonly believed that treatment efficacy is related to stimulus dose relative to ST, but higher stimuli also increase unwanted side effects. Most patients undergoing ECT take concomitant psychotropic drugs, but little information is available on how these drugs affect ST. Our study aimed to analyze the relationship between ST and psychotropic drugs in patients treated with ECT.

**Methods:** We retrospectively reviewed the medical charts of 58 patients who received ECT at Korea University Hospital between February 2009 and June 2015. Patients were excluded if treatment was aborted due to side effects or any other reasons before the 10<sup>th</sup> sessions and 43 subjects were included in the final analysis. ECT was administered with concurrent antipsychotics and antidepressants. 67.4 percent of subjects were diagnosed as schizophrenia and 20.9 percent of subjects were diagnosed as major depressive disorder. We used stepwise multivariate correlation analyses for examining the associations between ST and psychotropic drugs. Data are presented as initial ST, the difference in ST between the first and 10th sessions ( $\Delta$ ST10th), and the mean difference in ST between the first and last sessions (mean  $\Delta$ STlast).

**Results:** Patients took an average of 1.91 (SD=1.02, range 0–5) different psychotropics during ECT. The mean numbers of antipsychotics and antidepressants used were 1.53 (SD=0.74, range 0–3) and 0.37 (SD=0.76, range 0–4). Multivariate regression analyses showed positive correlations between initial ST and the total chlorpromazine-equivalent dose of antipsychotics ( $\beta$  = 0.363,  $p$  < 0.05). The total fluoxetine-equivalent dose of antidepressants was positively correlated to  $\Delta$ ST10th ( $\beta$  = 0.486,  $p$  < 0.05) and mean  $\Delta$ STlast ( $\beta$  = 0.472,  $p$  < 0.01).

**Conclusions:** Our study elucidated possible effects of psychotropics on ST in patients undergoing ECT. We revealed that larger doses of antipsychotics are associated with higher initial ST, whereas higher doses of antidepressants are associated with stronger shifts of ST during ECT.

## PM165

### Lower glutamate level in temporo-parietal area may predict a better response to tDCS in schizophrenia: A pilot study

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#### Objective

Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation technique which uses a weak electric current from electrodes across the scalp to modulate targeted brain areas. It has been suggested that tDCS may be useful in reducing psychotic symptoms such as auditory hallucination. The aim of this study was to find alteration of key neurotransmitters in schizophrenia in temporo-parietal area (TPA) after tDCS intervention, using magnetic resonance spectroscopy (MRS) technique.

#### Methods

Ten schizophrenia patients with auditory hallucination were recruited from the outpatient clinic of Seoul National University Hospital (SNUH). The anode was placed over the left dorsolateral prefrontal cortex (DLPFC), and the cathode was placed over the left TPA. Patients underwent MRS scan with the very short echo time phase rotation STEAM sequence before and after the tDCS sessions, respectively.

#### Results

Seven of the participants completed MRS scans before and after the tDCS sessions. Positive and Negative Symptom Scale (PANSS) total and general psychopathology scale showed a significant improvement after tDCS. There was no significant difference between glutamate/creatinine (Cr) level before and after tDCS sessions. However, a significant positive correlation between the pre-tDCS glutamate/Cr value in left TPA and the improvement in auditory hallucination measured by Auditory Hallucination Rating Scale (AHRS) after tDCS was found.

#### Conclusion

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The results of this investigation show that the schizophrenia patients whose auditory hallucination benefits the most from tDCS treatment had lower glutamate/Cr level in left TPA. Previous studies regarding the relationship between glutamatergic system and treatment response mostly have only focused on the frontal area and striatum. However, this study suggests a potential role of glutamatergic system in TPA in predicting treatment response of auditory hallucination.

## PM166

### Prediction of response to transcranial direct current stimulation by near-infrared spectroscopy in schizophrenia

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#### Objectives

Transcranial direct current stimulation (tDCS) has been shown to be effective in treating some of the symptoms of schizophrenia. In the current study, we sought to determine whether oxy-hemoglobin ([oxy-Hb]), measured by near-infrared spectroscopy (NIRS), is associated with effects of transcranial direct current stimulation (tDCS) on psychotic symptoms of schizophrenia.

#### Methods

Twenty-six patients underwent tDCS (2 mA x 20 min) two times per day for five consecutive days. The anodal electrode was placed over the left dorsolateral prefrontal cortex while the cathodal electrode was placed over the right supraorbital region.

#### Results

One month after the last administration of tDCS, positive, but not negative symptoms, evaluated by the Positive and Negative Syndrome Scale (PANSS), were significantly improved. At baseline, regional [oxy-Hb] concentrations in the brain were measured by a 52-channel NIRS instrument. Significant negative correlation was demonstrated between [oxy-Hb] concentrations of left temporoparietal regions throughout verbal fluency tasks vs. changes of PANSS Positive and Negative subscale scores.

#### Conclusions

This is the first study to demonstrate the correlation between the response of neural activity to cognitive tasks at baseline and the ability of tDCS to improve positive and negative psychotic symptoms. Our observations suggest that NIRS provides a marker to predict the response to treatment with tDCS in schizophrenia.

## PM167

### Genome-wide association analysis of psychopathological dimensions in bipolar disorder and schizophrenia

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**Background:** Genome-wide association studies (GWAS) provided an unprecedented tool to delve into the molecular underpinnings of psychiatric disorders. Available findings have blurred the boundaries of classic nosography and established the importance of investigating psychopathological dimensions that cut across different psychiatric diseases.

**Aim:** We investigated the association between single nucleotide polymorphisms (SNPs) and psychopathological domains in patients with schizophrenia (SCZ) and bipolar disorders (BD).

**Methods:** Patients with SCZ (total n=228) and BD (total n=226) were genotyped using the Infinium PsychArray. Genotype imputation was performed using Minimac3 and the Haplotype Reference Consortium (HRC) panel as reference. Phenotypes were onset age, lifetime alcohol/drug misuse, number of episodes and measures of psychopathological dimensions during an acute phase (depression, positive symptoms, suicidal ideation, insight of disease). We performed standard quality control on genome-wide data. Covariates were age, gender, illness duration and population principal components. Analyses were carried out using additive genetic models and linear or logistic regression.

**Results:** 7,805,186 and 7,524,911 polymorphisms were included in the analyses for SCZ and BD, respectively. No association reached the genome-wide significance threshold ( $p < 5e-08$ ). Suggestive signals ( $p < 5e-06$ ) were identified for depression and positive symptoms. For depression, suggestive non-significant signals were in intergenic polymorphisms within 5p15 in SCZ, while in BD they were located in intron polymorphisms of DFNB31 and MIR5684 genes. Suggestive non-significant signals for positive symptoms were found for intron polymorphisms within KCNIP4 and SPOCK3 genes in BD, for a 3'-UTR variant in MTUS1 gene and an intron polymorphism within BNIP3L gene in SCZ.

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**Conclusions:** DFNB31 was previously associated with susceptibility to BD. KCNIP4 and SPOCK3 show pleiotropic effects across neuropsychiatric disorders (ADHD, personality disorders, cognitive impairment), while they were not previously associated with SCZ or BD. The next steps of our study will be a gene-level analysis and a meta-analysis of SCZ and BD samples.

## PM168

### Association of RUNX2 gene polymorphisms with schizophrenia in Korean population

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**Introduction:** GABAergic dysfunction is present in the hippocampus in schizophrenia. Recent studies of the hippocampus have suggested that a network of genes is associated with GABA dysfunction in schizophrenia. Runt related transcription factor 2 (RUNX2) gene is a member of the RUNX family of transcription factors and encodes a nuclear protein with an Runt DNA-binding domain. Transcription factors are involved in cell growth and differentiation, and in some studies, RUNX2 gene expression was shown to be down-regulated in schizophrenia. In this study, we investigated the genetic association between schizophrenia and single nucleotide polymorphisms (SNPs) of the RUNX2 gene.

**Methods:** For SNPs (rs2677108, rs6905689, rs12333172, and rs16873437) of the RUNX2 gene considering their heterozygosity and minor allele frequency were genotyped in 218 schizophrenia patients and 373 control subjects. The genotypes of SNPs were performed by direct sequencing. All patients were evaluated by the Operational Criteria Checklist for Psychotic Illness. Multiple logistic regression models (that is, co-dominant, dominant, and recessive) were performed to generate odds ratios, 95% confidence intervals, and *p* values.

**Results:** The genotype frequencies of three SNPs showed significant association between schizophrenia and controls [rs12333172, *p*=0.009, OR=0.29, in the recessive model (T/T vs. C/C+C/T); rs16873437, *p*=0.03, OR=1.46, in the dominant model (G/T+G/G vs. T/T); rs6905689, *p*=0.02, OR=1.49, in the dominant model (C/T+T/T vs. C/C)].

**Conclusions:** These results suggest that RUNX2 gene polymorphisms may have influence upon the risk of developing schizophrenia in Korean population

**Key Words:** RUNX2, schizophrenia, polymorphism

## PM169

### Association between CCND2 gene polymorphisms and the risk of schizophrenia in Korean population

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**Introduction:** There is considerable evidence that schizophrenia is associated with subtle alterations in cell cycle dynamics, shortening of the cell cycle period, and increased expression of G1/S phase cyclins. Cyclin D2 (CCND2) protein encoded by this gene belongs to the highly conserved cyclin family, whose members are characterized by a dramatic periodicity in protein abundance through the cell cycle. Cyclins function as regulators of CDK kinases. In addition, several studies showed that abnormal expressions of several cell cycle-related genes are associated with schizophrenia. Therefore, we examined whether genetic polymorphisms of CCND2 gene is associated with schizophrenia in Korean population by analyzing the genotype and allele frequencies.

**Methods:** Three single nucleotide polymorphisms (SNPs) (rs7304270, rs3217805, and rs3812821) of the CCND2 gene considering their heterozygosity and minor allele frequency were genotyped in 185 schizophrenia patients and 303 control subjects. The genotypes of SNPs were performed by direct sequencing. Multiple logistic regression models were employed to calculate odds ratios (ORs), their 95% confidence intervals (CI) and corresponding *p* values, controlling for age and gender as co-variables. In the logistic regression analysis for each SNP, we compared three different models of gene expression (co-dominant model, dominant model and recessive model).

**Results:** SNP rs7304270 showed significant difference in the allele frequencies between schizophrenia and controls (*p*=0.002). The genotype frequencies of rs7304270 showed significant association between schizophrenia and controls (*p*=0.003 in the co-dominant model; *p*=0.003 in the recessive model). There was no significant association between other two SNP polymorphisms and schizophrenia.

**Conclusions:** Our study found that CCND2 gene polymorphism may have susceptibility to schizophrenia in Korean population

**Key Words:** CCND2, schizophrenia, polymorphism

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## PM170

### Concomitant Use of Alcohol and Benzodiazepine Hypnotics in Psychiatric Outpatients: A Questionnaire Survey

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#### Objective

Concomitant use of benzodiazepines and alcohol seems prevalent in clinical settings. However, previous studies have not focused solely on psychiatric patients. The objectives of this study were three-fold: (1) to investigate the prevalence of concomitant use of benzodiazepine hypnotics and alcohol in psychiatric outpatients, (2) to assess the extent of awareness on the side of their psychiatrists about concomitant use, and (3) to examine clinical characteristics of the concomitant users.

#### Methods

A questionnaire survey was carried out for outpatients with schizophrenia, depression, and insomnia (International Classification of Diseases, 10<sup>th</sup> edition) who were receiving benzodiazepine hypnotics in psychiatric hospitals and clinics in Tokyo and Kanagawa, Japan. Participants were asked to fill in a sleeping diary for seven days in which use of hypnotics and alcohol was also recorded. In addition, their treating psychiatrists were asked as to whether they thought their patients concomitantly using them. CAGE test was used to assess their drinking problems. Other assessments included Brief Psychiatric Rating Scale for schizophrenia and Montgomery-Asberg Depression Rating Scale for depression and insomnia.

#### Results

Eight-eight patients (mean±SD age, 53.6±14.2 years: 46 females: schizophrenia [n=34], depression [n=27], insomnia [n=27]) participated in this study. The prevalence of concomitant use of hypnotics and alcohol were 40.0% (35/88), although only 31.4% (11/35) of their psychiatrists suspected the concomitant use. CAGE total scores were significantly higher in concomitant users than the others (mean±SD, 1.2±1.3 vs 0.3±0.7, p<0.001). Other characteristics including symptom severities and dosages of prescribed psychotropics were not different between the two groups.

#### Conclusions

Nearly half of the patients concomitantly used benzodiazepine hypnotics and alcohol, which was frequently overlooked by their psychiatrists. It should be noted that such concomitant use occurs regardless of

illness severity. CAGE test may be useful to screen such concomitant users.

## PM171

### The effect of Suvorexant introduction on hypnotic prescription of schizophrenic patients

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**【Introduction】** Patients with schizophrenia often present insomnia, and hypnotics are one of the most commonly used drugs with antipsychotic drugs. Medication therapy for insomnia is mainly tolerated benzodiazepines, but in recent years its dependence and abuse have become a social problem. Under these circumstances, Suvorexant, a receptor antagonist for orexin that controls sleep and wakefulness, was released in Japan, three years passed. This time, we investigated the effect of Suvorexant introduction on hypnotic prescription of schizophrenic patients and its tolerability and report on it.

**【Method】** Targeted schizophrenic patients who introduced Suvorexant in December 2014 - December 2015 at Okehazama Hospital Fujita Kokoro Care Center. The age, gender, prescription medication name and dose, and side effects of the subject patient were investigated backwardly from the medical record for 2 years from the start of prescription of Suvorexant. As for this survey, we handled personal information carefully and made sufficient ethical consideration.

**【Results】** 74 subjects (inpatient / outpatient: 42/32, male / female: 30/44), average age 47.2 years old (inpatient / outpatient: 50.0 / 43.5, male / female: 46.8 / 47.5). The 1 year continuation rate of Suvorexant was 60.8% (inpatient / outpatient: 69.0% / 50.0%) and the 2 year continuation rate was 48.6% (inpatient / outpatient: 57.1% / 37.5%). The frequency of occurrence of side effects was low, and the most common was somnolence.

**【Discussion】** From this survey, it turned out that Suvorexant is frequently used in elderly inpatient. This seems to be due to the characteristics of the patient with chief complaint of midwake awakening, difficulty falling asleep, and the drug characteristics of Suvorexant controlling wakefulness. From now on, it seems necessary for pharmacists to actively support Suvorexant toward safer and more appropriate medication therapy.

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## PM172

### Fronto-Striatal Functional Connectivity and Striatal Dopamine Capacity in Treatment-Responsive and -Resistant Schizophrenia

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**Background:** Schizophrenia is thought to be a heterogeneous disorder and evidences reflect categorically distinct subtypes according to the antipsychotic treatment response. Altered frontostriatal functional connectivity (FC) in schizophrenia and its correlation with antipsychotic treatment response also suggests divergence of underlying pathophysiologic mechanism. Meanwhile, the observations that prefrontal activity correlates with striatal dopaminergic function, has led to the hypothesis that disrupted frontostriatal FC would be related with altered dopaminergic pathway in schizophrenia. The aim of this study was to investigate the relationship between frontostriatal FC and striatal dopaminergic activity in patients with schizophrenia according to responsiveness to first-line antipsychotic drug.

**Method:** 24 symptomatically stable patients with schizophrenia were recruited from Seoul National University Hospital, 12 of which responded to first-line antipsychotic drugs (first-line AP group) and 12 stable under clozapine (clozapine group), along with 12 matched health controls. All participants underwent resting-state functional MRI and [<sup>18</sup>F]DOPA positron emission tomography.

**Results:** There was no significant difference in the total PANSS score between the first-line AP group and the clozapine group (mean difference=0.67, s.e.=3.21, df=33, p=1.000). Voxel-based analysis found significant negative correlation between frontal FC to the left associative striatum and the  $k_i^{cer}$  in the corresponding region in first-line AP group but not in clozapine group or healthy control. Additional region of interest analysis confirmed the result (control group:  $R^2=0.032$ ,  $p=0.572$ ; first-line AP group:  $R^2=0.551$ ,  $p=0.005$ ; clozapine group:  $R^2=0.108$ ,  $p=0.297$ ) and the correlation coefficients were significantly different between first-line AP group and clozapine group ( $z=-2.75$ ,  $p=0.006$ ).

**Conclusions:** Different patterns of relationship between striatal dopamine capacity and frontostriatal FC observed in this study indicate different pathophysiology underlying schizophrenia according to antipsychotics treatment-responsiveness.

**Key words:** Schizophrenia, Functional connectivity, Dopamine, resting-state functional MRI, PET

## PM173

### Functional neuroanatomy of negative schema: comparison between patients with schizophrenia and healthy controls using fMRI

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**Objective:** Negative schema is one of the factors related to the formation of psychotic symptoms in patients with schizophrenia. We investigated functional neuroanatomy of the negative schema in patients with schizophrenia and healthy controls using task fMRI.

**Methods:** We recruited patients with schizophrenia (n=102) and healthy controls (n=41). Schema-evoking task consisted of two conditions: active conditions were four different types of sentences describing positive or negative characteristics of self or others, ie., describing positive- or negative-self or -others schema. Neutral condition consisted of sentences about general common knowledge. We compared the differences of brain activation between groups using active minus neutral contrast.

**Results:** The mean ages and sex ratios of patients with schizophrenia and healthy controls were  $33.38 \pm 10.02$  and  $33.98 \pm 8.53$  years, and 53/47 and 59/41%, respectively. Significant difference was only seen in the contrast of negative-self condition minus neutral condition. Compared with healthy controls, significant hyperactivations (thresholded at  $p < 0.05$ , FDR corrected, cluster size  $> 20$ ) in the putamen and lateral globus pallidus were observed in patients with schizophrenia. Patients with schizophrenia were less activated (thresholded at  $p < 0.05$ , FDR corrected, cluster size  $> 20$ ) in the right superior temporal gyrus and insular than healthy controls.

**Conclusions:** Our results indicate that negative-self schema in patients with schizophrenia may be associated with an alteration of neural activation in the striatum,

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superior temporal gyrus, and insula. The relevance of the findings is discussed in terms of understanding the pathogenesis of psychotic symptoms.

## PM174

### Effect of oxytocin on trust behaviour and neural circuitry of trust in Schizophrenia

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#### Background

Oxytocin, a neuropeptide plays a critical role in social cognitive functions. Impaired social behaviour including decreased trust in other humans is a characteristic feature of schizophrenia. While the effect of oxytocin on emotion recognition is examined in schizophrenia, its effect on trust behaviour and changes in neural circuits of trust has not been examined. Hence we examined the effect of oxytocin on neural circuitry of trust using a fMRI.

#### Methodology

Twenty-five male patients with Schizophrenia and twenty healthy volunteers underwent fMRI scans using 3T scanner while performing a multi round trust game. Sixteen patients participated in second phase of the study in which they underwent two more scans in which they received 24 IU of intranasal oxytocin or saline placebo 30 minutes before the scan. Participants performed a multi round trust game and invested in human counterpart or a computer lottery. A feedback was given midway through the game whether the trust was reciprocated or not.

#### Results

Patients with schizophrenia, compared to healthy volunteers, invested significantly less amount in trust trials, in particular post feedback trials. Patients had higher activation in right insular cortex, right orbitofrontal cortex, and left inferior frontal cortex. On administration of oxytocin, compared to placebo, no significant change in behavior was noted. However, patients showed increased activation in right anterior cerebellum extending to the parastriate cortex in the oxytocin condition compared to the placebo condition.

#### Conclusions

Study findings indicate decreased trust behaviour in patients with schizophrenia. Higher activation of insula in post feedback trials indicates higher risk aversion in patients. While single dose oxytocin did not have effects at

behavioural level, changes in brain activation during fMRI suggest possible neuromodulatory effect of oxytocin. These findings suggest the need for future studies with longer duration and multi-dose oxytocin administration to examine the effect at behavioural level.

**Keywords:** Schizophrenia, Trust, Oxytocin, fMRI, social cognition

## PM175

### Increased D<sub>2/3</sub> receptor availability in the retina of medication-naïve patients with schizophrenia. A [<sup>11</sup>C]-(+)-PHNO PET study.

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The retina has been known as a dopamine-rich organ for decades. Dopamine has been implicated in bright light adaptation, mainly through electrical decoupling of horizontal cells in the retina, thus decreasing the size of receptive fields.

Patients with schizophrenia have been shown to exhibit distortions of brightness contrast and motion perception, which appear to be alleviated by administration of D<sub>2/3</sub> receptor blocking compounds. These observations of an altered dopamine function in patients with schizophrenia indicate that schizophrenia specific midbrain dopamine dysfunction could also be observed in the retina.

We have assessed D<sub>2/3</sub> receptor availability in medication naïve patients with schizophrenia and healthy volunteers without prior exposure to psychostimulant drugs employing [<sup>11</sup>C]-(+)-PHNO positron emission tomography (PET) scans without intervention as well as after oral administration of 0.4 mg/kg body weight d-amphetamine sulfate. [<sup>11</sup>C]-(+)-PHNO is a D<sub>2/3</sub> receptor selective agonist radioligand that has been shown to be sensitive to alterations of endogenous dopamine levels.

Patients with schizophrenia display elevated levels of radioligand binding in the retina irrespective of

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amphetamine ingestion, with crude amphetamine effect being undetectable in our sample.

Considering only subjects with a reliable [ $^{11}\text{C}$ ]-(+)-PHNO kinetic model fit (binding-potentials ( $\text{BP}_{\text{ND5}}$ )  $>0.2$ ), a strong positive correlation between retinal and substantia nigra/ventral tegmental area  $\text{BP}_{\text{ND5}}$  was observed in patients with and without prior amphetamine ingestion but not in healthy volunteers. This indicates that pre-synaptic dopamine dysregulation in schizophrenia affects dopaminergic neurons in the retina and basal ganglia alike, while in healthy subjects these systems seem to be regulated differently.

These findings may serve to establish the retina, so to say, as an outpost of the brain in which disease specific alterations of neurotransmission can be observed in non invasive ways, e.g. optic coherence tomography. This may, in the future, lead to rapidly obtainable biomarkers for dopamine dysregulation in schizophrenia.

## PM176

### Hallucinations in Schizophrenia and Parkinson's disease: illustration of common pathway

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**Background:** Hallucinations have been described in various clinical populations. In schizophrenic patients (SCZ)<sup>1</sup>, hallucinations are hallmark symptoms. In Parkinson's disease (PD), the descriptions of hallucination modalities are sparse<sup>2</sup>. Hallucinations can be evaluated using The Psycho-Sensory hAllucinations Scale (PSAS)<sup>3</sup> which is a multimodal hetero-evaluation scale that includes four domains (auditory, visual, olfactory/gustatory, and coenesthetic modalities). This study aimed to explore the phenomenology of hallucinations in 100 SCZ and 100 PD patients using the PSAS. Is this phenomenology homogenous and/or disease specific? And what about repercussion on patients?

**Methods:** To identify groups of subjects with similar hallucinations characteristics and independently from pathological groups, factorial analyses (multiple correspondence analysis confirmed by hierarchical clustering) were performed. Comparison between groups on characteristics and repercussion index (frequency, duration, negative aspects, conviction, impact and control of each hallucinations) were made between clusters of subjects.

**Results:** Regarding phenomenology of hallucinations, a pronounced clustering structure within patients has been observed. Three groups with a low inter-group-recovery rate (24%) were determined. The majority of G1 group

( $n=88$ ) are PD patients (82%), majority of G2 group ( $n=19$ ) are SCZ patients (89%) but G3 group ( $n=93$ ) is a more mixed pathological group (72% PD vs 28% SCZ). All groups have specific pathway phenomenon but no significantly difference in the control on hallucinations.

**Discussion:** We confirmed that there's no strict overlap between pathology and hallucinations phenomenology that might be a good lead to precise mechanisms of hallucinations. More researches are needed to understand the complexity of the neurological process involved.

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## PM177

### MEG study of cross-frequency coupling in auditory cortex in early vs. chronic phase schizophrenia.

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#### Study Objectives

Cognitive impairments in schizophrenia patients are associated with cortical oscillatory disturbances. These include gamma oscillatory disturbances as well as possible disturbances in cross-frequency coupling (CFC), the modulation of high-frequency oscillations by lower frequency oscillations. The aim of this study was to CFC in the auditory cortex during 40 Hz steady-state stimulation, and their potential disturbance in schizophrenia patients.

#### Methods

Early ( $N=13$ ) and chronic ( $N=15$ ) schizophrenia patients were compared to healthy controls ( $N=17$ ) during the presentation of a 40 Hz auditory click train stimuli (1000 ms), recorded using magnetoencephalography (MEG). Data were processed using the MNE toolbox and source localization using dynamic statistical parametric maps (dSPM) method generated dynamic imaging of coherent source (DICS) estimates. Employing hybrid



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anatomical/functional regions of interest (ROI) across temporal cortices, bilaterally, we assessed CFC by computing the mutual information between the delta phase (2 Hz) and the gamma amplitude (40 Hz) during the steady state entrainment response.

## Summary of Results

Steady state gamma power showed an overall reduction in schizophrenia patients (healthy controls > early; healthy controls > chronic), as well as an interaction between hemisphere and group (healthy controls right > left hemisphere). The left hemisphere showed no differences between groups. All groups demonstrated coupling between gamma amplitude and delta phase, but there were no differences observed between groups or hemispheres.

## Conclusions

This is the first study to investigate source-localized cross-frequency neuronal interactions within the auditory cortex of schizophrenia patients. Despite decreased gamma oscillatory power, CFC appears to be intact in patients at both early and chronic phases of illness. Thus, while there may exist local circuitry disturbances that impair the ability to entrain activity to high frequency stimuli, the modulation of such activity by lower frequency activity may be relatively intact in the illness.

## PM178

### Psychopharmacological treatment and length of stay in psychiatric hospitals among patients with schizophrenia: a systematic review

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## Aims

While factors that have effects on the length of stay (LOS) in psychiatric hospitals have been discussed in the literature, most of them have mainly focused on socio-economic and demographic characteristics. The objective of this study was to examine associations between psychopharmacological treatment and LOS in psychiatric hospitals among patients with schizophrenia.

## Methods

We conducted a systematic literature search for studies examining factors associated with LOS in psychiatric hospitals among patients with schizophrenia in July 2017,

using PubMed with the following search terms: "length of stay" and (schizophrenia or psychosis). After the initial search, articles that evaluated associations between psychopharmacological treatment and LOS were identified. Reports written in English were included.

## Results

An initial search yielded 1724 studies, and 1711 studies were excluded for the following reasons: lack of actual evaluation of LOS among patients with schizophrenia (n=795), other diagnoses (n=218), focuses on welfare system (n=381), health economics (n=42), outpatient treatment (n=36), and forensic psychiatry (n=28), reviews (n=197), and nursing research (n=14). Associations between psychopharmacological treatment and LOS were examined in the remaining 13 articles. All of them were observational studies, and there were no controlled trials. Use of long-acting injectable (LAI) antipsychotics and clozapine was associated with a shorter LOS, respectively, whereas patients on polypharmacy showed a longer LOS.

## Conclusion

Psychopharmacotherapy with LAI antipsychotics, clozapine, and polypharmacy seem to be associated with LOS among patients with schizophrenia. On the other hand, data regarding the impact of pharmacotherapy on LOS in this population are very limited both in number and scope, which clearly warrants further investigations.

## PM179

### Comparison of emotional cognition assessed with fear conditioning by interpersonal conflicts in patients with depression and schizophrenia and healthy subjects

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## [Objective]

While emotional cognition has been implicated in various psychiatric illnesses, data are still scarce regarding its similarities and differences among diagnoses. We compared emotional cognition of patients with depression, schizophrenia, and healthy individuals by measuring skin conductance response (SCR) to the interpersonal stimuli.

## [Methods]

Twenty female patients each with depression and schizophrenia and 20 healthy female individuals underwent fear conditioning experiments in response to

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two types of stimuli: an aversive sound, and a picture of an actor's face with recorded unpleasant verbal messages. The paradigm consisted of three consecutive phases: habituation, acquisition, and extinction. Conditioned response was quantified by a differential SCR calculated as changes in SCR amplitudes to conditioned stimuli (CS) paired with unconditioned stimuli (CS+) subtracted by those to CS unpaired with unconditioned stimuli (CS-). Multiple regression analysis was performed to examine the effects of clinical characteristics on the differential SCR.

## **[Results]**

Patients with depression successfully showed fear conditioning in both conditions, and they exhibited slower extinction in the interpersonal condition. The Emotion Regulation Questionnaire (ERQ) expressive suppression score was positively associated with the differential SCR during the early extinction phase whereas the ERQ cognitive reappraisal score showed a negative association. Moreover, the use of antidepressants was negatively associated with the differential SCR during the late extinction phase. On the other hand, no differences in SCRs were observed between CS+ and CS- during the acquisition phase in both conditions in schizophrenia. In addition, the Positive and Negative Syndrome Scale negative syndrome score was negatively associated with the differential SCR to the interpersonal condition.

## **[Conclusions]**

The intrinsic impairment in the emotional processing was implicated in female patients with schizophrenia, especially among those who prominently demonstrated negative symptoms. Antidepressants and emotional self-control attainable through cognitive behavioral therapy may serve to alleviate personal negative conflicts in depression.

## **PM180**

### **Usefulness of pharmacists to accompany visit nursing on prevention of re-hospitalization in patients with schizophrenia: an interventional pre / post study**

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## **Background;**

Although patients with schizophrenia are managed their medication in hospital, after discharge, there is no one to manage patient's medication. Consequently, they stop taking medication and result in re-hospitalization. It is necessary for the patients to receive care by a medical staff not only in hospital but also after discharge.

The purpose of this study is to investigate whether participation in pharmacist's home-visit nursing can prevent the patients from re-hospitalization.

## **Methods;**

An interventional study of 43 patients with schizophrenia (diagnosed by DSM-IV criteria) was conducted. The inclusion criteria are receiving home-visit nursing by medical staff without pharmacists and multiple hospitalization (two or more hospitalization, 100 or more in-patient days, three or more psychiatric emergency department visits, or 3 months or more of no-show to out-patient clinic appointment in last 2 years). An intervention by pharmacists is to participate in a usual home-visit nursing. Duration of the intervention is for 6months, pharmacists performed it at least once a month.

The primary outcome was re-hospitalization rate. An EQ-5D, DAI-10, CGI-S, and dose of antipsychotics were obtained as secondary outcomes. Except re-hospitalization rate, data were collected at before and last home-visit nursing by pharmacists.

## **Result and Discussion;**

Of the 43 subjects, only 5 patients (11.6%) were re-hospitalized at 6 months after discharge. In Japan, it is reported that the re-hospitalization rate for patients with schizophrenia at 6 months after discharge is about 30%.

DAI-10 (before: 3.9, after: 5.4,  $p=0.02$ ) and dose of antipsychotics as CP equivalents (before: 914.4 mg, after: 832.1mg,  $p=0.04$ ) were significantly differences between before- and after-intervention. There was an improvement trend in EQ-5D converted data (before: 0.8, after: 0.9,  $p=0.09$ ) and CGI-S (before: 4.1, after: 3.7,  $p=0.07$ ).

These results might be suggested that intervention of pharmacists is useful for patients with schizophrenia to prevent to re-hospitalize.

## **PM181**

### **Difference in executive function among with patients with schizophrenia, their first-degree relatives and healthy subjects**

Yuzuru Kataoka<sup>1</sup>, Kazutaka Ohi<sup>1,2</sup>, Takamitsu Shimada<sup>1</sup>, Aki Kuwata<sup>1</sup>, Hiroaki Okubo<sup>1</sup>, Kohei Kimura<sup>1</sup>, Toshiki Yasuyama<sup>1</sup>, Takashi Uehara<sup>1</sup> and Yasuhiro Kawasaki<sup>1</sup>

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**Background:** Schizophrenia is a severe psychiatric disorder with high heritability. Patients with schizophrenia (SCZ) exhibit severe impairments in executive function compared with healthy controls (HC). The Wisconsin Card Sorting Test (WCST) is a set-switching task used extensively to study impaired executive function in SCZ. Previous studies indicated that SCZ had worse performance in the WCST, especially in the perseveration (which is the behavioral result of a lack of appropriate set switching) category than HC. However, few study investigated whether unaffected their first-degree relatives (FR) show worse executive function, mainly perseveration, compared with HC. In this study, we investigated difference in executive function using the WCST among SCZ, unaffected FR and HC.

**Methods:** To evaluate perseveration of executive function in SCZ ( $n=96$ ), unaffected FR ( $n=53$ ) and HC ( $n=86$ ), we used perseverative errors of Nelson (PEN) in the WCST. The difference among SCZ, FR and HC was analyzed using analysis of covariance (ANCOVA), PEN as a dependent variable, diagnosis as an independent variable and years of education, gender and age as covariates.

**Results:** There was significant difference in perseverative performance of the executive function among three diagnostic groups ( $F_{2,229}=4.47$ ,  $p=9.53 \times 10^{-3}$ ). *Post-hoc* analysis showed that FR as well as SCZ had worse perseverative performance than HC ( $p<0.033$ ). There was no significant difference in the performance between FR and SCZ ( $p>0.05$ ).

**Conclusion:** Despite onset of schizophrenia, perseverative function may be impaired in individuals with genetic components of schizophrenia, i.e. FR as well as SCZ, compared with neuropsychiatrically healthy individuals without the genetic components.

## PM182

### Association between clinician's attitude to patient and medication adherence in schizophrenia

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**Background:** Finding out the determinants that influence medication non-adherence in schizophrenia is an important issue. Although various factors affecting

medication non adherence have been extensively studied, clinician related features limited yet. In this study, we investigated the association between clinician's attitude to patient and medication adherence in schizophrenia.

**Methods:** We conducted a cross-sectional study of 55 patients with stable schizophrenia who were admitted to the outpatient clinic of a university hospital in Korea. Adherence rate and the clinician's attitude to patient were assessed with self-report questionnaires by patient. Korean version Medication Adherence Rating Scale (KMARS) and Korean version of scale to assess the therapeutic relationship (STAR\_K) were used. Korean version of STAR\_K has 12 items. Demographic and clinical data including symptom severity, insight and medication side effect were also collected. Spearman's correlation and multiple linear regression were performed. **Results:** STAR\_K supportive attitude score showed significant correlations with KMARS score ( $r=0.401$ ,  $p<0.05$ ) but STAR\_K collaborative attitude score didn't. With the results of regression analysis, STAR\_K supportive attitude score significantly predicted KMARS score after adjusting symptom severity, insight and medication side effect ( $\beta = 0.379$ ,  $P<0.01$ ).

**Conclusions:** Patients who felt supportive of the clinician were more likely to adhere to the medication. Clinician's warm and emotional approach to schizophrenia patient might be important to maintain medication adherence.

Keywords: Clinician's attitude. Medication adherence. Schizophrenia.

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## PM183

### Differences in Quality of Life among patients with schizophrenia, their first-degree relatives and healthy subjects

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**Background:** Schizophrenia is a severe psychiatric disorder with high heritability. Patients with schizophrenia (SCZ) exhibit impairments of Quality of Life (QoL) compared with healthy controls (HC). The impaired QoL

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are important outcome factors in the treatment of SCZ because QoL are independent factors from psychiatric symptoms. However, no study investigated whether their first-degree relatives (FR) as well as SCZ show impairments of QoL compared with HC. The aim of this study was to investigate differences in QoL among SCZ, unaffected their FR, and HC.

**Methods:** Subjective QoL [(i) Psychosocial, (ii) Motivation/energy and (iii) Symptoms/side-effects] were evaluated in SCZ ( $n=132$ ), unaffected FR ( $n=62$ ) and HC ( $n=99$ ) using the Schizophrenia Quality of Life Scale (SQLS). The differences among SCZ, FR and HC were assessed using analysis of covariance (ANCOVA), with QoL as a dependent variable, diagnosis as an independent variable and gender and age as covariates.

**Results:** There were significant differences in the three SQLS scales among three diagnostic groups (Psychosocial,  $F_{2,288}=54.4$ ,  $p=8.86 \times 10^{-21}$ ; Motivation/energy,  $F_{2,288}=37.7$ ,  $p=2.86 \times 10^{-15}$  and Symptoms/side-effects,  $F_{2,288}=28.7$ ,  $p=4.41 \times 10^{-12}$ ). *Post-hoc* analysis showed that SCZ had lower three SQLS scales than FR ( $p < 3.16 \times 10^{-4}$ ) and HC ( $p < 4.80 \times 10^{-12}$ ). Remarkably, FR had lower psychosocial scale than HC ( $p=4 \times 10^{-3}$ ). In contrast, there were no differences in the motivation/energy or symptoms/side-effects between FR and HC after applying Bonferroni correction ( $\alpha=0.05/3$ ,  $p > 0.017$ ).

**Conclusions:** Of three QoL scale impaired in SCZ, psychosocial scale may be an intermediate phenotype for schizophrenia. Further studies are needed to evaluate the heritability and stability of QoL, particularly psychosocial scale, in SCZ.

## PM184

### A 1.5-year longitudinal study on social activity in schizophrenia

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**Background:** Patients with schizophrenia exhibit impairments of social activity as well as intelligence quotient (IQ), daily-living skill and social function. The social activity is a high-order outcome of their lives. The purpose of current study is to evaluate longitudinally the effects of current IQ, daily-living skill, social function, psychiatric symptoms (positive and negative symptoms) and medications (chlorpromazine- and biperiden-equivalents) on social activity in patients with schizophrenia. In addition, we attempted to identify the specific factor that predicts the longitudinal change of social activity.

**Methods:** Sixty-five patients with schizophrenia were assessed at two time points [time2 (T2, follow-up)-time1 (T1; Baseline)=1.71±0.79 years]. Social activity, current IQ, daily-living skill and social function were assessed using the Social Activity Assessment (SAA; hr/week), Wechsler Adult Intelligence Scale-Third edition (WAIS-III), UCSD Performance-based Skills Assessment (UPSA) and Social Functioning Scale (SFS), respectively.

**Results:** Current IQ, daily-living skill, social function and social activity were significantly improved between T1 and T2 ( $t=2.0-4.4$ ,  $p=0.048-3.60 \times 10^{-5}$ ). Current IQ, daily-living skill and social function were positively correlated with social activity (lowest  $p=1.30 \times 10^{-5}$ ), and psychiatric symptoms were negatively correlated with social activity over time (lowest  $p=3.26 \times 10^{-9}$ ). The longitudinal change of social function was independently positively correlated with the change of social activity ( $B=0.13$ ,  $p=0.036$ ), and the correlation was still significant after including longitudinal changes of other factors ( $B=0.16$ ,  $p=0.021$ ). The longitudinal changes of other factors did not directly predict the change of social activity ( $p > 0.05$ ).

**Conclusions:** These findings highlight that social activity would be closely affected by social function compared with other factors.

**Keywords:** schizophrenia; social activity; social function; daily-living skill; current IQ; longitudinal study

## PM185

### Differences in social functioning among schizophrenia patients, their first-degree relatives and healthy subjects

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**Background:** Impaired social functioning is a core feature in patients with schizophrenia (SCZ). Individuals at a clinically high risk for SCZ show deficits in social functioning even during the pre-psychotic phase of the illness, suggesting that social deficits are present long

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before the onset of psychotic symptoms. Furthermore, it is considered that the interpersonal communication aspect of social functioning is prominently impaired in SCZ. However, few studies investigated the genetic basis of impaired social functioning. To date, no study has examined that impaired social functioning is a genetic continuum among SCZ, their first-degree relatives (FR) healthy controls (HC). In this study, we investigated differences in the total score and the detailed subscales of social functioning assessed by the Social Functioning Scale (SFS) among SCZ, FR and HC.

**Methods:** we first investigated differences in the total of social functioning assessed by SFS among SCZ ( $n=131$ ), FR ( $n=35$ ) and HC ( $n=91$ ). Then, we investigated differences in the seven subscales of the SFS among SCZ, FR and HC.

**Results:** In the total and all subscales of the SFS, SCZ showed lower scores than FR and HC. In addition, FR had intermediately impaired interpersonal communication between SCZ and HC.

**Conclusions:** Our findings demonstrate a social functioning continuum among SCZ, FR and HC and suggest that poor interpersonal communication is one of the intermediate phenotypes of SCZ.

## PM186

### Pharmacogenetics of tardive dyskinesia in schizophrenia: the role of muscarinic receptors

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Tardive dyskinesia (TD) is an important side effect of antipsychotics. Its pathogenesis has not been completely elucidated, but may be related to neurotoxic damage of extrapyramidal indirect striatopallidal pathway neurons (1-3). The authors try to verify the validity of a newly proposed hypothetical model implying the involvement of acetylcholine (muscarinic) M receptors in the development of TD by studying specific genetic factors.

The aim of the study is to determine possible associations between muscarinic receptor genes (*CHRM1*, *CHRM2*, *CHRM4*) polymorphisms and TD in patients with schizophrenia.

After obtaining approval of the study protocol by the institutes ethical committee, 472 patients with schizophrenia (121 patients with and 351 patients without

TD) were recruited after obtaining informed consent. TD was assessed cross-sectionally by the Abnormal Involuntary Movement Scale (AIMS). Determination of a set of 22 allelic variants of *CHRM1*, *CHRM2* and *CHRM4* was performed by polymerase chain reaction in real time (PCR-RT) with specific primers. Frequency distribution of the study sample was tested in accordance with Hardy-Weinberg equilibrium. To assess the association of different genotypes with the disorder, odds ratio (OR) were calculated.

Significant frequency reduction of CC genotype of gene *CHRM2* (rs2061174) were found in patients with TD in comparison to group without TD ( $\chi^2=6.027$ ,  $p=0.04$ ). A similar situation is observed with *CHRM2* polymorphism rs1824024 - frequency of GG genotype is lower in TD patients compared to group without it ( $\chi^2=6.161$ ,  $p=0.046$ ). The allele C and genotype CC have predisposition effects on the development of TD (OR1=1.41, 95% CI: 1.02 – 1.93;  $\chi^2=4.45$ ,  $p=0.039$  and OR2=2.54, 95% CI: 1.17 – 5.51;  $\chi^2=6.03$ ,  $p=0.048$ ).

This study identified associations between *CHRM2* variations and TD. *CHRM2* are inhibitory muscarinic autoreceptors of striatal cholinergic interneurons affecting the activity of both direct and indirect extrapyramidal pathway. The exact role of the *CHRM2* requires further study.

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## PM187

### Childhood maltreatment and inflammation in First-Episode Psychosis and unaffected siblings: Results from the STREAM study in Brazil

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We investigated: (1) plasma levels of IL-1 $\beta$ , IL-6, IFN- $\gamma$ , TNF- $\alpha$ , IL-4, IL-10, TGF- $\beta$  in first-episode psychosis (FEP), their unaffected siblings and population-based controls; (2) the association between subtypes of childhood trauma and inflammation in psychosis. This study is part of the epidemiological investigation "Schizophrenia and Other Psychoses Translational Research: Environment and Molecular Biology" (STREAM), conducted in Ribeirão Preto (São Paulo, Brazil), as part of the consortium "European Gene-Environment Interplay Study" (EU-GEI)<sup>1</sup>. We recruited 159 FEP (64.8% males; mean age: 30.2 $\pm$ 12.1), 75 siblings (30.7% males; mean age: 31.3 $\pm$ 11.0) and 257 controls (51.0% males; mean age: 31.5 $\pm$ 11.2). We used the Childhood Trauma Questionnaire and Multiplex Bead Array (Luminex; pg/mL). We performed Univariate ANOVA including gender and age. The groups differed in IL-6, TNF- $\alpha$ , IL-10, IL-1 $\beta$  and TGF- $\beta$  ( $p < 0.001$ ). FEP had significantly higher levels of IL-6, TNF- $\alpha$ , IL-10 and TGF- $\beta$  when compared with controls ( $p < 0.001$ ). Compared with their siblings, patients had higher levels of TNF- $\alpha$ , IL-10, and TGF- $\beta$  ( $p < 0.05$ ), and a trend to higher IL-6 ( $p = 0.062$ ). Siblings presented decreased IL-1 $\beta$  when compared with controls ( $p = 0.002$ ). There was a significant group by gender interaction for TNF- $\alpha$  ( $p = 0.042$ ) and TGF- $\beta$  ( $p = 0.007$ ). Female controls presented decreased levels of TNF- $\alpha$  ( $p < 0.001$ ) and TGF- $\beta$  ( $p = 0.010$ ) when compared with male controls, whereas female siblings presented higher levels of TGF- $\beta$  ( $p = 0.043$ ) when compared with male siblings. FEP patients with physical abuse had higher levels of TGF- $\beta$  when compared with FEP without physical abuse ( $p = 0.022$ ); furthermore, higher severity of physical abuse was associated with higher levels of TGF- $\beta$  ( $p = 0.017$ ). This is the first study to investigate childhood trauma subtypes on inflammation in a large population-based sample of FEP<sup>2,3</sup>. We will next investigate other factors moderating inflammation.

**Keywords:** childhood trauma, cytokines, inflammation, first-episode psychosis

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## PM188

### Signs of impaired blood-brain barrier function and lower IgG synthesis within the central nervous system in patients with schizophrenia or related psychosis, compared to in controls

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**Objective:** Evidence has accumulated, pointing to that an inflammatory, possibly autoimmune-mediated process in the central nervous system (CNS), and by way of an aberrant immune system, may underlie the development of schizophrenia (1-3). Therefore, the aim of this study was to evaluate patients with schizophrenia or related psychosis for blood-brain barrier (BBB) function and immunoglobulin (Ig)G synthesis within the CNS.

**Methods:** Fifteen patients, diagnosed with schizophrenia or schizoaffective disorder and on long-term treatment with antipsychotics, and 12 controls were investigated with lumbar puncture and blood sampling. Cerebrospinal fluid (CSF) and serum/plasma (S/P) were analysed for albumin and IgG by standard laboratory methods, and the ratio of CSF-albumin to P-albumin (marker of BBB function) and the IgG index (marker of CNS IgG synthesis) were calculated. Additionally, the patients were assessed for clinical symptoms with the Positive and Negative Syndrome Scale for schizophrenia.

**Results:** The ratio of CSF-albumin to P-albumin was higher and the IgG index was lower in patients, than in controls ( $p=0.045$  and  $p=0.001$ , respectively). Moreover, subgroup analyses showed that patients in partial symptom remission had higher ratio of CSF-albumin to P-albumin,

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than patients in full symptom remission, and that patients with heredity for schizophrenia or related psychosis had lower IgG index, than patients without heredity. No correlations were found between the ratio of CSF-albumin to P-albumin or IgG index and patients' age, smoking habits, duration of psychotic disorder or current antipsychotic treatment.

**Conclusions:** In this study we show that patients with schizophrenia or related psychosis have impaired BBB function and lower IgG synthesis within the CNS, compared to controls. These findings support the view that a pathological process within the CNS, combined with an aberrant immune system, may underlie the development of schizophrenia.

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## PM189

### Clinical and functional correlates of Vitamin D deficiency in patients with schizophrenia

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**Objectives:** Vitamin-D regulates phosphorus-calcium homeostasis and has immunological and neurotrophic functions. Its deficiency has been associated to schizophrenia, although the nature of this relationship remains unclear. We hypothesized that subjects with schizophrenia, a poorer function and more severe symptoms will present lower levels of vitamin-D. The objective was to evaluate the frequency and clinical correlates of vitamin-D deficiency in patients with schizophrenia

**Methods:** Transversal study that included adult patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder from the outpatient Mental Health Unit in "El Bierzo" Hospital (Ponferrada, Spain).

Variables included previous history, ICG-severity, SANS, SAPS, Beck Depression Inventory (BDI), UKU side effects and the Personal and Social Performance Scale (PSP),

anthropometrics, and fasting blood analysis. Vitamin D levels were assessed with the luminescence immunoassay method.

Vitamin-D deficiency frequency was compared to other clinical samples in the area. Spearman correlations, Mann-Whitney U tests, and Chi square tests were used to evaluate associations

**Results:** 51 subjects (33 males) were included. Vitamin-D was insufficient (<30ng/mL) in 78% of the patients (46% deficiency <20 ng/mL and 26% severe deficiency <12ng/mL) and 56% of general subjects (8636 subjects,  $\chi^2$ : 9.77;  $p=0.018$ )

Vitamin-D was correlated to PSP functionality dimensions of self-care ( $r:-0.313$ ;  $p=0.027$ ), social activities ( $r:-0.303$ ;  $p=0.032$ ) and personal and social activities ( $r:-0.399$ ;  $p=0.004$ ) and to Total PSP score ( $r:0.349$ ;  $p=0.014$ ). They were also negatively correlated to SAPS formal thought disorder ( $r:-0.287$ ;  $p=0.048$ ). Severe deficits were associated to higher PTH values ( $z:-2.281$ ;  $p=0.023$ ), SANS Attention Score ( $z:-1.965$ ;  $p=0.049$ ), lower adherence to treatment ( $\chi^2:8.598$ ;  $p=0.014$ ) and suicide attempts ( $\chi^2:5.821$ ;  $p=0.016$ ).

**Conclusions:** Vitamin-D alterations in patients with schizophrenia were frequent and were associated to a higher degree of functional deficits. Together with other metabolic factors, the evaluation of vitamin D should be considered in regular assessments of schizophrenia as a risk group.

## PM190

### Neuronal cell-surface autoantibodies in first episode patients with schizophrenia

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**Objective:** Previous studies have reported serum IgA and IgM anti-N-methyl-D-aspartate receptor (NMDAR)-antibodies in a variety of neuropsychiatric disorders (schizophrenia, affective disorders, stroke, Parkinson's disease, amyotrophic lateral sclerosis, personality disorder) (1). The aim of this study is to assess the prevalence of IgG, IgA, and IgM NMDAR-antibodies in patients newly diagnosed with schizophrenia and NMDAR-encephalitis. Furthermore, we determined whether new anti-neuronal antibodies against yet uncharacterized neuronal cell-surface antigens are involved in acute psychosis.

**Method:** We prospectively collected serum of eight patients with schizophrenia (diagnosed according to DSM-

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IV, 5 female mean age 26 years, PANSS:54, 3 male mean age 22 years, PANSS: 68) with a first psychotic episode within the last three years and who currently displayed psychotic symptoms. In addition, we retrospectively reviewed initial serum and CSF samples of three patients with NMDAR-encephalitis and presentation with acute psychosis (3 female, mean age 24 years). Anti-NMDAR IgG, IgA, and IgM antibodies were tested with fixed in-house cell-based assays. Screening for novel anti-neuronal antibodies was performed with indirect immunohistochemistry on rat brain (2).

**Results:** In first episode patients with schizophrenia serum IgG, IgA, and IgM NMDAR-antibodies were negative. In patients with NMDAR-encephalitis serum IgG NMDAR-antibodies were positive in 3/3, IgA in 1/3, and IgM in 0/3. In contrast, all tested CSF samples were positive for IgG, IgA, and IgM NMDAR-antibodies. Screening for novel neuronal cell-surface antigens in schizophrenia patients was negative.

**Conclusion:**

Anti-NMDAR IgG antibodies are highly sensitive and specific markers for anti-NMDAR-encephalitis. Comparison of serum and CSF revealed different proportions of IgG, IgA, and IgM NMDAR-antibodies in NMDAR-encephalitis patients. Our data suggest, that systematic CSF testing will be necessary to study the clinical significance of IgA and IgM NMDAR-antibodies in patients with psychiatric illnesses. Higher sample sizes to confirm this preliminary data are clearly needed.

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## PM191

### **Influence of benzodiazepine medications and GABAA receptor function on the pentobarbital-induced sleep behaviour of lipopolysaccharide-treated mice**

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The activation of peripheral inflammation modulates changes in psychological behaviour. Lipopolysaccharide (LPS) is widely used to systematically stimulate the immune system. Benzodiazepine receptor agonists are the most frequent type of drug administered for insomnia. Benzodiazepine receptor agonists are high-risk drugs known to induce postoperative delirium in patients undergoing surgery. These drugs alter benzodiazepine-gamma-aminobutyric acid (GABA) receptor functions under systemic inflammatory conditions. We sought to investigate whether benzodiazepine receptor agonists influence pentobarbital-induced sleep duration due to changes in benzodiazepine-GABA receptor functions using a mouse model of LPS-induced inflammation. Male ICR mice were administered LPS. We assessed the pentobarbital-induced sleep duration 24 hours after LPS treatment in mice. Additionally, we performed immunohistochemistry to determine the microglial response and examined the serum IL-6 and TNF- $\alpha$  concentrations in mice. Benzodiazepine receptor agonists (diazepam and brotizolam) and a GABA<sub>A</sub> receptor agonist (muscimol) produced significantly greater increases in pentobarbital-induced sleep duration in LPS-treated mice than those in saline-treated mice. These effects were blocked by bicuculline, a GABA<sub>A</sub> receptor antagonist. LPS significantly increased the number of ionized calcium binding adapter molecule-1 (Iba-1)-positive hippocampal cells 2 and 24 h after treatment. Minocycline significantly reduced the effect of diazepam on increasing pentobarbital-induced sleep duration. Furthermore, compared with LPS treatment, minocycline significantly decreased the number of Iba-1-positive cells. Based on the findings of the current study, benzodiazepine receptor agonists enhance pentobarbital-induced sleep duration to a greater extent under inflammatory conditions than that under normal conditions, and these effects might be related to the GABA<sub>A</sub> receptor.

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### **Add-on therapy with tandospirone, a serotonin 1A receptor partial agonistic anxiolytic, is useful for dose-tapering of concomitant benzodiazepines in psychiatric patients using long-term benzodiazepines.**

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**Objective:** We aim to assess if add-on treatment of tandospirone is useful for dose-tapering and



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discontinuation of long-term used concomitant benzodiazepines (BZD) in psychiatric patients.

**Methods:** In this open label study, hospitalized 8 patients with schizophrenia and 2 patients with bipolar I disorder, who had been receiving BZD hypnotics continuously 12 months or more, were enrolled. They were prescribed tandospirone, and then gradually tapered off their usual BZD treatment for 12 weeks. Simultaneously, participants received medication counseling by pharmacists every week, and the patients' symptom and interviewed comments were recorded. Changes in the taking amount of antipsychotics, anticholinergics and BZDs were investigated and calculated as follows: equivalent milligrams of chlorpromazine (CP equivalent), biperiden (BP equivalent) and diazepam (DAP equivalent), respectively. Furthermore, the Clinical Global Impression of Change (CGI-C) was evaluated between the start date of tandospirone (baseline) and the discontinuation date of BZD hypnotic agent or after 12 weeks in uninteruptable cases(endpoint).

**Results:** Significant decrease of DAP equivalent ( $P < 0.0001$ ) and BP equivalent ( $P = 0.045$ ) were found. Especially, DAP equivalent decreased dramatically as follows: DAP equivalent at baseline was  $15.5 \pm 8.9\text{mg}$  (mean  $\pm$  standard deviation) and that at endpoint was  $3.0 \pm 5.4\text{mg}$ . On the other hand, no changes in the CP equivalent were observed. Eight of ten patients achieved withdrawal from their usual BZD treatment within 12 weeks, and two patients were able to reduce by approximately 50% in DAP equivalent at endpoint compared to that at baseline. Six of eight patients who achieved withdrawal from BZD treatment showed improvement in the CGI-C value, and there was no patient who aggravated a mental condition.

**Conclusions:** It was suggested that management of tapering and discontinuation of BZD in psychiatric patients using long term BZD could be promoted by co-prescription of tandospirone during BZD tapering.

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### Relationship between withdrawal symptoms of benzodiazepine sleeping pills and background factors

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Background factors causing withdrawal symptoms after withdrawal from benzodiazepine (BZ) sleeping pills were evaluated using the withdrawal symptom rating scale

prepared by this research group. We examined the relation with the sleep rating scale, life function evaluation scale, and the dependence symptom evaluation scale, all of which were used conventionally.

The subjects were 349 patients taking sleeping pills due to insomnia who visited Tokyo Women's Medical University Hospital and research cooperation agencies. Among these, data from 330 patients were analyzed. The severity of withdrawal symptoms was classified into two groups based on a rating scale: those with a score  $\leq 6$  and those with a score  $\geq 7$ . The scores on the abovementioned scales were compared between groups. There was no significant difference between the two groups regarding sex, age, and medication period. This research was conducted with the approval of the ethics committee of the Tokyo Women's Medical University Hospital.

In the serious group, where the patients had a score of 7 or more on the rating scale, the number of medications was higher, as was the severity of dependence symptoms evaluated using the Bendep-SQ, CIWA-B, and the CGI scales. Furthermore, in the serious group, insomnia symptoms, hyperarousal, and the functional impairment of daily life were more severe; the quality of life was more markedly deteriorated.

The severity of withdrawal symptoms of sleeping pills was thus shown to be related to the severity of insomnia, hyperarousal, insomnia on stress loading, daily living functions, and quality of life.

It is therefore suggested that improvement in sleep disorder, psychology, living environment, and physical condition is important to prevent withdrawal symptoms due to benzodiazepines.

## PM194

### Sleep disorders in older adults and elderly following the catastrophic stressful life events

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In this paper we will discuss on sleep disorders in older adults and aged people following the catastrophes and stressful life events, and then note very shortly some treatments.

Sleep disorders and insomnia, sometimes accompanied with headache, have been known throughout the history of humanity and traditional medicine. In our time, diverse psychosocial and environmental factors such as wars (ex. Iran Irak, Israel. Palestine) also some psycho-socio-political events, acts of terrorism (New York, Paris, Nice, London ...) and others have shocked the world with numerous

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material, human damages and victims. Many of these catastrophic acts and stressful life events, with their pathological effects, can bring consequently anxiety and depression. Sleep disorders and insomnia resulting from anxiety (or terror as observed in certain persons), are very common, underdiagnosed, and become a significant source of major pain complaints in older adults and geriatric population. Some modifications in sleep patterns, during normal ageing process, as well as in retired people, may not be considered a part of pathological process of ageing; however, some factors like psychosomatical problems, death of spouse or loss of a child or other dear member family etc. can be related to pathological processes, and produce disturbances in circadian rhythm and consequently lead to sleep disorder.

Based on his teaching experiences and clinical observations at Mental Health Centers, as well as theoretical studies (particularly during these three last decades) the author presents the results of his clinical researches on the subject of his paper. Our studies and lectures in University Hospitals: (St. Anne: H. Loo J.P. Olié 2008, Lariboisière: C. Lidy and others 1996-98 - La Salpêtrière: J.M. Thurin et al 2004) have enriched this research.

The experiences and research have shown that anxiety and depression exert serious pathological effects, not only on the cognitive system as noted elsewhere (Rabbani H. ICAP, Paris 2014) and harmful influences on the cardiovascular system (Rabbani H, ICHB Paris 2016), but have also pathological effects on internal organs, such as the pineal gland and its "melatonin" hormone secretion which is considered as stimulator system (pace-maker-like) to regulate the rhythm of wake-sleep.

Major depression, anxiety and trauma, resulting of catastrophic stressful life event, such as wars, acts of terrorism (New York, Nice and Paris), or others, when accumulating and occurring together, can perturb not only the circadian rhythm system, but in some extreme situations (such as inability to cope with stress or suffering, facing economic crisis and failure etc.), in some cases as noted elsewhere (Rabbani H. Medical Psychology 1991) they can also engender behavior and personality disorders and finally lead to suicide.

The efficacy of melatonin to improve the quality of sleep is well established however the author would propose if possible, to maximize the dosage.

Keywords : sleep disorders, post-traumatic stress disorder, melatonin

## PM195

### Psychotropic medication and long-term suicide risk in a nationwide population-based cohort study in South Korea

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**Objectives:** We investigated the effects of psychotropic medication on the long-term risk of suicide in the general population of South Korea.

**Method:** We analyzed a National Health Insurance Service-National Sample Cohort (NHIS-NSC) database in South Korea. A total of 300,232 individuals were followed for up to 12 years. We obtained information on history of psychotropic medication (antidepressants, antipsychotics, benzodiazepine and zolpidem). We conducted a competing risk survival analysis to estimate the risk of completed suicide.

**Results:** 725 individuals (241/100,000) died by suicide in the follow-up period. The history of benzodiazepine use was associated with an increased long-term risk of completed suicide (adjusted Hazard Ratio [aHR] = 1.287, 95% confidence interval [CI] = 1.075-1.541,  $P = 0.006$ ) after controlling medical illness, psychiatric disorders and other psychotropic medications. Antidepressants, antipsychotics and zolpidem were not associated with higher suicide risk nor had they any protective effect for completed suicide.

**Conclusion:** We found the association between suicide risk and benzodiazepine. Our findings may enable more focused suicide surveillance in population efforts. In light of the increasing societal burden of suicide, further research is needed to develop precise suicide prediction.

**Keywords:** Suicide; risk factor; cohort study

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## PM196

### Prison Adolescent Suicide Risk factors.

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#### **Validation of Azerbaijan version of the Columbia-Suicide Severity Rating Scale (C-SSRS).**

**Objective:** This study focused to the reliability and validity the psychometric properties of an Azerbaijan version of the Columbia Suicide Severity Scale (Az-CSSRS) on the adolescent suicidal behavior. Clinician and nonclinician raters showed strong interrater reliability using the C-SSRS (Kerr DC<sup>1</sup>, Gibson B, Leve LD, Degarmo DS). Experts accentuated the importance of using nomenclature for suicidal behaviors (Silverman, Berman, Sanddal, O'Carroll, & Joiner, 2007; O'Carroll, Berman, Maris, Moscicki, Tanney, & Silverman, 1996). The Columbia Suicide Severity Rating Scale (C-SSRS) is one such tool for assessing suicidal thoughts and behaviors and also can be used to assess suicidal behavior across shorter timeframes (e.g., past month), and separately assesses suicidal ideation. The is a reliable and valid instrument for assessing suicidal ideation and behaviour in daily clinical practice and research settings. Psychometrically validated screening instruments are essential to any screening program. To effectively identify suicidal youths, a screening instrument should be assessed in relation to its sensitivity (ability to correctly identify those who are suicidal), specificity (ability to correctly identify those who are not suicidal), positive predictive value (proportion of those who screen positive who are true positives), and the negative predictive value (the probability that a person who screens negative is correctly identified as not at risk of suicide) (Peña & Caine, 2006).

Earlier research has shown that the signs that commonly precede a suicide attempt include substance abuse and a communication of intent (Chiles, Strosahl, Cowden, & Graham, 1986), as well as severe anxiety or extreme agitation (Busch, Fawcett, & Jacobs, 2003; Simon, 2006). The high incidence of youth self-directed violence in Azerbaijan Republic represents widespread and devastating outcomes that often have severe interpersonal and economic consequences. This article reviews the literature on suicide prevention screening, warning signs, and risk factors to gain a better understanding of evidence-based screening strategies and discuss the implications for school social workers, counselors, and psychologists. It focuses on the identification of research-based information and explication of potential means for guiding preventive screening and clinical practice with suicidal adolescents. Suicide ideators were more likely to

have contacted a mental health professional. Implications for suicide risk assessment and intervention are discussed.

**Purpose:** The purpose of this study was: 1) the examine rater/clinician-administered versions of the Columbia-Suicide Severity Rating Scale (C-SSRS) for research assess severity and intensity of suicidal ideation, types of suicidal behaviors, and lethality of suicide attempts at time points and over time periods that are typical for randomized control trials 2) Recognition and consideration of the developmental and contextual factors associated with adolescent suicidal behavior will help researchers in developing the next generation of interventions for suicidal teens and will help clinicians in implementing developmentally sensitive care in the treatment of suicidal behaviors among adolescents. (Stephanie S. Daniel, PhD and David B. Goldston, PhD)

**Method:** Data are from a cross-sectional validation study. The study measures were: C-SSRS and the Hamilton Depression Rating Scale (HDRS).

**Result:** *Construct validity:* Pearson coefficient between the C-SSRS severity (C-Sev) and intensity (C-Int) of ideation subscale scores was 0.?? (P<???) for the total sample. Likewise, Pearson coefficient between C-Sev score and HDRS item ? was ? (P<???). *Discriminant validity:* Significant differences were found in C-Sev and C-Int scores between patients with and without suicide attempt (P<???). The C-Sev score discriminated between patients based on HDRS item ? (P<???.). *Sensitivity to change:* Linear regression showed that a one-unit decrease in HDRS item 3 corresponded to a decrease of ??? units in the C-Sev score (P=???.). A one-unit change in HDRS item ? corresponded to a change of ??? on the C-Int assessments (P=???.). Cronbach's alpha was ??? for C-Int. The principal component analysis identified ? components that explain ???% of the total variance (C-Int).

**Conclusion:** The data support that the Az-C-SSRS is a reliable and valid instrument for assessing suicidal ideation and behavior daily clinical practice and research settings.

#### **Resources:**

- Al-Halabí S<sup>1</sup>, Sáiz PA<sup>2</sup>, Burón P<sup>1</sup>, Garrido M<sup>3</sup>, Benabarre A<sup>4</sup>, Jiménez E<sup>5</sup>, Cervilla J<sup>6</sup>, Navarrete MI<sup>6</sup>, Díaz-Mesa EM<sup>7</sup>, García-Álvarez L<sup>7</sup>, Muñiz J<sup>8</sup>, Posner K<sup>9</sup>, Oquendo MA<sup>9</sup>, García-Portilla MP<sup>10</sup>, Bobes J<sup>2</sup> Validation of a Spanish version of the Columbia-Suicide Severity Rating Scale (C-SSRS). [PubMed]
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• [Stephanie S. Daniel](#), PhD and [David B. Goldston](#), PhD Interventions for Suicidal Youth: A Review of the Literature and Developmental Considerations

## PM197

### The association between suicide attempts and *Toxoplasma gondii* infection

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**Background/Objective:** Suicide attempts are one of the powerful predictor of suicide. Possible mechanisms by which *Toxoplasma gondii* (*T. gondii*) may affect human behavior and it may also cause humans to attempt suicide. Several studies found that seroprevalence of *T.gondii* is associated with increased suicide rates. To our knowledge there was no similar research in Korean population. This article aimed to overview of the evidence of a potential pathophysiological relationship between depression, suicide, and the *T. gondii* infection in Korea.

**Method:** One-hundred fifty five psychiatric patients with history of suicide attempt (aged 18-80 years) and one-hundred thirty five healthy control individuals (aged 22 to 59 years) were examined with enzyme-linked immunoassays and fluorescent antibody technique for *Toxoplasma gondii* seropositivity and antibody titers. The group of suicide attempters were interviewed the history of suicide attempt during lifetime and evaluated using HAMD (Hamilton rating scale for depression), C-SSRS

(Columbia Suicide Severity Rating Scale), STAI (State-Trait Anxiety Inventory) and BIS (Barratt Impulsive Scale).

**Result:** Seroprevalences of *Toxoplasma* IgG and IgM in the cases and the healthy controls were not significantly different. IgG antibodies were found in 21 (13.5%) of 135 suicide attempters and in 8 (5.9%) of the 135 controls ( $p = 0.011$ ). There was only 1 control individual shows IgM seropositive. In contrast, the *Toxoplasma* IgG levels higher than 150 IU/ml were more frequently observed in the cases than in the controls (33.3% vs. 25%, respectively;  $p = 0.04$ ). The *Toxoplasma*-seropositive suicide attempt patients had higher HAMD score on depressed mood (3.33 vs 2.68,  $p=0.001$ ) and feelings of guilt (2.50 vs 1.85,  $p=0.009$ ) subscale and total score than the seronegative attempter. *T.gondii* seropositive status was associated with higher C-SSRS in severity (3.85 vs 3.22,  $p=0.003$ ) and lethality (2.75 vs 2.23,  $p=0.012$ ) subscale. *T.gondii* IgG seropositivity was significantly associated with higher STAI-X1(state anxiety) scores among suicide attempt group. The lifetime prevalence of suicidal attempt was not different between IgG seropositive and negative. In BIS, seropositive group were higher than seronegative group but did not show significant differences (72.95 vs 69.44,  $p=0.281$ )

**Conclusion:** These results suggested significant association between *T.gondii* infection and psychiatric problems in suicidality. The depressed mood, guilty ideation and state anxiety considered as endophenotypes for suicidal self-directed violence. And the severity and lethality of self-mutilation are associated with suicide completion. These findings could be further investigated as prognostic and treatment targets in *T.gondii* seropositive individuals at risk for suicidal behavior.

## PM198

### Naturally absorbed omega fatty acids, lithium, and suicide-related

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**Background:** Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (omega-3 fatty acids) have been found to be effective for depression which often leads to suicide, while the reported effects of arachidonic acid (omega-6 fatty acid) on suicide-related behaviours are

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conflicting and yet to be determined. Lithium (even trace levels found in tap water) is reportedly associated with lower suicide rates, but this association is not fully established at present. To date, the studies that have investigated these various factors on suicide-related events have examined them separately. Here, we aimed to comprehensively investigate the effects of naturally absorbed EPA, DHA, arachidonic acid and lithium in relation to suicide attempt and deliberate self-harm, with adjustment for each other.

**Methods:** We analyzed plasma EPA, DHA, arachidonic acid levels and serum lithium levels of 197 patients including 33 patients with suicide attempts, 18 patients with deliberate self-harm, and 146 control patients.

**Findings:** Multivariate logistic regression analysis with adjustment for age, gender, EPA, DHA, arachidonic acid and log-transformed lithium levels revealed that the positive association with DHA levels (adjusted odds ratio [OR] 1.026, 95% CI 1.010-1.043,  $p=0.002$ ) and the negative associations with EPA (adjusted OR 0.972, 95% CI 0.947-0.997,  $p=0.031$ ) and log-transformed lithium levels (adjusted OR ratio 0.156, 95% CI 0.038-0.644,  $p=0.01$ ) were significant in patients with suicide attempts than in control patients. The analysis also demonstrated that the positive association with arachidonic acid levels (adjusted OR 1.015, 95% CI 1.005-1.025,  $p=0.004$ ) was significant in patients with deliberate self-harm than in control patients.

**Interpretation:** The present findings suggest that, as naturally absorbed nutrients, higher EPA and higher lithium levels may be associated with less suicide attempt, and that higher arachidonic acid levels may be associated with more deliberate self-harm.

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## PM199

### Suicidal Behavior and Thyroid Pathology, Lima-Peru

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**OBJECTIVE:** To study incidence of thyroid pathology (TP) in patients with suicidal behavior (SB), assisted in a mental health institute, 2015-2016. **METHOD:** Descriptive and longitudinal trial, assessing patients with SB suffering TP, by a multidiscipline team, Medical, Endocrinology evaluation and DSM IV-RT criteria. **RESULTS:** From 1100 patients seen by SB, 34 were diagnosed as a TP, it is: 3.1%, 2 males (5.9%), 32 females (94.1%); 32 (94.1%) pats. made a suicide attempt, 2 of them: (5.9%) completed suicide. By groups of age: 18-33 y.o: 10 pats. (31.4%); 34-

49 y.o: 16 (47.1%), 50 or more y.o: 8 pats. (23.5%). Major diagnosis was Hypothyroidism: 23 pats. (67.6%), then Hyperthyroidism: 11 (32.3%). First psychiatric diagnosis was Major Depressive Disorder (MDD): 24 pats (70.6%), Bipolar Disorder (BD): 5 pats: (14.7%); OCD: 2 (5.9%), GAD: 3 (8.8%). Co-morbidity was found in 16 pats (47%): between MDD and BPD in 9: (26.5%), MDD/Alcohol Abuse in 6: (14.7%), and MDD/Pathological Gambling in 1 patient: (2.4%). The 2 females who completed suicide were 45 and 48 y.o, with diagnoses: Hypothyroidism associated to Depression and Alcoholism. 19 pats (59.4%) did not take any treatment for TP, other 13: (40.6%) were in sub-therapeutic doses. **CONCLUSION:** According trial, 3% of patients with SB suffered any TP, mostly Hypothyroidism, generally associated to MDD; in near half of them a co-morbidity was found; more than half was not under treatment. **BIBLIOGRAPHY:** 1.- Pompili M., et al (2012) Prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients., *Psychiatry Research*, Vol 200, Issues 2-3, pp 389-394. 2.- Duval F., et al (2010) Thyroid axis activity and suicidal behavior in depressed patients, *Psychoneuroendocrinology*, Vol 35, Issue 7, pp 1045-1054, Elsevier.

## PM200

### Escitalopram Attenuates Fear Stress-Induced Increase in Amygdala Dopamine According to Dopaminergic Sensitisation: Implications of Fine-Tuning Action of Selective Serotonin Reuptake Inhibitors on Emotional Processing

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Serotonin reuptake inhibitors modulate the serotonergic pathways of the nervous system and are widely used for treating psychiatric conditions such as anxiety and depression. Although these conditions are closely related to the dopaminergic system, the effect of serotonin reuptake inhibitors on dopamine levels and its consequent impact on emotional processing is unclear. Previous studies on methamphetamine-sensitized rats (behavioural models of stress vulnerability) have shown increased release of dopamine in response to conditioned stress in the amygdala, which is the key control centre for emotional memory and conditioned fear stress. This biochemical abnormality was proposed to underlie the

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pathophysiology of stress vulnerability. Here we examined the effect of escitalopram, a highly selective serotonin reuptake inhibitor, on fear-related behaviour, basal dopamine release and dopamine release in response to conditioned fear stress in the amygdala of model rats. Male Sprague-Dawley rats received 2 mg/kg/day of methamphetamine for 10 days to sensitise them to the drug, and a fear-conditioning paradigm was instituted to model psychological stress. Dopamine changes in the amygdala in response to systemic administration of escitalopram followed by conditioned fear stress were measured using microdialysis and high-performance liquid chromatography. Basal dopamine release in the amygdala was increased by escitalopram in non-sensitised rats but not in methamphetamine-sensitised rats. Escitalopram attenuated dopamine release in response to the fear-conditioned stimulus in both sensitised and non-sensitised rats. The extent of suppression in methamphetamine-sensitised rats was greater than that in non-sensitised rats. These findings suggest that serotonin reuptake inhibitors indirectly stabilise the dopaminergic pathway and modulate emotional processing in the amygdala.

## PM201

### An atlas-based whole brain tractography study in major depressive disorder and bipolar disorder.

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**Background:** Tractography is the method for delineating the structure of cerebral white matter in vivo, yet few studies have directly compared white matter tracts using tractography between major depressive disorder and bipolar disorder.

**Objective:** We examine 54 regions of the white matter separated by atlas-based segmentation in major depressive disorder and bipolar disorder using whole brain tractography method, to clarify the specific neural change in both diseases.

**Method:** Diffusional tensor imaging (DTI) data were acquired on a 3 Tesla scanner in 30 euthymic major depressive disorder, 30 euthymic bipolar disorder and 30 healthy controls. We employed an atlas-based whole brain tractography, then calculated fractional anisotropy (FA) along each tract.

**Result:** Bipolar disorder had significantly lower mean FA values in the bilateral cingulum bundle and the bilateral body of corpus callosum compared to major depressive

disorder and healthy control; in the right column and body of fornix compared to major depressive disorder; and in the left column and body of fornix and the bilateral genu of corpus callosum compared to healthy control.

**Conclusion:** We observed specific white matter changes in bipolar disorder compared to major depressive disorder. These changes may be involved in the pathophysiology of bipolar disorder.

## PM202

### Neuroprotective effect of lithium at therapeutic and subtherapeutic doses in GSK3beta autonomous pathways at primary hippocampal neurons cell culture

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**Introduction:** Low lithium concentration has a significant positive effect in synaptic plasticity and reduces cell toxicity. Lithium negatively regulates the expression and activity of glycogen synthase kinase 3b (GSK3b). GSK3b have different partners based on protein-protein interaction databases, here on called as the "GSKoma". The aim of the study is to evaluate the enrichment of the GSKoma in differentially expressed genes related to neuroprotection in hippocampal neurons with different doses of lithium. **Methods:** Primary cultures of hippocampal neurons were treated for 7 days with lithium (0.02mM, 0.2mM and 2mM). The Agilent860k microarray platform were used. The samples were analyzed in the MeV, with a delta of 1.4 and FDR of 5% and R v3.4. GSKoma was constructed using PathCard and String program. **Results:** Up regulated genes were identified: 8 (0.02mM), 126 (0.2mM) and 739 (2mM). Down-regulated genes were identified: 36 (0.02mM), 1132 (0.2mM) and 1603 (2mM). GSKoma was made up of 182 proteins that directly interact with GSK3b. The results showed that probably GSK3b is not the main route of different doses of lithium on gene expression, since there was no significant enrichment of the GSKoma using MSET. Analyses of biological processes showed that the 0.02mM dose was

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related to: cortex tangential migration; forebrain degeneration of neurons and forebrain differentiation; the dose of 0.2mM ion transport, metal ions transport, ion transmembrane transport; 2mM response to stimulus and response to organic substance. Whereas the biological processes related to GSK3b block were: response to organic substance; response to oxygen containing compound; response to endogenous stimulus and response to organic cyclic compound. *Conclusion:* GSK3b pathway did not appear as the main event for the response to treatment with lithium in therapeutic and subtherapeutic doses.

## PM203

### Paternal *Pax6* haploinsufficiency precociously accelerated vocal communication deficits by advanced paternal aging

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Epidemiological studies have indicated that advanced paternal age is a risk for elevated rates of various psychiatric disorders such as schizophrenia, autism, early onset of bipolar disorder, reduced IQ, and impaired social functioning in adolescence in their offspring. Both genetic and epigenetic mechanisms are assumed to be involved in these transgenerational effects. Here we revealed that advanced paternal age caused vocal communication deficits and that paternal *Pax6* haploinsufficiency precociously induced the deficits in F1 offspring. The vocal communication deficits were abolished when F2 offspring was born to young F1 male mice, suggesting involvement of epigenetic mechanisms rather than genetic mutations. We also identified a common change of H3K79 trimethylation (H3K79me3) in both wild type (WT) and *Pax6* mutant spermatocytes and sperm. Furthermore, a notable association was observed between H3K79 tri-methylation of sperm versus age of male mice, and versus vocal communication deficits in offspring. These results suggest that altered regulation of gene expression by H3K79me3 might be considered to be pathophysiological basis of vocal communication deficits by advanced paternal aging. Currently, we attempt to identify in the aged sperm target genes whose expression is regulated by H3K79me3, and to examine epigenetic phenotypes within the brain.

## PM204

### Protective effects of *Huperzia Serrata* against oxidative damage and cognitive dysfunction

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**Objective;** Alzheimer's disease (AD) is characterized by progressive cognitive decline, and accumulation of amyloid  $\beta$  protein (A $\beta$ ) is considered as an important factor in onset of AD. In AD, the amount of acetylcholine, which is one of neurotransmitters, is decreased. In addition, accumulation of A $\beta$  is closely related to the occurrence of oxidative stress, and oxidative stress is thought to promote neuronal cell death. In this study, we examined the protective effect of *Huperzia Serrata*, which has been used in traditional Chinese herbal medicine, against neuronal cell death and cognitive dysfunction.

**Methods;** We induced cell death in mouse hippocampal cells (HT22 cells) by A $\beta$  and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). The cell protective effects of *Huperzia Serrata* were examined by nuclear staining. The ratio of dead cells to total cells was used as an indicator of protective effects. Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitory activity were measured by Ellman's method using mouse brain homogenate and mouse serum, respectively. The effect on cognitive function was evaluated by Y maze test and passive avoidance test using male ICR mice. *Huperzia serrata* (50, 100 mg/kg) was administered orally once a day. Passive avoidance test was performed on day 12 to day 14, and Y maze test on day 13.

**Results;** *Huperzia Serrata* showed protective effects in a concentration dependent manner against cell death induced by A $\beta$  and H<sub>2</sub>O<sub>2</sub>. *Huperzia Serrata* showed inhibitory effects on AChE activity (IC<sub>50</sub> = 69.1  $\mu$ g/ml), but not BuChE activity (> 100  $\mu$ g/ml). In Y maze test and passive avoidance test, *Huperzia serrata* (100 mg/kg) significantly ameliorated arm alteration and latency, respectively.

**Conclusion;** These results suggest that *Huperzia serrata* ameliorates cognitive dysfunction by the inhibitory effects

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on AChE activity and the protective effects on oxidative damage.

**Policy of Full Disclosure:** None

## PM205

### Data driven assessment of pharmacological MRI data investigating an acute selective serotonin reuptake inhibitor challenge

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**Objective:** Pharmacological MRI (phMRI) enables the evaluation of the brain's response to drug interventions, which may yield important insights in psychiatric treatment regimens [1]. Model-based strategies have the disadvantage of neglecting the possibility that different brain regions may show a different drug response, whereas data driven analysis methods like clustering allow for a model-free evaluation [2-4].

**Methods:** Twenty-one healthy volunteers ( $28.09 \pm 8.51$  years, 12 male) completed two PET/MR sessions in a Siemens mMR scanner. Subjects were randomly assigned receiving an intravenous selective serotonin reuptake inhibitor (SSRI) challenge (citalopram) in the first session and placebo in the second or *vice versa*. Resting-state functional MRI (rsfMRI) measurements were performed simultaneously with the SSRI infusion (8 mg over 8 min) as to assess the pharmacological response over a 40 minute period. K-means clustering was used where the optimal number of unique clusters was estimated via the Bayesian information criterion. The percent signal change between conditions over time for each cluster was calculated separately for verum and placebo and averaged separately. The signals were then analyzed for differences between both verum and placebo.

**Results:** Two of the 14 clusters showed changes in the verum time-course signals after SSRI application in comparison to placebo. These clusters were located in the frontal and orbitofrontal parts of the brain. The frontal cluster exhibited an exponential increase in the signal

directly after SSRI application. The orbitofrontal cluster, however, showed a biphasic pattern with a drop and a delayed exponential increase in the verum signal after the baseline. In both clusters the placebo signal followed a general linear trend over time.

**Conclusion:** The data driven, assessment of phMRI revealed regionally specific and distinct signal responses to a single SSRI challenge. Such an approach could help in the understanding of neuronal responses to different pharmacological compounds.

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of the Medical University of Vienna, a grant from the Else Kröner-Fresenius-Stiftung (2014\_A192) and funding by SIEMENS (CA-ID: C00214938/06).

## PM206

### The Pharmacological treatment of major depressive episodes with mixed features

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**Objectives:** We reviewed clinical studies investigating the pharmacological treatment of major depressive episodes (MDEs) with mixed features diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

**Methods:** We systematically reviewed published randomized controlled trials (RCTs) on the



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pharmacological treatment of MDEs with mixed features associated with mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD). We searched the PubMed, Cochrane Library, and ClinicalTrials.gov databases through December 2017 with the following key word combinations linked with the word OR: (a) mixed or mixed state, mixed features, DMX, mixed depression; (b) depressive, major depressive, MDE, MDD, bipolar, bipolar depression; and (c) antidepressant, antipsychotic, mood stabilizer, anticonvulsant, treatment, medication, algorithm, guideline, pharmacological. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

**Results:** We found few double-blind, placebo-controlled, randomized trials on pharmacological treatments for MDEs with mixed features. Of the 36 articles assessed for eligibility, 11 investigated MDEs with mixed features in mood disorders: 7 assessed the efficacy of antipsychotic drugs (lurasidone and ziprasidone) in the acute phase of MDD with mixed features, although 5 of these were post hoc analyses based on large RCTs. Three studies compared antipsychotic drugs (olanzapine, lurasidone, and ziprasidone) with placebo, and one study assessed the efficacy of combination therapy (olanzapine + fluoxetine) in the acute phase of BD with mixed features.

**Conclusion:** Investigations of pharmacological treatments for MDEs with mixed features have focused on antipsychotic drugs, although evidence of their efficacy is lacking. Additional well-designed clinical trials of treatments for MDEs with mixed features are needed.

## PM207

### Role of SCN1A and SCN2A gene polymorphisms in epilepsy syndromes-a study from India

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**Background:** Epilepsy is the most common heterogeneous neurological disorder affecting approximately 50 million people worldwide [WHO]. Juvenile myoclonic epilepsy (JME) is a common form of idiopathic generalized epilepsy syndrome representing 5-10% of all epilepsy cases [Hsin YL, 2007]. Lennox-Gastaut syndrome (LGS) is one of the most severe epileptic encephalopathies of childhood onset, the cause of which may be symptomatic, i.e secondary to an underlying brain disorder or cryptogenic, i.e with no known cause. Sodium channels are integral membrane proteins which play a

central role in neuronal membrane excitability and action potential generation. Alpha subunit of voltage gated sodium channels encoded by SCN1A, SCN2A and other genes is pivotal for neuronal signaling. It was planned to analyze the roles of SCN1A Thr1067Ala and SCN2A Arg19Lys polymorphisms in the pathophysiology and risk JME and LGS in the Indian population.

**Methods:** A total of 50 JME patients, 50 LGS Patients and 100 age and sex matched healthy volunteers were recruited in this study. The genotyping of SCN1A Thr1067Ala i.e 3184 A>G (rs2298771) and SCN2A Arg19Lys i.e 56 G>A (rs17183814) polymorphism was performed by Polymerase Chain Reaction- Restriction Fragment Length Polymorphism (PCR-RFLP) analysis.

**Results:** The SCN1A Thr1067Ala polymorphism genotypic distribution in LGS was significantly different from the normal population (P=0.008), with mutant homozygous (GG) plus heterozygous (AG) genotypes' percentage in LGS patients (16%) being lower than in healthy controls (24%). Frequency of the mutant 'G' allele of this SNP in LGS patients was 0.1, while it was 0.2 in control subjects (P=0.04). These observations which suggest a protective role of SCN1A Thr1067Ala polymorphism in LGS, were in sync with computation of an odds ratio of 0.21 (95% CI 0.07 to 0.66, p=0.005) for the GG genotype in LGS patients. Though no correlation of SCN1A Thr1067Ala SNP with the severity of disease phenotype in LGS viz. frequency/duration of seizures etc. was noted, a conflicting finding was the significant association of its mutant genotypes with an early age of onset of the syndrome (p=0.007). Contrary to the findings in SCN1A Thr1067Ala, in case of SCN2A Arg19Lys polymorphism, though a significantly different genotypic distribution was present in LGS, in comparison to normal population (p=0.03), the mutant homozygous (AA) and heterozygous (GA) combined percentage in LGS patients (16%) was greater than in healthy controls (11%). This was complemented by observation of an odds ratio of 4.24 (95% CI 1.15 to 15.55, p=0.029, in case of LGS patients with heterozygous (GA) genotype, indicative of an increased disease susceptibility. Unlike LGS, in JME patients no significant differences in genotypic/allelic frequencies of SCN1A Thr1067Ala and SCN2A Arg19Lys polymorphisms were noted and the associated odds ratios for mutant genotypes were also non-significant.

**Conclusion:** The SCN1A Thr1067Ala and SCN2A Arg19Lys polymorphisms may play contrary roles in the pathophysiology of LGS. Inheritance of SCN1A Thr1067Ala mutant allele decreases the susceptibility for LGS occurrence, and may hamper Na<sup>+</sup> channels opening and neuronal excitability. On the other hand, the mutant allele of SCN2A Arg19Lys polymorphism confers an increased risk for development of LGS, consequent to a likely facilitatory effect on action potential generation and

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misfiring in neurons. Neither of these two SCNA SNPs appear to influence the pathogenesis/susceptibility to JME.

## PM208

### rs6738544 SNP of STAT4 and rs2298170 SNP of STAT6 associate with nicotine dependence

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Cigarette smoking is identified as a strong established risk factor of pancreatic cancer and parental passive smoking is associated with more severe atopic dermatitis in children. Furthermore, certain atopy-related variants including rs6738544 single nucleotide polymorphism (SNP) of *STAT4* gene was associated with pancreas cancer risk. Thus, the reported association exists between smoking and pancreatic cancer or atopy severity, atopy related *STAT4* and pancreatic cancer. However, the relationship between *STAT4* and smoking has not been reported.

To investigate the relationship between *STAT4* and smoking, we statistically analyzed 498 samples on rs6738544 SNP of *STAT4* using the Fagerstrom Test for Nicotine Dependence (FTND), Tobacco Dependence Screener, and number of cigarettes smoked per day as indices of nicotine dependence. Among these indices, only FTND showed significant association with the rs6738544 SNP ( $P = 0.030$ ) by a contingency table analysis in a genotypic model using the samples divided into low dependence group (FTND<4) and high dependence group (FTND $\geq$ 4). Rate of CC genotype was smaller in high dependence group (62%) than in low dependence group (72%). Similar to the previous report on CC genotype for reduced pancreas cancer risk, these results indicate the possibility that CC genotype relates to low dependency on nicotine.

Since the *STAT4* and *STAT6* pathways have essential roles in pancreatitis-associated lung injury based on a former report, we extracted three SNPs around *STAT6* gene (including 10 kbp upstream and downstream) from GWAS results of 148 samples. rs2298170 of *STAT6* showed an association with FTND ( $P = 0.019$ ) and a trend toward association after Bonferroni correction ( $P = 0.058$ ). In the

other 350 samples or total 498 samples, the SNP significantly associated with FTND ( $P = 0.034$ ,  $P = 0.007$ , respectively), suggesting that rs2298170 of *STAT6* relates to FTND.

Together, rs6738544 of *STAT4* and rs2298170 of *STAT6* associate with nicotine dependence.

## PM209

### Comparison of glucose metabolism and blood oxygenation during neuronal activation

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**Objective:** Neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) enable the assessment of glucose and oxygen demands, which are essential aspects of brain energy metabolism. However, PET imaging of neuronal activation required two separate scans: one at baseline and one during task performance. We have recently validated an approach to investigate task-specific glucose metabolism with a single PET scan [1]. The aim of this study was to directly compare these two metrics with simultaneous PET/MR imaging.

**Methods:** 20 healthy subjects underwent one PET/MR scan with constant infusion of [<sup>18</sup>F]FDG and fMRI acquisition. Task performance included right finger tapping and presentation of landscape movies in four blocks. Task-specific glucose metabolism [1] and fMRI percent signal changes (PSC) [2] were quantified as described previously.

**Results:** Task-specific changes showed different PSC but similar statistics for glucose metabolism (PSC=23.3% and 24.2%, peak t-value=18.3 and 18.7) and fMRI (PSC=1.8% and 1.1%, t-value=17.6 and 16.0) in the primary visual and motor cortices, respectively (all  $p < 0.05$  FWE-corrected). However, secondary brain regions such as the supplementary motor area, cerebellum and secondary visual areas were only observed with fMRI. There was no significant correlation between glucose metabolism and fMRI PSC in the primary visual and motor cortices.

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**Conclusion:** Neuronal activation can be robustly detected by both functional PET and MR imaging. However, the mismatch between the methods regarding PSC, secondary brain regions and the lack of correlation indicate that glucose consumption and blood oxygenation represent important complementary information of brain energy metabolism.

**References:**

[1] Hahn et al. JNM 57: 1933-1940, 2016.

[2] Luo et al. NeuroImage 19: 1014-1032, 2003.

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## PM210

### Oxytocin modulation of resting state regional cerebral blood flow (rCBF): comparing the effects of intranasal and intravenous methods of administration

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**Introduction:**

To illuminate the pathways through which synthetic oxytocin exerts its effects in the living human brain, we compared two methods of intranasal administration (standard spray vs PARI SINUS nebulizer, expected to maximize oxytocin deposition in the olfactory region - putatively involved in direct nose-to-brain transportation) to intravenous administration.

**Methods:**

16 healthy males received 40IU of oxytocin intranasally (through a spray or a nebulizer), 10IU intravenously, or placebo, in 4 visits, in a triple-dummy, double-blind, placebo-controlled, crossover design. We visualized and quantified (mL blood/100 g tissue/min) oxytocin-induced changes in rCBF, and hence neuronal activation, using arterial spin labelling in a 3T scanner, in eight 8-min CBF maps. Blood samples for plasma oxytocin quantification were collected at baseline and throughout the observation

period. We used mass univariate analysis and conducted cluster level inference ( $P_{FWE} < .05$ ).

**Results:**

The intranasal administration methods did not differ in their pharmacokinetic profiles. As expected, when administered intravenously, plasma oxytocin was significantly elevated throughout the observation period, compared to intranasal administration. Preliminary analyses demonstrated that the two intranasal methods resulted in markedly different patterns of increases in rCBF (**intranasal spray**: anterior insula, superior frontal gyrus, superior temporal gyrus; **nebuliser**: robust increases in rCBF at the precuneus at multiple time points). These increases in rCBF could not be accounted by plasma levels of synthetic oxytocin. However, significant decreases in rCBF over the amygdala and dorsal ACC using intranasal spray could be explained by increases in plasma oxytocin.

**Conclusions:**

The two different methods of intranasal administration resulted in distinct changes in rCBF despite achieving similar changes in plasmatic oxytocin, suggesting that they may differ in the achieved bioavailability of oxytocin in the brain. Our evidence is partially consistent with the notion of a direct nose-to-brain pathway, but also suggests that some of the effects of intranasal oxytocin may be due to peripheral signalling.

## PM211

### Hyaluronan Binding Protein Involved in Hyaluronan Depolymerization (HYBID, KIAA1199) is responsible for hyaluronan turn over in mouse central nerve system.

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**Objective:** HYBID (Hyaluronan Binding Protein Involved in Hyaluronan Depolymerization, KIAA1199) is a hyaluronan (HA) binding protein, which plays a crucial roles for depolymerization of HA in skin and synovial fibroblasts. In our previous study, we have demonstrated that HYBID mRNA expressed in the brain, especially hippocampus and cerebellum in wild-type mice. HYBID knockout (KO) mice showed decreased memory abilities in a novel object

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recognition test and Morris water maze test. In this study, we examined whether HYBID expression is involved in HA turn over in the central nervous system.

**Methods:** To investigate the expression levels of HA in hippocampus, the sandwich assay using HA binding protein was performed. The size distribution of HA in the brain tissue was determined by size-exclusion column chromatography. HA staining using HA binding protein was carried out to visualize the HA expression in the brain tissue.

**Results:** The sandwich assay demonstrated that the expression levels of HA in hippocampus of HYBID KO mice are significantly 2.5-fold higher than those of wild-type mice. In addition, the size of HA molecular weight in hippocampus of the HYBID KO mice was larger than that of the wild-type mice. HA staining showed an accumulation of HA in the brain tissue of the HYBID KO mice.

**Conclusion:** These data indicated that high molecular weight HA is accumulated in the hippocampus of the HYBID KO mice, and suggested that regulation of HA size distribution mediated by HYBID may be crucial for brain function, including memory and learning.

**Policy of Full Disclosure:** None.  
(251/300 words)

## PM212

### Periaqueductal gray glutamatergic transmission mediates depressive-like behaviors in the remission of visceral pain

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Chronic pain is often accompanied by psychological disorders. Clinical results showing patients with Irritable Bowel Syndrome (IBS) were highly associated with psychological mood disorders, including depression, even in the remission of IBS (1). The reasons of psychological symptoms still occur at the remission from IBS are largely unknown. Most recently, glutamatergic neurotransmission in periaqueductal gray (PAG) was identified to mediate stress-induced depressive-like behaviors (2). In the present

study, we investigated the role of PAG in mediating depressive-like behaviors after 7 days dextran sulfate sodium (DSS)-induced visceral pain, and with additional 7 days water replacement recovery period.

DSS treatment that increased stool consistency, bleeding, and abdominal hypersensitivity, comparing with control rats. After additional 7 days water replacement, visceral abnormalities were disappeared. Body weight and colon length were decreased in DSS-treated rats, and recovery from additional 7 days water replacement. Furthermore, DSS treatment induced the depressive-like behaviors measured by tail-suspension test and sucrose preference test, even with additional water replacement. Results indicated that depressive-like behaviors still occurred in the remission of IBS animal model. Moreover, the amplitude and frequency of miniature excitatory postsynaptic current (mEPSC) in PAG were impaired after DSS treatment, and impaired with additional water replacement as well. Intra-PAG injection of glutamate receptor 1 (GluR1) antagonist evoked animal depressive-like behaviors, and injection of glutamatergic receptor agonist or (2R,6R)-hydroxynorketamine that reversed DSS-induced depressive-like behaviors. Results suggested that PAG glutamatergic neurotransmission play a crucial role in regulating depressive-like behaviors in remission phase of DSS-induced visceral pain. The current study gave a new insight understanding why psychological symptoms are still occurred in the remission of IBS. Our study might provide a good nucleus-specific target for developing medical intervention for psychological disorders in recovery of chronic pain.

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2. Ho YC et al. (2017) Periaqueductal gray glutamatergic transmission governs chronic stress-induced depression. *Neuropsychopharmacology.* doi: 10.1038/npp.2017.199.

## PM213

### Involvement of miR-132 in PACAP-dependent morphological changes of dendritic spines

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**[Objective]** Pituitary adenylate cyclase-activating polypeptide (PACAP) is a multifunctional neuropeptide implicated as a risk factor for psychiatric conditions, including schizophrenia and stress-related disorders (1). Accumulating evidence suggests that psychiatric disorders are associated with dendritic spine abnormalities (2). In this study, we therefore examined the role of exogenous and endogenous PACAP in the formation and maturation of dendritic spines.

**[Methods]** After PACAP treatment, dendritic spine morphology and miRNA/mRNA expression levels were analyzed in primary cultured neurons. Moreover, miRNA-tomato lentivirus was transfected in the hippocampal CA1 of mouse brain and determined the spine density.

**[Results]** PACAP increased the size and density of dendritic spines in primary cultured hippocampal neurons. Concomitantly, PACAP increased miR-132 expression and decreased the mRNA expression levels of p250GAP which is involved in spine formation and a target protein of miR-132. In PACAP-deficient mice, the volume of PSD-95 puncta was decreased compared with wild-type mice. Golgi staining revealed decreased spine density and atypical morphology of hippocampal CA1 neurons in PACAP-deficient mice. Overexpression of miR-132 resulted in altered hippocampal spine density.

**[Conclusions]** These results show that PACAP is implicated in spine formation and maturation, in which miR-132 and p250GAP might be involved, and suggest that dysfunction of PACAP signaling may contribute to the pathogenesis of psychiatric disorders at least partly through dendritic spine abnormalities.

- (1) Hashimoto et al. *Curr Pharm Des.* 2011;17(10):985-9  
(2) Penzes et al. *Nature Neurosci.* 2011;14(3):285-93

## PM214

### Cobalt chloride exposure in neonatal rats induce behavioral alterations: an new animal model of schizophrenia?

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Perinatal hypoxia is a well-known risk factor for the development of schizophrenia (SQZ). Animal models submitted to hypoxia show behavioral and neurochemical changes suggestive of SQZ which can be observed when

rats are young and that remains in adulthood. Cobalt chloride (CoCl<sub>2</sub>) is a compound that produces chemical hypoxia, however its effects on behavioral parameters of rats are poorly understood. The aim of the present study was to evaluate the behaviors of adult rats submitted to neonatal administration of CoCl<sub>2</sub>. Seven postnatal day (PND) Wistar rats received CoCl<sub>2</sub> (CC) or saline (CTR). At 90 PND, the rats were observed in the locomotion (LO), social interaction (SI) and contextual conditioned fear (CFC) tests, as well as the effects of haloperidol in reverting the alterations caused by CoCl<sub>2</sub> exposure. Animals treated with CoCl<sub>2</sub> in perinatal period showed hyperlocomotion (CTR: 81.5; CC: 165.5; p=0.004), deficits in social interaction (CTR: 234; CC: 127.8; p=0.024) and in CFC (CTR: 164.36; CC: 113.6; p=0.049). In order to evaluate the pharmacological validity criterion of this animal model, animals were treated with haloperidol. All these alterations were reverted by haloperidol (LO - CC: 126.5; HAL: 28.25; p=0.003; SI - CC: 174.5; HAL: 457.5; p=0.0001; CFC - CC: 132; HAL: 197.17; p=0.029). These results suggest that CoCl<sub>2</sub> can induce behavioral alterations related with schizophrenia which can be reverted by haloperidol administration.

## PM215

### Examination of the effects of carbonyl stress elicited by GLO1 gene knockout in human iPSC cells

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Carbonyl stress is a central mediator of advanced glycation end product (AGE) formation. Toxic reactive carbonyl compounds such as  $\alpha$ -oxoaldehydes (e.g., methylglyoxal, glyoxal and 3-deoxyglucosone) are formed from sugars, lipids and amino acids. Accumulation of such reactive carbonyl compounds, referred to as carbonyl stress, results in the modification of proteins by AGEs like pentosidine. Cellular removal of AGEs hinges largely on the activity of the zinc metalloenzyme glyoxalase I (GLO1). Recent studies have revealed that carbonyl stress, along with dysfunction of GLO1, plays an important role not only in systemic diseases such as diabetes mellitus, but also in neuropsychiatric disorders including schizophrenia, mood disorder, autism and Alzheimer disease. Regarding schizophrenia, it has been reported that subset of patients showed increases in plasma AGEs and that offspring from

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diabetic mothers showed 7-fold increased risk for schizophrenia, suggesting that carbonyl stress in neurodevelopment could be future schizophrenia risk. To obtain insight into abnormalities in neurodevelopmental trajectories of schizophrenia by carbonyl stress, analyses of human induced pluripotent stem cells (hiPSCs) should be informative. Here, we established hiPSCs from schizophrenia patients with the *GLO1* frameshift mutation and *GLO1*-deficient hiPSCs from control iPSC lines by gene editing using CRISPR-Cas9. Neurosphere size, neurosphere number, neural differentiation efficiency and expression of neural stem cell marker (*SOX1*) were significantly reduced in the patient-derived iPSCs and *GLO1*-deficient hiPSCs. Furthermore, these iPSCs showed increase of carboxymethyllysine (CML) modification of a certain protein. CML is one of AGEs. Reduction of carbonyl stress by adding piridoxamine to patient-derived iPSCs and *GLO1*-deficient hiPSCs partially restored neural differentiation efficiency and decreased CML modification. These results suggest that carbonyl stress may affect neurodevelopmental process.

## PM216

### Analysis of sphingolipids in schizophrenia: postmortem brain study

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Schizophrenia is a severe mental disorder with a lifetime risk of about 1%, characterized by positive symptoms, negative symptoms and cognitive deficits. It has been thought that schizophrenia is caused by environmental and genetic factors, and their complicated interactions. However, detailed mechanism of schizophrenia pathophysiology, in particular in terms of metabolomics pathways, is unknown. Recently, some clinical studies reported altered metabolism of lipids and serine in bloods of schizophrenia patients.

Sphingolipids are lipids synthesized from serine, and important mediators involved in various functions, such as apoptosis, proliferation, and stress responses. Recently, it was reported that sphingolipid levels were changed in postmortem brains, erythrocytes and skin from schizophrenia patients. To investigate the role of sphingolipids in schizophrenia pathology, we analyzed sphingolipids of postmortem brains (region: Brodmann area 8 and corpus callosum) from schizophrenia patients. Our mass spectrometry-based lipidomics approach detected a decrease in sphingolipid content in the corpus

callosum of schizophrenia patients. The sphingolipid content was not correlated with therapeutic drug dose, and sphingolipid content was not changed in mouse brains after the treatment of an antipsychotic drug, excluding potential confounding effects of drugs. In addition, the expression of genes for sphingolipid metabolic enzymes was significantly changed in the corpus callosum between controls and schizophrenia patients. Furthermore, the expression levels of some sphingolipid receptors were increased in schizophrenia. From these findings, it is suggested that dysregulation of sphingolipid-mediated functions may underlie schizophrenia pathophysiology.

## PM217

### Paranoid Schizophrenia versus Residual Schizophrenia: Neuropsychological Aspects

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Neuropsychological aspects of psychotic disorders have still not been examined enough [1,2]. Identification of these features can help in the treatment and diagnosis of this disorder.

**Objective:** The essence of this research is to evaluate neuropsychological features of patients with paranoid and residual schizophrenia by applying neuropsychological tests.

**Methods:** The research included 80 subjects, inpatients with paranoid schizophrenia (n=40) and inpatients with residual schizophrenia (n=40). All subjects were tested with the following tests: a set of methods for neuropsychological evaluation (Balashova E.Y., Kovyazina M.S.), Positive and Negative Syndrome Scale (PANSS), Trail Making Test (TMT), Rey Complex Figure (RCF).

**Results:** level of negative symptomatology in patients with residual schizophrenia is significantly higher than  $35.6 \pm 4.2$  points (PANSS), compared with patients with paranoid schizophrenia  $21.1 \pm 3.1$  points. 78% of patients with paranoid schizophrenia and 83% of patients, according to neuropsychological research, there is a tendency for neglect of the left side of space.

**Table 1 - Achievements of the groups in neuropsychological tests (Mean±SD)**

Variable	Paranoid schizophrenia	Residual schizophrenia
TMT A	78.29±13.83	89.16±13.12
TMT B	140.73±30.34	149.95±25.32
RCF C	19.78±5.64	16.77±2.68
RCF 40'	11.30±3.05	7.22±1.02

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SD – standard deviation; TMT – Trail Making Test; RCF – Rey Complex Figure; RCF C – copying of the RCF; RCF 40' – postponed visual memory.

**Conclusion:** scores in the group of patients with residual schizophrenia are significantly higher and indicate a deficit in the frontal and temporal lobes (Table 1). These changes against the background of the tendency for neglect of the left side of space in 80.5% of cases allow us to assume the primary role of interhemispheric interaction and deficit of stimulation of the frontal and temporal lobes. Neuropsychological approach allows us to objectify the depth and severity of psychopathological symptoms. The deficit of stimulation of the frontal and temporal lobes is one of the factors which determine subtype and the final state. The use of neuropsychological approaches and results of this research allow optimizing the programs of therapy and psychosocial rehabilitation.

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- 2) [Seltzer J](#), [Conrad C](#), [Cassens G](#). Neuropsychological profiles in schizophrenia: paranoid versus undifferentiated distinctions. [Schizophr Res](#). 1997 Feb 7;23(2):131-8.

## PM218

### Impaired cerebellar development in mice overexpressing VGF nerve growth factor inducible (VGF) via promoting MAPK signaling

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**Objective:** VGF nerve growth factor inducible (VGF) is a neuropeptide precursor induced by brain-derived neurotrophic factor and nerve growth factor. In the previous reports, VGF is increased in prefrontal cortex and cerebrospinal fluid, and copy number variant is found on chromosome 7q22.1, in which VGF gene is located, in patients with schizophrenia. In our previous study, VGF-overexpressing mice exhibited schizophrenia-like behaviors and smaller brain weight. Brain developmental abnormality is one of causes on mental illnesses. Research on brain development is important for discovery of pathogenesis of mental illnesses. In the present study, we investigated the role of VGF on cerebellar development.

**Methods:** We performed histological analysis of cerebellum with sagittal sections of adult and postnatal

day 3 mice by Nissl staining. To investigate cerebellar development, we performed immunostaining with antibodies of immature and mature granule cell markers (neuronal nuclei, Ki-67, and phospho histone H3: pHH3). To investigate the mechanism underlying these histological changes, we investigated MAPK (Trk and Erk), Wnt (active  $\beta$ -catenin), and Sonic Hedgehog (Gli2) signaling by Western blot. Finally, we performed rotarod and footprint tests using adult mice to investigate motor function of mice.

**Results:** In adult mice, VGF-overexpressing mice exhibited smaller cerebellar size, especially granule layer, which contains granule cells. In postnatal day 3 mice, the size reduction of whole cerebellum and external granule layer and decrease of the number of mature granule cells (NeuN-positive cells) were found in VGF-overexpressing mice. Additionally, the number of proliferative granule cell precursors (pHH3-positive cells) was occurred in VGF-overexpressing mice. Phosphorylation of Trk and Erk1 were increased in cerebellum of postnatal day 3 VGF-overexpressing mice. Finally, adult VGF-overexpressing mice exhibited motor disability.

**Conclusion:** VGF is implicated with the development of cerebellar granule cells via promoting MAPK signaling, and affects the motor function in adult stage.

**Policy of Full Disclosure:** None

## PM219

### Genetic Associations with Suicide Attempt Severity

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**Background:** In 2015, the World Health Organization estimated that 788,089 people died by suicide worldwide, making it one of the leading causes of death. For every death by suicide there are as many as 25 suicide attempts, the occurrence of which is one of the strongest known clinical predictors of death by suicide. Despite this outside impact on mortality, the genetic influences on suicide attempt are poorly understood. We performed a genome-wide association study (GWAS) on the severity of suicide attempt to investigate genetic influences.

**Methods:** A total of 6320 subjects were interviewed using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA), from which we derived a quantitative phenotype for suicide attempt severity. Genome Wide Efficient Mixed Model Association (GEMMA) was used to identify single nucleotide polymorphisms (SNPs) associated with suicide attempt severity in two cohorts of European Americans (EAs) (Yale-Penn 1 n=1225, Yale-Penn 2 n=1214) and two cohorts of African Americans (AAs) (Yale-Penn 1 n=253, Yale-Penn 2 n=1351). The summary statistics from Yale-Penn1 and Yale-Penn2 were meta-analyzed by population (EAs n=2439, AAs n=3881).

**Results:** One independent signal was found in EAs, with 34 genome-wide significant (GWS) SNPs in high LD over a 44-kb region. The SNPs mapped in and around the "Lactate Dehydrogenase B" (*LDHB*) gene. The lead SNP (rs1677091, MAF=0.30, p=1.07E-08) was directly genotyped in both cohorts. Three GWS associations were found in AAs, 22 kb upstream of *ARNTL2* (rs683813, MAF=0.04, p=2.07E-08), 29 kb from *FAH* (rs72740082, MAF=0.03, p=2.36E-08), and an intergenic region on chromosome 18 (rs11876255, MAF=0.03, p=4.61E-08).

**Conclusions:** To our knowledge, this is the first GWAS of suicide attempt severity. We identified several GWS SNPs near genes involved in anaerobic energy production (*LDHB*), circadian clock regulation (*ARNTL2*), and the catabolism of tyrosine (*FAH*). These findings provide evidence of genetic risk factors for suicide attempt severity.

## PM220

### The Effect of Primary Cannabinoid Pre-Exposure on the Addictive Potential of Psychostimulant Drugs

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**Objective:** According to the Gateway drug theory, the risk of problematic drug use and drug addiction increases significantly in people who are experienced with marijuana, more specifically, with its psychoactive component – delta-9-tetrahydrocannabinol (THC). However, it has been shown in experimental studies that the cannabinoid, cannabidiol (CBD) can moderate some of THC's behavioural effects. We tested whether pre-exposure to cannabinoids (CBD, THC) affected subsequent development of amphetamine (AMPH) addiction in male Wistar rats.

**Method:** Conditioned place preference (CPP) was used to evaluate (i) the addictive potential of AMPH (1 mg/kg) without cannabinoid pre-exposure, and (ii) AMPH's addictive potential following pre-treatment with escalating (every two days) doses of THC (2, 4, 8 mg/kg) or CBD (5, 10, 20 mg/kg). Data were analysed using repeated measures ANOVA.

**Results:** AMPH group without cannabinoid pre-exposure spent significantly longer time in the AMPH-paired compartment, which was potentiated by pre-exposure to cannabinoids (THC or CBD).

**Conclusions:** At least in the animal model, THC and CBD have a same considerable effect on the development of addiction to the psychostimulant drug, AMPH. Both cannabinoids led to sensitisation and increased the addictive potential of AMPH. These findings suggest that further research is needed and will be followed with experiments at a neurotransmitter level.

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## PM221

### Spine density in the nucleus accumbens is differentially changed after rat gambling task with different housing condition



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**Background and aims:** Poor decision-making is closely related to symptoms of various psychiatric disorders. Rat gambling task (rGT) adopts the basic principle of Iowa Gambling Task. Dendritic spine is a key structure for structural plasticity in the brain, and its morphology dynamically changes through the learning process. Here we examined how housing condition and choice preference appeared in rGT contributes to morphological change of dendritic spines in the nucleus accumbens (NAc).

**Methods:** Rats were housed as isolated or paired, and trained in a touch screen chamber to learn the relationships between 4 different light signals on the screen and accompanied reward outcomes or punishments set up with different schedules. Once they show a stabilized pattern of preference upon free choice, rats were separated as risk-averse or risk-seeking group according to their preference of choice. Then, NAc tissues were immunostained with antibodies against GFP proteins and confocal imaging was conducted. With Neuronstudio Software, spine density was counted and its morphological differences were identified.

**Results:** We observed that rGT alone with pair-housing, whether it turned out to be risk-averse or risk-seeking, did not contribute to show any difference in spine density compared to control group. However, when combined with isolation-housing, rGT showed increased number of total and thin spine density only in risk-seeking compared to control groups.

**Conclusions:** These results indicate that trait (risky choice preference) and environment (isolated housing) inter-influence to contribute to morphological changes of dendritic spines in the NAc, and may suggest that these changes might underlie maladaptive decision making.

**Keywords:** pathological gambling, decision making, nucleus accumbens, spine

## PM222

### Enhancing adult hippocampal neurogenesis with lysophosphatidic acid: A proposal for erasing cocaine contextual memory

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**Aims.** Stimulating adult hippocampal neurogenesis (AHN) has been uncovered as a promising approach in the manipulation of retrograde memories. This work aims to study whether increasing AHN with lysophosphatidic acid (LPA, an endogenous lysophospholipid with proneurogenic actions) promotes the forgetting of previously established cocaine-contextual associations.

**Methods.** C57BL/6J mice previously trained in a cocaine-induced Conditioned Place Preference (CPP) paradigm were submitted to 23 days of withdrawal, during which they received repeated intracerebroventricular infusions of LPA, ki16425 (a selective LPA<sub>1/3</sub> receptors antagonist) or vehicle solution. Then, the CPP maintenance was assessed, and the causal role of AHN in this process was evaluated using a mediation analysis. In a complementary experiment, wild-type and LPA<sub>1</sub>-null mice were acutely infused with LPA or ki16425 to determine the involvement of the LPA<sub>1</sub> receptor in the *in vivo* proneurogenic actions of LPA.

**Results.** The chronic LPA treatment significantly weakened the long-term retention of a previously acquired cocaine-CPP memory, an effect clearly mediated by a LPA-induced increase in the number of adult-born dentate granule cells. In contrast, the ki16425-treated mice displayed aberrant responses of initially decreased CPP retention that progressively increased CPP across the extinction sessions, in absence of effects on AHN. The histological studies suggested that the proneurogenic actions of LPA were related to the enhancement of cell proliferation and critically depended on the LPA<sub>1</sub> receptor function.

**Conclusions.** Our results suggest that the LPA/LPA<sub>1</sub>-pathway acts as a potent *in vivo* modulator of AHN, and highlight the usefulness of a post-learning increase of adult-born hippocampal neurons as a strategy to promote the forgetting of cocaine-context associations. Enhancing AHN may lead to the renewal of the hippocampal circuitry, which might clear memories of previous cocaine experiences and, at the same time, facilitate the learning of new information, thus ameliorating the defective cognition frequently displayed by cocaine addicts.

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## PM223

### Galanin N-terminal fragment (1-15) decreases the voluntary alcohol intake in rats.

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Galanin (GAL) is involved in drug abuse and addiction including alcohol intake. In this work, we have analysed the role of the N-terminal GAL fragment (1-15) [GAL(1-15)] in voluntary ethanol consumption in rats using the two-bottle choice paradigm as well as compare the effects of GAL(1-15) with GAL.

The two-bottle choice test was used to determine the voluntary ethanol consumption of rats (Castilla-Ortega *et al.*, 2016). Three sets of experiments were conducted. In the first set of experiments, a dose-response curve of GAL(1-15) was performed. Groups of rats (n=7-9) received i.c.v. GAL(1-15) 1 nmol, 3 nmol or vehicle 2, 14 and 24 hours before the measures. In the second set of experiments, the effects in two-bottle choice test of GAL 3 nmol, and GAL(1-15) 3 nmol were compared. In the last set of experiments rats received i.c.v. GAL(1-15) 3nmol combined with GALR2 antagonist M871 3 nmol 2 hours before the measures.

GAL(1-15) 3nmol significantly decreased the alcohol intake 2 (p<0.05), 14 (p<0.05) and 24 (p<0.05) hours after its administration. Moreover, 2 hours after i.c.v. GAL(1-15) 3nmol a significantly decreased by 90% in preference was observed (p<0.05). This effect was maintained 24hours. GAL(1-15) also significantly reduced the alcohol intake (p<0.05) and preference (p<0.05) compared with GAL. GALR2 antagonist M871 significantly blocked the decreased in the ethanol intake (p<0.05) and preference (p<0.05) induced by GAL(1-15) 2 hours after its administration.

These results indicates that GAL(1-15) induces a strong reduction in preference and alcohol consumption in rat, showing a differential role than GAL. These results may give basis for the development of novel therapeutic strategies using GAL(1-15) for treatment of alcohol addiction.

This study was supported by Spanish SAF2016-79008-P and PPIT.UMA.B1.2017/17.

## PM224

### The acute effects of Deschlorketamine in animal model

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Deschlorketamine (2-methylamino-2-phenylcyclohexanone, also known as DXE, DCK, O-PCM) is a novel synthetic dissociative substance that has been sold online as a designer drug. DCK has exactly the same structure as ketamine although without the chlorine substituent on the phenyl ring. DCK has very brief history of human usage and literature about its behavioral effects remain scarce. Hence in this study deschlorketamine (5, 10, and 30 mg/kg subcutaneously, s.c.) was used in male Wistar rats across two behavioral/physiological procedures and in two temporal windows from administration (15 and 60 min) in order to test: locomotor effects in the open field and sensorimotor gating in the test of prepulse inhibition (PPI). DCK increased overall locomotion. It also decrease the amount of time spent in the center of open field arena in dose 5 mg/kg in both temporal windows and dose 10 mg/kg only in 60 min from administration. DCK also disturb PPI in all doses. To conclude, deschlorketamine has stimulant properties, increase exploration and/or decreased anxiety in the open field arena in low doses and also has psychomimetic effect.

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## PM225

### Attenuation of the formation of CPP by methamphetamine in Shati/Nat8l overexpressed mice in the prefrontal cortex.

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## **[Background and objective]**

Shati/Nat8l is a novel *N*-acetyltransferase identified in the brain of mice treated with methamphetamine. Shati/Nat8l generates *N*-acetyltransferase from aspartate and acetyl-CoA. Shati/Nat8l mRNA is expressed in various brain areas including prefrontal cortex (PFC) which shows high levels compared to other brain regions. Recent studies showed that Shati/Nat8l overexpression in the nucleus accumbens (NAc) attenuates methamphetamine (METH) response. Meanwhile, it is reported that after METH self-administration and during reinstatement, dopamine (DA) and glutamate dysregulation were observed in PFC and nucleus accumbens of rats. However, the mechanism underlying mPFC control over reward system and the function of Shati/Nat8l in mPFC have not been clarified. In this research we try to clarify the function of the medial prefrontal Shati/Nat8l in METH addiction.

## **[Methods]**

We induced Shati/Nat8l mPFC overexpressed mice using AAV vector and GFP mice (control) and confirmed the overexpression by qRT-PCR after 3 weeks. Next, we performed conditioned place preference (CPP) and locomotor activity (LA) after saline or METH subcutaneous injection. Finally, we performed immunohistochemistry using GFP antibody to confirm the connection of mPFC to the limbic system.

## **[Results]**

qRT-PCR experiment showed a significant increase of Shati/Nat8l mRNA in the mPFC of mice injected with AAV vector containing Shati/Nat8l, and interestingly in CPP experiment Shati/Nat8l overexpressed mice showed a reduced response to methamphetamine stimulation compared to control mice, however, no difference was observed in locomotor activity. Additionally, immunohistochemistry of mice injected with GFP in mPFC showed green fluorescence in different brain regions mainly in NAc, which explain a clear projection of mPFC neurons into the NAc.

## **[Conclusion]**

From these experiments, we can conclude that Shati/Nat8l overexpression in the mPFC reduces the addictive effect of methamphetamine as observed in CPP experiment but not the LA which might be due to specific projections from the mPFC to the NAc.

## **PM226**

### **Gene expression profile of dopamine-deficient mouse brain for underlying molecular pathology in psychiatric disorders**

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Dopamine dysfunction has been implicated in many psychiatric disorders such as Parkinson's disease, addiction, ADHD, and schizophrenia. Dopamine neurons project to some distinct areas via mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways. Dopaminergic neurons are also regulated from other neurotransmitters' systems including other monoaminergic, cholinergic, glutaminergic, and GABAergic neurons. Therefore, dopamine imbalance is hypothesized to alter these neurotransmissions but also gene expressions related to dopamine and other neurotransmitters. In this study, we analyzed transcriptome profiling in dopamine-deficient mice for underlying molecular pathology of psychiatric disorders.

Dopamine-deficient mice were generated by tyrosine hydroxylase (Th) gene knockout with Th transgene under a dopamine  $\beta$ -hydroxylase gene promoter. Gene expression profiles in the brains of dopamine-deficient mice were analyzed with Illumina MouseRef-8 Expression BeadChips. The gene expression of the aromatic L-amino acid decarboxylase, an enzyme of dopamine and serotonin synthesis was increased, but gene expression of monoamine-metabolizing enzymes, catechol-O-methyltransferase and monoamine oxidase A/B were not altered in dopamine-deficient mice. In contrast, choline acetyltransferase gene expression was decreased and acetylcholinesterase gene expression was unaltered in the basal ganglia of dopamine-deficient mice. The gene expressions of histidine decarboxylase and diamine oxidase of the histamine biosynthesis pathway were increased and decreased, respectively, in the brainstem of dopamine-deficient mice. These data suggest that serotonergic and histaminergic neurotransmissions may be activated while on the contrary cholinergic neurons may be inactivated in dopamine-deficient mice.

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## PM227

### Attenuation pharmacological effects of methamphetamine by Piccolo knockdown in the nucleus accumbens in mice

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We found "PCLO" as a molecule which increases the expression in the nucleus accumbens (NAc) of mice continuously administered Methamphetamine (METH). Piccolo, a protein encoded by PCLO, was reported that it is involved in dopaminergic neurons and single nucleotide polymorphism of addiction related-diseases, and that PCLO itself is involved in many psychiatric diseases. METH is one of the stimulants distributed worldwide. It is known that the number of repetitive users much more increase and their dependence in many case, however the medication of METH addiction is not established. Therefore, searching for new effective molecules related to METH addiction is important. In this study, we investigated the physiological function of Piccolo against the pharmacological action of METH by suppressing the expression of Piccolo in the NAc that is important a brain region for drug dependence.

We generated the Piccolo-specific knockdown mice (miPiccolo mice) and Mock mice by injecting adeno-associated virus (AAV) vector including Piccolo miRNA and AAV-mock. Using these mice, we performed several behavior tests such locomotor activity test, conditioned place preference (CPP) test. Furthermore we measured dopamine and GABA changes using in vivo microdialysis methods.

METH-induced locomotor activity of miPiccolo mice were reduced compared with Mock mice. METH-induced CPP formation was also decreased in miPiccolo mice. In microdialysis experiments, the basal level of dopamine in the NAc was significantly decreased in miPiccolo mice. Furthermore the amount of extracellular GABA from NAc tended to decrease in miPiccolo mice.

These results suggested that Piccolo in the NAc regulates neurotransmitters system and METH dependence related behaviors. Our findings might develop a novel clinical methods for METH dependence.

## PM228

### Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit expression and receptor binding in patients with addictive disorders: A systematic review of human postmortem studies

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**Objectives:** Altered trafficking of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors has been reported in animal models of addiction. The aim of this study was to synthesize data of human postmortem studies that investigated the AMPA receptor expression in patients with addiction.

**Methods:** We conducted a systematic literature search for postmortem studies examining the expression of AMPA receptor subunits or receptor binding in patients with addiction compared to healthy controls in October 2017, using PubMed and Embase with the following search terms: (( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) or AMPA or AMPAR) AND (alcohol\* or narco\* or addiction). Cross-reference and hand searches were also performed.

**Results:** An initial search yielded 910 studies; of these, 11 articles were relevant (1-11). All these studies examined AMPA receptor subunit transcript or protein expression, or AMPA receptor binding levels, and compared them between addictive patients and controls. Seven and four studies included alcohol use disorders (AUD) (1-7) and heroin/cocaine abusers (8-11), respectively. The most frequently investigated region was hippocampus (3 studies), amygdala (3 studies), and putamen (3 studies). In summary, 2 out of the 3 studies showed an increase in the expression of AMPA receptors in the hippocampus (2, 5) while the other study found no change (6). Two studies that examined amygdala demonstrated a decreased expression or receptor binding in this region (4, 7), and no change was found in the other (10). Concerning putamen, two studies showed no significant change (1, 9) whereas overexpression of receptor was observed in the other (8).

**Conclusions:** Findings of AMPA receptor subunit expression and receptor binding in patients with addiction were inconsistent among studies, except hippocampus and amygdala. Moreover, attention to date has been

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confined to AUD and heroin/cocaine abuse. Postmortem studies are prone to physiological degenerative changes after death. These limitations clearly emphasize the need of examination in the living human brains.

(Word count: 300)

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overdose victims. *Journal of neurochemistry*. 2003;85:911-924.

## PM229

### Involvement of enhanced 5-HT<sub>2A</sub> receptor function on doxorubicin and cyclophosphamide-induced anxiety-like behavior in rats

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We examined the influence of combination treatment with doxorubicin and cyclophosphamide, a traditional chemotherapy for breast cancer, on anxiety-like behavior in rats. Furthermore, we evaluated the serotonin (5-HT) receptor subtypes functions on the chemotherapy-induced anxiety-like behavior. Doxorubicin and cyclophosphamide were injected intraperitoneally once per week for 2 weeks. This treatment produced anxiety-like behavior using the light-dark test of rats. In addition, we measured 5-HT<sub>2A</sub> receptor in the frontal cortex and 5-HT<sub>1A</sub> receptor in the hippocampus, and 5-HT<sub>1A</sub> receptor and 5-HT<sub>2A</sub> receptor-mediated behavioral response in rats. Results Doxorubicin and cyclophosphamide produced anxiety-like behavior in light-dark test of rats. The combination treatment with doxorubicin and cyclophosphamide significantly increased ( $\pm$ )-DOI, 5-HT<sub>2A</sub> receptor agonist-induced wet-dog shakes, and 5-HT<sub>2A</sub> receptor protein in the frontal cortex. The anxiety-like behavior significantly inhibited by mirtazapine, 5-HT<sub>2A</sub> receptor antagonist/5-HT<sub>1A</sub> receptor agonist properties, and tandospirone, partial 5-HT<sub>1A</sub> receptor agonist, but not fluoxetine, selective serotonin reuptake inhibitor. Chemotherapy for the combination treatment with doxorubicin and cyclophosphamide-induced anxiety-like behavior is mediated by the hyperfunction of 5-HT<sub>2A</sub> receptor subtypes. It is possible that the effect of 5-HT<sub>2A</sub> receptor antagonistic or 5-HT<sub>1A</sub> receptor agonistic activity can be useful in chemotherapy-induced anxiety disorder.

## PM230

### Orexin A antagonist SB-408124 reduces anxiety signs via extrahypothalamic CRF in a rat PTSD model

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Corticoliberin (CRF) isn't only regulates hypothalamic-pituitary-adrenal axis activity, but also functions as a

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neurotransmitter in extrahypothalamic brain regions like amygdala, implicated in the emotional responses to stress. The CRF system provides an input to orexin neurons and can modulate the activity of orexinergic neurons in stress response. Some data showed the role of orexin-A in extinction of aversive memory. The orexin system was shown to participate in stress-induced behavior connected with the extended amygdala structures, like central nucleus of the amygdala. The objective was to study the effects of orexin-A antagonist SB-408124 in rats after predator-induced stress using behavioral tests and its effects on CRF level in amygdala.

Groups consist of 10 male Wistar rats (180-200g). The control animals were intact and 2 groups were exposed to a predator-induced stress. One experimental group received selective orexin-A antagonist SB-408124 20µg/20 µl intranasally for 7 days. Other groups received a saline. All animals were tested in the elevated plus maze (EPM) and resident-intruder test. After behavioral tests, the amygdala samples were taken for immunoassay. Data were analyzed with nonparametric ANOVA and Dunn's test, using the SPSS.

In the EPM, control rats spent 92.2±28.1 sec in the light arms. The predator-induced stress reduced it to 19.0±6.8 sec ( $p < 0.01$ ). Administration of SB-408124 restored it to 53.2±19.7 sec. In the resident-intruder test, the control rats demonstrated 14.0±2.6 communicative and 7.5±5.3 freezing acts. These indexes became the same after stress (13.6±3.3 communicative, 6.6±2.9 freezing acts). Administration of SB-408124 significantly decreased freezing to 1.3±0.6 acts in stressed rats.

The CRF level was lower in stressed rats (439.2±73 pg/mg protein vs 611.5±10 pg/mg protein in control). Administration of SB408124 restored it to 576±9 pg/mg protein.

SB-408124 reduced anxiety and restored CRF level in amygdala after predator-induced stress. These data showed the existence of feedback between extrahypothalamic CRF and orexin system.

## PM231

### **5-HT2A receptor antagonism unmasks a marked immobility-reducing effect of acute SSRI administration in a contextual fear paradigm**

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Acute administration of a selective serotonin reuptake inhibitor (SSRI) may exert both anxiolytic and anxiety-

enhancing effects in various animal models. While the mechanisms behind this apparently dual effect of serotonin reuptake inhibition on anxiety-like behavior are still not understood, one possibility might be that some serotonergic receptor subtypes can exert an anxiety-like response whereas other receptor subtypes may mediate an anxiolytic influence, the relative impact of the different receptor subtypes being dependent e.g. on the experimental paradigm. In this experiment, we studied the effect of acute administration of an SSRI, escitalopram (5 mg/kg), with or without co-administration of the 5-HT2A receptor antagonist MDL100907 (3 mg/kg), on the expression of contextual conditioned fear, manifested as complete immobility, in rat. Whereas SSRI per se did not influence immobility, and whereas MDL100907 caused only a modest immobility-reducing effect ( $p = 0.01$ ), the combination of escitalopram and MDL100907 resulted in a marked reduction in immobility ( $p < 0.000001$  vs saline;  $p = 0.01$  vs MDL100907 alone). The results suggest that enhanced extracellular levels of serotonin obtained by acute SSRI administration may activate fear-reducing postsynaptic receptors, but that this effect is counteracted by the simultaneous activation of 5-HT2A receptors exerting the opposite effect. Also, it suggests that adding a 5-HT2A antagonist to an SSRIs may result in an earlier therapeutic onset in the treatment of anxiety disorders.

## PM232

### **An anxiogenic-like response to predator odour in rats depend on baseline temperament and can be prevented by SSRI treatment**

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University of Gothenburg

**Objective:** Preclinical models of affective disorders generally aim to model aspects of animal behaviour that are reasonable to associate with e.g. (excessive) human fear. However, some stressors may have limited relevance in the ecological context of the species investigated, and it may be that certain stressors, such as cues that indicate predator presence, elicit behavioural responses that better model human disorders. We here investigate the interaction of anxiety-like behaviour as assayed in the elevated plus-maze (EPM), response to predator odour, and central serotonergic activity. **Methods:** Experiment I: 60 rats were subdivided according to baseline anxiety-like behaviour, exposed to cat odour and, two weeks later, again tested in the EPM. Animals were then sacrificed and brains harvested for gene expression analyses. Experiment II: 120 rats were subdivided as above, and randomised to either chow containing the selective serotonin reuptake inhibitor (SSRI) escitalopram, or control chow. Animals

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were exposed to cat odour after four weeks of treatment, and subjected to a second EPM session after a further two weeks. **Summary:** Experiment I: Predator odour had a strong anxiogenic-like effect in the 1/3 of animals displaying the highest baseline 'anxiety'. No effect was seen in less 'anxious' animals. Experiment II: As in experiment I, an anxiogenic-like effect of cat odour was specific to animals displaying high baseline 'anxiety', an effect prevented by SSRI treatment. **Conclusions:** These experiments i) strengthen the position that the EPM reflects ecologically relevant aspects of rodent behaviour ii) underline the value of taking individual behavioural differences into account iii) indicate that experimentally assayed anxiety-like behaviour may be related to differential foraging strategies in response to presence of predators and iv) suggest that serotonergic mechanisms contribute to these differences, and to behavioural predator response mechanisms in murids in general. Possible clinical implications exist for anxiety disorders and post-traumatic stress disorder.

## PM233

### **Overexpression of sigma-1 receptor rescues (G4C2)RNA repeats-mediated defect in the nucleocytoplasmic transport of Ran GTPase: implication in ALS**

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The GGGGCC ( $G_4C_2$ ) hexanucleotide repeat expansions within *chromosome 9 open reading frame 72 (C9ORF72)* have been characterized as the most common genetic abnormality in amyotrophic lateral sclerosis (ALS). Expanded  $G_4C_2$  repeats led to the mislocalization of nuclear pore complex (NPC) component protein nucleoporins in *C9ORF72* motor cortex as well as the nucleocytoplasmic transport defect of Ran GTPase in patient-derived induced pluripotent stem cells (iPSCs) neurons.  $G_4C_2$  repeat expansions can directly interact with Ran GTPase-activating protein 1 (RanGAP1), leading to the nucleocytoplasmic transport disruption by impairing the nucleus/cytosol (N/C) gradient of Ran GTPase. Therefore, understanding how  $G_4C_2$  repeat expansions work in the NPC is important for treatment of ALS/FTD patients. Our results showed that sigma-1 receptors (Sig-1Rs) bind to FG-repeat NPC nucleoporins and increase their half-life. Immunoprecipitation assay and fluorescence confocal microscopy revealed that Sig-1Rs interact with RanGAP1 in the nuclear envelopes. The biotin labeled  $G_4C_2$  RNA repeats interacted with the recombinant glutathione S-transferase (GST)-tagged Sig-1Rs proteins in the GST pull-

down assay. We also found here that by using the RNA fluorescence in situ hybridization (RNA-FISH) assay that Sig-1Rs partly colocalize with Cy3-labeled  $G_4C_2$  RNA repeats in the perinuclear region. Interestingly, the overexpression of Sig-1Rs can attenuate the defect of N/C ratio of RanGTPase caused by the  $G_4C_2$  repeats. Our results propose a novel mechanism whereby increasing the level of Sig-1Rs in the NPC by pharmacological or cellular biological means may represent a novel avenue for treating the *C9ORF72*  $G_4C_2$ -repeats subtype of ALS (This work was supported by IRP/NIDA/NIH/DHHS)

## PM234

### **Distinguishing Quantitative Electroencephalogram Findings between Panic Disorder and Generalized Anxiety Disorder**

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**Objectives:** Generalized anxiety disorder (GAD) and panic disorder (PD) are common diagnoses in anxiety disorders. However, it is difficult to distinguish GAD from PD. Neurobehavioral markers that differentiate GAD and PD would be helpful in ongoing efforts to refine classification schemes based on neurobiological measures. The aim of this study was to determine the distinguishing neurophysiological characteristics between GAD and PD using quantitative analysis of an electroencephalogram (QEEG).

**Methods:** The study included 36 patients with GAD and 25 patients with PD. Resting (eye closed) vigilance controlled EEG recordings were assessed at 64 electrode sites according to the international 10/20 system. QEEG were compared between GAD and PD groups by frequency bands (delta 1-3 Hz, theta 4-7 Hz, alpha 8-12 Hz, beta 12-25 Hz, high beta 25-30 Hz, gamma 30-40 Hz and total 1-40 Hz) made by spectral analysis.

**Results:** The absolute powers of theta and alpha bands at the frontal area differed between GAD and PD group. The absolute power of the theta activity was decreased in FP1 and FP2 ( $p < 0.05$ ) and the absolute power of the alpha activity was decreased in F3 ( $p < 0.05$ ) in cases with GAD compared to PD.

**Conclusions:** The differences in QEEG power in our investigation suggest that underlying pathophysiologic mechanisms may be different between GAD and PD. The findings that the decreased absolute powers of the theta and alpha activity at the frontal area in GAD may be the main neurophysiological characteristics of the GAD.

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## PM235

### Amelioration of Scopolamine-induced Attention Deficit by the Extracts from the Brown Alga *Ecklonia Stolonifera* Okamura

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**Objective:** Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder. Since a current pharmacotherapeutic strategy of ADHD relies on psychostimulants, developing an alternative, safer pharmacological strategy would be desired. Phlorotannins of the brown alga *Ecklonia Stolonifera* Okamura are the acetylcholinesterase inhibitor (Yoon et al., 2008, Fish Sci). In this study, we investigated whether *Ecklonia Stolonifera* Okamura (ESO) improved attention deficit induced by scopolamine (SCO) in mice.

**Methods:** Attention deficit in mice was assessed using the object exploration test that we have previously designed (Lee and Goto, 2011, Plos One). In this test, durations of object exploration in the open field chamber were measured as index of attention spans. Attention deficits were induced in mice with SCO (1 mg/kg, i.p.) administration. The effects of the ESO were examined with pre-treatments of the extracts (100 mg/kg/day, p.o.) 30 minutes before SCO administration.

**Results:** Mice receiving SCO exhibited shorter attention spans (0.53 +/- 0.11 sec per visit to the objects; n=4) than saline-treated control mice (1.19 +/- 0.25 sec; n=7), indicating impairments on sustained attention. Pre-treatments of the ESO extracts significantly prolonged attention spans (0.74 +/- 0.10 sec; n=5) compared to that of mice with SCO administration alone, although its attention span in mice with ESO+SCO was still shorter than that of control mice.

**Conclusions:** These results suggest that ESO may be a useful substance for improvement of attention deficits observed in psychiatric and neurological disorders such as ADHD and Alzheimer's disease.

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## PM236

### Effects of lithium on immune activation in an animal model of mania

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**Keywords:** Bipolar disorder, lithium, immune activation.

**INTRODUCTION:** Bipolar disorder has been associated with high rates of medical comorbidities. Multiple biological pathways appear to be involved in the connection between bipolar disorder and these comorbidities, and inflammation is gathering further importance. Evidence suggest that lithium, the gold standard treatment for this illness, has anti-inflammatory properties. However, no study investigated the effects of lithium on inflammatory markers after an immune challenge in an animal model of mania. **OBJECTIVE:** To evaluate whether an animal model of mania induced by lisdexanfetamine dimesylate exhibits an inflammatory profile and whether there is a cumulative effect on immune activation of subsequent stimuli by lipopolysaccharides in this model. Moreover, we evaluated the action of lithium on inflammatory factors. **METHODS:** Adult male Wistar rats were submitted to the animal model of mania. After the open-field test, they were given lipopolysaccharides to cause systemic immune activation. Subsequently, the animals had their blood collected, and their serum levels of inflammatory markers (TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IL-10, and iNOS) were measured. **RESULTS:** Lisdexanfetamine dimesylate induced hyperactivity in the animals, but did not increase any inflammatory marker. As expected, lipopolysaccharides increased the levels of inflammatory mediators. Lithium prevented the increase in iNOS levels in animals submitted to immune activation, but had no effect on cytokine levels after the lipopolysaccharides challenge. **CONCLUSIONS:** Based on these results, the potential anti-inflammatory effects of lithium on this animal model of mania were inconclusive. Nonetheless, lithium prevented an increase in serum iNOS levels caused by lipopolysaccharides.



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## PM238

### Sustained administration of cariprazine increases norepinephrine but not serotonin and dopamine neuronal activity in rats

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**Introduction:** Cariprazine (US: Vraylar<sup>®</sup>, Europe: Reagila<sup>®</sup>) is approved to treat adults with schizophrenia (US and Europe) and manic or mixed episodes associated with bipolar I disorder (US). It is an orally active and potent dopamine (DA) D<sub>3</sub>-preferring D<sub>3</sub>/D<sub>2</sub> receptor partial agonist that also displays *in vitro* partial agonism at serotonin (5-HT) 5-HT<sub>1A</sub> receptors and antagonism at 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors (Kiss et al., 2010). Due to the involvement of monoamine systems in the pathophysiology and therapeutics of major depressive episodes, this study investigated the *in vivo* electrophysiological effects of 2- and 14-day administration of cariprazine on the activity of locus coeruleus (LC) norepinephrine (NE), ventral tegmental area (VTA) DA and dorsal raphe nucleus (DRN) 5-HT neurons.

**Methods:** Male Sprague-Dawley rats received subcutaneous injections of cariprazine (0.6 mg/kg/day) for 2 and 14 days. *In vivo* single-unit electrophysiological recordings were conducted in the LC, VTA and DRN under chloral hydrate anesthesia.

**Results:** Administration of cariprazine for 2 and 14 days increased NE neuronal firing activity (by 27% and 61%, respectively;  $P < .05$ ) compared to the control group. Moreover, 14- but not 2-day administration of cariprazine increased the percentage of bursting NE neurons by 114% ( $P < .001$ ) compared to the control group. Cariprazine did not affect the firing and bursting activities of DA and 5-HT neurons.

**Discussion:** This study provided evidence that NE neuronal activity can be specifically augmented by repeated cariprazine administration. This enhancement is not related to blockade of  $\alpha_2$ -adrenergic autoreceptors on NE neurons since cariprazine has low *in vitro* binding affinity for and does not alter the responsiveness of these receptors (Blier et al., 2017). A potential increase in NE neurotransmission may contribute, at least in part, to the antidepressant response obtained with cariprazine in both clinical and preclinical studies, as well as its procognitive effects observed in animal models.

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Keywords: Cariprazine, norepinephrine, electrophysiology

## PM239

### Rapamycin ameliorates impairment of social interaction in the mice exposed in utero to valproic acid

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by social deficits. Various genetic and/or environmental factors have been investigated in studies for ASD. However, the efficient treatment for impairment of social interaction in ASD has not been established. Valproic acid (VPA) is an anti-epileptic drug. Pregnant mothers treated with VPA often deliver their children with ASD. Rodent pups exposed *in utero* to VPA have been used as an animal model of ASD. Recent studies reported that aberrant mTOR signaling pathway may cause ASD-like behaviors in VPA-exposed animals. The mTOR signaling pathway regulates neuronal cell proliferation and synaptogenesis. Overactivation of the mTOR signaling has been implicated in the pathogenesis of particular forms of syndromic ASDs, such as tuberous sclerosis complex (TSC). Rapamycin, an mTOR complex inhibitor, improves social deficits in *Tsc* heterozygous mice. These studies suggest that activated mTOR signaling pathway is involved in ASD and rapamycin is a potential therapeutic drug. Therefore, we aimed to clarify the effect of rapamycin treatment in social deficits in VPA-exposed

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animals. We injected VPA into pregnant mice and used the pups as ASD model. The pups were injected with rapamycin or vehicle and a social interaction test was conducted after rapamycin treatment in 5-6 weeks (adolescence) or 10-11 weeks (adult) mice. The mouse whole brains were scarified after the social interaction test on adult and microarray and western blots analyses were performed. We found that rapamycin treatment improved social deficits in the VPA-exposed mice both in adolescence and adult, and aberrant gene expression was detected in the VPA-exposed mice. We also found that rapamycin treatment recovered changes in expression of gene associated with ASD-like behavior and ratio of phosphorylation of S6. These results suggest that rapamycin is effective for treatment of non-syndromic ASD that is caused by aberrant mTOR signaling pathway.

## PM240

### Effects of modafinil on feedback-dependent reinforcement learning

Authors: Zhenyu Wei, Jialin Li, Xi Yang, Keith M. Kendrick, Benjamin Becker

Presenter: Zhenyu Wei

Modafinil has been shown to enhance cognitive performance in healthy individuals and patients with neurocognitive disorders. Previous research predominantly focused on prefrontal executive functions, effects in the domain of adaptive reinforcement learning yet remain to be determined. The present study employed a randomized placebo-controlled double-blind design to examine effects of a single dose of modafinil (200mg, p.o.) on feedback-dependent reward learning (NCT03426202, clinicaltrials.gov). Healthy male participants were randomly allocated to receive either modafinil ( $n = 29$ ) or placebo ( $n = 30$ ) and subsequently completed a classic feedback-based reinforcement learning paradigm. The paradigm included four blocks presenting two new symbols per block. One symbol was associated with a high reward probability (80%) and one associated with a low reward probability (20%). Subjects had to learn the contingencies through trial and error from feedback. Relative to the placebo group, participants in the modafinil group demonstrated a significant lower accuracy ( $t_{(57)} = 2.205$ ,  $p < 0.05$ ) and a trend for increased response times ( $t_{(57)} = -1.977$ ,  $p = 0.056$ ). Subsequent computational modelling of task behavior revealed similar learning rates ( $\alpha$ ) in the groups ( $t_{(57)} = 0.631$ ,  $p > 0.05$ ), yet a marginal higher temperature parameter ( $\beta$ ) in the modafinil group ( $t_{(57)} = -1.92$ ,  $p = 0.064$ ), suggesting less consistent choice behavior following modafinil. Importantly, in post assessment interviews participants were not able to

identify better than chance whether they had received modafinil or placebo ( $p > 0.05$ ). Together, the present findings suggest that modafinil has the potential to decrease adaptive reinforcement learning capability in healthy male subjects.

## PM241

### Oxidative damage and mitochondrial dysfunction in autism model rats

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Autism spectrum disorders (ASD) are a neurodevelopmental disease represented by social communication deficits and learning disability. Oxidative stress and mitochondrial dysfunction in the brain are implicated in ASD brain pathology. It is well known that prenatal exposure to anticonvulsant valproic acid (VPA) increases the risk of postnatal ASD (1). We here addressed questions whether oxidative stress and mitochondrial dysfunction are involved in autism-like behaviors in prenatally VPA-exposed rats (VPA rats). **[Methods]** Pregnant rats were treated with oral administration of VPA (600 mg/kg) at E12.5, and male pups after birth were used for postnatal analyses. **(i)** Behavioral tasks were carried out at 5-6 weeks of age to assess social and learning abilities. **(ii)** At 8 weeks of age, oxidative stress and mitochondrial function were assessed in the hippocampus of VPA rats. **(iii)** Some VPA rats were subjected to chronic administration (3 to 8 weeks of age) with orally 5-aminolevulinic acid (ALA; 30 mg/kg), a precursor of protoporphyrin IX, or intranasally oxytocin (OXT; 12  $\mu$ g/kg), a neuronal hormone in ASD patients. **[Results]** **(i)** Prenatal VPA exposed rats (VPA rats) impaired social and learning abilities, assessed by social interaction, Y maze, and novel object recognition tasks. **(ii)** Immunohistochemical analyses revealed elevated lipid peroxidation in the hippocampus of VPA rats, suggesting oxidatively damaged. Moreover, enzymatic activities of both complex I and II of mitochondrial electron transport chain were decreased, whereas the complex IV activity was conversely elevated in the hippocampus of VPA rats. ATP levels in the hippocampus was also decreased in VPA rats. **(iii)** Autism-like behaviors observed in VPA rats were improved by both oral ALA and intranasal OXT administration. **[Conclusions]** Taken together, oral ALA administration rescues oxidative stress and mitochondrial energetic disturbance in the brain, thereby ameliorating autism-like behaviors in VPA rats, like OXT. (1) *CNS Neurosci & Therap* 2016;22:845-853.

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## PM242

### Evaluation of Naringenin & its Surface Modified Nanocarriers as Neurotherapeutic for Autism Spectrum Disorders (ASD)

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**Objective:** Autism Spectrum Disorders (ASD) involve stimulation of neuroinflammatory cascades triggered by oxidative stress and mitochondrial dysfunction. Phytochemicals can serve as adjunct therapeutic interventions in attenuation of neuroinflammatory cascade. A major limitation of these phytochemicals is very low bioavailability and limited brain permeability. The objective of the present study was to evaluate neurotherapeutic potential of naringenin, its uncoated as well as glutathione and tween 80 coated nanocarriers against inflammatory cascades in an experimental paradigm of ASD in rats.

**Method:** ASD like phenotype was induced by infusion of 1M Propanoic acid (PPA) (4 $\mu$ l) into the anterior portion of the lateral ventricle in Sprague Dawley rats. Naringenin (25, 50 and 100 mg/kg), naringenin loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles (25 mg/kg), glutathione (GSH) and tween 80 coated naringenin nanoparticles (25 mg/kg), blank nanoparticles as well as minocycline (50 mg/kg) were administered orally for 28 days. Various neurobehavioural tests such as social interaction, stereotypy, locomotor activity, anxiety, novelty, depression, spatial learning, memory, repetitive and pervasive behaviour were performed. In addition, biochemical tests for oxidative stress, mitochondrial complexes, blood brain barrier (BBB) permeability, TNF- $\alpha$ , MMP-9, HSP-70 and P-glycoprotein (Pgp) were also assessed. Pearson correlation was applied between various neurobehavioural tests and neuroinflammatory markers

**Results:** Naringenin (25, 50 & 100 mg/kg), naringenin loaded PLGA nanoparticles (25 mg/kg), glutathione and tween 80 coated naringenin loaded PLGA nanoparticles (25 mg/kg) significantly and dose dependently restored behavioural as well as biochemical deficits in PPA induced ASD-like phenotype in rats. Glutathione (GSH) and tween 80 coated naringenin loaded nanoparticles not only enhanced the bioavailability of naringenin but also its brain targeting potential by inhibition of Pgp at a lower dose of 25 mg/kg. Naringenin (100 mg/kg) and its uncoated as well as coated nanocarriers (25 mg/kg) demonstrated comparable pharmacological efficacy with minocycline (50 mg/kg).

**Conclusion:** The major outcome of this study is that glutathione and tween 80 coated naringenin loaded

PLGA nanoparticles serve as multifactorial neurotherapeutics for management of ASD like phenotypes by virtue of enhanced brain delivery. Therefore, it has a strong clinical potential to be utilized as an adjunct neurotherapeutic approach in attenuating the neuropsychopathology associated with ASD.

**Keywords:** Autism spectrum disorders (ASD), naringenin, neurobehavioural, naringenin loaded PLGA nanoparticles, glutathione (GSH), tween 80

## PM243

### Behavioral impairment via delay myelination development in the prefrontal cortex of SHATI/NAT8L knockout mice

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We found SHATI/NAT8L in the mice brain of mice treated with methamphetamine. SHATI is *N*-acetyltransferase 8-like protein (NAT8L) that produces *N*-acetylaspartate (NAA) from aspartate and acetyl-CoA in the neuron. We produced SHATI/NAT8L knockout (*Shati*<sup>-/-</sup>) mouse that demonstrated behavioral deficits. The reason is still not clarified. It is possible that the developmental impairment results from deletion of SHATI/NAT8L in the mouse brain, because NAA is involved in myelination through lipid synthesis in the oligodendrocytes. However, it remains unclear whether SHATI/NAT8L is involved in brain development.

We investigated mRNA level of *Shati/Nat8l* in developmental stage by using real-time RT-PCR. We also evaluated the difference in MBP level of *Shati*<sup>-/-</sup> and *Shati*<sup>+/+</sup> mice by immunohistochemistry and Western blotting. Next, we conducted administration of glyceryltriacetate (GTA), which metabolized to acetate and distributed to the brain rapidly after oral administration, to *Shati*<sup>-/-</sup> and *Shati*<sup>+/+</sup> mice from juvenile, followed by performing locomotor activity, three chamber social interaction test and elevated-plus maze test. Furthermore, we observed G-ratio to confirm whether GTA treatment influences on myelination in the brain of *Shati*<sup>-/-</sup> and *Shati*<sup>+/+</sup> mice by using electron microscopy.

We found that the expression of *Shati/Nat8l* mRNA was increased with brain development in mice, and that there was a reduction in the MBP level in the prefrontal cortex of juvenile, but not adult, *Shati*<sup>-/-</sup> mice. Next, We found that deletion of SHATI/NAT8L induces several behavioral deficits in mice, and that GTA treatment ameliorates the behavioral impairments and normalizes the reduced protein level of MBP in juvenile *Shati*<sup>-/-</sup> mice.

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These findings suggest that SHATI/NAT8L is involved in myelination in the juvenile mouse brain via supplementation of acetate derived from NAA. Thus, reduction of SHATI/NAT8L induces developmental disorders.

## PM244

### A study of the Mixture of Rhubarb and Salvia Miltiorrhiza, Tanshinone II A on the prevention and treatment of AD

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**Objective:** Rhubarb and salvia miltiorrhiza (DD) are both traditional Chinese medicine, Tanshinone II A is the extracted substances that is a monomer, observe their effects on Alzheimer's disease.

**Methods:** In this study, using two different methods are used to observe AD model rats.

1. The AD model was established in rats by intraperitoneal injection of D-galactose and aluminum consecutively, and then analysis of the effect of IETM on AD rats were divided into 3 groups randomly. The level of LPS and tau protein were quantified by ELISA. The level of A $\beta$ 1-40 was observed by immunohistochemistry. The expression of APP, PS1, BACE gene were measured by RT-PCR.

2. The AD model was established by A $\beta$ 1-42 stereotactic injection into lateral cerebral ventricle, and the drug intervention was carried out by intraperitoneal injection of tanshinone II A sodium sulfonate. To observe the effects of tanshinone II A on microglia and the expression of the related inflammatory factor IL-1 $\beta$ , TNF- $\alpha$  and plasma endotoxin by immunohistochemistry and ELISA.

**Results:** 1. The results of DD showed that the levels of LPS and tau protein and the expression of APP, PS1, BACE gene were increased in AD model group.

2. The results showed that the plasma endotoxin level in the AD model group was significantly. The levels of IL-1 $\beta$  and TNF- $\alpha$  in AD group were significantly higher than those in control group, and the level of IL-1 $\beta$  and TNF- $\alpha$  in TS II A group was lower than that in AD group. Immunohistochemistry to detect the microglia: The results showed that compared with the control group, cortex Iba-1 positive cells (microglia) in AD group had large volume with the neurite retracted, and the quantity was increased significantly.

**Conclusions:** These results implicate that the rat model of Alzheimer's disease is accompanied IETM and the DD, tanshinone II A may be a useful treatment against Alzheimer's disease by reducing the level of LPS. But DD seems to be more cheap and practical.

## PM245

### Effects of Tanshinone II A on a rat model of Alzheimer's disease with intestinal endotoxemia (IETM)

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**Objective:** To establish a rat model of Alzheimer's disease, to observe the effect of Tanshinone II A on learning and memory, plasma endotoxin (LPS), microglial cells and the expression of the related inflammatory factors of AD rats.

**Methods:** 36 male SD rats were randomly divided into control group, AD group and Tanshinone II A group, 12 rats in each group. The AD model was established by A $\beta$ 1-42 stereotactic injection into lateral cerebral ventricle, and the drug intervention was carried out by intraperitoneal injection of Tanshinone II A sodium sulfonate. Rat behavioral tests to detect by Morris water maze. To observe the effects of Tanshinone II A on microglia and the expression of the related IL-1 $\beta$ , TNF- $\alpha$  and plasma LPS by immunohistochemistry and ELISA.

**Results:** 1. Morris water maze: the escape latency of AD rats was longer than that in control group, compared with the AD model group, the escape latency of Tanshinone II A group was significantly decreased.

2. ELISA for the detection of LPS and IL-1 $\beta$ , TNF- $\alpha$ : The results showed that the plasma LPS level in the AD model group was significantly higher than that in the control group, compared with the AD group, the plasma LPS level in Tanshinone II A group was decreased, and the results were statistically significant. The levels of IL-1 $\beta$  and TNF- $\alpha$  in AD group were significantly higher than those in control group, and the level of IL-1 $\beta$  and TNF- $\alpha$  in Tanshinone II A group was lower than that in AD group.

3. Immunohistochemistry to detect the microglia: The results showed that compared with the control group, cortex Iba-1 positive cells (microglia) in AD group had large volume with the neurite retracted, and the quantity was increased significantly. Compared with the model group, the cerebral cortex microglia of Tanshinone II A group became smaller, and the number was significantly decreased.

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**Conclusions:** Tanshinone IIA probably reduced inflammatory response in AD rats with IETM by decreasing the level of LPS, inhibiting the hyperplasia of microglia, and reducing the expression of IL-1 $\beta$  and TNF- $\alpha$  to play a protective role in AD.

**Key words:** Alzheimer's disease; Intestinal endotoxemia; Tanshinone II A

## PM246

### Study on Donepezil on Alzheimer's disease rats' model with intestinal endotoxemia (IETM)

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**Objective:** We establish the rat models of Alzheimer's disease to observe the effect of donepezil on the ability of learning and memory, plasma endotoxin and the expression of the related inflammatory factors in AD rats, in order to explore the possible mechanism of donepezil on AD rats with intestinal endotoxemia (IETM).

**Methods:** 18 male SD rats were randomly divided into control group, AD group and donepezil group, 6 rats in each group. The AD model was established by A $\beta$ 1-42 stereotactic injection into lateral cerebral ventricle, and the drug intervention was carried out by intraperitoneal injection of donepezil. Morris water maze was carried to detect the influence of donepezil on the learning and memory of AD rats. ELISA was used to observe the effects of donepezil on the expression of LPS, IL-1 $\beta$  and TNF- $\alpha$ .

**Results:** 1. Behavioral tests by Morris water maze: the escape latency of AD rats was longer than that in control group ( $P < 0.05$ ), Compared with the AD model group, the escape latency of donepezil group was significantly decreased ( $P < 0.05$ ).

2. ELISA for the detection of LPS, IL-1 $\beta$  and TNF- $\alpha$ : The results showed that the plasma endotoxin (LPS) level in the AD model group was significantly higher than that in the control group ( $P < 0.05$ ). Compared with the AD group, the level of plasma endotoxin in donepezil group had no significant difference. The levels of IL-1 $\beta$  and TNF- $\alpha$  in AD group were significantly higher than those in control group ( $P < 0.05$ ), and the level of IL-1 $\beta$  and TNF- $\alpha$  in donepezil group was lower than that in AD group.

**Conclusions:** 1. The level of plasma LPS, IL-1 $\beta$  and TNF- $\alpha$  were significantly increased in AD group, which indicated that the rats in AD group occurred IETM.

2. The levels of IL-1 $\beta$  and TNF- $\alpha$  in donepezil group were lower than that in AD group, But there was no significant

difference in plasma LPS levels between the AD group and the donepezil group, Which indicating that donepezil can not reduce the level of LPS in the AD rats with IETM, but can reduce the inflammatory factor levels of IL-1 $\beta$  and TNF- $\alpha$  in AD rats with IETM.

**Key words:** Alzheimer's disease; Intestinal endotoxemia; Donepezil

## PM247

### Functional expression of choline transporter-like proteins in human neural stem cells and its link to self-renewal system and neural differentiation

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Neural stem cells (NSCs) are self-renewing, multipotent stem cells of the nervous system, which can differentiate into neurons, oligodendrocytes, and astrocytes. Recently, stem cell-based therapies for central nervous system diseases and disorders have attracted much attention. Therefore, more understanding of its cell function is needed. Choline is a quaternary amine that is essential to all cells. It is used as a precursor of both the neurotransmitter acetylcholine and S-adenosylmethionine (SAM), a methyl donor, and is needed for the synthesis of the major membrane phospholipids phosphatidylcholine and sphingomyelin. To date, little is known about the uptake system for choline and the functional expression of choline transporters in human neural stem cells (hNSCs). We examined the molecular and functional characteristics of choline uptake in hNSCs. We found that both choline transporter-like protein 1 (CTL1) and CTL2 mRNAs and proteins were highly expressed in hNSCs, while high-affinity choline transporter 1 mRNA was not expressed. CTL1 and CTL2 were located in the plasma membrane and mitochondria, respectively. Choline uptake was saturable and mediated by a single transport system, which is both Na<sup>+</sup>-independent and pH-dependent. In addition, choline uptake was inhibited by choline uptake inhibitor hemicholinium-3 (HC-3), in a concentration-dependent manner. HC-3 inhibited cell proliferation, decreased cell viability, and increased caspase-3/7 activity. Inhibition of choline uptake by HC-3 blocked neuronal differentiation. We conclude that extracellular choline is mainly transported via CTL1, which relies on a directed H<sup>+</sup> gradient as a driving force. Furthermore, CTL2 may be involved in choline uptake in mitochondria, which is the rate-limiting step in SAM synthesis and DNA methylation.

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The impediment of choline uptake may inhibit the self-renewal system and neural differentiation of hNSCs.

## PM248

### Sexual differences of cognitive impairment induced by deletion of Shati/Nat8l

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**Background:** Shati/Nat8l significantly increased in the nucleus accumbens (NAc) of mice after repeated methamphetamine (METH) treatment. We reported that the expression of Shati/Nat8l mRNA is increased following brain development in mice, while there is the reduction in the myelin basic protein (MBP) level in the prefrontal cortex of juvenile, but not adult, Shat/Nat8l knockout (Shati KO) mice. These findings have suggested that Shati/Nat8l has essential roles in neuronal function. In this study, we carried out various behavioral and electrophysiological study using Shati KO mice to clarify the contribution of Shati/Nat8l on the cognitive function in mice.

**Methods:** We assessed the validity of behavioral test using Shati KO mice and wild type (WT) mice. Next, we prepared hippocampal slices from Shati KO and WT mice, and recorded the evoked field excitatory postsynaptic potentials and long-term potentiation (LTP) using MED64 systems.

**Results:** In the open field test, Shati KO mice showed higher basal locomotor activity. Shati KO mice avoided social interaction with unfamiliar mice compared with WT mice. In the elevated plus maze test, Shati KO mice spent much longer time in open arms than WT mice. These behavioral changes were observed both male and female Shati KO mice. Interestingly, impairment of cognitive dysfunction in the Y-maze and novel object recognition were observed only in Shati KO female mice. Furthermore, injection of adeno associated virus vector of Shati/Nat8l into hippocampal CA3 region of Shati KO ameliorated these cognitive dysfunctions in the female mice. Also in the electrophysiology test, the LTP of Shati KO mice were significantly decreased compared with wild type mice of both male and female mice.

**Conclusions:** These results suggest that Shati/Nat8l would be associated with cognitive function with sexual differences.

## PM249

### Multiple modality monitoring of animals in toxicology studies allows more precise preclinical assessment of PD/PK/toxicity for early clinical dose selection.

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The results of nonclinical toxicology studies are used for dose selection and exposure capping in early clinical development programs. In the case of central nervous system compounds, determination of plasma drug levels during a toxicology study may not reflect levels in the brain that are associated with adverse effects. This may be especially problematic when the brain is both the pharmacologic and toxicological target organ. The current study was conducted to more thoroughly characterize the exposure and toxicologic profiles of TAK-653, a novel potentiator of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors.

Adult male and female cynomolgus monkeys were dosed with TAK-653 daily for 13 weeks in a GLP-compliant study. During the first 28 days and at mid- and end of study, animals were monitored continuously for behavior via videography and for electroencephalographic/electromyographic (EEG / EMG) activity via telemetry. Day 1, 29, and end of study blood draws were taken for assessment of plasma drug levels. Unscheduled blood draws also were performed at the time of observed convulsions. At the end of study, blood, cerebrospinal fluid (CSF), and brain TAK-653 levels were assessed.

Study results indicated the following: tremors occurred in all treatment groups, including vehicle controls, and were not accompanied by changes in the EEG activity suggestive of epileptiform activity; some, but not all, convulsions were associated with a seizure-like EEG profile. Throughout the study, plasma drug levels were highest in animals that convulsed; brain and CSF levels at the end of study also were highest in these animals. These results allowed more precise characterization of plasma exposures at the time of a (clinical) convulsion, and to determine that tremors were not, in and of themselves, adverse. This information was used for dose selection and exposure capping in Phase1 trials [1].

For more information please see companion posters on TAK-653.

Reference

Authier,S, Delatte MS, Kallman MJ, Stevens J. Markgraf C. EEG in non-clinical drug safety assessments: Current and emerging considerations. J Pharma Toxicol Meth. 2016;81:274-285,

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## PM250

### Acute intermittent porphyria – pathogenic principles and neurobiological mechanisms

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#### Background

Acute intermittent porphyria (AIP) is a rare hereditary metabolic disorder with a dysfunctional heme biosynthetic pathway caused by porphobilinogen-deaminase (PBGD) deficiency. The consequence is an accumulation of the toxic intermediates, particularly aminolevulinic-acid (ALA) and porphobilinogen which are causing the symptoms of peripheral neuropathy, tremor, ataxia and psychiatric manifestations. While neuropsychiatric conditions are reported in up to 50% of the patients, the underlying neuropathological mechanisms are poorly understood.

#### Aims

1. Examine the emotional behavioral phenotype of PBGD-deficient (KI) mice.
2. Investigate whether behavioral disturbances in PBGD-deficient mice are associated with disrupted adult hippocampal neurogenesis and altered hippocampal functional activity.
3. Elucidate the signal transduction systems involved in behavioral and neurogenic deficits in PBGD-deficient mice.

#### Methods

By using behavioral, immunohistochemical, ex-vivo electrophysiological, biochemical and molecular approaches we investigate the potential behavioral, neurogenic and molecular deficits in the PBGD mouse model.

#### Results

The genetic mouse model showed an enhanced depression-like-behavior in KI as compared to WT littermates as well as impaired motor-coordination. Adult hippocampal neurogenesis was evaluated where KI mice showed significantly reduced hippocampal progenitor cell proliferation and the differentiation of cells into mature neurons was decreased in KI mice resulting in more cells of KI are in the early stages and less in the postmitotic phases compared to WT mice.

#### Conclusion

This first experimental assessment of the role of emotional disturbances in the pathogenesis of AIP and the planned molecular approaches may aid in the identification of therapeutically targets for preventive and symptomatic treatment of patients suffering from AIP.

## PM251

### Role of 5-HT1A receptors in the effect of galanin(1-15) on fluoxetine-mediated action in the forced swimming test

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Galanin N-terminal fragment (1-15) [GAL(1-15)] modulates the antidepressant effects induced by the 5-HT1A receptor (5-HT1AR) agonist in the forced swimming test (FST) and the binding characteristics and mRNA levels of 5-HT1AR in the dorsal hippocampus and dorsal raphe (DR).

Recently, we observed that GAL(1-15) enhanced the antidepressant-like effects induced by Fluoxetine (FLX) in the FST. In this work, we have studied whether the effects of GAL(1-15) on FLX action were mediated via 5-HT1AR, analyzing the effect of the 5-HT1AR antagonist WAY100635 in this effect and if the binding characteristics and mRNA levels of 5-HT1AR in the DR and dorsal hippocampus are modified by GAL(1-15)+FLX.

Groups of rats (n=6-8) received three injections of sc FLX(10mg/kg) and 15 minutes before the FST a single icv injection of GAL(1-15) (1nmol) and 5HT1AR antagonist WAY100635(6nmol) icv alone or in combination.

We also analyzed the effects of GAL(1-15)+FLX in the binding characteristics of the 5-HT1AR agonist [<sup>3</sup>H]-8-OH-DPAT and 5-HT1A mRNA levels in the DR, CA1 and Dentate Gyrus (DG).

WAY100635 significantly blocked the reduction in immobility time (p<0.05), and the increase in swimming time (p<0.01) induced by GAL(1-15)+FLX in the FST.

GAL(1-15)+FLX produced a significant increase in the 5HT1AR mRNA levels in CA1 (p<0.05) and DG (p<0.05). This effect was not observed in the DR. Moreover, GAL(1-15)+FLX produced a significant decrease in the Kd value (p<0.01) and in the Bmax value (p<0.05) of [<sup>3</sup>H]-8-OH-DPAT in the DG. These effects were not observed in the CA1 or in the DR.

These results indicate that 5HT1AR participates in the GAL(1-15)/FLX interactions in the FST and the mechanism underlying affected the binding characteristics and the

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mRNA levels of 5-HT1AR specifically in the dorsal hippocampus. The heteroreceptor 5-HT1AR-GALR1-GALR2 located in the dorsal hippocampus may be the target for GAL(1-15).

This work was supported by SAF2016-79008-P; PSI2013-44901-P.

## PM252

### Maternal fluoxetine treatment causes glutamatergic and GABAergic dysregulation in the cortex of adolescent offspring

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Approximately 10% of pregnant women are prescribed antidepressant drugs such as the selective serotonin reuptake inhibitor (SSRI), fluoxetine, for the treatment of depression. Recent evidence suggests that perinatal SSRI exposure can cause long lasting changes to offspring neurochemistry and behaviour. However it is not known what effects perinatal SSRI exposure has on development of the main excitatory and inhibitory neurotransmitter systems. In this study we aimed to determine the effects of developmental fluoxetine exposure on glutamatergic and GABAergic markers, using a rodent model of depression. Wistar-Kyoto (established model of depression; WKY) and Sprague-Dawley (healthy model; SD) rodent dams were treated with fluoxetine (10mg/kg/day) from gestational day 0 to postnatal day (PND) 14. Brains of male offspring were collected at PND14 and PND42 (adolescence) and the prefrontal cortex and hippocampus were dissected. NMDA glutamate receptor subunits (NR1, NR2A, NR2B) and GABAergic markers (GAD67 and Parvalbumin) were then measured via immunoblotting. Fluoxetine exposed offspring showed increased NR2B protein in the prefrontal cortex at PND14. There were no other changes in the measured glutamatergic or GABAergic markers at this age. In contrast, fluoxetine exposed offspring exhibited reductions in NR1 and NR2A NMDA receptor subunits in the prefrontal cortex at PND42. Expression of the interneuron marker, parvalbumin, was also reduced at PND42 in the prefrontal cortex of fluoxetine-exposed offspring. Maternal fluoxetine exposure did not alter these glutamatergic or GABAergic markers in the hippocampus at PND14 or 42. Overall, these findings show that maternal fluoxetine treatment caused delayed alterations in glutamatergic and GABAergic markers in the prefrontal cortex in both SD and WKY offspring. This work contributes to our understanding of the effects of

maternal antidepressant use on offspring neurobiology. It will be important in future studies to determine whether these same delayed effects occur in female offspring.

## PM253

### Flotillin-1 interacts with the serotonin transporter and modulates susceptibility to depression-like behavior

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#### Background

Aberrant serotonergic neurotransmission in the brain is considered at the core of the pathomechanisms involved in neuropsychiatric disorders. Gene by environment interactions contributing to the development of depression involve modulation of the availability and functional activity of the serotonin transporter (SERT).

#### Methods

Using behavioral, in-vivo electrophysiological, biochemical and molecular approaches we determined the involvement of Flotillin-1, a novel SERT interacting protein in the vulnerability to stress-induced depression-like behavior.

#### Results

We showed that Flotillin-1 and SERT localize at the same protein complex and that genetic Flotillin-1 depletion augments the sensitivity to the effects of chronic corticosterone treatment (CORT) on depression-like behavior in the Novelty Suppressed Feeding Test. The behavioral results were paralleled by concomitant CORT-induced alterations in the activity of serotonergic neurons, expressional levels of SERT and alterations of the glucocorticoid receptor transport machinery in a Flotillin-1-dependent manner.

#### Conclusions

We propose a role for Flotillin-1 as susceptibility factor for depression and suggest chronic stress-induced, Flotillin-1-dependent regulation of SERT expression and function at the core of the molecular mechanisms involved.



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## PM254

### Strain dependent effects of chronic stress on microRNAs expression in mice

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Small, regulatory, noncoding microRNAs (miRNAs) may contribute to the development of depression and its treatment. MiRNAs are enriched in the brain regions where they play a role in synaptic plasticity. We previously reported that chronic stress-elicited downregulation of miRNA-124 in the hippocampus is associated with depression-like behavior (Higuchi et al., *J. Neurosci* 2016). To further understand the effects of stress episodes on the gene expression network, we measured miRNAs levels in the ventral hippocampus of two strains of mice, each of which demonstrated different behavioral responses to stress. We subjected C57BL/6J (B6) and DBA/2 (DBA) mice to subchronic social defeat stress (smSDS) episodes. These episodes consisted of brief confrontations with aggressive male mice over a period of 7 days. Non-defeated control mice were not exposed to the aggressive mice. We found normal sociality of B6 mice exposed to smSDS, as compared to non-defeated control B6 mice. In contrast, DBA mice exposed to smSDS demonstrated a significantly less social interaction than non-defeated DBA mice. Thus, we developed B6 and DBA mice as stress-resilient and stress-susceptible strains, respectively. We then measured miRNA levels within ventral hippocampus tissues in stressed and non-stressed B6 and DBA mice. Small RNA-seq revealed a unique change in miRNA expression between stress-resilient B6 and stress-susceptible DBA mice. Pathway analysis revealed that the both p38 MAPK and Wnt signaling pathways are strongly associated with stress susceptibility. This study suggests that miRNA expression, influenced by genetic and environmental factors, may contribute to behavioral responses to stress. Moreover, our data suggest potential targets for treatment of stress-related disorders.

**Keywords:** Chronic stress, Depression, microRNAs

## PM255

### Extracellular glutamate levels in the rat prefrontal cortex after treatment with different N-methyl-D-aspartate receptor antagonists

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NMDA-R antagonists have been described as potential novel treatment options in the therapy of treatment-resistant depression (TRD). However their efficacy in humans differ. The non-selective NMDA-R antagonist ketamine was shown to have fast-onset and long-lasting antidepressant effects in patients; accompanied by transient psychotomimetic symptoms. Antidepressant effects without psychotomimetic side effects have been described in the clinic for the NR2B-subtype selective NMDA-R antagonist traxoprodil. On the other hand, another NMDA-R blocker, the low-trapping channel blocker lanicemine, failed to show fast-onset antidepressant effects in the clinic. One mechanism by which ketamine is hypothesized to elicit its antidepressant effects is by normalizing the reduced prefrontocortical connectivity described in patients suffering from depression. Additionally, preclinical data indicate subtype-dependent differences of NMDA-R blockers on glutamate concentrations in the prefrontal cortex (PFC). Therefore, we investigated acute changes in glutamate concentration elicited by treatment with these NMDA-R blockers in the prefrontal cortex (PFC) of rats, using glutamate voltammetry, a technique with high temporal resolution and sensitivity.

S-ketamine elicited a significant increase in glutamate in the PFC at 10 mg/kg, a dose which achieves the clinically relevant plasma exposure; these effects were blocked by co-treatment with lamotrigine. The same effect could be observed after treatment with traxoprodil, at a dose that elicits antidepressant-like effects in mice and men. Lanicemine, on the other hand, failed to increase glutamate in the PFC at doses up to 30fold of clinically active C<sub>max</sub>. Therefore, the increase in prefrontal glutamate levels described here may be a relevant indicator for antidepressant-like effects of compounds with a ketamine-like mode of action.

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## PM256

### D-lysergic acid diethylamide (LSD) reverses depressive-like behavior and serotonergic (5-HT) neurotransmission impairments in a murine model of chronic stress.

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**Background:** The hallucinogen d-lysergic acid diethylamide (LSD) has recently generated interest due to clinical findings reporting its beneficial mood-enhancing properties, although its effects on brain regions associated with mood have not been examined. Our previous studies demonstrated that LSD at low doses (5-20 µg/kg) decreases the activity of serotonin (5-HT) neurons in Dorsal Raphe Nucleus (DRN) and at higher doses (60-120 µg/kg) the dopaminergic neuronal activity in Ventral Tegmental Area, suggesting a psychotic-like effect at higher doses. Thus, we investigated the effect of low-dose of LSD in a mouse model of chronic stress (CS), employing behavioural paradigms of depression and *in vivo* electrophysiological recordings.

**Methods:** CS paradigm: 8-week old male C57BL/6J mice were placed in restrainers for 2 hours/day, over 14 days. Control (CTL) mice remained undisturbed in their cages. Between day 7 to day 14, CTL and CS mice received subcutaneous (s.c.) injections of LSD (15 or 30 µg/kg/day) or vehicle (veh); on day 15, mice were tested employing Open Field Test (OFT), Forced Swim Test (FST), Novelty Suppressed Feeding (NSF) and *in-vivo* extracellular recordings of 5-HT DRN neurons.

**Results:** CS mice showed decreased time and number of entrance in the center in OFT, vs CTL mice ( $p < 0.05$ ). LSD (30 µg/kg) normalized these values to CTL ( $p = 0.024$ ). CS group showed increased immobility time versus (vs) CTL in FST ( $p = 0.009$ ) and LSD (30 µg/kg) decreased immobility time, vs veh ( $p = 0.006$ ). LSD (15 and 30, µg/kg) reduced the latency to feed in CS mice ( $p < 0.001$ ) in NSF, increased after stress. Finally, CS mice showed a decreased 5-HT DRN firing rates vs CTL ( $p < 0.05$ ). LSD (15 and 30 µg/kg) increased neuronal activity to CTL group levels ( $p < 0.05$ ).

**Conclusion:** This study demonstrates that low doses of LSD improves depressive-like behaviour restoring the low 5-HT firing activity induced by CS.

## PM257

### Comparing all-cause mortality and external causes of deaths in different definitions of treatment resistant depression

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#### Background

Currently there is no generally accepted definition of treatment resistant depression (TRD). It is known that depression is associated with an increased mortality, but few studies have examined the mortality among the subgroup classified with TRD.

#### Objective

The aim of this study was to compare the all-cause and external cause mortality applying different definitions of TRD using Swedish register data.

#### Methods

A cohort of Major depressive disorder patients with antidepressant treatment was identified in the National Swedish Patient Register and the Swedish Prescribed Drug Register ( $n = 127,108$ ). During follow-up between 2006 and 2014, the mortality was examined among these patients using four different definitions of TRD; a customized algorithm made at Karolinska Institutet (KI-TRD,  $n = 16,453$ ), the European Staging Model (ESM,  $n = 12,059$ ), Massachusetts General Hospital Staging Method (MGH-s,  $n = 19,486$ ) and the Maudsley Staging Model (MSM,  $n = 24,112$ ).

Odds ratios (OR) with 95% confidence intervals (CI) were calculated for mortality from all causes and external causes of death. Analyses were adjusted for sex and age.

#### Results

The percentage of all-cause mortality were in KI-TRD 6.4%, ESM 6.7%, MSM 6.2% and MGHs 5.9%, while the percentage of external-cause of death were KI-TRD 1.9%, ESM 2.0%, MSM 1.8% and MGHs 1.6%.

Using KI-TRD definition as reference, adjusted ORs for all-cause mortality were for EMS: 1.00 (95%CI 0.92-1.10), MSM: 0.98 (0.90-1.06) and MGHs: 0.96 (0.89-1.04). The adjusted ORs for external-cause of death were EMS: 1.04 (95%CI 0.88-1.16), MSM: 0.93 (0.80-1.09) and MGHs: 0.84 (0.72-0.98) compared to KI-TRD.

#### Conclusion

There was no significant difference in all-cause mortality between the different definitions of TRD. However, a lower

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risk for death by external cause among the patients identified through MGH-s. The results suggest that various definitions of TRD applied in national health registers identify patients with a similar all-cause mortality, but a somewhat varying mortality from external causes.

## PM258

### Definitions of treatment resistant depression: A comparison between different methods in a register based environment

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#### Background

Major depressive disorder (MDD) which fails to respond to an adequate course of treatment is commonly named treatment resistant depression (TRD). However, there is no single accepted definition of how to operationalize TRD, although most definitions include at least two failed treatment attempts as a common denominator.

#### Objective

The aim of this study was to compare different definitions of TRD and their operational characteristics using Swedish register data.

#### Methods

All patients with a depressive disorder diagnosis in the National Swedish Patient Register and a filled prescription of an antidepressant in the Swedish Prescribed Drug Register during 2006-2014 were identified.

Four approaches of defining TRD were used: a customized TRD algorithm made at Karolinska Institutet (KI-TRD), and, adapted for register study, the European Staging Model (ESM) Massachusetts General Hospital Staging Method (MGH-s) and the Maudsley Staging Model (MSM). Parameters which vary between those TRD definitions include number of treatment failures, augmentation and adequate treatment length.

The cohorts established by the different TRD definitions were compared by the proportion of MDD patients meeting the TRD criteria and the number of days from the first antidepressant prescription until being identified as having TRD.

#### Results

In total 127,108 MDD patients with a prescribed antidepressant treatment were identified, among these the highest proportion of patients identified as TRD was found

in MGH-s (16.0%) followed by MSM (15.3%), KI-TRD (12.9%) and ESM (9.5%).

The least number of days until being identified with TRD was found in MSM (median 197 days; IQR 136-271), while ESM had the most number of days (216 days; 156-291).

#### Conclusion

The proportion of patients with MDD with TRD ranged between 9.5% and 16.0% which was noticeably lower than previously reported. No clear differences were apparent between the different TRD definitions in terms of days until meeting TRD criteria.

## PM259

### The long-lasting antidepressant effects and the cognitive impairment effects of (R)-ketamine are abolished in NMDA receptor GluN2D subunit knockout mice

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**Background:** The *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine exerts rapid and sustained antidepressant effects in depressed patients. Ketamine is a racemic mixture of equal amounts of enantiomers, (*R*)-ketamine and (*S*)-ketamine. The neural mechanisms that underlie different effects of these enantiomers remain unclear. We previously reported that phencyclidine, an NMDA receptor antagonist, significantly increased locomotor activity, caused motor impairment, and increased extracellular dopamine levels in wildtype but not GluN2D, one of NMDA receptor subunits, knockout (KO) mice. Further, GluN2D-KO mice did not develop ketamine-induced locomotor sensitization. However, roles of GluN2D in the antidepressant effects and the cognitive impairment effects of ketamine are still unknown. The present study investigated the role of GluN2D in the effects of ketamine and its enantiomers.

**Methods:** We investigated the rapid and sustained antidepressant effects of enantiomers of ketamine in GluN2D-KO mice using tail-suspension test (TST). The cognitive impairment effects of enantiomers of ketamine were also investigated using novel object recognition test (NORT).

**Results:** Intraperitoneal administration of ketamine or its enantiomers 10 min before the TST exerted significant antidepressant effects on restraint stress-induced depression in both wildtype and GluN2D-KO mice. The antidepressant effects of (*RS*)-ketamine and (*S*)-ketamine were sustained 96 h after the injection in both wildtype

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and GluN2D-KO mice, whereas such sustained antidepressant effects of (*R*)-ketamine were only observed in wildtype mice. In the NORT, the cognitive impairment effects of (*RS*)-ketamine and (*S*)-ketamine were observed in both wildtype and GluN2D-KO mice, whereas such cognitive impairment effects of (*R*)-ketamine were only observed in wildtype mice.

**Conclusions:** The present results suggest that GluN2D plays an important role in the sustained antidepressant effects and the cognitive impairment effects but not rapid antidepressant effects of (*R*)-ketamine, whereas this submit does not appear to be involved in the antidepressant effects and the cognitive impairment effects of (*RS*)-ketamine or (*S*)-ketamine.

## PM260

### **Structural interference at Ser743 in AMPA-R is a key to lower the agonistic effect of AMPA-R potentiators**

Akiyoshi Kunugi, Maiko Tanaka, Atsushi Suzuki, Yasukazu Tajima, Noriko Suzuki, Motohisa Suzuki, Shinji Nakamura, Haruhiko Kuno, Akihiro Yokota, Satoshi Sogabe, Yohei Kosugi, Yasuyuki Awasaki, Tomohiro Kaku, and Haruhide Kimura

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Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor (AMPA-R) potentiators could be promising as therapeutic drugs for psychiatric and neurological diseases. However, AMPA-R potentiators such as LY451646 and LY451395 carry risks of narrow bell-shaped dose-responses and seizure. In our previous study, LY451395 showed agonistic effects in primary neurons. We discovered an AMPA-R potentiator, HBT1, with lower agonistic effects compared with LY451395. HBT1 and LY451395 bound to a pocket in the ligand-binding domain (LBD) of AMPA-R with different binding modes. Thus, optimization of HBT1-site binders with careful consideration for the relationship between binding mode and functional outcome could be a promising strategy for discovering novel AMPA-R potentiators with lower agonistic effects. Here, we report that structural interference at Ser743 in AMPA-R is a key to lower the agonistic effect of AMPA-R potentiators containing dihydropyridothiadiazine 2,2-dioxides skeleton. We screened a chemical library by a binding assay using [<sup>3</sup>H]-HBT1 and GluA2o LBD protein and identified dihydropyridothiadiazine 2,2-dioxides. Two Dihydropyridothiadiazine 2,2-dioxide derivatives, Compound-1 and Compound-2, had similar binding affinity to AMPA-R and induced Ca<sup>2+</sup> influx in a glutamate-

dependent manner in cell lines expressing AMPA-R. Interestingly, Compound-1 had lower agonistic effect than Compound-2 in primary neurons. Compound-1, but not Compound-2, bound to AMPA-R in a glutamate-dependent manner. X-ray crystallography and mutation studies revealed that Ser743 prevented Compound-1, but not Compound-2, from binding in the “apo” agonist-free state (channel-closed state) due to steric interference. Thus, design of dihydropyridothiadiazine 2,2-dioxides with no or little binding affinity to the LBD in the channel-closed state by the steric interference at Ser743 may lead to the discovery of AMPA-R potentiators with lower agonistic effect.

## PM261

### **TAK-653, an AMPA receptor potentiator, produces an antidepressant-like effect with potential fast onset of action like ketamine**

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The N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine has rapid-onset and sustained antidepressant activity, that produces a response in two thirds of patients with treatment-resistant depression (TRD). However, its use is associated with unwanted side effects such as psychotomimetic effects. Activation of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and subsequent activation of the mammalian target of rapamycin (mTOR) signaling pathway have been thought to contribute to the antidepressant efficacy of ketamine. Here, we present findings on a potent and selective AMPA receptor potentiator with a minimal agonistic effect, TAK-653, that suggest it may have antidepressant-like effects in the absence of psychotomimetic activity. In rat primary cortical neurons, TAK-653 at 0.1 and 1  $\mu$ M significantly increased levels of phosphorylated and activated forms of mTOR and p70S6 kinase as well as their upstream regulators Akt and extracellular signal-regulated kinase (ERK). Likewise, TAK-653 at 0.1 and 1  $\mu$ M significantly increased brain derived neurotrophic factor (BDNF) protein levels. In vivo antidepressant-like effects were evaluated using the rat reduction of submissive behavior model (RSBM). Ketamine at 30 mg/kg, i.p. reduced submissive behavior in rats 24 h after treatment; this effect was blocked by pretreatment with the AMPA receptor antagonist NBQX at 10 mg/kg, i.p., indicating that the antidepressant-like effect of ketamine is likely to be through AMPA receptor activation. Consistent with this finding, repeated treatment of rats

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with TAK-653 at 0.1 and 1 mg/kg, p.o. significantly reduced dominance levels in the RSBM. Unlike ketamine, however, TAK-653 did not induce a hyperlocomotor response in rats, which has been one of the behavioral changes linked with psychotomimetic side effects in humans. These findings suggest that TAK-653 may be a promising drug for the treatment of major depressive disorders including TRD with the potential for a superior safety profile.

## PM262

### **TAK-137 is an AMPA-R potentiator with lower risks of bell-shaped response and seizure**

Akiyoshi Kunugi, Maiko Tanaka, Atsushi Suzuki, Yasukazu Tajima, Noriko Suzuki, Motohisa Suzuki, Shinji Nakamura, Haruhiko Kuno, Akihiro Yokota, Satoshi Sogabe, Yohei Kosugi, Yasuyuki Awasaki, Tomohiro Kaku, and Haruhide Kimura

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Activation of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA-R) is a promising strategy to treat psychiatric and neurological diseases if issues of bell-shaped response and narrow safety margin against seizure can be overcome. Here, we report the discovery of TAK-137, 9-(4-Phenoxyphenyl)-3,4-dihydropyrido[2,1-c][1,2,4]thiadiazine 2,2-dioxide, as a novel AMPA-R potentiator with low risks of bell-shaped response and seizure. We previously reported that structural interference at Ser743 in AMPA-R is a key to lower the agonistic effect of AMPA-R potentiators containing dihydropyridothiadiazine 2,2-dioxides skeleton (Poster #2871). With this structural insight, TAK-137 was discovered as a novel AMPA-R potentiator with a lower agonistic effect than an AMPA-R potentiator LY451646 in rat primary neurons. TAK-137 induced brain-derived neurotrophic factor (BDNF) in neurons in rodents and potentially improved cognition in both rats and monkeys. Compared to LY451646, TAK-137 had a wider safety margin against seizure, and enhanced neural activation and neural progenitor proliferation over a broader range of doses in rodents. These results may open the door for the development of AMPA-R potentiators as therapeutic drugs for psychiatric and neurological diseases.

## PM263

### **Identification of BDNF-enhancing targets by phenotypic screening modalities**

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Brain derived neurotrophic factor (BDNF) is a growth factor expressed by glutamatergic neurons and critically involved in synaptic plasticity of the adult brain. Since decreased expression of BDNF levels have been described in patients suffering from depression, schizophrenia, or Alzheimer's disease, the activation of the BDNF receptor TrkB has been considered as an attractive drug target, which so far failed due to the lack of suitable chemical matter, required to penetrate the blood brain barrier.

As an alternative strategy, we aim here to identify targets which result in increased BDNF-expression. This however is hampered by the complex regulation of BDNF-expression, exemplified by the presence of eleven exons and nine functional promoters generating more than 20 different mRNA species which are used in a context- and region-specific manner. Thus, we decided for an agnostic approach aiming to identify targets by means of phenotypic screening modalities: First, we validated primary neurons, derived from mice as a suitable in vitro system allowing the identification of targets with annotated compound libraries. In addition we characterized a fluorescent reporter expressing BDNF-P2A-SV40-NLS-EGFP in vitro, which aims in fluorescent labelling of neuronal nuclei without affecting BDNF trafficking. This reporter is currently being used to develop a transgenic mouse knocked into the endogenous BDNF locus, aiming to run a pooled genetic RNAi screen, using lentiviral vectors

Key words: BDNF- TrkB- phenotypic screening- primary neurons- drug target

## PM264

### **Ketamine and Ro 25-6981 reverse behavioral disturbances induced by zinc deficiency**

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Major depressive disorder (MDD) is a serious medical problem of a modern society. The etiology of MDD is a very diverse, thus treatment of this illness is difficult and often ineffective. Recently, the researchers have focused attention on the relationship between MDD and nutrition. It is well known that deficiency of some elements is associated with MDD. In particular, it has been reported that the lower level of zinc can be associated with severity of depression symptoms. Our previous preclinical studies showed that chronic treatment with fluoxetine and amitriptyline reversed pro-depressive behavior observed in rats with zinc deficiency (ZnD) evoked by administration of fodder containing the reduced level of zinc.

In the present studies we showed that single dose of amitriptyline did not reverse the increased immobility time in the forced swim test (FST) in ZnD rats. In contrast to that, the single dose of atypical fast acting antidepressant compounds like ketamine (global NMDAR antagonist) and Ro 25-6981 (a selective antagonist of the GluN2B subunit of NMDAR) decreased immobility time in the FST in ZnD rats. Additionally both ketamine and Ro 25-6981 increased sucrose intake in ZnD rats in the sucrose intake test. These effects were associated with the changes in the levels of synaptic proteins.

In conclusion, results obtained in our studies indicate that behavioral changes induced by ZnD are sensitive to pharmacological strategies used in the treatment of MDD. It may suggest that physiological disturbances induced by ZnD are similar to physiological processes responsible for MDD.

This study was supported by the grant 2015/19/B/NZ4/01890 from the National Science Centre, Poland

## PM265

### **Ketamine promotes early changes in dendritic morphology in the hippocampus of a genetic rat model displaying depressive-like behavior.**

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## **Background**

Psychiatric disorders constitute a major burden for society in terms of productivity and years lost to disability. Recently it was shown that ketamine (KET), a non-competitive NMDA receptor antagonist, induces a rapid and sustained antidepressant effect in treatment-resistant patients. However, the mechanism by which KET ameliorates depressive symptoms is still unclear.

Here we used the Flinders Sensitive Line (FSL) rat, and its control strain the Flinders Resistant Line (FRL) rat to investigate morphological and molecular changes in the hippocampus that may be involved in the rapid antidepressant-like effect of KET.

## **Methods**

To validate the antidepressant-like effects of KET at 1 h post injection, we exposed the rats to the forced swim test. For morphological analysis, one hemisphere per animal was processed for the Golgi-cox staining. Molecular studies were performed on the contralateral hemisphere.

## **Results**

We found that FSL rats exhibited higher immobility times ( $p < 0.001$ ) while KET treatment reduced immobility times ( $p < 0.0001$ ). Moreover, the swimming behavior was lower in FSL rats compared to FRL ( $p < 0.01$ ) and it was higher in FSL rats treated with KET compared to FSL vehicle ( $p < 0.05$ ). These data demonstrate an antidepressant-like effect of KET only 1 h after injection.

Regarding the morphological study, we found a significant increase in the number and density of spines in the apical dendrites ( $p < 0.01$ ) in FSL rats treated with KET. We also found an overall decrease in the basal dendritic length in the FSL rats ( $p < 0.05$ ) and an effect of KET treatment on spine number in FSL rats treated with KET ( $p < 0.05$ ).

At synaptical level, KET decreased the phosphorylation of cofilin and the NMDAR2A subunit level while it increased the HOMER 3 level.

## **Conclusion**

These data suggest that morphological and synaptic reorganization of both apical and basal dendrites may be involved in the fast antidepressant-like effect of KET.

## PM266

### **Functional connectivity of the subgenual cingulate cortex - Impact of genotypic variation**

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**Background:** Deregulation of the subgenual cortex (SGC) has been frequently linked to psychiatric disorders,

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especially mood disorders. However, it has not been researched thoroughly how genetic variations influence connectivity patterns of the SGC with the other components of the limbic system.

**Aims:** The aim of the study is to investigate the influence of 5 SNPs (5-HTTLPR, rs6265, rs988748, rs1030068 and rs988712) on the functional connectivity (FC) of the SGC with the limbic system.

**Methods:** 100 participants (healthy control participants, depressed patients without psychotic symptoms and depressed patients with psychotic symptoms) were included in this study. Functional magnetic resonance imaging (fMRI) scans were collected to observe low-frequency resting-state functional connectivity patterns. Standard clinical scales (Hamilton Depression scale, Brief Psychiatric Rating Scale) and overnight cortisol measurements were carried out. DNA was analyzed using saliva collected with the Oragene Kit.

**Results:** In the stepwise regression model which included all investigated SNPs, sex, age, BPRS and HAMD score, BDNF rs988748 was the only factor left ( $p=0.0034$ ;  $R$  square 0,62/ adjusted  $R$  square 0,49). More rare forms of this SNP were found to be associated with a lower connectivity of the SGC with the other 33 investigated brain regions.

**Conclusions:** This study shows that BDNF rs988748 influences FC of the SCG which is from scientific and clinical relevance as this brain region is involved in the origin and perpetuation of mood disorders. Further studies are needed to replicate this finding and to analyze the clinical impact in the depth. It would be also crucial to learn more about the effect of this allelic variation on cognitive function, memory and other neuropsychiatric disorders.

## PM267

### Quinolinic acid as pro-oxidant in depression: Implications through Nrf2 activity in hippocampus of restrain-stressed rats

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**Background:** Quinolinic acid (QA), a neurotoxic metabolite of kynurenine pathway exert neurotoxic effects in depression. It has been found that QA might increase reactive oxygen species through NMDA activation or directly through QA-iron reaction but the exact

mechanism is not clear. Enhancing nuclear translocation of endogenous antioxidant transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2) has been found to restore redox homeostasis and decrease vulnerability to depression.

**Aim:** With this background present study was designed to investigate the role of QA as pro-oxidant in depression by modulating nuclear translocation of Nrf2.

**Materials and Methods:** Restrain-stress model was used to induce depression in male wistar rats (7-8 week old). Animals were restrained for 2 hours daily for 7 days. Animals were divided into three groups: control, restrain-stress group and restrain-stress + UPF-648 (Kynurenine monooxygenase inhibitor, inhibit QA synthesis). Locomotor activity was evaluated in open field test and quantification of Nrf2 mRNA expression in hippocampus was done by qPCR. Serotonin (5-HT) and 5-Hydroxyindole acetic acid (5-HIAA) concentrations were quantified in hippocampus using Liquid Chromatography-Mass Spectroscopy.

**Results:** Restrain stress increases Nrf2 mRNA expression in the hippocampus of stressed animals and UPF-648 treatment prevent the activation of Nrf2. Restrain stress also increases serotonin turnover in hippocampus of stressed group and UPF-648 microinjection in hippocampus prevent increase in 5-HIAA and decrease in 5-HT levels in restrain-stressed rats.

**Conclusion:** QA increases oxidative stress by modulating Nrf2 activity in stressed conditions and hence act as pro-oxidant in depression.

## PM268

### Effect of chronic treatment with desipramine or milnacipran on the glycogen synthase kinase-3 phosphorylation in cerebral prefrontal cortex: study in alpha1B-adrenergic receptor knockout mice

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**Objective:** Glycogen synthase kinase-3 (GSK-3) has been linked among others to the mechanisms of mood regulation and the effects of psychotropic drugs [3]. GSK-3, the constitutively active multi-substrate serine/threonine kinase, exists in two isoforms: GSK-3alpha and GSK-3beta. Their different actions and regulation have begun to be identified [2]. The alpha1-adrenergic receptor family consists of three subtypes, alpha1A, alpha1B and alpha1D, which differ in their efficacy in evoking intracellular signals

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and transcriptional profiles [4]. The involvement of alpha1A-adrenergic receptors in regulation of GSK-3beta was found in the *in vitro* model of rat-1 fibroblasts [1].

**Methods:** We assessed phosphorylation of GSK-3 (pGSK-3) isoforms alpha and beta and the protein kinase B/AKT by Western Blot analyses. The expression of kinases protein was evaluated in prefrontal cortex dissected from brains of mice after chronic treatment (21 days) with antidepressant drugs, desipramine (20 mg/kg, i.p.) or milnacipran (30 mg/kg, i.p.). The study was performed in male and female mice devoid of the alpha1B-adrenergic receptor and in wild type controls.

**Results:** We found that both of chronically given antidepressant drugs increased the phosphorylation of GSK-3alpha and GSK-3beta, but the effects of the drugs were varied depending on animal sex and genotype. In females the main effect of genotype was observed in pGSK-3alpha while in males such an effect was noticed in case of pGSK-3beta. The total expression of both GSK-3 isoforms was not affected regardless of evaluated drug treatments. Antidepressant-induced changes in GSK-3 phosphorylation were not accompanied by modulation of AKT phosphorylation or its expression which remained at the saline control level.

**Conclusions:** Our findings provide new insight into the mechanisms of GSK-3 regulation by chronically given antidepressants and suggest that central alpha1B-adrenergic receptor is involved to some extent in such a regulation. (*This research was supported by National Science Centre, Poland, grant no. 2015/17/B/NZ7/03018*)

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## PM269

### Role of Kir4.1 channels in modulating BDNF expression in astrocytes

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Inwardly rectifying potassium (Kir) 4.1 channels are specifically expressed in astrocytes and regulate neuronal excitability by modulating the spatial potassium buffering activity. It is now known that loss-of-function mutations of the gene encoding Kir4.1 or down-regulation of Kir4.1 expression causes neural hyperexcitation due to elevated extracellular potassium and glutamate levels by the disruption of spatial potassium buffering. However, pathophysiological role and mechanism of astrocytic Kir4.1 dysfunction in the development of neuropsychiatric disorders are still unknown. In this study, we evaluated the effects of Kir4.1 dysfunction (blockade and knockdown of Kir4.1 channels) on the expression of BDNF, a key molecule modulating brain functions and neuropsychiatric disorders, in astrocyte primary cultures. For blockade of Kir4.1 channels, we tested several antidepressant agents which reportedly bound to and blocked Kir4.1 channels in a subunit-specific manner (*Brain Res.*, 1178, 44-51, 2007; *Mol. Pharmacol.*, 75, 1287-1295, 2009). Treatment of astrocytes with fluoxetine enhanced BDNF mRNA expression in a concentration-dependent manner and increased the BDNF protein level. Other antidepressants (e.g., sertraline and imipramine) also increased the expression of BDNF mRNA with relative potencies similar to those for inhibition of Kir4.1 channels. In addition, suppression of Kir4.1 expression by the transfection of small interfering RNA (siRNA) targeting Kir4.1 significantly increased the mRNA and protein levels of BDNF. The BDNF induction by Kir4.1 siRNA transfection was suppressed by the MEK1/2 inhibitor U0126, but only slightly by the p38 MAPK inhibitor SB202190 or the JNK inhibitor SP600125. Our results show that inhibition of Kir4.1 channels facilitates BDNF expression in astrocytes primarily by activating the Ras/Raf/MEK/ERK pathway, which may lead to the development of neuropsychiatric disorders (depression and epilepsy).



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## PM270

### Association of serum levels of endogenous estrogen receptor $\beta$ with depression and body weight

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We have recently reported that administration of estrogen receptor  $\beta$  (ER $\beta$ ) agonists reduced body weight gain and depressive-like behavior in ovariectomized mice. In the present study, we examined the associations of depression and body weight with endogenous ER $\beta$  ligands using previously reported data of 10 male and 13 female patients with depression (mean age [standard deviation] 67.4 [7.38] and 68.8 [6.95] years, respectively) and 12 male and 16 female healthy controls (65.7 [6.01] and 60.6 [2.42] years, respectively). Serum levels of the following 4 endogeneous ER $\beta$  ligands were measured: 5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol (3 $\beta$  Adiol), 7 $\alpha$ -hydroxydehydroepiandrosterone (7 $\alpha$ -OH-DHEA), androstenediol ( $\Delta$ 5-diol), Dehydroepiandrosterone (DHEA), 17 $\beta$ -estradiol (E2), and cortisol were also measured. Principal component analysis of the above 7 serum hormone levels revealed 2 principal components that respectively explained 46.4% and 26.9% of the original variance of the data. All the 7 hormones comprised the first principal component with loadings ranging from -0.93 to -0.44. By contrast, 7 $\alpha$ -OH-DHEA and DHEA had negative loadings ranging from -0.83 to -0.67 and E2 had positive loading of 0.61 on the second principal component. Two-way analysis of variance with sex and depression diagnosis as independent variables showed that high first principal component score was significantly associated with female sex ( $P < 0.001$ ) while high second principal component score was significantly associated with male sex and depression ( $P < 0.001$  and  $P = 0.016$ , respectively). Neither component scores were significantly associated with body weight or body mass index when controlled for sex. Our reanalysis of previously published data did not reveal association of endogenous ER $\beta$  ligands with body weight. However, our findings suggest the association between serum levels of endogenous ER $\beta$  ligands and depression.

## PM271

### Protective Effect of Formononetin and Biochanin A against Fluoxetine induced hepatic damage via curtailment of apoptosis and oxidative stress

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Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is used as a first line therapy in depression. Beside the asymptomatic less severe side effects, the cases of fluoxetine induced hepatotoxicity and acute hepatitis have also been reported as an uncommon adverse event. Alternative and complementary medicine has gained global attention because of their widespread applications of Chinese traditional medicine for treating many diseases. Therefore, the present study was inquested to enumerate the *in vitro* and *in vivo* hepatoprotective potential of formononetin (FMN) and biochanin A (BCA) against fluoxetine induced hepatocellular detriment. Human hepatocyte cell line were pre-treated with either vehicle or both the isoflavones (50 $\mu$ M) followed by incubation with fluoxetine (50  $\mu$ M) for 48h. For implementation of *in vivo* study, rats were exposed to both FMN (100mg/kg; *p.o.*) and BCA (100mg/kg; *p.o.*) followed by administration of fluoxetine (10mg/kg; *i.p.*). The FMN and BCA restored the deficits in fluoxetine induced cellular damage. Both the dietary flavones also improved the biochemical and antioxidant status in the liver tissue by decreasing the lipid peroxidation and inducing the reduced glutathione release in tissue. Pre-treatment with FMN and BCA also ameliorated the increased levels of biochemical markers of liver (SGOT, SGPT and ALP) which prove the capability of both the flavones to be protective against hepatotoxicity induced by fluoxetine. FMN and BCA also attenuated the fluoxetine induced Bax and caspase-3 activation and downregulate the expression of Bcl<sub>2</sub>. Alteration in the levels of inflammatory markers i.e., NO, COX, LOX, TNF- $\alpha$ , various ILs were also observed in both hepatic tissue and plasma. Consequently, FMN and BCA exerts hepatoprotective effect through modulating the oxidative stress, inflammation, apoptosis and reversing the tissue degeneration suggesting its therapeutic role in hepatotoxicity and other hepatocellular diseases.

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## PM272

### **Increased cyclophilin A expression in the anterior cingulate cortex of subjects with major depressive disorder**

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A growing body of evidence suggests that inflammatory protein levels are altered in the central nervous system of patients with mood disorders. Cyclophilin A (PPIA), a major immunosuppressant drug target, regulates the expression of several key inflammatory proteins. Furthermore, drugs that bind to PPIA can induce depressive side effects in patients with inflammatory disorders. However, it is unclear whether PPIA is involved in the pathophysiology of mood disorders. We investigated whether PPIA mRNA expression is altered in subjects with major depressive disorders (MDD) or bipolar disorders (BD) compared to controls, in Brodmann area (BA) 24, a brain region that is important in controlling mood.

Human post-mortem brain tissue was obtained from the Victorian Brain Bank Network. RNA was extracted from BA24 (anterior cingulate cortex) tissue, obtained post-mortem from subjects with MDD ( $n = 20$ ), BD ( $n = 18$ ), and non-psychiatric controls ( $n = 20$ ). The RNA was reverse transcribed and expression levels were quantified using qPCR with SYBR green chemistry in a Bio-Rad iQ5 Real-Time PCR Detection System. Reactions were performed in triplicate, and relative quantities of PPIA mRNA expression were normalized to the geometric mean quantities of two stably expressed reference genes.

PPIA mRNA expression was increased in BA24 from MDD subjects compared to controls ( $p < 0.001$ ). There was no significant difference in PPIA mRNA expression in BD compared to controls. Furthermore, there was no significant variation in age, sex, and post-mortem interval across diagnostic cohorts.

We have shown that the level of PPIA mRNA expression is increased in BA24 from subjects with MDD, but not subjects with BD. These findings indicate that increased expression of PPIA could contribute to the pathophysiology of MDD. The diagnostic specificity of these findings has implications for understanding the biochemical differences underlying MDD and BD.

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PT273	Preclinical	Depression
PT274	Preclinical	Epilepsy
PT275-PT283	Preclinical	Others
PT284-PT287	Preclinical	Pain
PT288	Preclinical	Personality Disorders
PT289	Preclinical	Post Traumatic Stress Disorders
PT290-PT308	Preclinical	Schizophrenia
PT309	Preclinical	Sleep Disorders
PT310	Preclinical	Suicide
PT311	Translational	Anxiety Disorders
PT313-PT318	Translational	Bipolar Disorders
PT319	Translational	Dementia
PT320-PT328	Translational	Depression
PT329	Others	Depression
PT330-PT331	Translational	Depression
PT332	Translational	Epilepsy
PT333-PT338	Translational	Others
PT340-PT341	Translational	Pain
PT342	Translational	Post Traumatic Stress Disorders
PT343-PT356	Translational	Schizophrenia
PT357-PT359	Translational	Suicide
PTL360	Clinical	Addictive Disorders
PTL361-PTL362	Clinical	Anxiety Disorders
PTL363-PTL364	Clinical	Attention Deficit Disorders
PTL365-PTL367	Clinical	Bipolar Disorders
PTL368	Clinical	Childhood & Adolescent Disorders
PTL369-PTL370	Clinical	Depression
PTL371	Translational	Suicide
PTL372-PTL375	Clinical	Depression
PTL376-PTL380	Clinical	Others
PTL381	Clinical	Personality Disorders
PTL382-PTL384	Clinical	Post Traumatic Stress Disorders
PTL385-PTL388	Clinical	Schizophrenia
PTL389-PTL391	Clinical	Suicide
PTL392-	Others	Addictive Disorders

## PTL393

PTL394	Others	Childhood & Adolescent Disorders
PTL395	Others	Others
PTL396	Preclinical	Anxiety Disorders
PTL397	Preclinical	Childhood & Adolescent Disorders
PTL398	Preclinical	Others
PTL400-PTL401	Preclinical	Schizophrenia
PTL402	Translational	Addictive Disorders
PTL403-PTL404	Translational	Depression
PTL404	Translational	Depression
PTL405	Translational	Post Traumatic Stress Disorders
PTL406	Translational	Schizophrenia
PTL407	Translational	Sleep Disorders

## PT273

### The Impact of Economic Problems on Depression of Single Mothers in Korea: A Comparative Study with Married Women

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**Objective:** Single parent families are faced with various social, economic, and psychological problems. The purpose of this study was to investigate the risk factors influencing depression in urban-dwelling single mothers.

**Methods:** Participants were 195 single mothers and 357 married mothers living in an urban community in South Korea. We collected the sociodemographic findings and psychological variables affecting depression in this population group. Participants completed self-report questionnaires including the following self-rating scales: the Global Assessment of Recent Stress, Center for Epidemiologic Studies-Depression scale (CES-D), the scale for Beck Suicidal Ideation, and the Korean version of the Alcohol Use Disorder Identification Test. For the current study's analysis, a CES-D point of 25 or above was classified into the depressed group. Multiple logistic regression analysis was performed to examine independent factors affecting single mothers' depression.

**Results:** The prevalence of depression in single mothers and control group showed a noticeable difference (33% and 8%, respectively). In single mothers group, younger age, low income, residence instability, more stress, high level of suicidal ideation, and more alcohol-related

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problems were associated with depression. After adjustment for covariates, living in rental housing (OR = 11.46, 95% CI 1.72-76.46) was an independent risk factor of depression in single mothers, while the impact of stress in single mothers group (OR = 1.16, 95% CI 1.09-1.24) was similar to those of married mothers group.

**Conclusions:** These findings suggest that practical economic assistance is urgently needed in order to prevent and manage depression in single mothers. A national welfare policy targeting economic difficulties have to be established to help mental health problems of single mothers.

## PT274

### **Prenatal exposure to valproic acid (VPA) is associated with altered neurocognitive functions and neurogenesis in dentate gyrus of offspring rats.**

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During pregnancy, epileptic patients must balance the maternal and fetal risks associated with seizures against the potential teratogenicity of antiepileptic drugs (AEDs). We investigated the alterations of neurocognitive behaviors and hippocampal neurogenesis in offspring after exposure of VPA during pregnancy in rats. We used pregnant female Wistar rats, and administered repeatedly intraperitoneally injections of VPA (100mg/kg/day [VPA100 group] or 200mg/kg/day [VPA200 group]) from embryonic day 12.5 to postnatal day (PD) 0. We injected Bromodeoxyuridine (BrdU) to offspring on PD29. After that, we performed behavioral tests (open field test [OF], elevated plus maze [EPM], Y-maze) and decapitated on PD30.

While no malformations were observed in offspring rats in VPA100 group, VPA200 group showed a distinctive malformation (crooked tail) in 66.6% of offspring. In comparison with the control group in OF, VPA200 group showed a more hyperactivity ( $p < 0.001$ ), but not a significant change in VPA100 group. In EPM test, a ratio in an open arm showed a significant increase in VPA groups than control groups ( $p < 0.05$ , both groups vs. control). There was no significant difference in both groups for alteration (%) in Y-maze test. BrdU-positive cells were significantly increased in VPA groups than control group dose-dependently ( $p < 0.05$  [control vs. VPA100 group],  $p < 0.001$  [control vs. VPA200 group] and  $p < 0.01$  [VPA100 group vs. VPA200 group]). There was a significant positive

correlation between spontaneous activities and BrdU-positive cells in all groups ( $R^2 = 0.184$ ,  $p = 0.025$ ).

In conclusion, malformation was detected even after ED12.5 with injection of VPA in high dosage (200mg/kg/day). Neurocognitive test may suggest a similar profile of attention deficit hyperactivity disorder (ADHD). Cell proliferations were increased in VPA-treated rats with a dose-response relationship. It raises a possibility that an increased cell proliferation in hippocampus may influence ADHD-like behavioral changes in offspring.

## PT275

### **The Roles of Serotonin on Conflicting Decision Making under Social Groups in Rodents**

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**Objective:** People often make conflicting decisions to conform social groups (Asch, 1956, Psychol Monogr) or obey to authority (Milgram, 1963, J Abnorm Soc Psychol) in social groups. The neural mechanisms how such social group environments cause conflicts on decision making have remained unclear. In this study, we investigated the roles of serotonin (5-HT) on conflicting decision making associated with social conformity and obedience, along with developments of novel behavioral tests, in mice under social groups.

**Methods:** We developed two behavioral tests to examine conflicting decision making associated with social obedience and conformity. The behavioral test for social obedience employed the paradigm of food access priority of mice in groups. The behavioral test for social conformity used the fear conditioning paradigm. Some mice in a group were subjected for cued fear conditioning, and housed together with non-conditioned mice. Subjects under the test received selective serotonin reuptake inhibitor (SSRI) or saline as a control treatment.

**Results:** In the behavioral test for social obedience, mice exhibited prioritized orders of food access, which correlated with social ranks of them in their groups. Thus, mice inhibited food access when they confronted against higher, but not lower, social rank opponents. SSRI administration attenuated such social inhibition in drug-administered mice, resulting in approximately equal frequency of food access regardless of opponent social ranks. In the behavioral test for social conformity, presentation of auditory tone used for fear conditioning induced freezing in conditioned, but not non-conditioned,

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mice when a number of conditioned mice was small in groups. However, when a number of conditioned mice were increased for more than a half of the groups, non-conditioned mice also exhibited significant freezing during the tone.

**Conclusions:** These results suggest that 5-HT transmission plays important roles on conflicting decision making caused by social group dynamics such as social conformity and obedience.

## PT276

### Protective role of Hemin against experimental role of Chronic Fatigue Syndrome in mice

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#### Background

Chronic fatigue syndrome (CFS) is an illness characterized by persistent and relapsing fatigue, often characterized by long-lasting and debilitating fatigue, myalgia, and impairment of neuro-cognitive functions along with other common symptoms.

**Objective** The present study was intended to explore the protective effect of hemin on experimental chronic fatigue stress in mice.

**Method & Result** Male albino mice (20–30 g) were subjected to swim stress induced fatigue in a force swimming test apparatus. Hemin (5 and 10 mg/kg, *i.p*) were administered daily for 21 days, after animals being subjected to force swimming test session of 10 min. Various behavioral tests (immobility period, locomotor activity, elevated plus maze test, mirror chamber and grip strength), biochemical parameters (lipid peroxidation, nitrite and glutathione levels), mitochondrial complex dysfunctions (complex I & II) and neurotransmitters estimation (DA, 5-HT and NE and their metabolites like DOPAC, 5-HIAA, HVA) levels were subsequently assessed through HPLC. Animals exposed to 10 min test session of forced swimming for 21 days showed a significant increase in immobility period indicating fatigue like behavior. Treatment with hemin (5 and 10 mg/kg) for 21 days significantly improved the decreased immobility period, increased locomotor activity, anxiety like behavior, oxidative defense, mitochondrial complex dysfunction and neurotransmitters level in brain.

**Conclusion** The present study highlights the protective role of hemin against chronic fatigue induced behavioral, biochemical and neurotransmitters alteration.

**Keywords-** Anxiety, Oxidative stress

## PT277

### Venlafaxine, but not fluoxetine reduces cuprizone-induced demyelination and neuroinflammation

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Antidepressants including serotonin-norepinephrine reuptake inhibitors [SNRIs] (e.g., venlafaxine and duloxetine) and selective serotonin reuptake inhibitors [SSRIs] (e.g., fluoxetine and sertraline) have been widely used to manage anxiety and depression symptoms in patients with multiple sclerosis (MS). However, the effects of SNRI and SSRI on the neuropathological progress of MS remain unclear. Here, we utilized a cuprizone-induced demyelination MS mouse model to examine the neuroprotective and anti-inflammatory effects of venlafaxine and fluoxetine on myelin deficits, oligodendrocyte death and astrocyte and microglia activations.

We examined the behavioral changes and brain pathologies in the mice received cuprizone (0.2%) with or without antidepressants for five weeks. Both antidepressants significantly reduced cuprizone-induced depression and anxiety-like behaviors, but only high-dose of venlafaxine alleviated cognitive impairment. Western blot and immunohistochemistry analysis showed that high dose venlafaxine reversed the myelin basic protein (MBP) and mature oligodendrocyte loss in the demyelinated brain. Both venlafaxine and fluoxetine decreased microglia and astrocyte activations associated with demyelination, but high dose venlafaxine demonstrated significant superior anti-inflammatory effects than fluoxetine. Our results indicate dose-dependent neuroprotective and anti-inflammatory effects of venlafaxine, which might be associated to provide its norepinephrine reuptake inhibition.

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PT278

## S100B Polymorphisms are Associated with Age of Onset of Parkinson's Disease

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**Background:** In this study we investigated the association between SNPs in the S100B gene and Parkinson's disease (PD) in two independent Swedish cohorts. The SNP rs9722 has previously been shown to be associated with higher S100B concentrations in serum and frontal cortex in humans. S100B is widely expressed in the central nervous system and has many functions such as regulating calcium homeostasis, inflammatory processes, cytoskeleton assembly/disassembly, protein phosphorylation and degradation, and cell proliferation and differentiation. Several of these functions have been suggested to be of importance for the pathophysiology of PD.

**Methods:** The SNPs rs9722, rs2239574, rs881827, rs9984765, and rs1051169 of the S100B gene were genotyped using the KASPar® PCR SNP genotyping system in a case-control study of two populations (431 PD patients and 465 controls, 195 PD patients and 378 controls, respectively). The association between the genotype and allelic distributions and PD risk was evaluated using Chi-Square and Cox proportional hazards test, as well as logistic regression. Linear regression and Cox proportional hazards tests were applied to assess the effect of the rs9722 genotypes on age of disease onset.

**Results:** The S100B SNPs tested were not associated with the risk of PD. However, in both cohorts, the T allele of rs9722 was significantly more common in early onset PD patients compared to late onset PD patients. The SNP rs9722 was significantly related to age of onset, and each T allele lowered disease onset with 4.9 years. In addition, allelic variants of rs881827, rs9984765, and rs1051169, were significantly more common in early-onset PD compared to late-onset PD in the pooled population.

**Conclusion:** rs9722, a functional SNP in the 3'-UTR of the S100B gene, was strongly associated with age of onset of PD.

PT279

## LSD increases social adaptation to opinions similar to one's own

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Inferring value from the reactions of others and adapting one's behavior to social group norms is an essential process in every-day decision making. However, the neuropharmacology of social influence processing is mostly unknown, although lysergic acid diethylamide (LSD) has been shown to alter social perception. To fill this knowledge gap, this study used LSD with and without ketanserin - a selective 5-HT<sub>2A</sub> receptor antagonist - pretreatment to investigate the role of the 5-HT<sub>2A</sub> receptor in social influence processing and decision making.

In a double-blind, randomized, cross-over study 23 healthy participants received 1)placebo+placebo, 2)placebo+LSD (100 µg po), and 3)ketanserin (40 mg po)+LSD in different sessions. Participants completed a task assessing social influence on aesthetic judgements, allowing the investigation of social feedback processing and decision making via fMRI and behavioral ratings. Adaptation to social norms was quantified by calculating the absolute value of the change between initial and final judgment in relation to the distance between initial judgment and the group norm for each trial.

Participants adapted their opinion more strongly to group norms in the high conflict (HC) than the low conflict (LC) condition under placebo and ketanserin+LSD. This pattern was reversed by LSD (all  $p < 0.05$ , Bonferroni corrected). Processing LC was associated with increased BOLD signal in the dorsal striatum in the LSD condition, while processing HC was associated with increased BOLD signal in the supplementary motor area in the placebo condition. No differences in BOLD signal were observed during decision making.

LSD increases adaptation to opinions similar to one's own, presumably via stimulation of 5-HT<sub>2A</sub> receptors. fMRI results reveal that this is attributable rather to alterations in social feedback processing than to decision making. The

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data shed light on the role of the 5-HT system in social influence processing and are important for the development of novel treatments in psychiatric disorders.

## PT280

### Deschloroketamine – a new ketamine analogue

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Arylcyclohexylamines belong to a group of New psychoactive substances (NPS), described as the dissociative anaesthetics. The most well-known members of the group are phencyclidine (PCP), ketamine and many of their analogues. Deschloroketamine (DXE) is one of the replacement of ketamine, mainly because of a ketamine sudden high price. This situation on street market is supposed to be a consequence of legislative changes in India which was the main source of ketamine according to US Department of State's International Narcotics Control Strategy Report from 2012.

The concern of this work was to identify and partially confirm DXE metabolites in urine samples. Thanks to a collaboration with the NIMH of the Czech Republic, urine samples of Wistar rats were collected within the behavioural study on DXE. Rats were subcutaneously administered with 30 mg/kg of DXE and the urine was collected for 24 h. One set of samples was plain diluted and the second set was hydrolysed before the dilution.

Metabolites were investigated owing to UHPLC-MS/MS system (QTOF MS). Electrospray ionization in positive mode was used within the non-target analysis with inclusion list.

To sum up the present study, DXE, dihydronordeschlorketamine, and nordeschlorketamine were confirmed thanks to in-house synthesized analytical standards. Glucuronides and minor metabolites were identified.

This study was funded by the Ministry of Interior of the Czech Republic (projects VI20172020056 and VI20152020048).

## PT281

### The pharmacological properties of the new psychoactive substance (±)-cis-4,4'-dimethylaminorex (4,4'-DMAR)

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#### BACKGROUND AND PURPOSE

(±)-cis-4,4'-Dimethylaminorex (4,4'-DMAR) is a psychostimulant that has been associated with 31 fatalities and other adverse events in Europe between June 2013 and February 2014. However, the pharmacology of 4,4'-DMAR remains largely unexplored.

#### EXPERIMENTAL APPROACH

We used *in vitro* uptake inhibition and transporter release assays to determine the effects of 4,4'-DMAR on human high-affinity transporters for dopamine (DAT), norepinephrine (NET) and serotonin (SERT). In addition, we assessed its binding affinities to monoamine receptors and transporters. Furthermore, we investigated the interaction of 4,4'-DMAR with the vesicular monoamine transporter 2 (VMAT2) in rat pheochromocytoma (PC12) cells and synaptic vesicles prepared from human striatum.

#### KEY RESULTS

4,4'-DMAR inhibited uptake mediated by human DAT, NET or SERT, respectively in the low micromolar range (IC<sub>50</sub> values < 2 μM). Release assays identified 4,4'-DMAR as a substrate type releaser, capable of inducing transporter-mediated reverse transport via DAT, NET and SERT. Furthermore, 4,4'-DMAR inhibited both the rat and human isoforms of VMAT2 at a potency similar to 3,4-methylenedioxymethylamphetamine (MDMA).

#### CONCLUSIONS AND IMPLICATIONS

This study identified 4,4'-DMAR as a potent serotonin-norepinephrine-dopamine releasing agent (SNDR). In contrast to the known effects of aminorex and 4-methylaminorex, 4,4'-DMAR exerts profound effects on human SERT. The latter finding is consistent with the idea that fatalities associated with its abuse may be linked to monoaminergic toxicity including serotonin syndrome. The activity at VMAT2 suggests that chronic abuse of 4,4'-DMAR may result in long-term neurotoxicity.

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## PT282

### Prenatal disruption of D1R-SynGAP complex impairs GABAergic interneuron migration and causes behavioural deficits in adulthood

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**Background:** The dopamine D1 receptor (D1R) plays a role in GABAergic interneuron migration. However, the molecular mechanism underlying this process and the pathophysiological consequences that occur when it is disrupted during prenatal development remain unclear. Synaptic Ras-GTPase activation protein (SynGAP) has been found to regulate GABAergic innervation. In this study, we investigated a potential protein-protein interaction between D1R and SynGAP, and its role in GABAergic interneuron migration and physiological consequences in the behaviors of adulthood.

**Methods:** co-immunoprecipitation and GST pull-down were carried out to investigate the D1R-SynGAP interaction and its regulation of D1R signaling. An interfering peptide (TAT-D1R<sub>pep</sub>) was developed and injected into pregnant mice during the occurrence of GABAergic interneuron migration. Immunofluorescent staining was used to analyze the distribution of GABAergic interneurons at various developmental stages. Locomotor, pre-pulse inhibition, visual discrimination and social behaviors were assessed to determine whether the prenatal impairment of GABAergic interneuron migration caused behavioral deficits in adulthood.

**Results:** we found a novel protein-protein interaction between the D1R and SynGAP, which facilitates D1R membrane expression, and D1R-mediated downstream signaling. These effects were blocked by TAT-D1R<sub>pep</sub>, which specifically disrupts the D1R-SynGAP interaction. Interestingly, disrupting this complex during embryonic development resulted in pronounced GABAergic interneuron tangential migration deficits, possibly due to altered actin and microtubule dynamics. More importantly, administration of TAT-D1R<sub>pep</sub> to pregnant mice led to abnormalities in locomotor activity, pre-pulse inhibition, sociability and visual discrimination in the offspring.

**Conclusions:** Our study discovered a novel protein-protein interaction between D1R and SynGAP, and this interaction plays a critical role in the prenatal GABAergic

interneuron migration and development of important behaviors in adulthood.

## PT283

### The role of the OX1R orexin antagonist SB-408124 on the lienocytogram of the spleen of animals

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The OX1R orexin antagonists are implicated in psychopharmacological researches as potential antialcoholic and anxiolytic drugs [1]. The requirements to safety of such drugs are very high because of its chronic use.

The objective was to study the effect of SB-408124, a OX1R orexin antagonist, on the spleen fingerprints (lienocytogram) and morphological changes of the blood cells in Wistar male. The studies were carried out on the populations of spleen cells concerning the genetic and toxic safety of the drug [1]. The changes in the cells were compared after intranasal single administration of the drug 200 µg in 20 µl (10 µl to each nostril) in the acute phase (24 h), in the subacute phase (20 µg in 20 µl, 28 days) and in the rehabilitation phase (2 weeks after withdrawal). The cut surface of spleen was carried over a slide and prints were made. Marking, fixing, coloring, drying of prints was made in the same way as blood smears. The prints were stained using Pappenheim's method, without prior drying [2]. Microkernels appeared in erythrocytes 1.8‰ and in lymphocytes 1.92‰ of peripheral blood. This shows that the eukaryotic organism reacts to the administration of the drug in the subacute phase, and the microkernels disappear in the rehabilitation phase. There is an increase of monocytes, lymphocytes, promyelocytes, polychromatophilic, oxyphilic normoblasts in the treated rats. The elimination of cells in both white and red blood during the rehabilitation phase (2 weeks) was observed. The study of blood-forming organs allow us to judge about the level of hematopoiesis. The spleen prints and its cells after drug administration were compared to the cells of the vascular bed of the blood. The results show that the hematopoietic organs at all stages of erythropoiesis are within the norm. Also the drug acts as a slight xenobiotic [3].



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## PT284

### **Astrocyte Activation in Locus Coeruleus Is Involved in Neuropathic Pain Exacerbation Mediated by Maternal Separation and Social Isolation Stress**

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Our previous studies demonstrated that emotional dysfunction associated with early life stress exacerbated nerve injury-induced mechanical allodynia. Sex differences were observed in several anxiety tests, but not in mechanical allodynia. To elucidate the mechanism underlying these findings, we have now investigated the involvement of astrocytes in emotional dysfunction and enhancement of nerve injury-induced mechanical allodynia in mice subjected to maternal separation combined with social isolation (MSSI) as an early life stress. We measured expression of glial fibrillary acidic protein (GFAP), an astrocyte maker, in each brain area by immunohistochemistry. GFAP expression in the locus coeruleus (LC) of female, but not of male mice, significantly increased after MSSI, corresponding to the behavioral changes at 7 and 12 weeks of age. Lipopolysaccharide (LPS)-treated astrocyte-derived supernatant was administered to local brain regions, including LC. Intra-LC injection of conditioned medium from cultured astrocytes treated with LPS increased GFAP expression, anxiety-like behavior and mechanical allodynia in both male and female mice. Furthermore, increases in anxiety-like behavior correlated with increased mechanical allodynia. These findings demonstrate that emotional dysfunction and enhanced nerve injury-induced

mechanical allodynia after exposure to MSSI are mediated, at least in part, by astrocyte activation in the LC. Male but not female mice may show resistance to MSSI stress during growth.

## PT285

### **The involvement of free fatty acid-GPR40/FFAR1 signaling in chronic social defeat stress-induced pain prolongation in C57BL/6J male mice**

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Emotional dysfunction such as depression or anxiety causes the development of chronic pain, and chronic pain also induces emotional dysfunction. Chronic pain which comorbid emotional dysfunction lead to impairment of quality of life. Some studies prove that n-3 fatty acids or fish oil attenuate pain and mood disorders, but its detail mechanism and relationship between chronic pain and emotional dysfunction is unknown. In this study, we tested that the involvement of brain GPR40/FFAR1 in social defeat (SD) stress-induced pain prolongation. Chronic SD stress mice showed decrease of social behavior in social interaction test and increase of anxiety behavior in elevated-plus maze test and open field test. Furthermore, chronic SD stress mice showed continuous induction of mechanical allodynia until 21 days after paw surgery. These mechanical allodynia were prolonged continuous infusion of GPR40/FFAR1 antagonist into the brain by osmotic mini-pump during chronic SD stress than those of vehicle treated mice of response to mechanical stimuli. Our findings suggest that fatty acids-GPR40/FFAR1 signaling might be important factor to regulate the pain prolongation induced after received emotional dysfunction.

## PT286

### **Low-doses of cannabidiol reduce neuropathic pain and associated anxious behavior by normalizing serotonergic activity**

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**Introduction:** There is a new interest in exploiting the therapeutic properties of cannabis and its constituents.

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Cannabidiol (CBD), the primary non-addictive component of cannabis, may possess antidepressant and analgesic effects mediated by pleiotropic interactions, including binding to the serotonin 5-HT<sub>1A</sub> receptor. We investigated the modulating effect of acute and chronic CBD on 5-HT Dorsal Raphe Nucleus (DRN) neurons and we tested its antinociceptive and anxiolytic properties on a neuropathic pain model in rats.

**Methods and Results:** Employing *in-vivo* single unit extracellular recordings, acute intravenous (i.v.) doses of CBD (0.1-1.0 mg/kg) decreased 5-HT DRN activity ( $p < 0.001$ ), effect prevented by pretreatment with 5-HT<sub>1A</sub> antagonist WAY 100635 (0.5 mg/kg, i.v.), but not with CB<sub>1</sub> antagonist AM 251 (1 mg/kg, i.v.) or TRPV1 antagonist capsazepine (1 mg/kg, i.v.), confirming CBD's strong activity at 5-HT<sub>1A</sub> but not at CB<sub>1</sub> or TRPV1. Subsequently, we investigated the analgesic effect of chronic subcutaneous (s.c.) treatment with CBD in the spared nerve injury (SNI) model of neuropathic pain, testing its effectiveness on the animal's associated anxiety and modulating effect of 5-HT DRN neurons. Using Von Frey filaments, CBD (5 mg/kg/day, s.c., for 7 days, administered 15 days after SNI surgery) prevented mechanical allodynia ( $p < 0.001$ ). SNI rats showed anxiety-like behavior in Elevated Plus Maze (EPM), Open Field Test (OFT) and Novelty Suppressed Feeding (NSF), but not depressive-like behavior in Force Swim Test (FST). CBD increased the time in open arms in EPM ( $p < 0.05$ ), number of entries in OFT ( $p < 0.05$ ) and reduced the latency to feed in NFS ( $p < 0.001$ ). CBD reduced the number of 5-HT DRN excitatory neurons responsive to mechanical stimulus, increased in SNI rats compared to sham.

**Conclusions:** These data suggest that short-term treatment with low-dose of CBD (5 mg/kg) has analgesic properties, reduces anxiety, and rescues the impairment of serotonergic neurotransmission observed under neuropathic pain conditions.

## PT287

### **Inhibition of peripheral macrophages by perineural administration of nicotinic acetylcholine receptor agonists suppresses spinal microglial activation, resulting in the improvement of neuropathic pain in mice**

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Neuro-immune interaction underlies chronic neuroinflammation and aberrant sensory processing resulting in the development of neuropathic pain. In this

study, we determined whether the inhibition of inflammatory macrophages by administration of  $\alpha 4\beta 2$  nicotinic acetylcholine receptor (nAChR) agonists improves neuropathic pain and affects microglial activation in the spinal dorsal horn (SDH) in male ICR mice. Neuropathic pain was rendered by partial sciatic nerve ligation (PSL). Flow cytometry revealed that CD11b<sup>+</sup> F4/80<sup>+</sup> macrophages were accumulated in the injured sciatic nerve (SCN) after PSL. TC-2559, a full agonist for  $\alpha 4\beta 2$  nAChR, suppressed the upregulation of interleukin-1 $\beta$  (IL-1 $\beta$ ) in the injured SCN after PSL. Moreover, TC-2559 attenuated lipopolysaccharide-induced upregulation of IL-1 $\beta$  in cultured macrophages, *in vitro*. Systemic (subcutaneous, s.c.) administration of TC-2559 during either the early (days 0–3) or middle (days 7–10) phase after PSL improved mechanical allodynia evaluated by the von Frey test. Moreover, local (perineural, p.n.) administration of TC-2559 and sazetidine A, a partial agonist for  $\alpha 4\beta 2$  nAChR, during either the early or middle phase of PSL improved mechanical allodynia, dose-dependently. However, p.n. administration of sazetidine A during the late (days 21–24) phase did not show the attenuating effect, whereas p.n. administration of TC-2559 during this phase relieved mechanical allodynia. Most importantly, p.n. administration of TC-2559 significantly suppressed morphological activation of Iba1<sup>+</sup> microglia and decreased the upregulation of inflammatory microglia-dominant molecules, such as CD68, interferon-regulatory factor 5, and IL-1 $\beta$  in the SDH after PSL, indicating that suppression of peripheral sensitization induced by p.n.  $\alpha 4\beta 2$  nAChR agonist also inhibited the central sensitization. These findings support the notion that pharmacological inhibition of inflammatory macrophages induced by peripheral administration of  $\alpha 4\beta 2$  nAChR agonist, could be nominated as a novel pharmacotherapy to relieve intractable neuropathic pain due to suppression of both peripheral and central sensitization.

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PT288

## Modulation of impulsive aggression through ventral hippocampus to ventromedial hypothalamus projection

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**Background:** Impulsive aggression is a sudden and uncontrollable violence, particularly under frustrated conditions, and is recognized as one of pathological symptoms in borderline personality disorder. It is well known that the activation of the ventromedial hypothalamus (VMH) elicits attack behaviors in mice. However, little is known about how brain regulates impulsive aggression. Clinical studies reported that subjects with borderline personality disorder have smaller volume and higher activation of the hippocampus. The ventral hippocampus (vHip) regulates emotional and motivated behaviors and has strong connections with hypothalamus. Thus, we hypothesized that the vHip modulates impulsive aggression through the VMH.

**Methods:** We infused a retrogradely fluorescent dye, the red retrobead, into the VMH to examine whether vHip projects to the VMH. To study the role of the vHip neurons projecting to the VMH, we used an adeno-associated viruses (AAV) to express a modified form of the human M4 muscarinic receptor (hM4Di) in the vHip. The hM4Di is activated only by clozapine-*N*-oxide (CNO) and triggers the Gi signaling pathway to inhibit neuronal activity. After 4~6 weeks of resting, CNO was infused into the VMH of transduced mice to inhibit the vHip terminals in the VMH.

**Results:** The signals of red retrobeads, which were infused into the VMH, co-localized with the acute stress-induced c-Fos expression in the vHip, suggesting that the vHip output projects to the VMH and this pathway is activated under acute stress conditions. After 4~6 weeks of the transduction with AAV5-hSyn-hM4Di-mCherry into the vHip, CNO infusion into the VMH decreased stress-induced attack behaviors in mice. The results indicate that hM4Di-mediated inhibition of the vHip terminals in the VMH suppresses attack behaviors in mice. **Conclusions:** Our findings provide the evidence that the vHip neurons projecting to the VMH modulates impulsive aggression in mice.

**Keywords:** aggression; ventral hippocampus; chemogenetic

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PT289

## A role for miR-132 in learned safety

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Learned safety is a fear inhibitory mechanism, which regulates fear responses, promotes episodes of safety and generates positive affective states. The molecular mechanisms of learned safety remain poorly understood, despite its potential as experimental model for several psychiatric illnesses, including post-traumatic stress disorder and depression.

Here, quantitative real time PCR based analysis of miRNA expression was applied to investigate expression of 22 miRNAs in the basolateral amygdala (BLA) of learned safety and learned fear trained mice. BLA levels of the safety-related miRNA miR-132 were enhanced by *in-vivo* transfection of a specific miRNA mimic and the relevance for learned safety was evaluated at the behavioral level and characterized electrophysiologically at the neuronal

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functional level in the BLA. Using a designated bioinformatic approach, potential miR-132 target genes were nominated and validated in *in-vitro* experiments.

Six safety-related miRNAs, including three members of the miR-132/-212 family, with differential expression in the BLA were identified. Enhancement of miR-132 levels in the BLA abolished the expression for learned safety and strengthened long-term potentiation at a fear synapse in the BLA. GAT1 and PTEN were validated as novel miR-132 target genes.

This is the first experimental evidence that amygdala miRNA expression is regulated in learned safety, which we suggest as relevant construct within the Research Domain Criteria (RDoC) matrix. We propose miR-132 as molecular "brake" and signature molecule to be considered in future preclinical and translational approaches testing the transdiagnostic relevance of learned safety as intermediate phenotype in fear and stress-related disorders.

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## PT290

### The impact of fatty-acid amide hydrolase inhibitors in an animal model of schizophrenia

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Several lines of evidence point to a close relationship between endocannabinoid system (ECS) and schizophrenia as cannabis use may precipitate or exacerbate the symptoms of this disease. The ECS is composed of CB1 and CB2 receptors, and their endogenous ligands. The best known endocannabinoids are anandamide and [2-arachidonoylglycerol](#), which are intracellularly degraded by fatty acid hydrolase (FAAH). Thus, the function of ECS might be modulated in a direct way, by ligands of CB receptors or indirectly by FAAH inhibitors.

The aim of the study was to determine the involvement of compounds which inhibit hydrolytic activity of FAAH, i.e., URB-597 and JZL-184 in mice. Schizophrenia-like behavior was assessed using an animal model of schizophrenia, based on psychotic properties of an N-methyl D-aspartate (NMDA) receptor antagonist MK-801. We studied an impact of MK-801 (0.1, 0.3, 0.6 mg/kg), URB-597 (0.1, 0.3, 1

mg/kg) and JZL-184 (1, 4, 8, 20, 40 mg/kg), administered alone or in combination on rodents' locomotion measured in actimeter cages.

Our results revealed that MK-801 (0.3 and 0.6 mg/kg) caused an expected growth of mice motility while URB-597 (0.1 and 0.3 mg/kg) or JZL-184 (4, 8, 20, and 40 mg/kg) induced hypolocomotion. After non-effective doses of FAAH inhibitors (1 mg/kg) we revealed that URB-597 had no significant impact on mice activity after MK-801, whereas JZL-184 intensified hyperlocomotion triggered by MK-801.

The results allow evaluating the possible relationship between ECS and positive symptoms of schizophrenia, focusing on the indirect modulation of ECS functioning, using FAAH inhibitors. We can suggest that compounds which modify ECS activity in the indirect way, might be a potential agent enhancing psychotic symptoms of schizophrenia in human.

## PT291

### Exploring participant-level trajectories of cognitive performance among patients with schizophrenia in a multi-national trial

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**Background:** It remains unclear whether the lack of clinical trial success and drug approval for cognitive impairment associated with schizophrenia (CIAS) is due to compounds being ineffective, or whether trial methodology itself has been a limiting factor in successfully demonstrating the efficacy of these agents. Schizophrenia is a heterogeneous disorder and whilst cognitive deficits are a core feature, the profile and degree of neuropsychological impairment can vary across patients. Though most individuals with schizophrenia exhibit some general cognitive impairment compared to antecedent expectations, such as premorbid intelligence, up to a quarter display cognitive performance in the 'normal' range. This may pose a problem for pro-cognitive drug trials in this population given that it potentially inflates baseline scores and reduces the scope to see improvement between treatment and placebo groups. In order to examine this potential issue, we investigated participant-level trajectories of cognitive performance

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among patients with schizophrenia enrolled in a multi-national, phase II clinical trial.

**Methods:** We conducted a post-hoc analysis of existing trial data from 463 patients with schizophrenia who participated in a randomized, double-blind, placebo-controlled trial. Patients met established diagnosis for schizophrenia (DSM-5), were clinically stable (non-acute) and had no more than moderate severity ratings on the Positive and Negative Syndrome Scale (PANSS). During the trial, participants completed two different neurocognitive test batteries, the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the MATRICS Consensus Cognitive Battery (MCCB), at 4 separate time points (screening, baseline, week 6 & week 12). Participant data were pooled across placebo and treatment groups to explore trajectories of cognitive performance, at the participant-level, across the course of the study.

**Results:** Linear mixed model analyses revealed that participants who performed within the 'normal range' at screening on cognitive tasks as measured by CANTAB, continued to perform well at baseline, week 6 and week 12, showing no significant change in their performance. By contrast, participants who performed below the normal range at screening, showed a significant improvement in their test performance across the remainder of the study. When compared in the context of MCCB, those participants who performed a standard deviation (SD) above the MCCB normative mean at screening, were also the participants who performed within the normal range on CANTAB. Approximately 25% of the overall sample were performing within a clinically normal cognitive range at screening.

**Discussion:** Substantial variability was evident in cognitive performance among the current sample of patients with schizophrenia. We identified a subsample of patients whose performance fell within a clinically normal range. Cognitive improvement was observed only in those who exhibited a deficit at screening, bringing into question whether the inclusion of unimpaired patients in clinical trials increases the risk of ceiling effects and minimizes chance to see change. Further analyses will determine the interaction between different cognitive trajectories and the treatment arms included in this trial to explore whether there are individuals with a particular cognitive profile who are most likely to respond to treatment. This has potentially important methodological implications in the search to find a drug to treat CIAS.

## PT292

### Elucidating the interaction between brain-derived neurotrophic factor (BDNF) and the dopamine D3 receptor in methamphetamine psychosis

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Methamphetamine abuse is associated with heightened risk of a psychosis similar to paranoid schizophrenia. Brain-derived neurotrophic factor (BDNF) has been implicated in neuronal adaptation to methamphetamine as well as pathways mediating psychosis. BDNF also modulates expression of the dopamine D3 receptor (D3R), which is involved in psychosis and methamphetamine sensitization. The main aim of this study was to elucidate brain mechanisms involved in methamphetamine psychosis. Specifically, we investigated the role of the D3R in changes in methamphetamine sensitization in mice with reduced BDNF expression.

We crossed BDNF heterozygous mice and D3R knockout mice to obtain wildtype, BDNF heterozygote, dopamine D3R knockout, and double mutant genotypes. Male and female mice were chronically treated with saline or methamphetamine during 6, 7 and 8 weeks of age on an escalating dose regime, after which they were left undisturbed for at least 2 weeks. Mice were then tested in automated photocells for changes in locomotor hyperactivity to an acute 3 mg/kg methamphetamine challenge.

As expected, acute methamphetamine increased locomotor activity ( $P < .001$ ) and this effect was enhanced in mice chronically pre-treated with the drug. In methamphetamine-pre-treated animals, the acute response to methamphetamine was significantly higher in BDNF heterozygotes compared to wildtype controls ( $P = 0.004$ ). This interaction seems reliant on D3 receptor availability as this enhancement of sensitization was lost in double mutant mice ( $P = 0.897$ ). Furthermore, these interactive effects were not observed in saline pre-treated mice, suggesting that the interplay between BDNF and downstream D3 signalling is particularly important during the sensitization phase of methamphetamine psychosis development.

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## PT293

### The protective effect of hemin against experimental chronic fatigue syndrome in mice: possible role of neurotransmitters

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Chronic fatigue syndrome (CFS) is an illness characterized by persistent and relapsing fatigue, often characterized by long-lasting and debilitating fatigue, myalgia, and impairment of neuro-cognitive functions along with other common symptoms.

**Objective** The present study was intended to explore the protective effect of hemin on experimental chronic fatigue stress in mice.

**Method & Result** Male albino mice (20–30 g) were subjected to swim stress induced fatigue in a force swimming test apparatus. Hemin (5 and 10 mg/kg, *i.p.*) were administered daily for 21 days, after animals being subjected to force swimming test session of 10 min. Various behavioral tests (immobility period, locomotor activity, elevated plus maze test, mirror chamber and grip strength), biochemical parameters (lipid peroxidation, nitrite and glutathione levels), mitochondrial complex dysfunctions (complex I & II) and neurotransmitters estimation (DA, 5-HT and NE and their metabolites like DOPAC, 5-HIAA, HVA) levels were subsequently assessed through HPLC. Animals exposed to 10 min test session of forced swimming for 21 days showed a significant increase in immobility period indicating fatigue like behavior. Treatment with hemin (5 and 10 mg/kg) for 21 days significantly improved the decreased immobility period, increased locomotor activity, anxiety like behavior, oxidative defense, mitochondrial complex dysfunction and neurotransmitters level in brain.

**Conclusion** The present study highlights the protective role of hemin against chronic fatigue induced behavioral, biochemical and neurotransmitters alteration.

## PT294

### Understanding the developmental profile of excitatory and inhibitory neurotransmission in a maternal immune activation model: Impact of cannabidiol treatment and therapeutic implications for schizophrenia

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**Background:** Maternal immune activation (MIA) during pregnancy is a risk factor for schizophrenia (Meyer and Feldon, 2012). An imbalance in the major excitatory (glutamate) and inhibitory (GABA) systems of the brain (which are important for cognition) may underlie the disorder (Yang and Tsai, 2017). We have shown that polyriboinosinic-polyribocytidilic (poly I:C) acid-induced MIA leads to cognitive impairment and social withdrawal in adult offspring that were ameliorated by cannabidiol (CBD) treatment (Osborne *et al.*, 2017a, 2017b). The aim of this study was to examine the developmental profile of excitatory/inhibitory neurotransmission in the poly I:C model, and determine whether CBD treatment could prevent any alterations.

**Methods:** Pregnant Sprague-Dawley rats were injected with poly I:C (4 mg/kg) or saline (control) at mid-late gestation (day 15). Male offspring were sacrificed at juvenile (postnatal day (PN) 14), adolescent (PN56) and adult (PN80) time points (n = 8/group). A cohort of control and poly I:C offspring (n = 8/group) were treated with CBD (10 mg/kg; *i.p.*) from PN56–80. The glutamatergic N-methyl-D-aspartate receptor (NMDAR), GABA<sub>A</sub> receptor (GABA<sub>A</sub>R) and glutamate decarboxylase 67 (GAD<sub>67</sub>) were examined in the prefrontal cortex and hippocampus.

**Results:** Control offspring displayed the expected pattern of NMDAR and GABA<sub>A</sub>R binding, and GAD<sub>67</sub> protein expression across development. Poly I:C offspring showed a similar developmental profile to controls at the juvenile and adolescent time points. In adulthood however, poly I:C offspring had lower GAD<sub>67</sub> levels (vs. controls) in the hippocampus, which was prevented by chronic CBD treatment. CBD administration did not significantly alter neurotransmission in control offspring.

**Conclusions:** Poly I:C exposure did not alter excitatory/inhibitory neurotransmission in juvenile or adolescent offspring, but did impair hippocampal GABA synthesis (GAD<sub>67</sub>) in adulthood, suggesting delayed onset of neurochemical alterations in this model. CBD treatment prevented poly I:C-induced GABAergic deficits in adulthood. Coupled with our behavioural findings, this

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suggests that CBD may have therapeutic potential for schizophrenia by increasing GABAergic tone.

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## PT295

### Synaptic vesicle protein 2A regulates the susceptibility to methamphetamine-induced hyperactivity in rats.

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Synaptic vesicle glycoprotein 2A (SV2A) is a prototype protein specifically expressed in the synaptic vesicles and facilitates action potential-dependent exocytosis of neurotransmitter. Although the precise mechanisms of SV2A in modulating synaptic release remain to be clarified, SV2A has been suggested to be involved in the development of psychotic disorders. In the present study, we investigated behavioral and *in vivo* microdialysis experiments using SV2A-mutant (*Sv2a*<sup>L174Q</sup>) rats, which carry a missense mutation (L174Q) in the *Sv2a* gene, to clarify the role of SV2A in modulating the susceptibility to methamphetamine (MAP)-induced hyperactivity. In behavioral studies showed that hyperactivity induced by the acute treatment with MPA (1 mg/kg, i.p.) was significantly enhanced by the *Sv2a*<sup>L174Q</sup> mutation, as compared to the control (F344) rats. In addition, development of supersensitivity (reverse tolerance) to the repeated MAP treatments (0.3 mg/kg/day, i.p., 12 days) was also significantly augmented by the *Sv2a*<sup>L174Q</sup> mutation. *In vivo* microdialysis study, dopamine release induced by MAP (100 μM) in the nucleus accumbens was markedly enhanced in *Sv2a*<sup>L174Q</sup> rats, compared with F344 rats, while the basal dopamine release remained unaltered.

Immunofluorescent double staining studies revealed that SV2A was co-stained with glutamate decarboxylase 67 (a GABAergic neuron marker), but not tyrosine hydroxylase (a dopaminergic neuron marker), both in *Sv2a*<sup>L174Q</sup> and F344 rats. In addition, the GABA<sub>A</sub> receptor antagonist bicuculline (BIC, 100 μM) applied through the dialysis probe completely suppressed the enhancement of dopamine release by the *Sv2a*<sup>L174Q</sup> mutation, implying a possible involvement of SV2A-GABA interaction. The present study demonstrates that dysfunction of SV2A by the *Sv2a*<sup>L174Q</sup> mutation augments the MAP susceptibility by enhancing dopamine release in the nucleus accumbens possibly via the interaction with GABA neurons. These results suggest that SV2A play a crucial role in regulating the vulnerability to neuropsychiatric disorders.

## PT296

### Development and validation of animal model for antipsychotics-induced metabolic alterations

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**Background:** Despite benefits, atypical antipsychotics (AAPs) produce troublesome metabolic adverse effects particularly weight gain, hyperphagia, dyslipidemia, hyperglycemia, insulin resistance and QT prolongation which further develops metabolic and cardiac complications. Currently used animal models of antipsychotics induced-weight gain (AIWG) only focuses on metabolic alteration in AAPs treated animals but none has reported the effects after induction of schizophrenia which mimics the exact clinical condition. **Aim:** The present study was aimed to develop and validate a new animal model to study AAPs-induced metabolic alterations in mice exhibiting schizophrenia like behavioral alterations following MK-801 treatment. **Methods:** Female BALB/c mice (weighing 18-25g) exhibiting schizophrenia like behavior after 5 days of MK-801 injection were administered olanzapine (3 and 6 mg/kg, per oral) and risperidone, (2 and 4 mg/kg, per oral) for six and four weeks respectively. Induction of schizophrenia like behaviors were assessed by open field test, sucrose preference test and novel object recognition test. Assessment of metabolic alterations were done into three categories viz. (i) Face validity (body weight, temperature,

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feed and water intake, organ weights), (ii) Predictive validity (metformin was used to reverse metabolic alteration produced by olanzapine and risperidone treatment). (iii) Construct validity (Serum Insulin, proinsulin, adiponectin, TNF- $\alpha$ , IL-6, Ghrelin levels). **Results:** Olanzapine and risperidone increased body weight in a time dependent manner. Olanzapine (6mg/kg) treatment well demonstrated validity of animal model for all three categories while risperidone failed to do so. Metformin (100 mg/kg) has reversed the metabolic and physiological alteration produced by olanzapine and risperidone treatment. Olanzapine and risperidone also reversed the schizophrenia like behavioral alterations produced by MK-801 injection. **Conclusion:** Our study concludes that treatment of schizophrenic mice with olanzapine (6mg/kg) for six weeks is a valid animal model to study AAPs-induced metabolic alterations.

**Key words:** Antipsychotics; weight gain, animal model, olanzapine, risperidone, metabolic syndrome.

## PT297

### Sex-dependent disruption of myelination in the neurodevelopmental model of schizophrenia

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#### Introduction

Numerous clinical studies show sex differences in the development and clinical manifestation of schizophrenia with higher incidence, earlier onset and more severe progression in men [1]. Similarly, there is emerging evidence for sex-dependent differences in white matter and myelin with their potential involvement in the

pathophysiology of schizophrenia [2]. However, these differences are not fully elucidated.

#### Methods

Both female and male rats, prenatally exposed to methylazoxymethanol acetate (MAM, 22 mg/kg) on gestational day 17 [3], were behaviorally tested to validate schizophrenia-like phenotype at adult age. Subsequently, the animals were subjected to magnetic resonance (DTI) with focus on white matter structures. Histological sections from collected brain samples were stained for myelin (luxol fast blue, LFB) and image analysis was performed on ultra-thin sections viewed in electron microscope (EM).

#### Results

Diffusion tensor imaging revealed decrease of fractional anisotropy ( $p=0.0157$ ) along with the increasing tendency of radial diffusivity ( $p=0.0635$ ) in the anterior commissure of male rats compared to control group. Qualitative LFB-stained sections as well as quantitative myelin ratio of EM images showed lower proportion of myelin in MAM-exposed male rats ( $p=0.0013$ ).

#### Discussion

Prenatal MAM exposure affects anterior commissure of adult rats in a sex-dependent manner. Simultaneous increase of fractional anisotropy and decrease of radial diffusivity could indicate changes in the structure of myelin sheath. These results are in accordance with histological and EM image analysis supporting myelination disruption only in the male population.

#### Conclusion

The MAM neurodevelopmental model of schizophrenia may be a useful tool for assessing the pharmacological effects of currently used and potential novel antipsychotics on myelination and white matter structures, with respect to sex-dependent specifics in the pathophysiology.

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## PT298

### **A systematic review of the consequences of maternal immune activation with poly I:C on neurotransmission in offspring: the need for a methodological consensus?**

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**Background:** Maternal immune activation (MIA) is a risk factor for neuropsychiatric disorders such as schizophrenia and can be modelled in rodents by administering synthetic virus polyinosinic-polycytidilic acid (poly I:C) to pregnant dams (Reisinger et al. 2015). The impact of poly I:C-induced MIA on offspring behaviour has been reviewed (Meyer & Feldon 2012); however, an understanding of the neurobiological changes that occur in offspring is lacking. Therefore, we conducted a systematic review of literature investigating the methods and neurodevelopmental effects of poly I:C administration on major neurotransmitter systems in offspring.

**Methods:** A systematic search of original research articles was conducted across major databases (PubMed, MEDLINE, Scopus and Web of Science). Studies were included if poly I:C was administered maternally and neurotransmission was assessed in the offspring. Studies that used neonatal poly I:C administration, did not measure neurotransmission, or investigated combined risk factors (e.g. genetic) were excluded.

**Results:** Twenty-seven articles (18 mouse; 9 rat) met criteria and were included. Studies showed that poly I:C induced region-specific alterations in dopaminergic (n=13), glutamatergic (n=14), GABAergic (n=11), serotonergic (n=7) and endocannabinoid (n=1) markers, mostly conducted in adult offspring. Methodologies differed across studies, including varied gestational timing (early vs. late gestation), dose (ranging 1 - 20 mg/kg), injection regime (single or repeated) and route of administration (intravenous vs. intraperitoneal). Consequently, results for poly I:C effects on neurotransmission are inconsistent, especially between studies that employed different gestational timing.

**Conclusions:** Overall, investigations of longitudinal alterations in offspring are limited, and the gestational

timing of poly I:C administration appears critical to the neurobiological phenotype of the offspring. Different results due to different methodologies raises the question of which neuropsychiatric disease is being modelled. Tracking the consequences of MIA on behaviour and neurotransmission over the course of neurodevelopment is required in order to provide meaningful insight into the pathogenesis and treatment of neuropsychiatric disorders.

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## PT299

### **Muscarinic M1/M4 receptor density alterations in the brain following cannabidiol treatment in a prenatal infection model of schizophrenia.**

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**Background:** Prenatal infection is a risk factor for schizophrenia and can be modelled in rodents with the synthetic virus, polyinosinic:polycytidilic (poly I:C) acid (Meyer and Feldon, 2012). We have previously shown that cannabidiol (CBD) treatment improves cognitive deficits and social interaction in the poly I:C model (Osborne *et al.*, 2017), but the mechanisms underlying these effects are unclear. The muscarinic M1 receptor (M1R) is involved in cognition and is down-regulated in a subset of schizophrenia patients (Scarr *et al.*, 2013). The aim of this study was to examine whether M1/M4R binding density is altered following CBD treatment in the poly I:C model.

**Methods:** Pregnant Sprague-Dawley rats were injected with poly I:C (4 mg/kg; i.v.) or saline on gestational day 15. Male offspring were treated for 3 weeks with CBD (10 mg/kg; i.p.) or vehicle, starting at postnatal day 56. Brain sections were incubated with [<sup>3</sup>H]pirenzepine to detect M1/M4R binding density in regions relevant to cognition and schizophrenia neuropathology (prefrontal and

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cingulate cortices, nucleus accumbens, caudate putamen and hippocampus).

**Results:** M1/M4R binding was observed in all regions, with the highest density in the nucleus accumbens. Poly I:C offspring showed reduced M1/M4R binding density across the brain regions examined (all  $p < 0.05$  vs controls). Chronic CBD treatment normalised M1/M4R binding density in poly I:C rats to control-like levels. CBD reduced M1/M4R binding in all brain regions examined ( $p < 0.05$ ), except the caudate putamen in control offspring.

**Conclusion:** Prenatal infection in rats reduced M1/M4R binding density similar to the post-mortem schizophrenia brain. CBD treatment in the model normalised M1/M4R binding density; however, the functional relevance of the reduction in the control CBD group is unknown. Overall, these results suggest that CBD may have therapeutic potential to normalise muscarinic receptor deficits in patients, but further research is required.

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## PT300

### Towards molecular insights into psychiatric disorders using affinity proteomics

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#### Background:

In the recent years, studies have shown a correlation between higher levels of autoantibodies and the frequency of autoimmune disease in patients with psychiatric disorders compared to healthy individuals. In this study we

used a targeted affinity proteomics approach to investigate the autoantibody repertoire of samples obtained from patients diagnosed with various psychiatric disorders and compared these with samples of healthy volunteers.

#### Methods:

In this study several psychiatric disorder associated cohorts, with different sample types have been used to study the autoantibody repertoire. In total we analysed more than 600 serum and 130 brain tissue samples in a first discovery phase. Based on this and previous in-house and external published studies of autoantibodies within psychiatry we selected 224 protein fragments from the Human Protein Atlas with a length of roughly 80 amino acids. Autoantibody profiling was performed using suspension bead array technology and IgG reactivity was measured in patients and controls.

#### Results:

Our findings indicate altered immune response in patients with chronic mental illness compared to healthy controls. In our study we identified potential predictive autoantibody signatures, presented with higher IgG reactivity in patients compared to healthy control samples.

#### Conclusions:

With our approach we were able to profile autoantibody repertoires in patients with psychiatric disorders. By further validating these putative autoimmunity targets, we could gain insights into the autoantigens associated to chronic mental illnesses.

#### References:

Zandian *et al.*: Untargeted screening for novel autoantibodies with prognostic value in first-episode psychosis; *Transl Psychiatry*. 2017 Jul 25;7(7):e1177

## PT301

### In vitro screening of antipsychotics using a neuronal network dysregulation model of psychosis

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**Background:** Dysregulation of neuronal networks has been suggested to underlie the cognitive and perceptual abnormalities observed in schizophrenia. We tested a new cellular model of psychosis where the NMDA antagonist and hallucinogenic drug phencyclidine (PCP) was used to emulate aberrant electrical activity that may occur in schizophrenia.

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**Methods:** Spontaneously active murine primary cortical networks cultured on microelectrode arrays (MEAs) were exposed to 0, 0.01, 0.1, 1, 10, and 50  $\mu\text{M}$  of PCP both in the absence and presence of the antipsychotic drugs aripiprazole 1  $\mu\text{M}$ , clozapine 1  $\mu\text{M}$ , and haloperidol 0.75  $\mu\text{M}$ , respectively.

**Results:** A concentration-dependent suppression of the spontaneous spike rate ( $\text{EC}_{50}$ : 0.01  $\mu\text{M}$ ) as well as of network synchronicity was observed following PCP exposure. All of the used antipsychotic drugs rescued this network inhibition and desynchronization, causing a right-shift of the dose concentration curve of PCP. At 0.01  $\mu\text{M}$  of PCP, the spike rate (spikes per minute) was  $52.4 \pm 5.7\%$  without an antipsychotic and (in the order of potency)  $85.8 \pm 8.4\%$  with aripiprazole,  $99.9 \pm 3.1\%$  with haloperidol, and  $107.6 \pm 4.4\%$  with clozapine, with reference to the initial native spiking activity.

**Conclusions:** Our studies provide proof-of-principle for the use of primary cortical networks grown on MEAs as an in vitro model of psychosis and an assay for screening drugs with a possible antipsychotic effect.

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## PT302

### Rapid augmentation of antipsychotic drugs by sodium nitroprusside (SNP). Behavioral assessment and effect on brain dopaminergic transmission in rats.

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#### Background

Recently, a single injection of the nitric oxide donor sodium nitroprusside (SNP) was found to induce a rapid (within 4 hours) and sustained (several weeks) antipsychotic effect in treatment-resistant schizophrenic patients [1]. Moreover, a single injection of SNP was found to produce a prolonged block of the psychotomimetic effects of phencyclidine or ketamine in rats [2], as well as to generate both rapid and persisting changes in brain synaptic plasticity, including enhanced excitatory

postsynaptic current (EPSC) responses and spine morphology in layer V pyramidal cells in rat medial prefrontal cortex (mPFC) brain slices [3]. Here we have studied the antipsychotic-like effect of SNP in rats using behavioral techniques, both when given alone and in combination with a sub-effective dose of risperidone (RISP). Correlative biochemical studies of regional dopamine release in the brain were also performed.

#### Methods

We used the conditioned avoidance response (CAR) test to investigate the antipsychotic-like efficacy, since this behavioral assay has shown a very high predictive validity to identify drugs with clinical antipsychotic activity, and in vivo microdialysis in freely moving animals to measure neurotransmitter efflux in the mPFC and the nucleus accumbens (NAc), respectively. Friedman's analysis of variance (ANOVA) followed up by Wilcoxon matched-pairs signed-ranks tests was used to analyse the CAR experiments and the microdialysis experiment was analyzed with two-way (treatment x time) repeated measures ANOVA followed by a planned comparisons test.

#### Results

RISP 0.25 mg/kg i.p. alone only caused 20% suppression of CAR, which is far below the degree of CAR suppression required to indicate a significant clinical antipsychotic effect, which is 70-80%. Addition of SNP 1, 1.5 and 2 mg/kg i.p. to RISP 0.25 mg/kg dramatically enhanced the antipsychotic-like effect to 67, 86 and 100% CAR suppression, respectively. However, addition of the highest dose of SNP, i.e. 2 mg/kg, resulted in escape failures indicating risk of non-specific side effects. SNP 2 mg/kg given alone generated only a small (11%) and clinically irrelevant CAR suppression. In the mPFC, addition of SNP 1 mg/kg significantly enhanced the risperidone-induced dopamine output, whereas there was no difference in the NAc in risperidone-induced dopamine output after SNP was added.

#### Conclusions

The present preclinical results support the clinical observation that a single injection of SNP can rapidly and dramatically augment the clinical efficacy of antipsychotic drugs in schizophrenia, albeit within a relatively narrow dose-range. SNP selectively increased risperidone-induced prefrontal dopamine release, while not increasing risperidone-induced dopamine release in the NAc. Therefore, the antipsychotic effect of SNP seems to be achieved by enhanced prefrontal dopamine output. Our results might imply that the very rapid and potent augmentation of the antipsychotic-like effect of risperidone by a single, low dose of SNP may be related to acute changes in brain synaptic function and morphology in pyramidal cells in the mPFC as previously described [3], and that the corresponding effects of the low dose may be potentiated by the concomitant administration of an

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antipsychotic drug. In this manner, both drugs could be administered in a lower dose, reducing the risk of side effects.

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## PT303

### **Polygenic risk for schizophrenia does not predict subclinical psychosis in adolescents**

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Family, twin and adoption studies have suggested a genetic link between schizophrenia and subclinical expressions of the disease. However, molecular genetic studies have found mixed evidence of a relationship between a schizophrenia genetic risk score and aspects of subclinical psychosis, with some results suggesting a positive relationship, whereas others found no or inverse relationships. We seek to clarify this by examining the relationship in a large cohort of children and young adults. Participants ( $n = 4767$ ) were part of the Philadelphia Neurodevelopmental Cohort, a publicly available resource designed to assess behavioural and biological factors contributing to mental illness in young adults (aged 8-21). A schizophrenia genetic risk score was determined using SNPs identified by the Psychiatric Genomics Consortium (PGC2). Regression analyses were used to test the association of the schizophrenia genetic risk score with positive psychosis symptoms, positive subclinical psychosis symptoms, negative subclinical psychosis symptoms, and combined subclinical symptoms. Models were adjusted for age, sex and ethnicity. All analyses were conducted in the whole sample, then separately in European Americans ( $n = 2566$ ) and African Americans ( $n = 1421$ ). The schizophrenia

genetic risk score was significantly associated with positive subclinical psychosis symptoms ( $B = .078$ ,  $p = .036$ ), negative subclinical psychosis symptoms ( $B = .099$ ,  $p = .007$ ), and combined subclinical symptoms ( $B = .102$ ,  $p = .006$ ), but not positive psychosis symptoms ( $B = .073$ ,  $p = .053$ ). No relationships remained significant when analyses were conducted in separate ethnic groups, indicating that the significant effects in the whole group likely reflect confounding from population stratification. This lack of association may reflect measurement error of the subclinical psychosis phenotype, measurement error related to construction of the schizophrenia GRS, bias in participant selection, or some combination of these. Alternatively, this result may reflect that subclinical psychosis is genetically unrelated to schizophrenia.

## PT304

### **A novel therapeutic target for neuropsychiatric disorders: The cerebellar alpha6-GABA-A receptor**

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The pathophysiological role of  $\alpha 6$  subunit-containing GABAA receptors ( $\alpha 6$ GABA<sub>A</sub>Rs), which are mainly expressed in cerebellar granule cells, remains unclear. Recently, we demonstrated that hispidulin, a flavonoid isolated from a local herb that remitted a patient's intractable motor tics, attenuated methamphetamine-induced hyperlocomotion in mice as a positive allosteric modulator (PAM) of cerebellar  $\alpha 6$ GABA<sub>A</sub>Rs. Here, using hispidulin and a selective  $\alpha 6$ GABA<sub>A</sub>R PAM, the pyrazoloquinolinone Compound 6, we revealed an unprecedented role of cerebellar  $\alpha 6$ GABA<sub>A</sub>Rs in disrupted prepulse inhibition (PPI), which reflects sensorimotor gating deficits manifested in several neuropsychiatric disorders. PPI disruptions were induced by methamphetamine and NMDA receptor blockers in mice. GABA<sub>A</sub>R modulatory effects of tested compounds were measured in *Xenopus* oocytes expressing recombinant

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$\alpha 6\beta 3\gamma 2sGABA_A$ Rs. Hispidulin given by *i.p.* or bilateral intra-cerebellar (*i.cb.*) injection significantly rescued PPI disruptions induced by methamphetamine, ketamine, MK-801 and phencyclidine. Intra-cerebellar effects of hispidulin were mimicked by Ro15-4513 and loreclezole (two  $\alpha 6GABA_A$ R PAMs), but not by diazepam (an  $\alpha 6GABA_A$ R-insensitive benzodiazepine), and were antagonized by furosemide (*i.cb.*), an  $\alpha 6GABA_A$ R antagonist. Importantly, Compound 6 (*i.p.*) also significantly rescued methamphetamine-induced PPI disruption in a manner prevented by furosemide (*i.cb.*). Both hispidulin and Compound 6 significantly potentiated  $\gamma$ -GABA<sub>A</sub>-mediated GABA currents. These results suggest that positively modulating cerebellar  $\alpha 6GABA_A$ Rs can rescue disrupted PPI via attenuating granule cell activity, and  $\alpha 6GABA_A$ R-selective PAMs are potential medicines for treating sensorimotor gating deficits in neuropsychiatric disorders. A mechanistic hypothesis is provided based on increasing evidence for a cerebellar contribution in cognitive functioning including sensorimotor gating.

## PT305

### **Allosteric modulation of muscarinic M<sub>1</sub> receptors is reduced in the hippocampus, striatum, and cortex of a sub-group of subjects with schizophrenia**

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#### **Background**

Evidence suggests positive allosteric modulators (PAM) of muscarinic M<sub>1</sub> receptors (CHRM1) could be a new treatment for schizophrenia (Conn et al., 2009). However, these agents may not be effective in a sub-group of subjects with schizophrenia identified as having low cortical muscarinic receptor availability, termed muscarinic receptor-deficit schizophrenia (MRDS; Scarr et al., 2009). Using the CHRM1 PAM, BQCA, we previously reported decreased responsiveness to allosteric modulation of the CHRM1 in the cortex (Brodmann's area (BA) 6) from subjects with MRDS (Dean et al., 2016). We have adapted this assay to use in situ radioligand binding and autoradiography to allow the measurement of BQCA's effects, both spatially and quantitatively, in complex CNS structures such as the hippocampus.

#### **Methods**

Hippocampal, striatal, and cortical (BA6) sections (20 $\mu$ m) were taken from 40 subjects with schizophrenia (20 MRDS and 20 subjects without a muscarinic receptor deficit (non-MRDS)) and 20 control subjects. We measured the binding of [<sup>3</sup>H]n-methylscopolamine ([<sup>3</sup>H]NMS) partially displaced by acetylcholine in the presence or absence of BQCA (BQCA-mediated binding).

#### **Results**

There was significant variation in BQCA-mediated binding in all regions by diagnosis (BA6:  $F_{2,56}=19.36$ ,  $p<0.0001$ ; striatum:  $F_{2,57}=8.166$ ,  $p=0.0008$ ; nine hippocampal sub-fields:  $F_{2,57}=3.9-15$ ,  $p=0.025-<0.0001$ ). Post-hoc analysis showed that compared to controls, BQCA-mediated binding was lower in MRDS, but not non-MRDS, in BA6 ( $p<0.0001$ , fold change: -0.64), the striatum ( $p=0.0007$ , fold change: -0.53), and nine hippocampal sub-fields ( $p=0.04-<0.0001$ , fold change: -0.65 - -0.89).

#### **Conclusion**

We have reproduced our membrane-based finding showing lower BQCA-mediated binding in BA6 from subjects with MRDS. Our data is the first evidence that in the striatum and hippocampus there is a loss of BQCA-mediated binding in subjects with MRDS. Our data support the argument that there is a decreased capacity for allosteric modulation of the CHRM1 in the hippocampus, cortex and striatum in MRDS and therefore these individuals may not respond optimally to this form of treatment.

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Scarr E, Cowie TF, Kanellakis S, Sundram S, Pantelis C, Dean B (2009) Decreased cortical muscarinic receptors define a subgroup of subjects with schizophrenia. *Molecular Psychiatry* 14:1017-1023.

## PT306

### **Increased Excitatory Amino Acid Transporter 1, isoform 1 (EAAT1) mRNA in subjects with schizophrenia**

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**Background:** Excitatory Amino Acid Transporter 1 (EAAT1) has been proposed to mediate the duration of glutamate receptor activation and prevent spill-over or glutamate excitotoxicity, through the perisynaptic binding and transportation of glutamate into glia. Using an Affymetrix™ microarray, we observed a 1.36 fold increase in EAAT1 mRNA expression in the prefrontal cortex (Brodmann's area (BA) 9) from subjects with schizophrenia (Scarr et al., 2016). The aim of the current study was to determine whether changes in EAAT1 mRNA levels occur in other cortical regions from subjects with schizophrenia, and whether the splice variants of EAAT1 (EAAT1a-c) contribute to the observed results.

**Method:** cDNA was prepared from tissue extracted post-mortem from BA44, BA46 and BA10 of subjects with schizophrenia (n=20) and non-psychiatric controls (n=18), obtained from the Victorian Brain Bank Network. PCR was performed using primers spanning the splice sites to determine which splice variants were expressed in the prefrontal cortex. EAAT1 mRNA levels were measured in subjects using qPCR, normalised to the geometric mean of two stably expressed reference genes.

**Results:** PCR detected only the presence of the full length EAAT1 mRNA in the prefrontal cortex. Normalised levels of EAAT1 mRNA were significantly higher in BA44 and BA10, but not BA46, from subjects with schizophrenia compared to age and sex matched controls (Mann Whitney test, BA44 fold increase: 1.50,  $p = 0.0017$ ; BA10 fold increase: 2.27,  $p = 0.0005$ ; BA46 fold increase: 0.91,  $p = 0.15$ ).

**Conclusion:** Our data suggests that widespread increases in EAAT1 mRNA in the prefrontal cortex are involved in the pathophysiology of schizophrenia, which cannot be attributed to the splice variants of EAAT1. These findings support a role for glia in glutamatergic dysfunction in schizophrenia and may have important implications for the treatment of the disorder.

#### Reference:

Scarr E, Udawela M, Thomas E, Dean B (2016) Changed gene expression in subjects with schizophrenia and low cortical muscarinic M1 receptors predicts disrupted upstream pathways interacting with that receptor. *Molecular psychiatry*.

#### PT307

##### **Diazepam suppresses the stress-induced dopaminergic release in the amygdala of methamphetamine-sensitized rat**

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Diazepam (7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one) is widely used in the treatment of various psychiatric disorders but is potentially overprescribed. The proper use of other psychotropic drugs is based on symptom classification and experience of clinicians. We conducted the present research to clarify the biological basis of the utility of diazepam in psychiatric medication, to support its more rational use.

We used rats with a vulnerability to stress caused by sensitization with methamphetamine ([RS]-N-methyl-1-phenylpropan-2-amine), which is regarded as a biological model of psychiatric disorders. We also exploited their susceptibility to conditioned fear stress and used the variation in the extracellular dopamine in the amygdala as the stress-load indicator. Using a surgical procedure, we inserted a probe into the amygdala, the anatomical center of affect. We then used microdialysis to sample dopamine for analysis. In other rats, we performed a behavioral experiment to observe the relationship between the variation in dopamine levels and freezing behavior.

After fear conditioning, diazepam suppressed the conditioned-stimulus-induced increase in extracellular dopamine in the normal amygdala as well as in the amygdala of methamphetamine-sensitized rats. However, administration of diazepam did not shorten freezing time in any group.

We previously reported similar phenomena with certain types of antipsychotic drugs and mood stabilizers. We suggest that these phenomena are important to the pharmacodynamics of all psychotropic drugs, and in this study, we report the biological basis of the pharmacodynamic effects of diazepam for the first time.

#### PT308

##### **Prolonged periods of social isolation from weaning is marked by an impaired blood-brain anti-inflammatory response**

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Post-weaning social isolation (pwSI) is used to study the neurobiology of schizophrenia<sup>1,2</sup>; yet, the investigation of blood-brain cytokines through this model remains scarce<sup>3</sup>. We investigated: a) IL-6, TNF- $\alpha$ , IL-10 at blood, prefrontal cortex and hippocampus of rats submitted to the pwSI, including their mRNA; b) the correlation between cytokines and locomotion at the open field in isolated animals. Male *Wistar* rats (n=10/group) were kept isolated (n = 1/cage) or grouped (n = 4/3 per cage) since weaning for 10 weeks. After, rats were submitted to the open field (20 min). Cytokines were measured using Milliplex MAP (pg/mL), and qRT-PCR performed using TaqMan. We used repeated measures ANOVA for behavioural analysis, and T test for cytokines analysis. There was a significant group & local & time interaction with isolated animals presenting hyperlocomotion at periphery and centre of the arena on the two first time-bins ( $p < 0.05$ ). Additionally, isolated rats had lower IL-10 ( $t = 2.265$ ;  $d.f = 17$ ;  $p = 0.044$ ;  $n = 9-10$ ) and lower IL-10 mRNA ( $t = 2.342$ ;  $d.f = 12$ ;  $p = 0.037$ ;  $n = 7$ ) blood levels when compared with controls. Likewise, IL-10 in the hippocampus of isolated rats was significantly lower ( $t = 2.318$ ;  $d.f = 15$ ;  $p = 0.035$ ;  $n = 8-9$ ). In the prefrontal cortex, isolated rats had reduced IL-6 ( $t = 2.280$ ;  $d.f = 16$ ;  $p = 0.037$ ;  $n = 9$ ), and reduced IL-6 mRNA ( $t = 2.234$ ;  $d.f = 17$ ;  $p = 0.039$ ;  $n = 9-10$ ). There was a significant negative correlation between locomotion and IL-10 in the hippocampus of isolated rats ( $\rho = -0.739$ ;  $p = 0.029$ ). Our study shows that prolonged periods of social isolation since weaning reduces IL-10 in rats, and this is translated from blood-to-brain. Reduced anti-inflammatory signalling may be critical for eliciting abnormal behaviour in adulthood.

**Keywords:** post-weaning social isolation; cytokines; early-life stress

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## PT309

### Receptor gene *npas2* rs4851377 polymorphism and its association with circadian rhythm in male population in Russia/Siberia: MONICA- psychosocial Study

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**Objective:** to study the prevalence and NPAS2 gene association with sleep disorders in male population in Russia/Siberia.

**Methods.** In 2014-2016 a random representative sample of the male population 25-44 years of one of the districts of Novosibirsk was examined. A random method was used to select 200 men (mean age= 35.5 years) who underwent psychosocial testing using the C.D. Jenkins scale "4-item Jenkins Sleep Questionnaire". In men, included in the study, the frequency distribution of genotypes rs4851377 of the NPAS2 gene was studied. Approved by Ethical Board. Differences in the frequency distribution of the rs4851377 of the NPAS2 gene between the groups were evaluated by the Chi square test ( $\chi^2$ ).

**Results.** Most of men needed 7 hours of sleep per day - 46.7%. The rates of those with an 8-hour sleep were 24.4%. Genotype C / C of gene NPAS2 rs4851377 is more common in those who slept in the day at least 8 hours (33.3%) and 9 hours (33.3%). Genotype C / T and T / T were in persons with 7- hour sleep (50% and 53.3%, respectively). Allele T carriers in 4.5-fold higher had 6 hours of sleep compared to the C allele carriers whose sleep was 9 hours. Allele T carriers had lower sleep duration (7 instead of 9 hours of sleep) in 4 times compared with allele C. **Conclusions** The findings suggest that site rs4851377 of gene-candidate NPAS2 determines need for sleep in men.

**Keywords:** NPAS2 gene rs4851377, sleep duration.

## PT310

### The influence of the Serotonin Transporter 5-HTTLPR polymorphism on Suicidal Behavior: a meta-analysis

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Suicidal Behavior is the second leading cause of death among youth worldwide (WHO, 2017) and the tenth among all age groups (CDC, 2017). Inherited genetic differences have a role in suicidality, as shown by family, adoption and twin studies, with heritability ranging from 30 to 55% (Brent DA et al., 2008; Voracek M et al., 2007). The SCL6A4 5-HTTLPR gene variant (Antypa et al., 2013), has been largely investigated for association with Suicidal Behavior (SB), with controversial results. Two early meta analyses reported opposite findings (Lin and Tsai, 2004; Li and He, 2007), while more recent ones showed significant associations though with some variability in the results (Clayden et al., 2012; Schild et al., 2013; de Medeiros Alves et al., 2015).

In this work we sought to determine whether the results of previous meta-analyses were confirmed or modified subsequently to the inclusion of more recent literature data.

Electronic literature search was performed to identify pertinent studies published until January 2018 using PubMed. Their reference lists were inspected to retrieve additional papers not indexed by MEDLINE. For meta-analyses, data were entered and analyzed through RevMan v5.3. Furthermore, sensitivity meta-analyses were performed considering ethnicity, gender, different phenotypes of SB and psychiatric diagnostic categories.

Our literature search yielded 156 articles on *SCL6A4* gene polymorphisms and SB association; among these, we identified 45 pertinent case-control studies.

Results are still under finalization and will be presented at the meeting. However preliminary analyses confirm a significant association ( $p < 0.01$ ) of 5-HTTLPR s variant with SB, though with a relevant degree of heterogeneity across clinical variables.

Our work contributes to clarify the contrasting previous evidences by taking into account most recent literature evidence. Nonetheless, many other modulators, including environmental factors and their interaction with the genome through epigenetics mechanisms may act to further increase the level of complexity.

## PT311

### **Unilateral Endothelin-1 injections into the medial prefrontal cortex and nucleus accumbens – a possible model for post-stroke depression and anxiety?**

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**Objective:** Post-stroke depression (PSD) and anxiety (PSA) commonly affect stroke survivors and are associated with poorer functional and cognitive recovery as well as higher mortality rates. Unfortunately, both diseases are usually undertreated and many cases may remain undiagnosed, indicating a need for a better understanding of the underlying mechanisms and improved treatments. Current animal models of PSD and PSA, which rely on middle cerebral artery occlusion to induce an infarct, may be confounded by associated motor deficits that can influence behavioral tests of depression and anxiety. The vasoconstrictor endothelin-1 (ET-1) can be used to induce small stroke lesions in specific brain areas. In the present study, we investigated the effect of unilateral microinjections of ET-1 into the nucleus accumbens (NA) and/or medial prefrontal cortex (mPFC) on anxiety- and depressive-like behavior.

**Methods:** ET-1 (or vehicle control) will be injected into the left NA and mPFC of adult male Sprague-Dawley rats using stereotaxic surgery. Animal behavior will be evaluated at 2 and 6 weeks post stroke using standard tests for locomotion (Open Field), anxiety (Elevated Plus Maze), and depression (Forced Swim Test).

**Results:** In a pilot study, we found that ET-1 injections into the left mPFC alone caused increased anxiety, with no effect on motor function or depressive-like behavior. We expect that unilateral lesions of the NA and mPFC will increase both anxiety- and depressive-like behavior without affecting motor function.

**Conclusions:** This is the first study specifically investigating the effect of unilateral ET-1 induced lesions of the mPFC and NC on anxiety- and depressive-like behavior in rats. Preliminary results indicate that an anxiety-like phenotype can be induced by ET-1-induced lesions to the left mPFC, suggesting that this animal model may be useful for studying post-stroke anxiety.

## PT313

### **The effect of prebiotics on mania-like behavior: a behavioral study in CLOCK transgenic mice**

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## Objectives

Prebiotics are non-digestible dietary fibers which when ingested alter the composition of the gastrointestinal microbiota. The gastrointestinal microbiota influences the brain through immunological, neurological and hormonal pathways. By manipulating the microbiota of the gastrointestinal tract these pathways can be indirectly influenced. Based on these observations we believe that prebiotics may potentially relieve manic episodes in bipolar disorder. The aim of the current study was to investigate the effect of prebiotics on the mania-like behavior seen in the CLOCKΔ19 transgenic mice.

## Methods

Male transgenic CLOCK mice (CLOCK) and their wildtype littermates (WT) were randomly allocated into three groups: control groups ( $n \geq 10$ ), lithium chloride (LiCl) groups ( $n \geq 12$ ) and prebiotics groups ( $n \geq 11$ ). The LiCl group was used as an effect reference to the prebiotics. After four weeks of treatment the animals were subjected to behavioral testing including the elevated plus maze (EPM). The elevated plus maze was used to estimate risk-taking behavior.

## Results

Preliminary results from the behavioral testing show that the untreated CLOCK animals showed increased risk-taking behavior in the EPM. Both prebiotics and LiCl attenuated this behavior by reducing the time spend in the open arms of the EPM. This reduction indicates a normalization of the risk-taking behavior seen in the CLOCK mice. The prebiotics showed an equivalent effect as LiCl on this behavioral estimate.

## Conclusions

LiCl is a common medication used in the treatment of bipolar disorder. LiCl normalizes the risk-taking behavior of the CLOCK mice, giving strength to the CLOCKΔ19 mice as an animal model of mania.

Prebiotics juxtaposed with LiCl showed an equivalent treatment effect on the risk-taking behavior of the CLOCK mice. These results are very promising, and gives strength to the hypothesis that prebiotics can attenuate the mania-like behavior seen in the CLOCK mice.

## PT314

### The effects of valproic acid on dopamine transporter availability in euthymic bipolar II disorder

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## Purpose:

Valproic acid (VPA) has been reported to decrease presynaptic dopamine (DA) synthesis capacity without altering D<sub>2</sub> receptor density. However, the effect of VPA on presynaptic DA transporters in bipolar disorder remains unclear. The current study aims to explore the effect of VPA on striatal DA transporter availability in euthymic bipolar II disorder.

## Method

14 patients (5 males) with DSM- IV bipolar II disorder treated with VPA were recruited in their euthymic state, with Young Mania Rating Scale (YMRS)  $\leq 7$  and Hamilton Rating Scale for Depression (HAM-D)  $\leq 12$ . Their striatal DA transporter availabilities, evaluated according to the ratio of [<sup>99m</sup>Tc] TRODAT-1 binding in the striatal area relative to occipital area, were obtained by using the single photon emission computed tomography.

## Result:

The mean YMRS and HAM-D were  $1.64 \pm 2.90$  and  $5.00 \pm 4.06$ . The mean serum VPA level was  $56.79 \pm 23.91 \mu\text{g/ml}$ . There was a significant negative correlation between the serum VPA level and striatal DA transporter availability. The clinical symptoms had no significant association with the VPA level and striatal dopamine transporter availability.

## Conclusion:

The reverse correlation suggests a down-regulating effect of VPA on striatal DA transporter level in euthymic bipolar II patients, which may be secondary to the effect of VPA on decreasing DA synthesis capacity.

## PT315

### DNA methylation analyses of the candidate genes identified by a methylome-wide association study revealed common epigenetic alterations in schizophrenia and bipolar disorder

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**Aim:** Gene-environmental interaction has been implicated in the pathogenesis of various mental disorders. Schizophrenia (SZ) and bipolar disorder (BD) are known to share genetic and environmental risk factors, and complex gene-environmental interactions may contribute to their pathophysiology. In contrast to high genetic overlap between SZ and BD, as revealed by genome-wide association studies, the extent of epigenetic overlap remains largely unknown. In this study, we explore if SZ and BD share epigenetic risk factors in the same manner as they share genetic components.

**Methods:** We performed DNA methylation analyses of the CpG sites in the top five candidate regions (*FAM63B*, *ARHGAP26*, *CTAGE11P*, *TBC1D22A*, and intergenic region (IR) in chromosome 16) reported in a previous methylome-wide association study (MWAS) of SZ, using whole blood samples from subjects with BD (N=450) and controls (N=457).

**Results:** Among the five candidate regions, the CpG sites in *FAM63B* and IR on chromosome 16 were significantly hypomethylated after Bonferroni correction in the samples from subjects with BD as well as SZ. On the other hand, only one of the three CpG sites in *TBC1D22A* were hypermethylated after Bonferroni correction in the samples from subjects with BD, in contrast to hypomethylation in the samples from subjects with SZ.

**Conclusion:** Hypomethylation of *FAM63B* and IR on chromosome 16 could be common epigenetic risk factors for SZ and BD. Further comprehensive epigenetic studies for BD such as MWAS will uncover the extent of similarity and uniqueness of epigenetic alterations.

## PT316

### Eye movements at the crossroads of attention and emotion processing in adults with Bipolar Disorder or ADHD.

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Introduction: Bipolar Disorder (BD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are two disorders with similar functional deficits and overlapping clinical presentations. Finding discrete biomarkers for each of these clinical entities is expected to improve diagnosis validity and outcomes. This study used eye movement

paradigms to distinguish adult patients with BD from patients with ADHD.

Methods. Adults, aged 18-62, with ADHD (n=22) and BD (n=20) performed an interleaved pro- and anti-saccade task modified to include task irrelevant emotional faces. The test variables were compared on their ability to accurately differentiate by diagnosis using supervised analytic techniques: a decision tree analysis and logistic regression.

Results. In our decision tree, two variables predicted diagnosis with an overall accuracy of 86%: multistep saccade trial percentage and direction error percentage. The logistic regression was similar; multistep saccade percentage (p=.015), error percentage (p=.025), and saccadic reaction time (p=.022) contributed to the model. Only saccadic reaction time (SRT) was impacted by emotional stimuli, specifically neutral faces. The logistic regression had 81% accuracy using these variables.

Conclusion. The integrity of the motor plan (multistep saccade trials) best discriminated ADHD from BD in these models, while measures of response disinhibition (direction errors) and processing speed (SRT) also differentiated them. Importantly, emotional stimuli played a role in modulating processing speed. Limited by a small sample size and the rather heterogeneous patient groups, these results provide a promising first step in capturing relevant physiologic dimensions to better distinguish patients with BD and ADHD using a cost effective method.

## PT317

### Clozapine metabolism and plasma levels in bipolar psychotic mood disorders: the effect of valproic acid and antidepressants

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The aim of the present study was to appraise retrospectively the influence of valproate (VPA) and antidepressants (ADs) on the steady-state plasma concentrations of clozapine (CLZ), the prototype of second-generation antipsychotics (SGAs), norclozapine (NCLZ, its main metabolite), their sum (NCLZ + CLZ) and ratio (NCLZ/CLZ) in 67 psychotic patients with a prevalent diagnosis of bipolar disorder (BD). Data were analyzed altogether and subdivided in four groups, according to pharmacological treatments: # 1 CLZ (n=21); # 2 CLZ plus antidepressants (ADs) (n=13); # 3 CLZ plus VPA (n=16); and #4 CLZ plus ADs plus VPA (n=17). Results showed significant positive correlations between CLZ plasma parameters (ng ml<sup>-1</sup>) and CLZ daily dosages (mg kg<sup>-1</sup> body weight) (n=67) (Spearman, r<sub>CLZ</sub>=0.49,

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$r_{NCLZ}=0.43, r_{sum}=0.52, P<.001; r_{ratio}=0.31, P=.011$ ). After the normalization of plasma parameters by given doses and natural log transformation, ANOVA factor analyses followed by pair-wise comparisons performed on the 4 groups and CLZ parameters, revealed significant drug effects on: 1) CLZ plasma levels, higher in group # 2 vs. group # 1; 2) NCLZ/CLZ ratios, lower in group # 2 vs. groups # 1 and # 3; moreover, significant drug x gender interactions were found in group # 3, while showing higher NCLZ levels and ratios in men than women. Despite its inherent limitations, this observational study confirms the significant increase of plasma CLZ concentrations and reduction of NCLZ/CLZ ratio when this drug is co-administrated with ADs (group # 2), a finding apparently counteracted by VPA (group # 4). The drug x gender interactions in patients concurrently taking CLZ and VPA (group # 3) warrant deepening by prospective and targeted investigations.

## PT318

### The Kynurenine Pathway and Mood Disorders: An Intersection of Monoaminergic, Glutamatergic and Immune Response

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**Background:** Growing evidence from preclinical and clinical studies supports the hypothesis that the underlying pathophysiology of depression implicates dysfunction in a wide array of systems, including the immune, monoaminergic and glutamatergic system. One potential confluence of these highly relevant systems is the kynurenine (Kyn) pathway of tryptophan (Trp) metabolism. Trp is a precursor to serotonin (5-HT), and its synthesis in the brain is highly dependent on the bio-availability of Trp in the plasma. Majority of Trp is metabolized into KYN via rate-limiting enzymes of tryptophan 2,3-dioxygenase, expressed mainly in periphery and indoleamine 2,3-dioxygenase (IDO) in the brain. Heightened inflammatory and stress responses may induce IDO increase production of KYN and shunt away serotonin, resulting in two major downstream byproducts: kynurenic acid (KynA) and quinolinic acid (QA); both are implicated in glutamatergic system modulation. This symposium will explore the impact of the glutamatergic modulator ketamine on the potential proinflammatory effects of KYN pathway activation in subjects with bipolar depression (BD).

**Methods:** This is a double-blind, randomize crossover trial assessing the efficacy of single dose of IV ketamine

(0.5 mg/kg) BD patients. We used specific ELISA and LC-MS-based metabolomics to characterize Kyn pathway analytes. We further tested whether baseline concentrations of the pro-or anti-inflammatory markers moderated changes in the KYN pathway and response to ketamine. Lastly, using a factor analysis model, we examined whether the KYN pathway moderated behavioral response to ketamine.

**Results:** Ketamine administration resulted in decreased IDO and increased both Kyn and KynA. At baseline, anti-inflammatory markers were inversely correlated with IDO concentration and positively related to Kyn concentration and Kyn/KynA. Some evidence for a predictive effect of QA was observed, such that higher baseline concentration was associated with more post-ketamine infusion improvement in depression symptoms.

**Conclusions:** Our report indicated that acute ketamine administration modulates the kynurenic pathway in BD patients. We show that ketamine significant lowers IDO, a critical component of the immunologically mediated component. It further drives conversion of Kyn to KynA, which has neuroprotective effect to the brain. Last, we show that ketamine modulates the role of inflammatory cytokines exert in the kynurenine pathway.

## PT319

### Genetic dissection of severity and onset modulators for Alzheimer's pathology in Down syndrome using cellular systems

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### Objectives

Trisomy of APP seems obviously responsible for extremely high incidence and early onset of AD pathology in Down syndrome (DS) brains. However, other genes on human chr21 likely modulate the age of onset, severity and modality of the clinical picture, as DS individuals have later or absent onset of clinical AD, and less intracerebral haemorrhage pathology, than euploid individuals with dupAPP. Our aim is to identify such modulator genes on chr21 using cellular models.

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## Methods

Neurons derived from isogenic hiPSCs we generated from a mosaic DS individual, unpublished iPSCs from segmental trisomy 21 DS and non-DS individuals, as well as from DS individuals with extremely early or late dementia onset are used in 2D, 3D and cerebral organoid paradigms. Optogenetic stimulation of Channelrhodopsin-2 engineered hiPSCs is used to determine the neuronal activity-dependent cellular phenotype modulation. CRISPR/Cas9 mediated reduction from trisomy to disomy for individual selected candidate genes on chr21 are performed on isogenic T21 iPSCs.

## Results

We detect T21-caused neurodevelopmental delay, increased  $\beta$ -amyloid and phospho-Tau presence, complex mitochondrial dysfunction, accelerated DNA damage and abnormal endosomes, and some of these phenotypes exacerbate in 3D and cerebral organoid paradigms, and/or can be reproduced in primary human neuroectodermal cells expanded and differentiated in vitro.

## Conclusions

Cellular phenotypes relevant for AD pathology caused by trisomy21 can be reproduced in iPSC-derived and primary NSC-derived neurons and differences sharpened by the use of cerebral organoid technology. Isogenic iPSCs allow detection of subtle changes in phenotypes (both pathogenic and protective) and evaluation of single gene's trisomy contribution using CRISPR/Cas9 editing.

## PT320

### Development of touchscreen-based objective evaluation methods for motivation using common marmoset

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**Background:** As some antidepressants are not effective in some patients with depression, a new drug for treatment-resistant depression (TRD) is required. Recent reports indicate a possibility that TRD is related to neuroinflammation in the central nervous system, so we are trying to make a new animal model of neuroinflammation-based depression using common marmosets. Methods to evaluate depression-like behaviors are required, but only a few methods using non-human primates have been reported. Patients with depression show multiple psychotic and somatic symptoms. As it is difficult to comprehensively evaluate depressive behavior in marmosets, we focused on "loss of motivation" which

affects quality of life in patients, and tried to make new evaluation methods which are close to the ones used in humans.

**Methods:** Nine common marmosets were used. The apparatus consisted of a 7-in. tablet and a USB-driven feeder was used to present stimuli and deliver rewards. In order to evaluate motivation, we made a progressive ratio task as follows. A Blue, yellow or red square was shown on the screen and marmosets touch it a certain number of times to get reward. The required number to get a reward was 1 at first then it was progressively increased to 30. The number of touches was used as index for motivation.

**Results:** We trained the marmosets on the task. Subsequently, the effects of reserpine were evaluated as a positive control because it induces depressive symptoms as a side effect in humans. We administered 60  $\mu$ g/kg once a day for three days and 24 hours after the final administration, the number of touch significantly decreased without any effects on motor function and appetite.

**Conclusions:** These results suggest that we could quantify motivation and detect the reserpine-induced depressive behavior. In the future, we will validate the above-mentioned pathological model using this evaluation system.

## PT322

### Epistasis in *HTR1A* and *BDNF* influences cortical 5-HT<sub>1A</sub> receptor binding: a PET study in 46 healthy subjects

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**Objective.** Genes involved in the serotonergic system as well as neuroplasticity have been major targets of neuropsychiatric research, especially in affective disorders. Two functional single nucleotide polymorphisms (SNPs), rs6295 of the serotonin 1A receptor gene (*HTR1A*) and rs6265 of brain-derived neurotrophic factor gene (*BDNF*), may impact transcriptional regulation and expression of

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the 5-HT<sub>1A</sub> receptor [1]. However, despite preclinical, clinical, imaging and postmortem evidence, the role of these SNPs is still not sufficiently understood [2, 3]. Here we investigated interaction effects of rs6295 and rs6265 on 5-HT<sub>1A</sub> receptor binding.

**Methods.** 46 healthy subjects were scanned with PET using the radioligand [*carbonyl*-<sup>11</sup>C]WAY-100635. Genotyping was performed for rs6265 of *BDNF* and rs6295 of *HTR1A*. Subjects showing a genotype with at least three risk alleles of both SNPs were compared to control genotypes. Cortical surface binding potential (BP<sub>ND</sub>) was computed for 32 cortical regions of interest (ROI) using FreeSurfer. Mixed model was applied to study effects of ROI and genotype. ANOVA was used for post hoc analyses.

**Results.** Considered separately, none of the SNPs showed significant effects on BP<sub>ND</sub>. High risk individuals with at least 3 risk alleles exhibited an increase in 5-HT<sub>1A</sub> receptor binding by an average of 17% (mean BP<sub>ND</sub> 3.56 ± 0.74 vs 2.96 ± 0.88). Mixed model produced an interaction effect of ROI and genotype on BP<sub>ND</sub> and differences could be demonstrated in 10 ROI post hoc.

**Conclusion.** The combination of disadvantageous allelic expression of rs6295 and rs6265 may result in increased 5-HT<sub>1A</sub> receptor binding in most cortical brain regions, a 5-HT<sub>1A</sub> receptor profile comparable to findings in depression. Based solely on healthy subjects, our results advocate further research on this genetic signature in affective disorders.

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## PT323

### A genome-wide association study identifies a novel locus associated with depressive state in the Japanese population

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**[Objective of the study]** Major depressive disorder (MDD) is a common, debilitating psychiatric disorder. Numerous efforts have been made to identify candidate genes contributing to MDD pathogenesis, and a recent mega-scale genome-wide association study (GWAS) identified 44 loci associated with MDD. However, the genetic etiologies of MDD remain unclear. To further understand the genetic basis of MDD, we conducted a GWAS in East Asia, wherein more than 10,000 Japanese ancestries were enrolled, and sought for MDD/depressive state susceptibility loci and their most proximal genes.

**[Methods used]** After quality control of genotypic data, a total of 229,276 SNPs were imputed using the 1000 Genomes data set. Participants completed a self-administered questionnaire on their medical history and health conditions that included the 6-item Kessler screening scale (K6 scale) for depressive state (cut-off point of 4/5; 3,982, depressive group [cases]; 6,350, non-depressive group [controls]).

**[Summary of results]** A genome-wide significant association ( $P = 7.6 \times 10^{-9}$ ) was observed for a locus in chromosome 20, an intronic region of *WAP-type four-disulfide core 11 (WFDC11)* belonging to the WFDC domain family, which was reported to play a regulatory role in inflammation.

**[Conclusions]** This is, to the best of our knowledge, the first large-scale GWAS on data from direct-to-consumer (DTC) genetic tests carried out in a population non-European-ancestry. The present study detected a novel locus significantly associated with depressive state, indicating that large-scale independent data of non-European ancestry can contribute to further revealing genetic basis for MDD.

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## PT324

### Brain connectivity changes by associative learning measured with resting-state fMRI as an approach to investigate treatment-induced neuroplastic changes

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**Objectives:** Standardized associative learning over a specific time period is associated with neuroplastic changes in brain structure and function measurable by magnetic resonance imaging (sMRI, fMRI).<sup>1</sup> Learning experience influences functional connectivity at rest.<sup>2</sup> These findings might be applicable in complementary treatment approaches for psychiatric diseases involving cognitive impairment.<sup>3, 4</sup> In this context, our aim was to show the effects of associative learning on resting-state brain connectivity using fMRI to provide a tool for future investigations in pharmacological fMRI.

**Methods:** Twelve healthy subjects were randomly assigned to two association learning paradigms, matching (1) Chinese characters with German words or (2) face dyads. In a longitudinal design, they participated in 2 MR measurements at 3T including 7 minutes of resting-state, separated by 3 weeks of computer-based learning. Global functional connectivity was estimated as the mean correlation of each voxel to the overall brain and compared between the two groups over time.

**Results:** We found no significant interaction effects, though findings depict significant main effects of time at the left parahippocampus/superior temporal pole ( $p_{\text{peak}}=0.007$ ), left supramarginal/superior temporal gyrus ( $p_{\text{cluster}}=0.006$ ,  $p_{\text{peak}}=0.022$ ) and mid cingulum/supplemental motor area ( $p_{\text{cluster}}=0.017$ ). Post-hoc t-tests confirmed that these areas all showed increased global functional connectivity at the 2nd measurement, independently of the learning paradigm.

**Conclusions:** The finding supports the hypothesis that standardized associative learning influences brain network connectivity at rest, in particular in the parahippocampus and in the temporal pole.<sup>5-7</sup> These regions are highly involved in learning and are found to be abnormal across different neuropsychiatric disorders.<sup>8</sup> Therefore, treatment-induced neuroplastic changes and differences between treatment regimes might be investigated based on associative learning paradigms as proposed in this study. This could present a valuable model for the interactions of

drugs (e.g., SSRIs) and standardized learning (e.g., by psychotherapy) due to neuroplastic processes.

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## PT325

### Prefrontal Neural Markers to Predict Antidepressant Treatment Outcome

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Major depressive disorder (MDD) is highly prevalent and current clinical procedures include no pretreatment information to detect patients that likely fail to recover from first-line serotonin reuptake inhibitors (SSRI). Hence, we aimed to determine neural prognostic predictors of treatment outcome (TO) that could personalize treatment

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and reduce suffering of MDD patients in a pharmaco MRI study.

Outpatients were scanned during cognitive task performance (*n*-back) before (d0), 4-8 hours (d1), 4 and 8 weeks (w4, w8) after initiation of open-label escitalopram treatment. This longitudinal design allows differentiating relatively stable trait-like predictors and state-like mediators. The latter might indicate a causal link between neural changes and TO.

The neural mediator of TO in the anterior medial prefrontal cortex (amPFC) revealed a reduced activity in case of clinical response and WM performance improvements. This supports the crucial role of the amPFC for the recovery from depression. Three prognostic predictors of TO were statistically significant: the activation in the dorsolateral PFC (dlPFC), the context-independent integration of the dlPFC with the amPFC and posterior cingulate cortex, and the context-dependent dlPFC integration with the parietal lobe. This prefrontal network might measure cognitive regulation processes predictive for later antidepressant response even prior treatment initiation.

Our encouraging results might propel the tremendous interest in predictive analytics in mental health closing the gap to precision medicine, better treatment and faster remission rates for MDD patients.

## PT326

### Increased cerebrospinal fluid fibrinogen and brain-blood barrier disruption in a subpopulation of psychiatric disorders

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Psychiatric disorders including major depressive disorder (MDD) presumably include heterogeneous subgroups with differing pathologies. We previously reported that a subpopulation of MDD patients had high CSF fibrinogen levels and white matter tract abnormalities. In the present study, we expanded our study by measuring CSF fibrinogen levels in a total of 387 samples from 108 MDD, 95 schizophrenia, 61 bipolar disorder (BD) patients and 127 controls. We found that 21 (19.4%) MDD, 13 (14.3%) schizophrenia, 6 (9.8%) BD patients and 1 (0.8%) control had abnormally high (>99percentile of controls) CSF fibrinogen levels. The frequency of high fibrinogen subjects was increased for these disorders compared to controls (MDD,  $p < 0.0001$ ; schizophrenia,  $p < 0.0001$ ; BD,

$p = 0.005$ , Fisher's exact test). In 97 samples from the Max Planck Institute of Psychiatry, 2 (10.0%) MDD, 3 (9.4%) schizophrenia, 4 (20%) BD patients and 1 (4.0%) control had abnormally high CSF fibrinogen levels. We also analyzed CSF fibrinogen levels in 17 patients who received electroconvulsive therapy (ECT). The fibrinogen levels significantly decreased after ECT ( $p = 0.04$ , paired t-test). We then measured the CSF/plasma albumin ratio (QAIB), a marker for blood-brain barrier (BBB) integrity, in 324 cases. The fibrinogen levels significantly correlated with QAIB (Spearman's  $\rho = 0.78$ ). Because fibrinogen levels are ~1000 times higher in plasma compared to CSF, the increased CSF fibrinogen levels in psychiatric patients might be an indication of BBB disruption. Our results suggest that a common pathophysiology may be present in a subpopulation of patients across the major psychiatric disorders that is represented by BBB disruption and increased CSF fibrinogen levels.

## PT327

### In vitro human lymphocyte activation fails to elucidate 5-HT<sub>2C</sub> receptor functioning

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**Background:** The gene encoding for the 5-hydroxytryptamine, type 2C receptor (HTR<sub>2C</sub>) displays several single nucleotide polymorphisms (SNPs), including rs6318, which has been associated with a variety of neuropsychiatric disorders and aberrant pharmacological effects of antipsychotic and antidepressant drugs. Whether this Cys23Ser missense mutation (rs6318) causes functional changes itself, is however not clearly supported by molecular evidence. Possibly, this SNP is in equilibrium with other HTR<sub>2C</sub> gene variants having functional consequences. Therefore, a clinical test to estimate the functional consequences of this SNP is needed. The authors tried to investigate whether a human ex vivo model based on HTR<sub>2C</sub> regulated Ca<sup>2+</sup> influx was suitable to estimate possible functional consequences of this rs6318 SNP.

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**Methods:** Human female peripheral mononuclear cells (PBMCs) were loaded with the FluoroForte® dye, whether or not after incubation with increasing concentrations of lipopolysaccharide (LPS). The effects on intracellular free calcium were measured after exposure to digitonin, ATP, histamine and various concentrations of the 5-HT<sub>2C</sub> receptor agonists,  $\alpha$ -methyl-5HT and MK-212.

**Results:** Neither  $\alpha$ -methyl-5HT nor MK-212 induced an intracellular free calcium ion increase at any of the concentrations tested. This was not measurably influenced by preincubation with LPS.

**Conclusions:** Measuring intracellular free calcium concentration in human lymphocytes cannot be used to assess the functionality of the rs6318 polymorphism in human patients. Another ex vivo or in vivo method remains to be identified to elucidate the consequences of rs6318 carriership in humans.

## PT328

### **Apathetic and agitated aspects of depression are differently associated with responses of hormones and nicotine craving to neurotransmitter challenge tests**

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Depression has formerly been divided into apathetic (inhibited) and agitated depression which can be mirrored by psychometric scales measuring fatigability/ asthenia (FA) and stress reactivity (SR) respectively. Asthenia in depression has been reported to derive from deficiency of dopamine (1), whereas responsiveness of the noradrenergic and serotonergic system have been described in relation to the anxiety and stress sensitive component of depression (2,3). In most drug challenge tests used for identifying neurotransmitter abnormalities, only magnitude of responses has been considered, but also response latency should be assessed because it might reflect differences between slow apathetic and fast irritable reactions of behavior. Since, furthermore, the three neurotransmitters and depression are relevant to smoking (4), the present experiment investigates if fatigability (FA) and stress reactivity (SR), measured by questionnaires in healthy individuals, can be separated by drug induced hormone responses and by drug induced cigarette craving

Method: 36 healthy male smokers assessed for FA and SR by questionnaires were tested under noradrenergic (NA), serotonergic (5-HT) and dopaminergic (DA)

pharmacological stimulation in a placebo controlled balanced crossover design. Placebo corrected time and size of drug induced hormone responses and behavioural measures of cigarette craving during nicotine deprivation were obtained.

Results revealed that both FA and SR were related to early 5-HT cortisol responses, indicating either supersensitivity of the HPA axis or postsynaptic 5-HT receptors, but only FA showed late and low DA prolactin responses indicating DA deficiency leading to slow full receptor occupancy. Smoking urge was increased by the noradrenergic drug merely in stress sensitive individuals, and larger prolactin responses to DA were associated with increased smoking urge.

Conclusions: Facets of depressiveness can be discriminated by neurotransmitter related hormone responses. Personality related differences in smoking motivation may be revealed by psychotropic drugs, and their underlying mechanisms may become evident by neurochemical responses to psychotropic drugs

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## PT329

### **Management of antidepressants in pregnancy and lactation**

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**OBJECTIVE:** Approaching the management of antidepressants in women during pregnancy, postpartum, lactation and mothering

**METHODS:** Related bibliographic review

**RESULTS:** We find studies that evaluate the effects on the fetus and neonate of mothers who have been exposed during pregnancy to antidepressant drugs (alterations in neurodevelopment, effects on birth weight, cancer, Autism, attention deficit disorder and hyperactivity ...). In many cases, the results are not statistically significant, it is considered that other factors could influence more than the direct contact with the drug or it is concluded that more studies would be necessary. For the management of antidepressants in clinical practice, the teratogenic classification of the FDA (Food and Drug Administration) is taken into account, with 5 categories (A, B, C, D, X). There are also risk classifications in the period of lactation.

**CONCLUSIONS:** Postpartum, breastfeeding and the period of mothering, is a period of high risk of onset of major depressive episodes. According to the literature, some antidepressants would be considered safer in pregnant women and during lactation, for example sertraline, is recommended as an appropriate option. In practice, it is essential to assess the benefit / risk in each case, taking into account the personal and family history and the medical-legal consequences.

## PT330

### Brain Glucose Uptake during Transcranial Direct Current Stimulation

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#### Introduction:

Transcranial direct current stimulation is a non-invasive electrical brain stimulation technique supposedly exerting actions on brain function by altering short-time and long-time synaptic activity. An antidepressant effect of tDCS in major depression was reported, yet clinical effect sizes appear to be inferior to SSRIs<sup>1</sup>. Moreover, critiques

questioned permeability of the current through the skull. Since *in vivo* mechanism of action studies are missing, we conducted a novel continuous infusion [<sup>18</sup>F]FDG PET study with simultaneous tDCS application to probe the impact of tDCS on simultaneous glucose metabolism.

#### Methods:

15 physically and mentally healthy subjects (7 female, average age=26.6) were measured with continuous infusion [<sup>18</sup>F]FDG PET twice. They received tDCS over bilateral dorsolateral prefrontal cortex (anode left, cathode right) with 0.5 mA, 1 mA and 2 mA active tDCS for 10 min in randomized order with 10 min inter-stimulus intervals each. The second PET-scan followed the same paradigm, yet sham tDCS (off). Dynamic glucose metabolism during tDCS was measured with continuous infusion [<sup>18</sup>F]FDG as recently demonstrated<sup>2</sup>. Active vs. sham was compared to by repeated measures ANOVA and post-hoc t-tests for each condition.

#### Results:

The repeated measures ANOVA did not yield a positive interaction between scan and stimulus intensity during stimulation (all  $p > 0.05$ ). Moreover, there was no significant difference in the regional cerebral metabolic rate of glucose in post-hoc t-tests between each of the stimulus intensity (all corrected  $p > 0.05$ ). Post-hoc exploratory analyses detected significantly increased rCMRglu in the right temporal cortex 5 min after stimulation in the inter-stimulus interval at 1 mA ( $pFDR = 0.03$ ).

#### Conclusion:

Our study failed to detect an effect of tDCS on simultaneously measured glucose metabolism, however indicated a trend towards a post-stimulation effect. This is congruent with literature on after-effects of tDCS on cortical excitability<sup>3</sup>. The result demand for mechanistic studies applying paradigms designed to test after-effects.

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## PT331

### The portuguese alimentary pattern, depression and the link

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**BACKGROUND:** Portugal is one of the european country with the highest rates of depression. The portuguese alimentary pattern is considered the Mediterranean diet type (that includes extra virgin olive oil, red wine, onions, garlic, coffee, nuts and seeds, fruit and berries) which is known for having antioxidant potential in vitro. The Mediterranean Adequacy Index- used to measure the degree of adhesion to the mediterranean alimentary pattern- has been decreasing since 1990 until now in Portugal. The composition and the metabolism of the gut microbiome is influenced by diet and the gut microbiome can modify exposures in ways that may be detrimental to the human host at various levels including increasing the risk of depression. Our aim was to investigate the evidence for the relation between the diet and depression, with a special interest in portuguese population.

**METHODS:** We examined key papers in order to identify prospective cohort studies that associated dietary patterns and the incidence of depression, particularly related to the mediterranean type of diet. Studies which related to the keyword were identified through PubMed, Medline, Google Scholar.

**RESULTS:** Studies that controlled for depression severity at baseline or that used a formal diagnosis as outcome did not yield statistically significant findings. Some studies found association between dietary improvements and changes in depressive symptoms.

**CONCLUSIONS:** There is some evidence in favour of the hypothesis that diet influences depression risk, however not all available results are consistent with this. More studies are necessary to increase the validity of findings in this field. In what concerns the portuguese population, there is no available data.

## PT332

### Relationship between ciliary neurotrophic factor concentration and severity of temporal-lobe epilepsy in women under the tereament with citicoline.

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**Objectives.** Role of neurotrophic factors is poorly understood in pathogenesis of epilepsya. Ciliary neurotrophic factor (CNTF) is neurotrophic cytokine from interleukin-6-family. CNTF is released (secreted) by astrocytes.

**Aim.** The aim of study was to analyze relationship between CNTF concentration in serum of patients with temporal-lobe epilepsy and severity of disease under the treatment of nootropic drug citicoline.

**Methods.** 36 women with temporal-lobe epilepsy were enrolled in study. Patients were divided into three groups (G1, G2, G3) depending on severity of disease: slowly progressing (G1), moderately progressing (G2), and progressing (G3) courses of disease. Each group included 12 patients selected randomly. Control group consisted of 35 healthy women. 500 mg of citicoline was injected i/m daily for 5 days on background of antiepileptic treatment. CNTF concentration in blood serum was assessed by ELISA method using Uniplan analyzer (Russia) and RsD systems (United States).

**Results.** At the beginning of study CNTF concentration in accordance with severity of disease was significantly higher: 14,3; 18,9 and 32,1 pg/mL in G1, G2 and G3 groups, respectively, in comparison with control level (3,4 pg/mL). After treatment CNTF concentration significantly decreased by 1,7 (8,3 pg); 1,5 (12,6 pg) and 1,3 (24,4 pg) times in G1, G2 and G3 groups, respectively, in comparison with the level before treatment.

**Conclusion.** Aggravation of clinical manifestation is accompanied by increase in CNTF levels in serum of patients with epilepsy. We hypothesize that CNTF is generated in response to pathological process, but immediately leaks into blood through damaged blood-brain barrier and does not exhibit neuroprotective action. Decrease of CNTF concentration in serum after citicoline treatment points out on repair of blood-brain barrier function and tendency to normalization of metabolic processes.

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PT333

## Striatal brain activity alterations in Tourette's Syndrome

### A meta-analysis of [<sup>11</sup>F] Fluorodeoxyglucose (FDG) PET studies

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#### Introduction

Despite intense research, the underlying mechanisms and the etiology of Tourette's syndrome remain unknown (1). Several functional imaging studies have pointed at a dysfunction of the basal ganglia, a striatal dopamine dysregulation and the involvement of cortical structures in the generation of tics (2). For a better understanding of neuronal circuits in Tourette's syndrome we performed a systematic review and meta-analysis of available [<sup>11</sup>F] Fluorodeoxyglucose (FDG) PET studies, which measure the glucose uptake of the brain, a proxy for brain activity (3) in striatum of Tourette's patients.

#### Methods

The bibliographic database Medline was systematically searched in March 2017 using the terms 'tourette' and 'PET', or 'neuroimaging'. The automated search results were narrowed to studies reporting on Tourette's syndrome evaluated with FDG PET reporting means and S.D. values. All statistical analyses were performed using the software package R 3.0.1 and the package metafor, as described previously (4). Briefly, standardized mean differences were calculated as Hedges' g. Meta-analysis was performed using a random-effects model.

#### Results

To date there are three studies evaluating the striatal glucose uptake in Tourette's syndrome by FDG PET imaging: Braun 1993 [16 Pat.], Eidelberg 1997 [10 Pat.], and Pourfar et. Feigin 2011 [12 Pat.] (5, 6, 7). Altogether 38 drug-free Tourette patients and 38 age and gender-matched healthy controls could be included in our meta-analytic approach. A comparison of glucose uptake in striatum (caudate and putamen) of Tourette patients and matched healthy controls was carried out. The Tourette patients showed significant lower FDG uptake in the striatum (mean -1,45 (95% CI =[-2,86; -0,03])). Detailed information is shown in a forest plot in figure 1.

#### Conclusion

Our results of lower brain activity measured by FDG PET in Tourette syndrome emphasize the theory of striatal alterations in Tourette patients.

#### Disclosure

Authors declare no conflict of interest with relation to this work.

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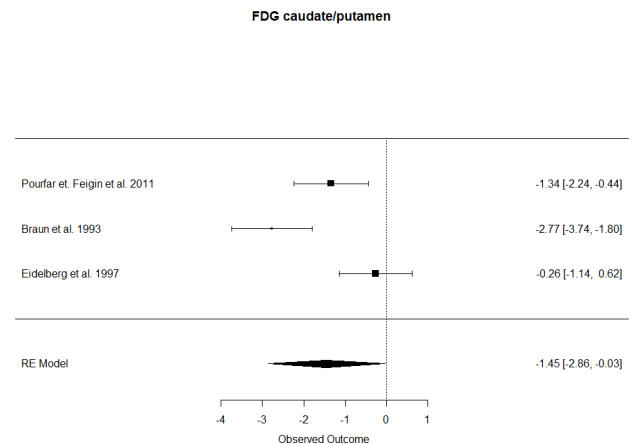


Fig.1. A forest plot for the striatum, revealing a sig. lower glucose uptake in Tourette patients compared to the control group.

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## PT334

### **In vivo dopamine D2 and D3 receptor binding measured with [<sup>11</sup>C]-(+)-PHNO and PET correlates with post-mortem mRNA expression**

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#### **Objective**

Associations between mRNA expression and positron emission tomography (PET) binding potentials have been investigated by means of transcriptome atlases, such as the Allen Human Brain Atlas (AHBA) [1]. Studies have shown strong correlations for several proteins, including the serotonergic system, the metabotropic glutamate receptor 1, as well as myelin-associated proteins [2, 3]. For the dopamine system, intermediate correlations between [<sup>11</sup>C]raclopride binding and dopamine D2 receptor mRNA expression were presented, alongside analyses for the dopamine transporter and DOPA decarboxylase, which showed rather low associations [4]. The purpose of this study was to investigate the association between gene expression of dopamine D2 and D3 receptors and in vivo protein distribution using the radioligand [<sup>11</sup>C]-(+)-PHNO and PET.

#### **Methods**

[<sup>11</sup>C]-(+)-PHNO binding potentials were derived from 27 healthy subjects, resulting in a signal comprising both D3 and D2 components. Virtually devoid of dopamine receptors, the cortical cerebellum was used as reference region to calculate parametric images. Analyses included subcortical regions of interest (thalamus, caudate, putamen, ventral striatum, hippocampus, substantia nigra and globus pallidus) as well as cortical regions. Gene expression values (log<sub>2</sub>) for dopamine D2 and D3 receptors were downloaded from the AHBA database. Subsequently, mRNA values and PET binding potentials were averaged within brain regions to perform correlation analyses

#### **Results**

Pearson's correlations of cortical and subcortical regions indicated a strong linear relationship between binding potentials and gene expression throughout the human brain for both receptors. For subcortical regions, correlation between [<sup>11</sup>C]-(+)-PHNO and mRNA was  $r=0.32$  for D2 and  $r=0.59$  for D3. Inclusion of cortical regions (in total 14 ROIs) yielded in correlation coefficients of  $r=0.81$  (D2) and  $r=0.90$  (D3).

#### **Conclusions**

Our results support reports that indicate spatial differences between dopamine D2 and D3 receptors throughout the

brain and affirm previous correlation analyses for dopamine D2 receptors imaged with [<sup>11</sup>C]raclopride.

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## PT335

### **Alterations of central metabotropic glutamate receptor 5 binding and glutamate concentrations by food intake**

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Glutamatergic neurotransmission in the brain is coupled with cerebral and possibly with systemic glucose metabolism, which could be affected by food intake. The current study aimed to investigate effects of food intake on metabotropic glutamate receptor 5 (mGluR5) binding and glutamate levels in the brains of living subjects.

Eleven healthy males underwent two clinical PET scans 3 hours apart using (*E*)-[<sup>11</sup>C]ABP688, a radioligand for mGluR5. Imaging sessions were performed with (n=5) or without (n=6) food intake between the two scans. Two MRS scans were also conducted, one before the first and the other after the second PET scan. Arterial blood was sampled during the PET scans to estimate mGluR5 binding as total distribution volume ( $V_T$ ). Glutamate concentrations in the right anterior and posterior insulae were measured using MRS data. To support the clinical PET findings, four awake rats underwent two PET scans on different days, one under control condition and the other under glucose-load (2g/kg p.o.) condition.

In assays of human subjects with food intake,  $V_T$  increased in the whole brain by 29% on average ( $p = 0.01$ ) and glutamate concentrations in the right posterior insula increased by 10% ( $p = 0.02$ ) between the first and second scans. By contrast,  $V_T$  decreased by 20% on average ( $p = 0.02$ ) and glutamate concentrations decreased by 8% ( $p = 0.01$ ) in the corresponding areas of subjects without food intake. Cerebral  $V_T$  was significantly and positively correlated with the blood glucose level (Pearson's  $r = 0.87$ ,  $p = 0.001$ ). In the rat experiment, intake of glucose alone was sufficient to increase mGluR5 binding by 18%.

These results indicate that plasma glucose levels are intimately involved in the dynamic activities of glutamate neurons represented by the mGluR5 status and glutamate metabolism in the brain, as cerebral glutamate neurotransmitter cycling is concurrent with aerobic glycolysis.

## PT336

### D-Amphetamine response in female subjects is mediated by sex hormones

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**Objective:** Sex hormones have been shown to impact brain development and the behavioral and neurochemical response to dopamine-increasing substances. So far, data suggest that estrogen facilitates the stimulating effects of d-amphetamine, while progesterone seems to inhibit them. The effect of hormonal contraception on d-amphetamine response remains unknown thus far. We studied the impact of sex hormones on the behavioral and neurochemical response to d-amphetamine in healthy females.

**Methods:** Ten stimulant-naïve female subjects underwent two positron emission tomography scans using the dopamine  $D_{2/3}$  receptor agonist radioligand [<sup>11</sup>C]-(+)-PHNO, the current gold standard for measuring changes in extracellular dopamine in the living human brain. Behavioral effects of d-amphetamine were assessed using the drug effects questionnaire (DEQ) and the subjective states questionnaire (SSQ). Blood was drawn and serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen, progesterone, and testosterone were measured. [<sup>11</sup>C]-(+)-PHNO  $BP_{ND}$  values were extracted from ventral striatum, putamen, caudate, globus pallidus, and substantia nigra/ventral tegmental area using the simplified reference tissue model (SRTM-2).

**Results:** We observed a positive correlation between the behavioral response to d-amphetamine and serum levels of LH, FSH, and estrogen with  $r^2$  values up to 0.65. There was no significant correlation with progesterone levels. Hormonal contraception seemed to attenuate the behavioral response to d-amphetamine. Sex hormone levels were not related to [<sup>11</sup>C]-(+)-PHNO binding.

**Discussion:** Our data speak in favor of a relevant impact of sex hormones, especially estrogen, on the behavioral response to d-amphetamine and suggest a blunting effect of anti-contraceptive hormones. Despite strong behavioral effects, sex hormones had no impact on [<sup>11</sup>C]-(+)-PHNO  $BP_{ND}$  values, which might suggest the existence of a non-dopaminergic pathway by which sex hormones modulate the behavioral response to d-amphetamine.

# CINP 2018: Poster Abstracts

## PT337

### Neuroprotective role of cannabidiol in brain disorders: a systematic review

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**Keywords:** Cannabidiol, neuroprotection, brain disorders

#### Background:

**Aim:** To study the neuroprotective role of cannabidiol (CBD) in neurology and psychiatry, we performed a systematic review to evaluate the effect of this medication in neuroinflammation, oxidative stress, neuroplasticity, cognition, behavior, sleep disturbances, pain, among other disorders. **Methods:** Following the PRISMA protocol we systematically searched PubMed, Scopus, and Web of Science for pre-clinical and clinical articles measuring neuroinflammation, peripheral inflammatory or oxidative stress markers associated to brain disorders, neuroplasticity assessed in vitro or in vivo with neurotrophic factors, neurophysiology, behavior in animal models of psychiatric and neurologic illnesses and cognition in humans. Two independent researchers screened the abstracts and the full papers. The consensus for cases of disagreement where made by the two researches after discussion. We extracted data and divided according different subjects (humans, animals, in vitro). The protocol of study was registered in PROSPERO under number 80518. **Results:** A total sample of 4,426 abstracts were screened, and 236 full papers were read. The most commonly articles found between the 146 remaining were pre-clinical (132; 90,41%) and the majority evaluated animal models of hypoxic-ischemic injury and multiple sclerosis. The cellular cultures where mostly related to the CBD effects on microglia. Studies with humans assessed different brains disorders, however the most studied was multiple sclerosis. About 86% of the papers described at least one neuroprotective action of CBD. **Conclusion:** We conclude that CBD presents a neuroprotective role in different brain disorders, based on pre-clinical and clinical evidence.

## PT338

### Prediction of the human whole-brain transcriptome for hypothesis generation and drug development

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#### Background

The study of gene expression in the human brain promises novel insights on brain function in health and disease. The Allen Human Brain Atlas (AHBA) constitutes the most comprehensive resource comprising mRNA microarray data of approximately 3700 samples collected from 6 brain donors. While high correlation with protein binding assessed with PET imaging has been established for several targets [1], extensive exploitation of this data is limited by its sparsity, sampling bias and the abundance of probes with varying sensitivity. We developed a method to assess transcription for each gene in the entire brain.

#### Methods

Samples from the AHBA were registered to surface space using FreeSurfer 5.1 [2]. For each gene, probes were averaged after discarding of probes which negatively affected relative structured variability of expression, i.e. introduced spatial randomness. For each gene, mRNA expression between brains was normalized based on average values in brain regions. Prediction of mRNA expression on the entire cortical surface was carried out using Gaussian process regression [3]. Validity of results was assessed using leave-one-out cross-validation by correlating observed and predicted expression.

#### Results

Comprehensive gene expression data for 18,686 genes was generated in FreeSurfer fsaverage surface space and MNI space. Only 816 genes exhibited high spatially structured variability of >50% of semivariance. Cross-validation showed minimal bias of  $\pm 0.016$  log<sub>2</sub> intensity and high correlation of validity of prediction results with spatial dependence for all genes on the cortical surface ( $r=0.91$ ).

#### Conclusions

The resulting data can be readily integrated with imaging data at vertex-wise resolution without bias arising from non-uniform sampling. Further, it allows for intuitive viewing of the distribution of transcription throughout the human brain. This may support hypothesis generation and drug development. A web application to provide this information to a greater audience will be made available on the website of our institute.

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## PT339

### **Oxytocin reactivity to an emotional challenge paradigm and relations to social-cognitive functions in healthy volunteers**

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#### **Objective**

Here we introduce an emotional challenge paradigm for measuring oxytocin (OT) reactivity in probands by analyzing a series of OT plasma levels before and after the challenge. For proof of principle, we examine whether variation in OT reactivity is associated with variation of social-cognitive functioning.

#### **Methods**

20 healthy male probands were recruited for the following study set-up: A venous catheter was applied to allow for serial blood draws in 5 min intervals for 30 min. 5 min after venipuncture an emotionally challenging but not disturbing video clip was shown to the probands of a man receiving a painful molar extraction at the dentist's.

OT was analysed in blood plasma using solid phase extraction followed by ELISA (Enzo). OT reactivity was calculated as the difference of plasma values at 25 min post challenge and baseline.

The following social-cognitive domains were measured: cognitive and emotional empathy using the Multifaceted Empathy Test and emotional face recognition using the Pictures of Facial Affect Test.

#### **Results**

On average, plasma OT was 67 pg/ml at baseline and increased significantly post challenge by 15 %. Low

plasma OT at baseline and high oxytocin reactivity were significantly correlated with emotional empathy, but not with cognitive empathy nor with facial affect recognition.

#### **Conclusion**

A short emotional video of a person experiencing pain can be used as a challenge paradigm for eliciting an increase of peripheral OT in healthy male subjects. The paradigm lends itself as a research tool for determining oxytocin reactivity in probands. The observed combination of low peripheral OT at baseline with high OT reactivity may be a psychoendocrine trait that is linked to higher emotional empathetic functioning, which should be studied further in psychiatric patients with compromised social cognition.

## PT340

### **Genome-wide association study identifies genetic polymorphisms associated with the analgesic effect of fentanyl in the preoperative cold pressor-induced pain test**

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**Objective:** Opioid analgesics are widely used for the treatment of moderate to severe pain. The analgesic effects of opioids are well known to vary among individuals. Such individual differences in opioid sensitivity may at least partly be attributable to genetic factors. The present study focused on the genetic factors that are associated with interindividual differences in opioid and pain sensitivity.

**Methods:** We conducted a multistage genome-wide association study (GWAS) in subjects who were scheduled to undergo mandibular sagittal split ramus osteotomy and were not medicated until they received fentanyl for the induction of anesthesia. We preoperatively conducted the cold pressor-induced pain test before and after fentanyl administration. Whole-genome genotyping was performed with iScan System (Illumina, San Diego, CA, USA) and mainly two kinds of BeadChip, Human1M v1.0 and Human1M-Duo v3.

**Results:** As a result of GWAS with approximately 300,000 polymorphic markers in surgical patients, the rs13093031 and rs12633508 single-nucleotide polymorphisms (SNPs) near the *LOC728432* gene region and rs6961071 SNP in the *tcag7.1213* gene region were significantly associated with the analgesic effect of fentanyl, based on differences

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in pain perception latency before and after fentanyl administration. The associations of these three SNPs that were identified in our exploratory study have not been previously reported. The two polymorphic loci (rs13093031 and rs12633508) were shown to be in strong linkage disequilibrium. Subjects with the G/G genotype of the rs13093031 and rs6961971 SNPs presented lower fentanyl-induced analgesia. However, no SNPs were identified as genome-wide significant in their associations with pain sensitivity.

**Conclusions:** Our findings provide a basis for investigating genetics-based analgesic sensitivity and personalized pain control, in which the G alleles of the rs13093031 and rs6961971 SNPs are associated with lower opioid sensitivity.

## PT341

### **Novel Modulators of Serotonin, Dopamine, and Mu Opiate Receptors for Substance Use Disorders Pain and Mood Disorders**

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#### **Objective**

A series of novel compounds has been discovered that bind 5-HT<sub>2A</sub>, D<sub>1</sub> and mu opiate receptors. This series is exemplified by ITI-333, which possesses low nanomolar affinity for 5-HT<sub>2A</sub>, D<sub>1</sub> and mu opiate receptors with Ki values of 8.3nM, 50nM and 11nM, respectively. Here, we report the pharmacological profile of ITI-333 as related to treatment of pain and substance use disorders.

#### **Methods**

The pharmacological profile of ITI-333 was explored using in vitro receptor binding and cell-based functional assays and in vivo tests of functional activity at 5-HT<sub>2A</sub>, D<sub>1</sub>, D<sub>2</sub>, and mu opiate receptors (MOP).

#### **Results**

ITI-333 binds with high affinity to 5-HT<sub>2A</sub>, D<sub>1</sub> and MOP receptors. At MOP receptors it acts a partial agonist and as a biased ligand, selectively activating the Gi over  $\beta$ -arrestin signaling pathways. MOP receptor partial agonism was confirmed demonstrating that the intrinsic efficacy of buprenorphine was higher than ITI-333. ITI-333 reduced morphine-induced hyperactivity and morphine-induced analgesia in the tail flick assay in mice. Mice treated with ITI-333 also exhibited potent, naloxone-sensitive analgesia. ITI-333 does not exhibit morphine-like dependency, withdrawal, constipation or decreased respiration but can ameliorate morphine-induced decreases in GI-motility. ITI-

333 blocks clinical signs associated with withdrawal from oxycodone dependency in mice.

#### **Conclusions**

The unique pharmacological profile of ITI-333, including potent 5-HT<sub>2A</sub> antagonism, D<sub>1</sub> activity and MOP partial agonism is predicted to translate into utility for addressing pain, dependence and psychiatric co-morbidities (e.g. depression, anxiety) accompanying a broad spectrum of substance use disorders, while reducing withdrawal symptoms without contributing to drug dependencies.

## PT342

### **Altered cerebellar microcircuit shapes emotional memory via cerebellothalamic connectivity**

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(\*equally contribution)

It has been overlooked that emotional processing is associated with bodily movement on the basis of neuronal circuits, particularly in fear memory consolidation and retrieval. To address this issue, we engineered local connectivity by targeting signal transducer and activator of transcription 3 (STAT3) in Purkinje cells. Herein, we found that STAT3 knockout(KO) group increases long-term fear memory and shows more exaggerated behavioral responses. During fear memory enhancement, long-term potentiation (LTP) is reframed to long-term depression (LTD) at parallel fiber-Purkinje cell synapses of STAT3 KO mice, indicating the reorganization of cerebellar microcircuits. The bidirectional synaptic plasticity in fear memory enhancement requires highly expressed *gluA1/2* subunits. In fear memory retrieval, STAT3 KO mice increase the neuronal activity in the paraventricular nucleus of thalamus where consolidated fear memory is distributed from altered local connectivity in cerebellum. These results demonstrate that altered cerebellar microcircuit regulates fear memory processing via cerebellothalamic connectivity.



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## PT343

### MiRNA-19 and the enhanced vulnerability of developing stress-related disorders: focus on the crucial role of this miRNA during neurodevelopment

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**BACKGROUND:** Early life stressful events are often associated with an increased risk of developing psychiatric disorders, such as psychosis, later in life [1;2]. However, not all the stress-exposed individuals suffer from such illnesses as they develop coping or resilience strategies. The molecular mechanisms underlying the vulnerability or resilience to stress remain unclear, but epigenetics, such as microRNAs (miRNAs), may be involved [3].

**AIM:** Since recent studies have identified miR-19 as a key regulator involved in neurodevelopment [4] and in Schizophrenia (SZ) [5], we investigated: i) the effects of stress early in life on the long-lasting modulation of miR-19; ii) the involvement of miR-19 in the vulnerability or resilience of developing psychosis.

**METHODS:** The family of miR-19 is composed of miR-19a and miR-19b that differ by one single nucleotide in the middle of the sequence. We measured by Real Time PCR the expression levels of both miRNAs in different tissues and models, such as: i) brain samples of prenatal stressed (PNS) and chronic mild stressed (CMS) rats, ii) human hippocampal progenitor stem (HPS) cells treated with cortisol and iii) blood samples from controls characterized for childhood trauma and SZ patients.

**RESULTS:** We found a significant downregulation of miR-19a and b in proliferating HPCs treated with cortisol as well as in the hippocampus of adult rats exposed to PNS. Similarly, CMS caused a significant downregulation in the levels of both miRNAs, but only in vulnerable rats. Alterations in miR-19 levels were observed also in blood of controls with a childhood trauma history and in SZ patients, as compared to their controls respectively.

**CONCLUSIONS:** MiR-19 is a target of stress and can influence the vulnerability of developing stress-related psychiatric disorders; thus, it can be useful in identifying subjects at high risk for psychosis. Moreover, therapies targeting miR-19 may help in preventing such stress-related vulnerability.

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## PT344

### To Compare P-glycoprotein Information of Psychotropics from Different Sources

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**Objective:** The efflux transporter P-glycoprotein exerts a profound effect on the disposition of psychotropics in the brain. The drug information related to P-glycoprotein is important in treating polymedicated elderly or drug resistant patients with mental illness, schizophrenia, bipolar disorder, major depression, epilepsy. **Methods:** Three sources were compared. One is the label information of approved drug collected from DailyMed (website of U.S. National Library of Medicine). Another is Drug Interaction Facts 2015. The other is data collected from articles published. A search was made in the database of Medline (via PubMed), over the last 18 years, using the keywords 'psychotropic' OR 'antipsychotic' OR 'antidepressant' OR 'antiepileptic,' combined independently with the terms 'P-glycoprotein' by means of the connector 'AND.' **Result:** There is insufficient information available on the psychotropic drug

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interactions related to P-glycoprotein in drug label. Drug Interaction Facts 2015 is a reliable and easy accessible source of P-glycoprotein information. A total of 152 review articles were found via PubMed. This source is comprehensive but time consuming. Most antipsychotics act various degrees of P-glycoprotein inhibition. Haloperidol is a potent P-glycoprotein inhibitor, while chlorpromazine functioning moderate. Some antidepressants, fluoxetine, paroxetine, sertraline, are moderate P-glycoprotein inhibitors. Several psychotropics including antipsychotics (amisulpride, aripiprazole, chlorpromazine, fluphenazine, haloperidol, olanzapine, pimozide, risperidone, **paliperidone**, trifluoperazine), antidepressants (amitriptyline, doxepine, nortriptyline, venlafaxine), and antiepileptics (felbamate, gabapentin, lamotrigine, phenobarbital and topiramate) are P-glycoprotein substrates. Some antiepileptics (levetiracetam, topiramate and phenytoin) at therapeutic doses are P-glycoprotein inducers. **Conclusion:** There is currently insufficient information available on the psychotropic drug interactions related to P-glycoprotein in drug label collected from DailyMed. Drug Interaction Facts 2015 is a reliable source of P-glycoprotein information.

## PT345

### The role of dopamine in social interactions

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The dopaminergic system is implied to be the central culprit in many psychiatric disorders that are characterized by the inability to form satisfying social interactions [1]. Yet despite the established role of dopaminergic neurons in approach and avoidance behavior in non-social settings [2], its role in social interactions is poorly understood. Neuroimaging studies suggest that brain areas densely innervated with dopaminergic neurons involved in basic reward processing overlap with brain areas responsible for social reward processing and facilitation of cooperative behavior [3].

We used a high dose of selective D2/3 dopamine receptor blocker to investigate the effects of the dopaminergic system on learning about and interacting with others. We administered either sulpiride or placebo to 80 participants that played the investor in a repeated trust game and developed a computational model of behavior to further dissect the underlying mechanisms.

Preliminary analysis show that sulpiride did not affect learning about the other person, but did lower the consistency of participants' choices. We found a similar effect in a non-social learning task [4], which supports the idea of overlapping processing of social and non-social information.

### References

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## PT346

### Long-term haloperidol changes in the striatum, prefrontal cortex and hippocampus of mice – a proteomics perspective

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Schizophrenia (SCZ) is a very serious and costly mental disease characterized by a combination of positive, negative and cognitive symptoms. Haloperidol, a first-generation antipsychotic, is thought to alleviate the positive symptoms essentially by antagonizing dopamine D2 receptors. Nonetheless, it is less clear which are the long-term molecular effects of this medication. Many studies have assessed the molecular alterations induced by antipsychotic medication in SCZ patients however, the reports from these studies are inconsistent and not able to assure if the identified changes are disease or drug-related or a consequence of chronic impairment.

The main aim of this study was to evaluate the molecular effects of chronic Haloperidol in mice striatum, prefrontal cortex and hippocampus. The proteomic content of the 3 tissues were analyzed after 15 and 30 days daily exposure to the antipsychotic drug by a state of the art liquid chromatography mass spectrometry relative quantification approach, SWATH. In total, over a thousand proteins were confidently quantified in each tissue. From these, some statistically meaningful differences were detected in each tissue, where stronger alterations were registered in prefrontal cortex and less pronounced alterations in the striatum. Using a principal component analysis with these significantly altered proteins it was possible to distinguish between the control and medicated groups. Moreover, when gene ontology analysis was performed for these proteins, several pathways are highlighted such as some metabolic processes, suggesting a possible metabolic shift, or even protein translation related pathways.

Altogether, these findings highlight several pathways affected in the 3 brain structures by haloperidol chronic treatment suggesting the long-term molecular mechanisms of action of the drug. This study may also depicts target molecular pathways for the investigation of psychotic disorders' physiology and its pharmacological treatment.

## PT347

### Metabolic status of patients with chronic schizophrenia under antipsychotic treatment

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**Aim.** To investigate antioxidant enzyme and monoamine oxidase (MAO) activities and level of middle-mass endotoxic molecules (MMEM) in red blood cells (RBC) and serum of schizophrenic (SCH) patients under pharmacotherapy with traditional antipsychotics.

**Methods.** There were investigated 26 schizophrenic patients. Biochemical parameters - glutathione peroxidase (GP), glutathione reductase (GR), glutathione-S-transferase (G-S-T), catalase (CAT), glucose-6-phosphate dehydrogenase (G-6-PD) and MAO activities and MMEM level (parameter of degree of endogenous intoxication) were estimated before and after 6 weeks of pharmacotherapy with traditional antipsychotics. Control group consists of 39 healthy persons.

**Results.** CAT activity of patients at admission was significantly higher than in controls. Treatment with antipsychotics normalized this index. GP activity did not change during treatment. H<sub>2</sub>O<sub>2</sub> is predominantly destroyed by CAT and not by GP. G-S-T activity was significantly lower before and after treatment in comparison with controls. G-6-PD activity was significantly lower at admission as compared with controls. After treatment G-6-PD activity continues to decline. GR activity was significantly higher before treatment and after pharmacotherapy its activity was significantly lower in comparison with values both at admission and in controls. MAO activity was twice higher at admission in comparison with controls. After treatment it decreased and was significantly lower then at admission and significantly higher in comparison with control values. MMEM level was higher at admission and showed tendency to decrease. There were revealed clinical improvement in 92% of patients after pharmacotherapy according to GCI Scale.

**Discussion.** Patients at admission were characterized by pronounced disturbance in monoamine metabolism and state of antioxidant defence. There are no signs of normalization of metabolic process in spite of improvement of clinical status of patients after pharmacotherapy.

## PT348

### Dynamics of metabolic changes in first-episode drug-naive schizophrenic patients under antipsychotic pharmacotherapy

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**Objectives.** The main tasks of biological psychiatry are identification of biomarkers of mental disorders.

**Aim.** To investigate metabolic parameters and degree of endogenous intoxication in first-episode drug-naïve schizophrenic (FES) patients in dynamics of psychopharmacotherapy.

**Methods.** Platelet monoamine oxidase (MAO) and semicarbazide-sensitive amine oxidase (SSAO) activities, serum concentrations of middle-mass endotoxic molecules (MMEM) and conformational parameters of serum albumin were measured in 26 FES patients and 15 healthy controls. FES patients received risperidone (3-6 mg/daily) during 45 days.

**Results.** Severity of the disorder prior treatment was 75.5 according to PANSS score. There were revealed significant increase in MAO activity and MMEM concentration and decrease of SSAO activity in comparison with controls. Regression analysis has showed a significant relationship of MAO, SSAO and MMEM parameters with values of PANSS score. Factor analysis has permitted us to suggest that MAO and SSAO are specific components of pathogenesis of FES. After 45 days of treatment the severity of disorder decreased to 58 points according to PANSS score. There were observed significant decrease of MAO activity after treatment in comparison with values before treatment, but these values were significantly higher than in controls. Decrease in MMEM concentration was insignificant. There were detected significant conformational changes of albumin molecule in FES patients before treatment using pulse laser fluorescent spectroscopy with subnanosecond resolution. Values of fluorescence decay amplitude of probe from albumin in FES patients after the treatment were practically on control level.

**Conclusion.** We suggest that platelet MAO activity and albumin conformational parameters can serve as potential biomarkers of efficacy of pharmacotherapy of first episode of schizophrenia.

## PT349

### Developing a method for detection of retrotransposon by next generation sequencing and its application to single brain cells

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**Specific objective of the study:** Recent several studies have revealed that the genome of brain cells contains several kinds of somatic mutations, such as single nucleotide variants, copy number variations and novel insertions of retrotransposons. These brain cell-specific somatic mutations may play an important role in the development of psychiatric diseases. We recently reported that the copy number of long interspersed nucleotide element (LINE-1) retrotransposon was higher in the neurons of patients with schizophrenia than in the neurons of healthy controls. The purpose of this study is to detect the somatic insertion sites of LINE-1 using human postmortem brains at the single cell level.

**Methods:** Here we developed a new method to identify the brain-specific LINE-1 insertion genomic site at the single cell level. Firstly, cell nuclei of several specific brain cell types were separated from human prefrontal cortex using nuclei sorting method. Whole genome amplification (WGA) using single nuclei was performed and WGA products with low allele dropout rate were selected. Genomic regions including 3' end of human LINE-1 (L1Hs) and adjacent regions were selectively amplified by adaptor-ligation PCR and sequenced by illumina MiSeq.

**Summary of results:** Using this method, we detected 79.2% (670/859) of LINE-1 found in the reference human genome sequence (hg38) and 64-74 of unknown non-reference somatic LINE-1 insertions in single neuronal nuclei from prefrontal cortex of a human without any psychiatric diseases. These newly inserted LINE-1 were validated by Sanger sequencing method.

**Conclusions reached:** Using the developed method, we successfully detected somatic LINE-1 insertion sites using single neuronal nuclei with high efficiency. We have been conducting a case-control study using postmortem brain samples from patients with schizophrenia and controls to clarify the role of somatic LINE-1 insertions in the pathogenesis of schizophrenia.

## PT350

### Molecular and genetic study of the discs, large homolog 1 of *Drosophila* (DLG1) in schizophrenia

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## Objective

*DLG1* gene encodes scaffold proteins interacting with the NMDA receptor that is hypothesized to be hypofunctional in schizophrenia. The involvement of *DLG1* gene in the pathophysiology of schizophrenia is strongly supported by the reports demonstrating microdeletion in 3q29, where *DLG1* gene resides, confers a 40-fold increase in the risk for schizophrenia. The present study aimed to investigate the molecular and genetic roles of *DLG1* in schizophrenia using postmortem brains and DNA samples.

## Methods

We first explored the complementary DNA library of the postmortem human cerebral cortex in an attempt to identify unreported *DLG1* splicing variants. Then, we investigated the gene expression of these variants in the postmortem brain tissues of patients with schizophrenia and bipolar disorder. Furthermore, we examined genetic association between *DLG1* gene and schizophrenia using a Japanese cohort

with 1,808 cases and 2,170 controls.

## Results

We found the reduced expression of a newly identified splicing variant of *DLG1*, in the Brodmann area 46 of the postmortem brains from patients with early onset schizophrenia. This variant, 3b(+) mRNA, has been shown to be transcribed from an unreported primate-specific 95 base-pair exon designated as Exon 3b. Moreover, the expressional levels of the 3b(+) mRNA depend upon the genotypes of the SNP rs3915512 located in the exonic splicing enhancer site of the Exon 3b. The genetic association analysis detected an association between schizophrenia and the SNP rs3915512. When stratified by onset age, the association was observed in non-early onset schizophrenia, whose onset-age selectivity is consistent with the postmortem study.

## Conclusions

The present study would provide a clue for molecular mechanisms on how genetic variations in *DLG1* gene affect its regulation in the glutamate system and lead to the disease onset around a specific stage of brain development. The onset-stratified approach proved its usefulness studies of heterogeneous disorders such as schizophrenia.

## PT351

### Quantifying dopamine receptor availability in the retina of humans using [<sup>11</sup>C]-(+)-PHNO

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	Estimated Parameters					Parameter Fits					
	SRTM					%Covariance					
	R <sub>1</sub>	K <sub>2</sub>	BP <sub>ND</sub>	K <sub>2</sub> '	K <sub>2a</sub>	R <sub>1</sub>	K <sub>2</sub>	BP <sub>ND</sub>	K <sub>2</sub> '	K <sub>2a</sub>	χ <sup>2</sup>
Mean	.25	.02	.73	.07	.01	2.88	5.95	31.29	8.10	13.76	1.62
S.D.	(.05)	(.004)	(.58)	(.02)	(.003)	(.83)	(1.83)	(27.68)	(2.19)	(6.06)	(.87)
Minimum	.17	.01	.04	.04	.00	1.82	2.74	6.76	4.34	5.40	.52
Maximum	.42	.03	2.32	.12	.02	6.54	10.33	141.24	13.38	42.74	4.28

<sup>3</sup>Department of



Table 2. MRTM Parameters & Model Fits.

	Estimated Parameters					Parameter Fits					
	MRTM					%Covariance					
	BP <sub>ND</sub>	K <sub>2</sub> '	-Vt/(Vrk2'b)	1/b	-Vt/(Vrk2'b)	BP <sub>ND</sub>	K <sub>2</sub> '	-Vt/(Vrk2'b)	1/b	-Vt/(Vrk2'b)	χ <sup>2</sup>
Mean	.81	.07	.0003	-.0002	.1806	33.37	45.24	11.36	22.52	38.93	.93
S.D.	(.57)	(.05)	(.0001)	(.0001)	(.36)	(27.29)	(83.08)	(10.96)	(17.50)	(81.65)	(.34)
Min.	.05	-.09	-	-	-	7.06	5.42	3.10	6.22	2.09	.35
Max.	2.69	.26	-	-	-	140.82	400.62	44.60	84.10	372.26	1.92

Psychiatry, University of Toronto

**Objectives:** [<sup>11</sup>C]-(+)-PHNO is an agonist radiotracer for dopamine (DA) D<sub>2/3</sub> receptors (D<sub>2/3</sub>R). We have observed significant uptake of [<sup>11</sup>C]-(+)-PHNO into the retina, a region rich in extrasynaptic

DA receptors (Figure 1). We wished to determine whether this uptake in the retina could be quantified with two reference tissue methods: the simplified reference tissue model (SRTM) and Ichise's Multilinear Reference Tissue Model (MRTM). We then explored whether [<sup>11</sup>C]-(+)-PHNO BP<sub>ND</sub> in the retina differed between neuroleptic naïve patients with schizophrenia and age and gender matched healthy controls.

**Methods:** [<sup>11</sup>C]-(+)-PHNO data from 49 healthy controls (μage: 39.96±14.36; 16 female) and 12 antipsychotic-naïve patients

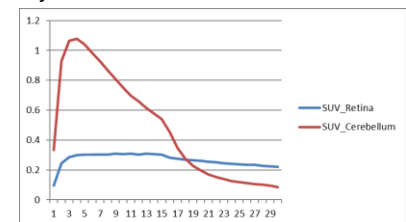


Figure 2. Averaged SUVs in each ROI.

with schizophrenia (μage: 25.75±6.25; 4 female) were analyzed. Time activity curves were extracted from the retina and cerebellum from manually drawn ROIs (author FC) (Figure 2).

**Results:** The estimated parameters and model fits using the SRTM and the MRTM, are presented in Table 1 and Table 2, respectively. The average measure interclass correlation coefficient (ICC) between the manually drawn SRTM and MRTM retina BP<sub>ND</sub> estimates was .91, with a 95% CI from .84 and .95 (F(48,48)=11.70, p<.0001). Retina BP<sub>ND</sub> did not differ between patients and matched controls measured with the SRTM (W=2, p=.97) and MRTM (W=16, p=.57).

**Conclusions:** It is possible to quantify DA receptor availability in the retina with [<sup>11</sup>C]-(+)-PHNO. Notably, BP<sub>ND</sub>'s and associated model fits fell within previously

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accepted ranges for other ROIs, such as the thalamus (average  $BP_{ND}$ , 95% CI): .36, .26-.49<sup>1</sup>; .44, .35-.54<sup>2</sup>. Future studies should conduct displacement studies to determine whether  $D_3R$  is expressed in the human retina. While it is possible to quantify retina  $BP_{ND}$  using reference tissue models, arterial kinetic modelling is warranted.

**References:** [1] Tziortzi et al. (2011). *NeuroImage*, 54, 264-277. [2] Searle et al (2013). *NeuroImage*, 68, 119-132.

## PT352

### Glutamatergic Neurometabolite Levels in Patients with Treatment-resistant Schizophrenia: a Cross-sectional 3T Proton MRS study

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**Objective:** In terms of response to antipsychotic treatment, patients with schizophrenia can be classified into three groups: (1) treatment-resistant patients who are clozapine (CLZ)-resistant (ultra-resistant schizophrenia [URS]), (2) treatment-resistant patients who are CLZ-responsive (non-URS), and (3) patients who respond to first-line antipsychotics (treatment non-resistant schizophrenia [TnRS]). The aim of this study was to compare glutamatergic neurometabolite levels in these three patient groups and healthy controls (HCs), using proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS).

**Method:** Glutamate (Glu) and glutamate+glutamine (Glx) levels were assessed in the caudate, the anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) using 3T <sup>1</sup>H-MRS (PRESS, TE=35ms). Neurometabolite levels were corrected for cerebrospinal fluid proportion of the voxels. Glutamatergic neurometabolite levels were compared between the groups using analyses of variance.

**Results:** Group differences were detected in the ACC Glx levels ( $F[3,96]=2.93$ ,  $p=0.038$ ); patients with URS showed higher ACC Glx levels than HCs ( $p=0.038$ ). There were no significant group differences in the caudate or DLPFC. When patients with URS and non-URS were combined into one group, this subset of patients showed higher Glu and Glx levels in the ACC compared to HCs ( $p=0.028$  and  $0.023$ , respectively).

**Conclusions:** Higher levels of glutamatergic neurometabolites in the ACC may be a biological marker of resistance to the first-line antipsychotic treatment that persists even after CLZ administration. Patients with treatment-resistant schizophrenia with higher ACC glutamatergic neurometabolite levels may benefit from early CLZ administration.

## PT353

### Frontostriatal functional connectivity and its relationship with striatal dopamine capacity in schizophrenia

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**Objective:** Schizophrenia is thought to be a heterogeneous disorder and evidences reflect categorically distinct subtypes according to the antipsychotic treatment response. Altered frontostriatal functional connectivity (FC) in schizophrenia and its correlation with antipsychotic treatment response also suggests divergence of underlying pathophysiologic mechanism. Meanwhile, the observations that prefrontal activity correlates with striatal dopaminergic function, has led to the hypothesis that disrupted frontostriatal FC would be related with altered dopaminergic pathway in schizophrenia. The aim of this study was to investigate the relationship between frontostriatal FC and striatal dopaminergic activity in patients with schizophrenia according to responsiveness to first-line antipsychotic drug.

**Method:** 24 symptomatically stable patients with schizophrenia were recruited from Seoul National University Hospital, 12 of which responded to first-line antipsychotic drugs (first-line AP group) and 12 stable under clozapine (clozapine group), along with 12 matched health controls. All participants underwent resting-state functional MRI and [<sup>18</sup>F]DOPA positron emission tomography.

**Results:** There was no significant difference in the total PANSS score between the first-line AP group and the clozapine group (mean difference=0.67, s.e.=3.21,  $df=33$ ,  $p=1.000$ ). Voxel-based analysis found significant negative correlation between frontal FC to the left associative striatum and the  $k_i^{cer}$  in the corresponding region in first-line AP group but not in clozapine group or healthy control. Additional region of interest analysis confirmed the result (control group:  $R^2=0.032$ ,  $p=0.572$ ; first-line AP group:  $R^2=0.551$ ,  $p=0.005$ ; clozapine group:  $R^2=0.108$ ,  $p=0.297$ ) and the correlation coefficients were significantly different between first-line AP group and clozapine group ( $z=-2.75$ ,  $p=0.006$ ).

**Conclusions:** Different patterns of relationship between striatal dopamine capacity and frontostriatal FC observed in this study indicate different pathophysiology underlying schizophrenia according to antipsychotics treatment-responsiveness.

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## PT354

### Cognitive Clustering in Schizophrenia Patients, their First-Degree Relatives and Healthy Subjects is Associated with Anterior Cingulate Cortex Volume

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Cognitive impairments are a core feature in schizophrenia patients (SCZ) and are also observed in first-degree relatives (FR) of SCZ. However, substantial variability in the impairments exists within and among SCZ, FR and healthy controls (HC). A cluster-analytic approach can group individuals based on profiles of traits and create more homogeneous groupings than predefined categories. Here, we investigated differences in the Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery (six subscales) among SCZ, unaffected FR and HC. To identify three homogeneous and meaningful cognitive groups regardless of categorical diagnoses (SCZ, FR and HC), cognitive clustering was performed, and differences in the BACS subscales among the cognitive cluster groups were investigated. Finally, the effects of diagnosis and cognition on brain volumes were examined. As expected, there were significant differences in the five BACS subscales among the diagnostic groups. The cluster-analytic approach generated three meaningful subgroups: (i) neuropsychologically normal, (ii) intermediate impaired and (iii) widespread impaired. The cognitive subgroups were mainly affected by the clinical diagnosis, and significant differences in all BACS subscales among clusters were found. The effects of the diagnosis and cognitive clusters on brain volumes overlapped in the frontal, temporal and limbic regions. Frontal and temporal volumes were mainly affected by the diagnosis, whereas the anterior cingulate cortex (ACC) volumes were affected by the additive effects of diagnosis and cognition. Our findings demonstrate a cognitive continuum among SCZ, FR and HC and support the concept of cognitive impairment and the related ACC volumes as intermediate phenotypes in SCZ.

## PT355

### Amphetamine-induced dopamine release and sensitization are regulated by the prefrontal cortex: A [<sup>11</sup>C]-(+)-PHNO PET study in healthy subjects and patients with schizophrenia

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**Objective:** Scientific evidence shows a dysregulation of the dopamine system in schizophrenia. An exaggerated behavioral response and increased release of dopamine after stimulant exposure led to the hypothesis that the dopamine system of patients with schizophrenia might be in a state of natural sensitization. Sensitization denotes an increased response after repeated exposure to a stimulus of constant intensity. Studying sensitization to amphetamine in healthy subjects could thus serve as useful tool for investigating neurobiological alterations underlying this severe psychiatric disorder. Since the neurodevelopmental hypothesis of schizophrenia postulates a dysfunctional regulation of the dopamine system by cortical regions, we investigated the relationship between volumetric parameters in the prefrontal cortex and release of dopamine after repeated exposure to amphetamine.

**Methods:** For measuring amphetamine-induced dopamine release in key dopaminergic brain regions, positron emission tomography using the dopamine D<sub>2/3</sub> receptor agonist radioligand [<sup>11</sup>C]-(+)-PHNO was performed in 23 healthy stimulant naïve subjects (11 females) and 16 medication- and stimulant naïve patients with first episode schizophrenia (5 females). All participants received one naïve and one post-amphetamine scan. Healthy subjects repeated this protocol after two amphetamine sensitization visits. For investigating the impact of the prefrontal cortex on

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amphetamine-induced dopamine release, T1 magnetic resonance imaging was performed in all subjects.

**Results:** After amphetamine sensitization, healthy subjects exhibited enhanced dopamine release, similar to what was found in patients with schizophrenia. In healthy subjects, we observed a negative relationship between prefrontal cortical volume and amphetamine-induced dopamine release before sensitization. No correlation was observed in healthy subjects after sensitization and in patients with schizophrenia.

**Discussion:** Our data demonstrate natural amphetamine sensitization in schizophrenia and support the hypothesis of a deficient regulation of the dopamine system by prefrontal cortical regions in the disorder.

## PT356

### Investigation of Mechanism of Increased Appetite after Olanzapine by sLORETA during Sleep

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Increased appetite is a frequent side effect of atypical antipsychotics like olanzapine and results in weight gain and an elevated risk of somatic disorders. The mechanisms of this side effect are widely unknown. The subgenual anterior cingulate cortex (sgACC) participates in the regulation of appetite and sleep and was tested by standardized low resolution brain electromagnetic tomography (sLORETA) whether olanzapine provides changes in healthy young subjects.

10 healthy, young male subjects underwent two 118 channel sleep-EEG recordings i) at baseline and ii) after treatment with olanzapine up to 10 mg for 7 days. We used artifact-free 5 min EEG clips from the first N3-sleep period for the EEG bands for various frequency bands including  $\alpha$  (8-12Hz). sLORETA is an EEG-based neuroimaging technique performing the inverse solution to quantify sgACC activity within predefined voxels. Appetite was assessed daily by a self-rated questionnaire.

In sgACC the current source density of  $\alpha$  frequency band increased significantly after olanzapine to 5.76 [SEM= 0.184] vs 5.42 [SEM= 0.128] at baseline ( $p < 0.005$ ). Sleep stage N3%TIB ( $p = 0.00033$ ) [N3 during baseline 17.3% ( $\pm 5.93\%$ ); N3 after treatment 26.33% ( $\pm 10.45\%$ )] and self-rated appetite ( $p = 0.0015$ ) increased after treatment (mean baseline appetite from 59.33% [SD=  $\pm 18.46\%$ ] to 70% [SD=  $\pm 17\%$ ]).

Our finding suggests that changed activity in the sgACC participates in the increase of appetite after olanzapine. Furthermore the capacity of sLORETA during sleep is

demonstrated. The increases of sleep stage N3 and of appetite after olanzapine are as expected.

## PT357

### Increased oxytocin gene expression levels in patients with suicidal ideations

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**Introduction:** In 2015, the WHO estimated 800 000 suicide deaths worldwide, making suicide the second leading cause of death among 15–29-year-olds (WHO). The identification of highly suicidal patients, both in and outside the hospital, still represents a challenge to physicians and health professionals, also reflecting the urgent need for a reliable and valid set of peripheral biomarkers (Kobeissy et al., 2012). In recent years, the neuropeptide oxytocin has been associated with psychiatric disorders such as Major Depression and Borderline Personality Disorder (Parker et al., 2010, Herpertz et al. 2015). Little is known about its expression in peripheral blood in suicidal patients. The present study attempts to elucidate the relationship between oxytocin and suicide ideations in a sample of affective disorder patients.

**Methods:** A total of 244 Caucasian affective disorder patients were recruited in the context of the Austrian Science Funds (FWF) funded study "VieSAD" (Vienna Study on Genetics in Suicidal Behavior in Affective Disorders) in the Medical University of Vienna and the University Hospital Tulln. Assessment of suicidality and severity of symptoms was performed by the SBQ-R (Suicide Behavior Questionnaire Revised) and the HRSD-17 (17-item Hamilton Rating Scale for Depression). Whole blood was drawn immediately after the standardized interview. Subsequently, gene expression levels for oxytocin (OXT) and endogenous control genes were quantified using Taqman qPCR method.



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**Results:** Severity of depression did not correlate with mRNA expression of oxytocin. Yet, comparing qPCR data in relation to suicidal ideations, we could show that patients with current suicidal ideations (SI) showed higher OXT mRNA levels ( $Z=-2.0$ ,  $p=0.04$ ), however not resisting FDR correction ( $p_{corr}=0.2$ ). Gender specific sub-analysis of the data suggests that the tendency originates from the female subsample ( $Z=-2.8$ ,  $p=0.004$ ,  $p_{corr}=0.02$ ).

**Conclusion:** The significant correlation of suicidal ideations with peripheral oxytocin mRNA levels in the female subsample suggests a role for oxytocin in the search for biomarkers for suicide prevention. These findings need to be replicated and re-evaluated with different populations.

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## PT358

### Risk factors associated with non-suicidal self-injuring behaviour and previous suicide attempts in a sample of affective disorder patients

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**INTRODUCTION:** More than 300 million people worldwide suffer from depression and more than 800.000 people die from suicide every year. In 2017, suicide was the second leading cause of death among 15-29 year-olds. {1,2} Depression, suicide attempts and Non-Suicidal Self-Injury (NSSI) seem to correlate; therefore, characterisations

of these subsamples are relevant in a clinical context in regards to detection and prevention of suicidal behaviour. {3,4,5}

In this study, we investigated risk factors associated with suicidal behaviour in affective disorder patients.

**PATIENTS AND METHODS:** 787 affective disorder patients (272 males, 515 females; 512 inpatients, 275 outpatients) were recruited in University hospitals and a rehab facility in Vienna and Lower Austria. Psychiatric diagnoses and demographic data were assessed via structured interviewing (Schedules for Clinical Assessment in Neuropsychiatry). To assess a history of NSSI and previous suicide attempts, patients completed the Viennese Suicide Risk Assessment Scale.

**RESULTS:** Patients with a history of NSSI showed significant associations with female sex, being single, non-religious and having a low income. Other significant correlations were smoking, being impulsive and having both a family and a personal history of suicide attempts, and having used a more violent method in prior suicide attempts.

A prior suicide attempt significantly correlates with being single, smoking, low income and impulsivity, plus a family history of suicide attempts. Other significant associations in this subsample include severe chronic disease, prior psychiatric hospitalisation and a history of NSSI.

**CONCLUSION:** We examined a large, homogenous sample of affective disorder patients, who pose one of the highest risk groups for suicide. {6} We were able to point to further important clinical and demographic risk factors which are associated with a history of NSSI and past suicide attempts and thus likely contribute to the future total suicide risk in patients with affective disorders.

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## PT359

### Specific alterations in epigenetic blood biomarkers to predict suicide attempts

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**Introduction:** Predicting suicidal behaviors is one of the most complex challenges of daily psychiatric practices. Alterations of RNA editing of neurotransmitter receptors and other proteins have been shown to be involved in etiology of different psychiatric disorders and linked to suicidal behavior.

**Objective:** The objective of the present study was to test whether longitudinal measurement of RNA editing profile of disease-relevant blood biomarkers can be used to predict patients at greatest risk of relapse.

**Methods:** A clinical study was performed to identify an RNA editing signature in blood of depressed patients with previous history of suicide attempts ( $n=28$ ) over a 6-month period. Patient's samples were drawn in PAXgene tubes at initial visit and 6 months later and analyzed on Alcediag's proprietary RNA editing platform using NGS. In parallel, clinical evaluations (Hamilton, MADRS and BDI) were performed.

**Results:** During follow-up, 8 patients out of 28 have reattempted suicide (RSA). In the 20 patients that did not reattempt suicide (NRSA), the BDI score showed significant improvement during follow up. On the other hand, clinical evaluations in the RSA patients did not show any improvement and even showed worsening of the MADRS score. In addition, all phosphodiesterase 8A (*PDE8A*) mRNA editing sites showed significant changes in the NRSA patients over time whereas no *PDE8A* mRNA editing sites were modified in the RSA patients, suggestively signing improvement of their mental state.

**Conclusions:** Longitudinal measures of RNA editing biomarkers in blood samples of patients can be useful for predicting future suicide attempts.

## PTL360

### 'Hot and cold' cognition in users of novel psychoactive substances

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**Objectives:** Novel psychoactive substances (NPS) (formerly 'legal highs') refer to new drugs that are designed to mimic the effects of 'classic' drugs of abuse. Recent reports point to an increase in the availability, use and harmful effects of these substances, particularly in young adult men. We investigated the effects of NPS use on cognitive and social-emotional functioning in a non-clinical drug-using population. **Methods:** Males reporting frequent NPS use (at least twice a month in the last three months) without any psychiatric disorder including current or past alcohol or substance dependence ( $n=30$ ) were compared with healthy drug-naïve males with low alcohol consumption ( $n=32$ ) on standardised neuropsychological measures from the CANTAB ('cold' cognition) and EMOTICOM ('hot' cognition) test batteries.

**Results:** The two groups were matched for basic demographic information including intelligence and years in education; alcohol and tobacco use; and trait measures of anxiety, depression, trauma and resilience. Types of NPS included hallucinogenics, depressants, stimulants and cannabinoids, with a high frequency of polydrug combinations. The NPS group reported significantly higher levels of sensation seeking ( $p<0.001$ ) and impulsiveness ( $p=0.03$ ). On the CANTAB test battery, the NPS group showed significantly impaired episodic memory ( $p=0.003$ ), spatial working memory ( $p=0.008$ ) and sustained attention ( $p=0.005$ ). On the EMOTICOM test battery, the NPS group was significantly more positively biased when interpreting social ambiguity ( $p=0.02$ ) and less sensitive to risk toward both reward ( $p=0.03$ ) and loss ( $p=0.008$ ). Across groups, risky behaviour was positively associated with higher sensation seeking toward reward ( $p=0.002$ ).

**Conclusions:** Frequent NPS users show significant cognitive impairments. The effects of different combinations of novel and illicit psychoactive substances and the severity of cognitive impairments in comparison with dependent users seeking treatment warrant further investigation.

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## PTL361

### Escitalopram in Adult Separation Anxiety Disorder

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Adult Separation Anxiety Disorder seems to be existing very common in psychiatric population. Recent studies indicate that it may coexist with anxiety disorders. There are not any relating the efficacy of medications in treating Adult Separation Anxiety Disorder.

**Method :** 19 patients from an outpatient unit in Istanbul with Adult Separation Anxiety Disorder is taken into the study open label study . The patients were rated with Separation Anxiety Disorder Symptom Inventory. The ratings were done successively every two months for a six months period. The patients were escitalopram within dose range of 10-20 mg. Two patients left the study.

**Results:** The mean dose of escitalopram was 13.4 mg and the scores of Separation Anxiety Symptom Inventory dropped from 30.4 to 17.26 after 6 months. The results were statistically significant

**Conclusion:** This preliminary open study shows that escitalopram may be promising treatment for Adult Separation Anxiety Disorder

## PTL362

### Non-verbal Memory impairment in Korean obsessive-compulsive disorder patients with checking type compulsions

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**Purpose:** To find evidence for specific correlation between checking symptoms and memory impairments, we compared memory within the OCD (Obsessive Compulsive Disorder) group. We divided the patient samples into two groups according to their compulsive symptoms evaluated by Yale-Brown Obsessive-Compulsive Scale (Y-BOCS): one with prominent 'cleaning' and other with 'checking' behavior.

**Methods:** 47 OCD subjects and 20 controls were tested. 47 were divided into two groups, 24 patients with predominantly 'checking' and 23 with 'cleaning'

compulsions. All went through memory tests with Rey-Osterrieth complex figure test (RCFT) for non-verbal memory function, and Hopkins Verbal Learning Test for verbal memory function.

**Results:** The immediate and delayed memory scores for RCFT were significantly lower in checking than in cleaning types and controls. Specifically, the 'checking' type showed significantly lower scores compared to 'cleaning' type and normal controls in 'immediate recall'.

There was a trend level correlation with Y-BOCS scores and RCFT 'delayed recall' scores in the 'checking' patients ( $\rho = -0.32$ ).

**Conclusion:** The non-verbal memory function in checking type OCD were significantly decreased. This non-verbal memory dysfunction showed trend level correlation with the severity of OC symptoms in checking type OCD. These results suggest that the development of checking compulsions in OCD might be associated with non-verbal memory dysfunction.

## PTL363

### Deficit in the delayed visuospatial memory in ADHD children

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**Objective:** the goal of this research was to examine the hypothesis that children with ADHD have a deficit in the delayed visuospatial memory.

**Participants and Methods:** the experimental group included 24 children with ADHD at the age 6–7. The control group included 24 typically developing children. The children from experimental and control group were matched for IQ, sex and age. Children from both groups were assessed with the Rey-Osterrieth Complex Figure in Copy, Immediate and Delayed Recall conditions.

**Results:** two-way ANOVA was used to reveal group differences in reproducing the Rey-Osterrieth Complex Figure in different conditions. We have not revealed significant differences ( $p < .05$ ) between children from experimental and control group in reproducing the Rey-Osterrieth Complex Figure in Copy and Immediate conditions. However, children with ADHD had weakness in the accurate reproduction and placement of specific design elements of Rey-Osterrieth Complex Figure in Delayed Recall condition.

**Conclusion:** in view of the obtained results, it can be assumed that children with ADHD have specific deficit in the delayed visuospatial memory.

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Funding: The research was supported by Act 211 Government of the Russian Federation, agreement 02.A03.21.0006

## PTL364

### **Influence of body-oriented therapy on executive abilities in preschool children with ADHD**

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**Objectives:** it is known that children with ADHD have deficit of executive abilities. The goal of this study was to reveal effect of body-oriented therapy on executive abilities in ADHD children. Particularly we compared the efficacy of two methods of treatment (body-oriented therapy for children vs. conventional motor exercises) in a randomized controlled pilot study.

**Methods:** 14 children with ADHD between 5 to 6 years of age were included and randomly assigned to treatment conditions according to a 2x2 cross-over design. The body-oriented therapy included the exercises from yoga and breathing techniques.

To assess the executive functions and attention in children we used 5 subtests from NEPSY (Tower, Auditory Attention and Response Set, Visual Attention, Statue, Design Fluency). Effects of treatment were analyzed by means of an ANOVA for repeated measurements.

**Results:** The ANOVA has revealed ( $p < .05$ ) that for all 5 subtests on executive functions and attention the body-oriented therapy was superior to the conventional motor training, with effect sizes in the medium-to-high range (0.49-0.89).

**Conclusions:** The findings from this pilot study suggest that body-oriented therapy can effectively influence the executive abilities in preschool children with attention-deficit hyperactivity disorder. However, it is necessary to do further research into the impact of body-oriented therapies on the prevention and treatment of ADHD in children.

The research was supported by Russian Foundation for Basic Research, grant № 15-06-06491A.

## PTL365

### **An interaction between carbamazepine, fluvoxamine and clozapine in a patient with bipolar depression**

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#### **Brief introduction:**

In the treatment of bipolar depression, classes of commonly used drugs include lithium, anticonvulsants and antipsychotics. In some refractory cases, antidepressants may also be considered a choice. A large portion of these available drugs could be metabolized by the cytochrome P450 enzyme (CYP). Previous studies have shown that carbamazepine (CBZ) can decrease plasma clozapine (CLZ) levels, while fluvoxamine (FVX) can increase plasma levels of CLZ. In addition, combined administration of FVX and CBZ may increase the risk of CBZ intoxication. Here, I report the drug interaction in a patient with bipolar depression with concomitant use of CBZ, CLZ and FVX.

#### **Case report:**

A case of a 46-year-old male with bipolar II disorder treated with quetiapine 800 mg and a controlled release of CBZ 400 mg daily. He was admitted to acute psychiatric service in March 2018 due to insomnia and worsening of dysthymic mood. He maintained a blood CBZ level of 8.86 ug/mL at admission (normal range: 4-12 ug/mL). I first added 50 mg of agomelatine per day for insomnia and depression but to no avail. Therefore, we administered 100 mg FVX combined with 100 mg CLZ in place of quetiapine and agomelatine. The consequence was wonderful in improving her symptoms except for dizziness that complained to the patient during the day. The blood CBZ level increased to 13.83 ug/mL after re-verification. I adjusted the dose of CLZ from 100 mg to 50 mg and used fast-acting CBZ instead of controlled release without a dosage of change. After adjustment, his dizziness improved and also retained efficacy in insomnia and depression with a blood level of CBZ of 12.82 ug/mL.

#### **Discussion:**

To our knowledge, this is the first case describing the concomitant use of CBZ, FVX and CLZ. Previous studies have suggested that FVX increased the plasma level of CLZ and CBZ by being an inhibitor of CYP1A2 and 3A4, respectively. On the other hand, CBZ decreased the plasma level of CLZ by being an inducer of CYP3A4. The increase in blood level of CBZ in this case could be explained mainly by the effect of FVX. Although FVX and CBZ have an opposite effect on CLZ, I proposed that the effect of FVX on CLZ was much higher than the effect of CBZ on CLZ, resulting in a less necessary dose of CLZ in this case. Formal pharmacokinetic studies examining the potential interaction between these three drugs are needed to confirm this finding. In summary, this case highlights the importance of monitoring plasma concentrations or

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clinical status when multiple drugs with CYP450 inhibition or induction actions are combined.

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Key words: bipolar depression, carbamazepine, fluvoxamine, clozapine, interaction  
Statistical summary:430

## PTL366

### Use of benzodiazepines and hypnotics in maintenance phase of patients with bipolar disorder in an outpatient setting

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#### Introduction:

Guidelines for the maintenance treatment of bipolar disorder generally do not include the use of hypnotics, in particular benzodiazepines. In the acute phase of mania, benzodiazepines are useful for anxiety, agitation and insomnia.

#### Aim:

The aim is to describe the use of hypnotics in patients with bipolar disorder in remission seen at an outpatient clinic in Singapore.

#### Methods:

The case notes of patients with bipolar disorder in remission, seen by a single psychiatrist (author) in an outpatient bipolar disorder clinic in a general hospital unit from Dec 2014 to Mar 2015 were studied. Data describing the age, sex, type of bipolar disorder and psychotropic medications prescribed, was obtained.

#### Results:

42 patients were included, of which 13 (31%) were male and 29 (69%) were female. The age ranged from 23 to 82, with mean age of 47 years. Of these 17 (40%) had Bipolar I and 25 (60%) had Bipolar II.

Almost all of patients with bipolar disorder in remission managed in an individual practice were on mood stabilisers. Atypical antipsychotics were more frequently prescribed compared to lithium. Lithium was used in combination with other mood stabilisers in all instances.

There were a total of 12 patients on long-term use of hypnotics (28.6%). Of these 4 were Bipolar I and 8 were Bipolar II. There were 6 patients on benzodiazepines; 1 on zolpidem; 1 on hydroxyzine; 1 on both benzodiazepines and zolpidem; 2 on both benzodiazepines and hydroxyzine; 1 on zolpidem, benzodiazepines and hydroxyzine. There was no pattern of escalating usage of hypnotics in all of them.

#### Conclusion:

About one third were prescribed hypnotics as adjunctive medication, mostly benzodiazepines. There was no evidence of substance dependence as a result of the use of hypnotics in this group of patients.

Benzodiazepines and hypnotics may be useful in bipolar patients who have continued psychosocial stressors and insomnia during the maintenance phase. With repeated exposure to stressors, there is habituation to the stressor with repeated and sustained hypothalamic pituitary adrenal (HPA) axis activation, which persists along with the secretion of cortisol. Restoring homeostasis to the HPA axis can be achieved with use of benzodiazepines, thus reducing the risk of relapse.

## PTL367

### Valproic Acid-Induced Hyperammonemic Encephalopathy and Coma: A Case Report

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**Objective:** Ornithine Transcarbamylase (OTC) deficiency is the most common form of urea cycle defects, disorders characterized by increased serum ammonia levels. Clinical symptoms of OTC deficiency include mental retardation, vomiting, lethargy, coma and cerebral edema [1] [2]. Valproic acid (VPA) is an antiepileptic drug and mood stabilizer that elevates ammonia levels and thus increases the risk of encephalopathy [3]. VPA-induced hyperammonemic encephalopathies without OTC deficiency are rare and usually reversible [4]. VPA is also known as a potential trigger of hyperammonemic crises in OTC deficiency patients [1].

**Methods:** We report the case of a 66-years-old female who was admitted to an intensive care unit of the General Hospital of Vienna due to coma of unknown origin. She

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had a history of bipolar disorder and was on a regular medication including VPA. An initial VPA level beyond the upper measurable limit of 2000 µmol/l confirmed the suspected diagnosis of VPA intoxication. Ammonia levels were shown to be above 680 µmol/l. After citrate hemofiltration and discontinuation of VPA, VPA serum levels were back to normal therapeutic range after 4 days. Similarly, ammonia levels declined rapidly. After regaining consciousness the patient was in a delirious and disoriented state for two days. When reoriented the patient and her husband confirmed that she had never overdosed VPA, and that she had had several incidents of coma of unknown origin in the past.

**Summary:** To determine OTC deficiency, a broad array of amino acids from plasma were analyzed and revealed strong evidence for OTC deficiency, with increased serum alanine and glutamine, and decreased serum arginine.

**Conclusion:** Even though treating OTC-deficient patients with VPA increases the risk for hyperammonemic encephalopathy, little is known about diagnosing and managing these patients [1]. Thus, identifying urea cycle deficiencies in VPA-treated patients is crucial to prevent exacerbation of life threatening symptoms.

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## PTL368

### Mindfulness training during pregnancy has positive effect on neurocognitive development of children

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**Background:** There is evidence that maternal anxiety during pregnancy affects child outcomes. However, there is lack of studies that have evaluated the effects of maternal psychosocial factors during pregnancy on child neurocognitive outcomes. This study evaluates the effect of the maternal mindfulness training during pregnancy on neurocognitive development in 7–8 years old children.

**Methods:** In the current study we included 28 women who participated in the maternal mindfulness training during pregnancy. The control group included 28 women who did not participate in this training during pregnancy. When the offspring of the target pregnancies were between 7 and 8 years of age, their neurocognitive development was assessed by Lurias's child neuropsychological assessment battery that enables to assess five functional domains, including executive abilities, language, memory, sensorimotor and visuospatial abilities.

**Results:** One-way ANOVA was used to reveal group differences in performing subtests from five functional domains of Luria's battery. We have revealed the significant differences ( $p < .05$ ) between groups in three functional domains. The children from the experimental group performed better on subtests from executive, language and memory functional domains.

**Conclusion:** These results suggest that maternal mindfulness training during pregnancy may have positive effect on neurocognitive development of children, particularly on the development of executive, language and memory abilities in children.

**Funding:** The research was supported by Act 211 Government of the Russian Federation, agreement 02.A03.21.0006.

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## PTL369

### Development and Validation of a Clinical Calculator to Predict Acute-Phase Antidepressant Outcomes Using Early Changes in Irritability and Depression Severity: Findings from CO-MED and SAMS Trials

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**Background:** This report evaluates improvement in irritability with antidepressant treatment and its prognostic utility in treatment-seeking adult outpatients with major depressive disorder (MDD).

**Methods:** Mixed model analyses tested changes in irritability [5-item irritability domain of Concise Associated Symptom Tracking scale CAST-IRR] from baseline to week-4 independent of depression severity [16-item Quick Inventory of Depressive Symptomatology Clinician-Rated (QIDS-C)] in the Combining Medications to Enhance Depression Outcomes (CO-MED) trial participants (n=664). An interactive calculator for remission (QIDS-C  $\leq$ 5) and no-meaningful-benefit (<30% QIDS-C reduction from baseline) at week-8 was developed in CO-MED trial participants with complete data (n=431) using logistic regression analyses, and independently validated in the Suicide Assessment and Methodology Study (SAMS, n=163).

**Results:** In CO-MED trial, irritability reduced significantly [effect size (ES)=1.06,  $p < 0.0001$ ] from baseline to week-4, independent of QIDS-C change (ES=0.36,  $p < 0.0001$ ). One standard deviation greater baseline-to-week-4 CAST-IRR reduction predicted 1.73 times higher likelihood of remission ( $p=0.0001$ ) and 0.72 times lower likelihood of no-meaningful-benefit ( $p=0.036$ ) at week-8, even after controlling for baseline QIDS-C and CAST-IRR and baseline-to-week-4 QIDS-C reduction. The remission and no-meaningful-benefit models had area under the curve (AUC) of 0.795 and 0.757. These models, were validated in SAMS (remission AUC=0.796 and no-meaningful-benefit AUC=0.842) and were used to develop an interactive calculator.

**Conclusion:** Irritability is an important symptom domain of MDD that is not fully reflected in measures of core depressive symptom severity. Early reductions in irritability when combined with depressive symptom severity changes provides a robust estimate of an individual MDD outpatient's likelihood of remission or no-meaningful-benefit in replicated analyses.

## PTL370

### Pre-treatment S100B Selectively Predicts Response to SSRI Monotherapy Vs. Antidepressant Combinations: Clinical Implications of Blood Brain Barrier Dysfunction

Manish Jha, Abu Minhajuddin, Bharathi Gadad, Madhukar Trivedi

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**Background:** Elevated S100 calcium binding protein B (S100B) levels in depressed patients may reflect greater blood brain barrier (BBB) dysfunction, which in turn can facilitate neuroinflammation and impair dopamine neurotransmission. We hypothesize that higher S100b levels will predict poorer outcomes with selective serotonin reuptake inhibitor (SSRI) medications as compared to combination containing dopaminergic antidepressant.

**Methods:** S100B was measured at baseline with enzyme-linked immunosorbent assay in Combining Medications to Enhance Depression Outcomes participants (n=153). Treatment arms included bupropion-plus-escitalopram, escitalopram-plus-placebo, and venlafaxine-plus-mirtazapine. Depression severity was measured with 16-item Quick Inventory of Depressive Symptomatology Self-Report and anhedonia was measured with 3 items of 30-item Inventory of Depressive Symptomatology. Differential changes in depression severity and anhedonia over acute-phase (baseline to week 12) in the three treatment arms were tested with logS100B-by-treatment-arm interaction in mixed model analyses after controlling for age, gender and body mass index.

**Results:** There was a significant logS100B-by-treatment-arm interaction for anhedonia ( $F=3.21$ ;  $df=2, 142$ ;  $p=0.04$ ) but not for overall depression severity ( $F=1.99$ ;  $df=2, 142$ ;  $p=0.14$ ). Higher logS100B levels were associated with smaller reductions in anhedonia (effect size=0.67,  $p=0.047$ ) in escitalopram monotherapy but not the other two arms. Correlation coefficients of anhedonia severity averaged over acute-phase (including baseline) with baseline S100B levels were 0.57, -0.19, and 0.22 for escitalopram monotherapy, bupropion-plus-escitalopram and venlafaxine-plus-mirtazapine arms.

**Conclusion:** High baseline S100B levels in depressed patients resulted in poorer response to escitalopram monotherapy. Addition of bupropion, a dopaminergic antidepressant, partially mitigated this effect. S100B is a promising target to identify novel therapeutics to reduce anhedonia in depressed patients.

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## PTL371

### Association of Th2-Cell Mediated Immune Response with Suicide Behavior in Adolescents and Young adults

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**Background:** Impaired T-cell mediated adaptive immune response have gained recent attention for their role in pathophysiology of depression and suicide behavior. In this report, we compared differences in levels of T-cell cytokines among adolescent and young adult participants at risk of major depressive disorder (MDD; at-risk), with confirmed diagnosis of MDD (with MDD diagnosis), and with diagnosis of MDD plus recent suicide behavior (with MDD and suicide behavior).

**Methods:** Plasma samples from at-risk (n=37), with MDD diagnosis (n=19), and with MDD and suicide behavior (n=28) participants (ages 10-25 years) were assayed for T helper (Th)1- [Interferon gamma (IFN- $\gamma$ ) and interleukin (IL) 2], Th2- (IL-4 and IL-10), and non-T- (IL-1 $\beta$ , IL-6, tumor necrosis factor alpha or TNF- $\alpha$ ) cell-related cytokines using a Bio-Rad multiplex (Bio-plex) assay. Level of inflammatory markers were compared among the three groups after log-transformation (due to non-normal distribution) using analyses of variance.

**Results:** Levels of IL-4 (F=14.92, df=2, 91, p<0.0001) and IL-10 (F=3.84, df=2, 91, p=0.025) differed significantly among the three groups. Participants with MDD and recent suicide behavior had lower IL-4 and IL-10 than those at-risk (IL-4 adjusted p<0.0001; IL-10 adjusted p=0.019). They had lower IL-4 (adjusted p=0.013) than those with MDD diagnosis but no suicide behavior. The three groups did not differ on levels of Th1- (IFN- $\gamma$  p=0.08; IL-2 p=0.12) and non-T- (IL-1  $\beta$  p=0.50; IL-6 p=0.13; TNF- $\alpha$  p=0.13) cell-related cytokines.

**Discussion:** Adolescent and young adult patients with recent suicide behavior exhibit lower Th2-cell related cytokines, suggesting an autoimmune process. Targeting inflammation presents a promising avenue to reduce suicide behavior.

## PTL372

### Dynamics of cognitive functioning in patients with major depressive disorder and anxiety-depressive disorders under the influence of antidepressant therapy

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**Objective.** Recent years the cognitive impairment considered not only as one of the main manifestations of mood disorders but the most significant criterion of treatment efficacy. Especially cognitive impairment causing social desadaptation and reduced quality of life in patients with major depressive disorder (MDD) and anxiety-depressive disorder (ADD).

**Methods.** We had analyzed the impact of antidepressant therapy on cognitive function in 110 patients with MDD (70 persons) and ADD (40 persons) by applying a cognitive tests battery. Randomization was in the ratio of 1: 1 to treatment groups amitriptyline ((reuptake inhibitor SERT and NET, receptor antagonist 5-HT<sub>2</sub>) and venlafaxine (reuptake inhibitor SERT and NET)

**Results.** The greatest severity of cognitive impairment in MDD patients was in visual gnosis (Hm=1.43; Sx=0.07) and tactile gnosis (Hm=1.51; Sx=0.07), attention (Hm=1.56; Sx=0.12), memory (Hm=1.76; Sx=0.12), visual-spatial functions (Hm=7.74; Sx=0.17). In ADD patients the most significant cognitive impairment was in visual (Hm=1.50; Sx=0.09) and tactile gnosis (Hm=1.55; Sx=0.09), memory (Hm=1.70; Sx=0.16), and visual-spatial functions (Hm=1.77; Sx=0.21).

In MDD patients the positive amitriptyline impact on dynamic, kinesthetic praksis, reciprocal interaction, visual and tactile gnosis wasn't statistically significant (p>0.05). Conversely, a positive venlafaxine therapeutic effect on cognitive function was statistically significant (p<0.05). ADD patients also had a positive amitriptyline effect on cognitive functioning (except gnosis and visual memory), but only as a trend. In contrast, the therapeutic effect of venlafaxine had a high level of probability (p<0.01). Venlafaxine was much more influenced visual gnosis (p<0.001) compared with tactile one (p<0.05).

**Conclusions.** The cognitive status of MDD patients remains indifferent to the action of classic antidepressant amitriptyline. Venlafaxine action extended to certain cognitive functions based on the specific pharmacological mechanism of action.



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## PTL373

### Optimized regimens of combined medications for the treatment of major depressive disorder : double-blind investigation

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**Introduction:** This study investigated if optimized dose regimens of escitalopram and bupropion combination treatment from treatment initiation can be superior to either drug alone in speed of onset, remission rate, and maintenance of therapeutic efficacy.

**Method:** Patients from a single site (N=85) within a larger double-blind 12-week trial (N=245)<sup>1</sup> showed a lower dropout rate (14% vs 40%) and used higher doses and therefore were analyzed separately. Escitalopram could be given up to 40 mg/day and bupropion up to 450 mg/day. After 12 weeks, non-remitters on a single drug received the other one in addition and in combination non-remitters escitalopram was switched for duloxetine for a 6-week period. A 6-month prolongation was implemented in remitters, maintaining the double-blind design throughout. Remission was defined as  $\leq 7$  on the HAM-D17.

**Results:** At week 2, combination treatment was superior in remission rate (5/28) compared to both bupropion (0/26) and escitalopram monotherapy (0/31) ( $p=.03$  and  $p=.02$  respectively). The week 12 remission rate of combination treatment showed a higher rate (15/28) relative to bupropion monotherapy (7/26;  $p=.04$ ), but not different from escitalopram monotherapy (11/31;  $p=.13$ ). The 6-week augmentation produced remission in 7/21 monotherapy non-remitters and 0/6 in the switch group. Remission was sustained in 28/31 patients in the 6-month maintenance.

**Discussion:** These results suggest that combination treatment from treatment initiation, using optimized regimens of escitalopram and bupropion is superior to either monotherapy in speed of onset. The addition of a second drug in non-remitters can lead to additional remissions, as shown with other combinations of medications.<sup>2,3</sup> Treatment prolongation using optimized regimens leads to low relapse rates.

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## PTL374

### Decrease in choline and N-acetyl aspartate levels in dorsolateral prefrontal cortex at the beginning of recovery phase are markers of increased risk of depressive episode recurrence under maintenance therapy – a proton magnetic resonance spectroscopy study

Keywords: depression, recurrence, magnetic resonance spectroscopy

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**Introduction:** The risk of recurrence after three depressive episodes approaches 100% in the absence of prophylactic treatment<sup>1</sup>. Brain metabolites measurable by proton magnetic resonance spectroscopy (1H-MRS) include N-acetyl aspartate (NAA), considered a putative marker of neuronal integrity<sup>2</sup> and functionality<sup>3,4</sup>, and choline (Cho), considered as a marker of cellular membrane turnover.

**Aim:** This study evaluates the change of 1H-MRS brain metabolite levels over the first 6 months of the index episode recovery phase in relation to the recurrence of the depressive episode in patients on maintenance therapy.

**Methods:** Changes in NAA and Cho in dorsolateral prefrontal cortex (DLPFC) were analysed in 48 patients with recurrent depression who underwent maintenance therapy with the same antidepressant during the maintenance period. 1H-MRS evaluations were performed at the start of the recovery phase and 6 months later. 1H-MRS parameters, together with descriptors of index episode and the course of depressive disorder were analysed by Cox Proportional Hazards (CPH) model.

**Results:** Decreases in NAA/Cr and Cho/Cr six months after the beginning of the recovery period appeared as time-independent risk factors for recurrence of depressive episode in patients who started with maintenance therapy. Changes in those brain metabolites were not related to the severity of symptoms, whereas MADRS score remained in

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average nearly the same over the first 6 months of maintenance therapy.

**Conclusion:** Patients with the decrease in NAA or Cho levels in DLPFC early in the recovery phase and while on maintenance therapy are exposed to doubled risk of recurrence of a depressive episode. Sustainable NAA and Cho levels at the beginning of the recovery phase may indicate increased brain resilience gained with antidepressant therapy. Contrary to that, decreases in NAA and Cho levels may point to only the trait-related temporal effect of therapy in another stratum of patients<sup>5</sup>.

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## PTL375

### Complex tic movements as a manifestation of psychotic depression: a case report

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Tics represent a heterogeneous group of entities defined as involuntary, repetitive, rapid, stereotyped movements, generally non-goal-directed. Depending on the number of muscle groups involved, tics can be classified as simple or complex. The ability of voluntarily suppressing the movements is one of the main features of tics. Anxiety, stress, mental or physical fatigue may impair this capacity and/or increase the severity of the symptomatology.

We present a case of an interesting and atypical manifestation of psychotic depression, with complex tic movements as pivotal symptomatology. No previously

report of the co-occurrence of this two entities was found in the literature.

A 55-year-old male patient with history of discrete simple facial tics since childhood, and no psychiatric history was admitted in the Neurology Department in the context of insidious development of complex tics (facial, axial and appendicular) associated with anxiety and insomnia. A thorough workup was performed in order to exclude other movement disorders. During the hospitalization period, the patient developed psychotic symptoms with suspiciousness and persecutory delusions. In the absence of other neurologic abnormalities, the patient was evaluated by a psychiatrist whom detected depressive symptomatology, namely depressive mood, thoughts of worthlessness and hopelessness, loss of appetite and recurrent thoughts about death. Therefore, antidepressant and antipsychotic treatment was initiated, with total remission of the complex tic movements and improvement of the mood disorder and psychotic symptoms.

This case is an example of how a prevalent disorder can be expressed by atypical and unexpected signs, highlighting the importance of a good anamnesis. In the presence of exuberant symptomatology we might sometimes underestimate other complains that may be important, delaying the correct diagnosis and, therefore, the appropriate treatment.

## PTL376

### Therapy of mental disorders in elderly patients with multimorbidity

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**Objective.** The multimorbidity state greatly complicates the process of supervision and increases the disease burden for the patient, especially elderly. They are forced to seek and to be observed by doctors of various specialties, which, in turn, raises the problem of excessive pharmacotherapy.

**Methods.** 238 gerontopsychiatric patients receiving standardized optimized treatment and psychotherapeutic intervention were evaluated by Cumulative Grade Ratings for Geriatric Patients (CIRS-G), Quality of Life Questionnaire (SF-36), Patient Satisfaction Questionnaire (PSQ). Optimization of standard pharmacotherapy means reducing the overall pharmacotherapeutic load, using psychotropic drugs somatotropic action and somatotropic drugs psychotropic action, combined medications. Psychotherapy included psycho-education, compliance therapy, and prevention pharmacomania training.

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**Results.** The elderly patients had a multimorbidity high level: totally 8.37 points; 3.83 categories; comorbidity index 2.2. The severity and number of concomitant diseases increased with age ( $p < 0.001$ ), but decreased with smoking ( $p = 0.001$ ) and associated with the life quality deterioration ( $p < 0.001$ ). The multimorbidity level and severity didn't depend on the main mental illness (dementia, schizophrenia, etc.). The average life quality was low (34.3 points). The tendency to life quality decrease was directly proportional to increase the concomitant diseases number ( $p < 0.001$ ), daily and periodic volume of pharmacotherapy ( $p = 0.037$ ); growth of patients' age ( $p < 0.001$ ). The medical care satisfaction level was 59.9 points. The complex therapy contributed to improving the life quality ( $p < 0.001$ ), patients' compliance ( $p = 0.007$ ), medical care satisfaction ( $p < 0.001$ ). Improved life quality was seen in younger patients with lower cognitive deficits ( $p < 0.001$ ). Medical care satisfaction improvement was associated with a greater number of medications in the stable therapy ( $p = 0.029$ ), and avoiding additional periodic meds ( $p = 0.015$ ).

**Conclusions.** In addition to rational pharmacotherapy of elderly patients with mental disorders and multimorbidity should be used the psychotherapy aimed at the patient's awareness of the disease and methods of treatment, creating a therapeutic alliance and prevent self-medication.

## PTL377

### **Folie à deux: if you do not search for it, you will never find it**

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Folie à deux, or "Shared Psychotic Disorder", is a relatively rare clinical condition characterised by shared of delusional ideas in closely related persons. Usually, the delusion is transferred from a "primary" patient, frequently diagnosed with delusional disorder, schizophrenia or affective disorder, to one "secondary" individual, usually with the co-morbid diagnosis of schizophrenia, depression, dementia, mental retardation or bipolar disorder.

We report an interesting case of folie à deux, in which a couple of a 46-year-old woman, diagnosed with delusional disorder and dependent personality disorder, and a 71-year-old man, with cognitive impairment and past morbid jealousy history, shared persecutory delusions involving their neighbours and the police.

This is an example of a case of folie à deux that would not have been identified if the patient's husband hadn't been present during the interview. An interview with a close

relative of the patient is not a standard procedure in all psychiatric appointments, due to the lack of time and availability of the physicians to observe the patients' relatives. When associated to the complex of comorbidities usually present, this may lead to an underdiagnosis of this entity. This could explain the scarcity of literature about this disorder, as opposed to its reported low lifetime prevalence. Thus, in the presence of a patient with a delusional disorder, evaluating the family dynamics in more detail may be fruitful.

## PTL378

### **Mindfulness training can reduce prenatal maternal stress**

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**Background:** Prenatal maternal stress is an important phenomenon. Evidence on this topic suggests that women who experience high stress during pregnancy are more likely to deliver preterm infants. The goal of this study was to evaluate the influence of mindfulness training on stress reduction during pregnancy.

**Methods:** In the current study we included 23 women who participated in the mindfulness training during pregnancy. The control group included 23 women who were in the reading control condition during pregnancy. Women were eligible to participate if they were experiencing elevated levels of perceived stress or pregnancy-specific anxiety (PSA), as indicated by responses to the Perceived Stress Scale and the PSA scale on a screening questionnaire. Women enrolled between 12 and 26 weeks gestation were randomly assigned to either the mindfulness training or to the reading control condition. Effects of training were analyzed by means of an ANOVA with repeated measurements.

**Results:** ANOVA has revealed ( $p < .05$ ) that women in the mindfulness intervention experienced larger decreases from pre- to postintervention in pregnancy-specific anxiety and pregnancy-related anxiety than participants in the reading control condition.

**Conclusion:** This pilot study suggests that mindfulness training during pregnancy may effectively reduce pregnancy-related anxiety. However, it is necessary to do further research on the impact of mindfulness training on stress reduction during pregnancy.

**Funding:** The research was supported by Act 211 Government of the Russian Federation, agreement 02.A03.21.0006.

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## PTL379

### **A study of delirium: its course and outcome in a tertiary care teaching hospital**

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#### **HYPOTHESIS:**

Delirium is the commonest reason for cross-consultation in a tertiary care teaching hospital. Owing to a lack of awareness regarding delirium, its diagnosis and treatment are often delayed. Moreover, patients are given sub-optimal doses of psychotropic drugs which further delays the recovery.

#### **METHODOLOGY:**

The study was conducted at the Punjab Institute of Medical Sciences, Jalandhar, Punjab (INDIA) which is a 500-bedded tertiary care teaching hospital. The study was conducted over a period of 21 months. The initial 18 months constituted the intake period. The last three months were, thus, the end follow-up period.

All indoor patients referred to the Department of Psychiatry and diagnosed to have delirium as per the ICD – 10 criteria were included.

The tools used to assess the patients were the Confusion Assessment Method, the Mini Mental Status Examination (M.M.S.E) and the Delirium Rating Scale (D.R.S.).

#### **ASSESSMENT OF THE PATIENT WAS CARRIED OUT AS FOLLOWS:**

The patients were assessed every 24 hours for the first seven days or till recovery from delirium, whichever was earlier, using M.M.S.E. and D.R.S. Subsequently, patients were assessed once every seven days using M.M.S.E. and D.R.S. At the end of three months, follow-up of each patient was done either by personal contact or telephonic contact.

#### **RESULTS AND CONCLUSIONS:**

The study sample consisted of 123 males and 27 females. The total number of admissions to the hospital during the period of study was 71,452. Thus the incidence of delirium works out to be 0.21 per cent.

A total of 468 etiologies were ascertained for 150 patients, a mean of 3.12 etiologies per patient. The mean duration of delirium was 6.95 days with onset 4.42 days after hospitalization.

The findings of this study would help us in formulating protocol suggestions for identification and management of delirium and to help non-specialists identify delirium early.

## PTL381

### **The subtle line between belief and psychosis (and its underlying ethical dilemma): a case report**

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Schizotypal personality disorder (SPD) is characterized by peculiarities of thought, perception, speech and behaviour, namely eccentric and bizarre thoughts and appearance, inappropriate affect and limited interpersonal interaction. Psychotic-like episodes, paranoid ideation, disorganized thinking, obsessive rumination and perceptual disturbances can occur.

With an estimated lifetime prevalence of 3-4%, SPD has been showed to confer higher risk of developing a psychotic disorder being, therefore, associated with potentially significant disability. Despite the relevance of this diagnosis, few studies have been conducted in order to evaluate the benefits of antipsychotic therapy in SPD. As so, no consensual clinical recommendations can be made. The aim of this study is to assess the ethical dilemma of introducing pharmacologic treatment in patients with SPD. For this purpose, along with a case report, we conducted a brief non-systematic review of literature.

We present a case of a 38-year-old male patient, with a post-graduate degree, with no past psychiatric history. He was involuntarily brought to the emergency room, due to insidious development of total social isolation and self-neglect (both in nutritional, hygiene and health care) over the last 7 years, in the context of a fulltime investigation of metaphysic and mystic theories, impairing his functionality in the remaining spheres of live. The patient fulfilled the diagnostic criteria for SPD, and showed poor insight into his condition.

In this case, towards the absence of clear psychotic symptoms or criteria for compulsory treatment, the decision of implementing pharmacotherapy was controversial. Notwithstanding, due to the evolution of the clinical condition, the benefits of starting pharmacological treatment seemed to outweigh its risks.

Further studies exploring the ethical dilemma of initiating pharmacotherapy in these patients and treatment guidelines are needed in order to reduce the bias that underlies the subjectivity of the physician's interpretation.

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## PTL382

### Altered white matter diffusivity of the cingulum angular bundle in PTSD

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Prior studies showed PTSD-related alterations in white matter integrity, but most have used region-based approaches. We address this limitation by investigating the relationship between PTSD severity and fractional anisotropy (FA) using a novel, tract-based approach. Structural and diffusion MRI were acquired from sixty-seven combat-exposed US Veterans and processed using FSL/FreeSurfer (TRACULA). Partial correlations were conducted between PTSD severity and FA of the cingulum and uncinate fasciculi covarying for age, sex, and head motion. Only FA of the left cingulum angular bundle (CAB) was positively correlated with PTSD symptom severity ( $r=0.433$ ,  $p=0.001$ ,  $df=57$ ) and remained significant after Bonferroni correction. This finding may imply greater organization of the CAB with increasing PTSD severity. The CAB connects directly to the cingulate cortex and the hippocampal subiculum, critical nodes of the default mode network, as well as being implicated in neurodegeneration pathology, decision-making, and executive functions, which may help explain previously shown alterations in this network in PTSD. Further study of white matter tract integrity in PTSD is warranted, particularly to investigate whether the CAB connections with both higher-order cognitive functioning and emotion processing regions contribute to the pathophysiology and comorbidity of PTSD.

## PTL383

### Psychiatric Symptoms and Responses in Students in the High School Exposed to the Sewol Ferry Disaster

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Two hundred and fifty 11th grade students and teachers from Danwon High School drowned during a school trip in the Sewol Ferry Disaster on April 16, 2014. The goal of this

study is to investigate the experiences of the psychiatrists who volunteered and provided psychiatric services to the students.

The study questionnaires were distributed retrospectively to psychiatric volunteers who conducted outreach at Danwon High School. We surveyed the pro bono psychiatrists about their experiences, including the students' chief complaints, psychiatric problems, and clinical diagnoses, as well as the psychiatrists' treatment recommendations.

We reached 72 (43.1%) of the 167 volunteers, and they reported on 212 (38.6%) of the 550 encounters. The common chief complaints were mental health problems, companion problems, and family problems. The most frequent psychiatric symptoms were anxiety (20.4%), depressive mood (13.6%), and concentration difficulty (13.5%). The most frequent clinical diagnoses of the students were normal reaction (38.8%), acute stress disorder (23.2%), adjustment disorder (17.0%), anxiety disorders (8.9%), and posttraumatic stress disorder (6.3%). More than half of the students needed "Additional counseling/therapy" (39.7%) or "Referral to psychiatric treatment" (13.7%)

During the acute aftermath of the Sewol Ferry Disaster, volunteer psychiatrists were able to provide services. These services included psychiatric assessments, crisis counseling, psychological first aid, and referrals for ongoing care. Although the systematic diagnoses could not be confirmed, more than half of the students were perceived to have a psychiatric diagnosis, and a substantial proportion of students needed further treatment. Future research should focus on the short- and long-term effects of psychiatric interventions and the characterization of postdisaster mental health needs and service provision patterns.

## PTL384

### Diagnostic approach to the mild traumatic brain injury verification in patients with PTSD

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**Background.** Many studies indicate the increasing of mild traumatic brain injury (mTBI) among other military injuries, which aren't diagnosed on time. However, mTBI have a negative psychosocial effect, reduce the possibility of successful adaptation and re-socialization, especially in combination with post-traumatic stress disorder (PTSD).

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**Methods.** We have studied 93 postdeployment persons men who participated in military conflict in eastern Ukraine for 3-40 months prior to the survey. In order to verify mTBI, the Boston Assessment of TBI-Lifetime (BAT-L) was used. - Scale for clinical diagnosis of PTSD (CAPS-5) was used for PTSD verification.

**Results.** mTBI is one of the most common injuries among veterans, but individual symptoms may be inaccurately associated with another disease. It may adversely affect diagnosis, treatment planning and recovery expectations. Epk Compliance with the accuracy of The verification' exactness is complicated with lack/ false information about mTBI; in the initial assessment delay; overlap of PTSD and mTBI symptoms; comorbidity of mental disorders and mTBI.

Our study found that according to BAT-L 63% had at least one mTBI throughout their lives. In 41.9% cases there was at least one military mTBI, but only 19.2% of people had mTBI documentary evidence and 17.2% persons did not seek medical assistance at all. Among military injuries 38.5% were blast-related, 43.6% - due to other military reasons, 17.9% had a combined injury mechanism. According to the CAPS-5 scale, 54.4% patients with mTBI had PTSD, and 45% had a adjustment disorders. Violations of attention were 86.8% of all surveyed, executive disfunction - 75.0%.

**Conclusions.** Boston's assessment of traumatic brain injury during life (BAT-L), PTSD clinical diagnostic scale (CAPS-5) and cognitive tests are useful for mTBI + PTSD diagnosis.

## PTL385

### **Robust anti-suicidal and antidepressant effects of S-ketamine in post-psychotic depression: A case report**

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**Key words:** schizophrenia, post-psychotic depression, ketamine

#### **Background:**

Rapid anti-suicidal and antidepressant effects of ketamine have repeatedly been reported in patients suffering from major depression (MD) (1-3). Antidepressant efficacy has also been confirmed in depressed patients with psychotic symptoms in their history (4). However, the administration

of ketamine in psychotic disorders has largely been avoided because of its potential to exacerbate dissociative or psychotic symptoms. Since up to 36 % of schizophrenia patients develop post-psychotic depression (5), effective treatment strategies are urgently needed in order to adequately manage this challenging clinical phenomenon.

#### **Methods and Results:**

We present a 30 years-old female inpatient (weight: 114 kg) suffering from schizophrenia with a severe and chronic disease course (DSM-5: 295.90). After full remission of positive symptoms she developed severe post-psychotic depression with concrete suicidal ideation not responding to conventional psychopharmacotherapy with venlafaxine 300 mg, pregabalin 600 mg and valproate 1000 mg per day in addition to clozapine 400 mg and risperidone 8 mg per day. Consequently, an augmentation treatment with intravenous S-ketamine 25 mg per application (=0,22 mg/kg) was initiated. Immediately after the first S-ketamine infusion we observed a robust anti-suicidal and antidepressant response lasting several days, which was accompanied by discrete dissociative phenomena, which, however, disappeared minutes after S-ketamine had been administered. Since intravenous S-ketamine was well tolerated by the patient, the application dose was increased to 37,5 mg (=0,33 mg/kg) and administered thrice weekly for 2 weeks. Consequently, a sustained remission of depressive symptoms and suicidality was achieved without any induction of psychotic symptoms.

#### **Discussion:**

Intravenous S-ketamine led to rapid anti-suicidal and antidepressant effects without any accompanying meaningful psychotic or dissociative phenomena in our schizophrenia patient. Hence, we encourage scientists and clinicians to widen the administration range of ketamine beyond the diagnosis of MD to improve the current understanding of the efficacy of ketamine in psychotic disorders.

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## PTL386

### Heritability and Familiality of Psychopathologic Dimensions in the Korean Families With Schizophrenia

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**Objectives:** Categorical syndrome such as schizophrenia could be the complex of many continuous mental structure phenotypes including several personality development/degeneration dimensions. This is the study to search heritability and familiality of SCL psychopathologic dimensions in the Korean schizophrenic LD(Linkage Disequilibrium) families.

**Methods:** We have recruited 204 probands(with schizophrenia) with their parents and siblings whenever possible. We have used SCL questionnaires for measuring psychopathologic dimensions. Heritabilities of symptomatic dimensions in total 543 family members were estimated using Sequential Oligogenic Linkage Analysis Routines(SOLAR). Psychopathologic dimensions in total family members were compared with those in 307 healthy unrelated controls for measuring the familialities using ANOVA analysis.

**Results:** Seven of the 10 SCL variables were significantly heritable and were included in the subsequent analyses. The three groups(control, unaffected 1<sup>st</sup> degree relative, case) were found to be significantly different with the expected order of average group scores for all heritable dimensions.

**Conclusion:** Our results show that the aberrations in several symptomatic dimensions could form the complexity of schizophrenic syndrome as a result of genetic-environment coactions or interactions in spite of some limitations(recruited family, phenotyping).

## PTL387

### Focus on apathy in schizophrenia: a review of non-pharmacological interventions and pharmacological approaches

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**Background** - Apathy/Avolition domain of negative symptoms is described as an impaired motivation and a reduced goal-directed behaviour. Given that apathy is highly associated with functional outcome, the development of therapeutic strategies should be a key goal in the care of patients with schizophrenia. Furthermore, apathy has been identified as a major limiting factor in psychosocial rehabilitation.

**Objective** - The aim of this review is to provide an update of the main clinical trials of pharmacological agents and non-pharmacological treatments targeting negative symptoms in schizophrenia, especially apathy.

**Method** - A systematic review of clinical trials focusing on apathy and avolition in schizophrenia, published between 1995 and 2018 was performed. Thirty-eight studies were selected and divided in two groups: 1/pharmacological therapeutics, 2/non-pharmacological approach.

**Results** - To our knowledge, no study defined specific treatment for apathy in schizophrenia as primary endpoint.

1/ Several pharmacological agents were reported to decrease negative symptoms, especially in the field of apathy: antidepressants (citalopram, mirtazapine), selective MAOreceptor inhibitor (rasagiline), antipsychotics (olanzapine, aripiprazole, amisulpride, risperidone, clozapine), psychostimulant (modafinil), antibiotics and anti-inflammatories (minocycline, pregnenolone), NMDA receptor antagonist (memantine), new agents (5-HT<sub>3</sub>, 5-HT<sub>2A</sub>agonists, brexpiprazole, bitopertin, selective agonist mGlu<sub>2/3</sub>receptor, alpha-7nicotinic agents) and dietary supplements (folates/vitamin B12, sodium benzoate).

2/ Several non-pharmacological approaches were also reported to improve apathy in schizophrenia, including neuromodulation (rTMS), behavioral and activity based approaches (music therapy, physical exercises, calligraphy) and cognitive stimulations (OPUS treatment, social skills training, positive emotion program for schizophrenia, cognitive psychotherapy and remediation).

**Conclusion** - Clinicians have existing options for treatment of negative symptoms linked to schizophrenia. However,

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considering the critical impact of apathy on psychosocial rehabilitation and quality of life, specific studies primarily focused on the apathy domain in schizophrenia are needed. Furthermore, reliable information regarding the distinction between primary (prior to treatment) and secondary (consecutive to drugs or depression) apathy is nowadays lacking.

## PTL388

### Risky co-operative behavior in Schizophrenia: A neuroeconomics examination

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**Background:** Clinical features of Schizophrenia, such as paranoid delusions, are characterized by impaired trust in others. This is reflected in societal interactions, especially while mutually rewarding co-operation is needed in a risky situation. Despite its significance, the nature of risky co-operation in Schizophrenia is under-examined.

**Objective:** Objective of the study was to evaluate risky co-operative behavior in Schizophrenia patients, compared to healthy individuals. We hypothesized that, in comparison to healthy controls, individuals with Schizophrenia would have lower risky co-operative behavior.

**Methods:** We used the modified, iterated stag-hunt game, a neuroeconomics paradigm, to assess risky co-operation in 27 Schizophrenia patients (age=33.07±1.21years;male:female=19:8) and 30 healthy controls (age=31.23±0.99years;male:female=17:13). They could invest either in a high risk-high reward co-operative strategy, which depends on the partner's cooperation or a low risk-low reward strategy independently. Subjects also completed tasks examining general risk-taking behavior, social preferences and mood status.

**Results:** Patients and healthy controls were matched on age and gender distribution ( $p>0.05$ ). Compared to healthy controls (84.33±4.57), Schizophrenia patients (42.96±1.04) had significantly lower baseline investment ( $t=8.83$ ;  $p<0.001$ ) indicating lower risky cooperation. Behavioral modification after feedback was also significantly lower in patients ( $t=2.51$ ;  $p=0.015$ ). On the other hand, schizophrenia patients (52.96±37.80) had significantly higher general risk-taking behavior compared to healthy controls (31.33±0.29) ( $t=2.72$ ;  $p=0.009$ ). Patients (52.6±8.82) also had significantly lower social preference score compared to controls (90.67±4.72), ( $t=3.80$ ;  $p<0.001$ ). Difference in risky co-operative behavior persisted despite controlling for the potential confounding

effect of lower social preference score ( $f=37.94$ ;  $p<0.001$ ). There was no correlation between investment, clinical variables and neurocognition ( $p>0.05$ )

**Conclusion:** The findings of this first study examining risky co-operative behavior in schizophrenia indicate that patients have lower co-operative behavior in a risky situation. The study provides a testable, ecologically valid paradigm for social behavior in Schizophrenia.

## PTL389

### Preliminary Evidence of a Suicidal Ideation-Specific Neural Signature of Synaptic Loss and Dysconnectivity in Posttraumatic Stress Disorder

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Suicide is a global phenomenon and a worldwide leading cause of death, yielding unimaginable burden for loved ones and significant socioeconomic toll. In the U.S., 20 military Veterans die by suicide each day, a rate two to six times that of their civilian counterparts. Suicidal ideation (SI), a cardinal precursor to death by suicide, occurs at a significantly greater frequency than death and causes immense burden, yet relatively little is known about its pathophysiology. This is especially so in the context of PTSD, a signature injury of the wars in Iraq and Afghanistan. Mounting evidence supports stress-related structural and functional neural alterations in SI and PTSD, thought to be the result of synaptic loss and dysconnectivity, yet few studies have examined SI in PTSD populations. Using high resolution MRI, cortical thickness and global brain connectivity (GBC) were evaluated in 31 combat-exposed Veterans with PTSD. SI was assessed with the Beck Scale for Suicidal Ideation. GLM analyses, controlling for age, depression, and PTSD symptom severity were used to evaluate any distinct effects of SI. Analyses demonstrated a widespread bilateral pattern of alterations in cortical thickness in SI, particularly in the prefrontal and parietal regions as well as regions in the limbic system including the insula, parahippocampal area, and cingulate. Altered GBC was found in three major intrinsic connectivity networks – the default mode, central executive, and salience networks. These preliminary analyses suggest SI may have a distinct neural signature of synaptic loss and dysconnectivity in areas implicated in reward processing, memory/cognition, empathy, and behavioral and emotional control. Further, these results underscore the invisible wounds of war and highlight a possible biomarker to aid in potentially distinguishing



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between those at increased risk for SI. This area of research has potential to inform novel prevention, identification/diagnostics, and treatment approaches with immense clinical implications.

## PTL390

### **A retrospective study of suicide reporting in Indian Newspaper: Are WHO Guidelines followed?**

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#### **AIMS AND OBJECTIVES:**

We aimed to assess and analyze the nature and extent of reporting of suicides in an Indian newspaper. We also intended to find out whether the nature and extent of reporting of suicide conformed to the guidelines laid out by the World Health Organization.

#### **MATERIALS AND METHODS:**

We carried out a retrospective study covering THE TIMES OF INDIA (English language National daily). The data was collected over a two month period from September 1, 2017 to October 31, 2017 with the help of an electronic search for the word "suicide" from the archives. The articles so collected were assessed by a team of two psychiatrists.

#### **CONCLUSIONS:**

Of the 384 suicide-related articles retrieved from the archives of THE TIMES OF INDIA, 92.2% were in the form of a news report of the incident while only 7.8% were in the form of an opinion or debate on the issue. 57.3% clippings used the word "suicide" in the headline, which should be avoided as per the W.H.O. guidelines. 53.1% of the articles used the term "committed suicide", which is not recommended. 27.1% of the articles gave a detailed description of the method used. 10.9% of the suicide-related articles were accompanied by one or more photographs. Out of them, 33.3% featured a photograph which made the location of the suicide clear and 9.5% carried a photograph which made the method of suicide clear. All of these are not recommended by the W.H.O. guidelines.

Surprisingly, none of the articles or news-items used the term "non-fatal suicide attempt" recommended by the W.H.O. guidelines. Only 8.85% articles gave information about where to seek help if any of the readers had suicidal ideas (another recommendation laid out by the W.H.O.). Only 10.9% articles sought an expert advice and only 12.5% talked of education about suicide warning signs and its prevention.

Our study is one of the initial studies carried out in India to study the extent to which W.H.O. guidelines on suicide reporting are complied with in newspapers published in India. The findings of our study underscore the need for research in impact of media reporting on suicides in India. Framing of media guidelines for suicide reporting in India is essential. Workshops need to be conducted all over India to sensitize the media and need to be repeated on a regular basis. Mental health professionals need to take the lead in educating the media about responsible suicide reporting.

## PTL391

### **Suicide attempt during postpartum in Psychiatry Emergency Room**

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**OBJECTIVE:** To study incidence of puerperal patients (1 year post partum)(PP) with suicide attempt, seen at Emergency Room( ER) of a Mental Health Institute in Lima (2015-2017).**METHOD:** Prospective trial , ICD -10 Diagnostic Criteria and Scale of Pierce for Suicidal Behavior, in female during PP state, aged 18-45 years, assisted by suicidal attempt in ER. **RESULTS:** Of 1700 females ,75 of them (4.4 %) were in PP period; being at first trimester 67 (89,3 %):According age: :18 to 25years old: 26 (34.7 %), 26- 33 y.o : 31 (42.7 %), 34-41 y.o: 15 (20.0 %) and 42 y.o or more: 2 (2.6 %). Civil Status: Separated : 31 (41,3 %), convivial:17 (22,7 %), single :16 (21,3 %), married : 9 (12.0 %) and widow :2 (2.7 %). Clinical Diagnoses : Major Depressive Disorder: 54 (72,0 %), Bipolar Disorder 8 (10,7 %) ,General Anxiety Disorder 5 ( 6,7 %) ,Obsessive Compulsive Disorder 2 ( 2.7 %), and Schizophrenia 6 (8.0 %). Co-morbid Diagnoses: Borderline Personality Disorder: 35 ( 46.7 %),Psychoactive Substance Disorder 5 ( 6.7 %).Motivation : Undesired pregnancy : 13 (17,3 %), Familial trouble : 18 (24,0 %), Conjugal conflicts : 39 (52.0 %), others: 5 (6.7 %). Method : overdose of tablets: 43 (57,3 %), self cutting: 16(21,3 %), poisons: 12( 16,0 %), hanging : 4( 5.3 %). At least 39 (52 %) patients made a previous suicidal attempt. Two females (2.6 %) made a Filicide.**CONCLUSION:** According this trial,PP period, mostly during first trimester, becomes a risk factor, associated especially to MDD, together with a conjugal or familial stressor for suicide attempt and also filicide.**BIBLIOGRAPHY:**1.-Comtois KA, et al (2008) Psychiatry risk factors associated with postpartum suicide attempt in Washington State, 1992-2001. Am J Obst Gynecol,199( 2): 120. 2.-Sanchez -Tapia FR, Ostolaza-Vite

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## PTL392

### **BDNF Gene is a Determinant of methadone dose on Heroin Dependence in Han Chinese**

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#### **Background**

Heroin dependence is a brain disease to involve complex genetic mechanisms. Methadone maintenance treatment has helped them to improve their health, family and social lives. We aimed to explore the genetic predisposition on low dose versus high dose methadone treatment in heroin-dependent patients.

#### **Method**

Two hundred and forty volunteers (209 men, 31 women), 120 below 60mg methadone and 120 above 60mg methadone daily dose, aged  $\geq 20$  years recruited from ethnically Han Chinese patients with methadone maintenance treatment in Taiwan. All subjects were genotyped via SEQUENOM MassARRAY System iPLEX SNP Genotyping for 46 single-nucleotide polymorphisms in genes encoding DRD1, DRD2, DRD3, SLC6A3, HTT, COMT, BDNF, CREBBP, OPRM1, GABRA2, PPARGC1A, GRM3, MTHFR, CYP3A4, and CYP2D6 at the Genomics Research Center, Academia Sinica. The association between genotypes and methadone dose status were tested by Cochran-Armitage trend test.

#### **Result**

Only one single-nucleotide polymorphisms in Brain-derived neurotrophic factor (BDNF) gene, namely at rs3763965 ( $p=0.024$ ,  $OR=1.51$ ), was significant on statistical analyses.

#### **Conclusion**

These findings suggest main determinant gene is BDNF about methadone dose for heroin dependence. However, this study enrolled Han Chinese participants only, it would be interesting to know whether our findings are applicable to other ethnic populations.

## PTL393

### **Spread via real or virtual paths? Exploring seven illicit drugs' probable transmission based on the poundage of drug seizing**

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#### **Background**

We delineated the illicit drugs' paths of transmission via smuggling or online transaction based on a nationwide database of drug seizing in Taiwan.

#### **Material and Method**

We used the open access database of National Police Agency, Ministry of the Interior in Taiwan. We analyzed 201,294 criminal cases with the date, location, and quantity of illicit drugs was seized from 2015 to 2017. We investigated the association between the weight of illicit drugs and the place where drug seizing located of seven drugs: heroin, amphetamine, ketamine, flunitrazepam, 3,4-Methylenedioxymethamphetamine (MDMA), marijuana, and cathinones. We used receiver operating characteristics (ROC) analysis to examine the discriminating ability of drug weight via possible online transaction or smuggling in airports or customs. We presented the area under the curve (AUC) of ROC and carried out C-statistics for the AUC of the parameters higher than 0.5 indicated that the weight of drugs had potential discriminating efficacy. We defined the significant prediction if the 95% CI of the AUC did not cross the 0.5, that is, the  $p$ -value was less than .05.

#### **Results**

Heroin (AUC = .739,  $p = .001$ ), amphetamine (AUC = .732,  $p < .001$ ), and cathinones (ACU = .748,  $p = .001$ ) have significant discriminating efficacy which implied the paths of transmission via online transaction. Whereas, heroin (AUC = .683  $p < .001$ ), ketamine (AUC = .841  $p < .001$ ), flunitrazepam (AUC = .826,  $p = .003$ ), marijuana (AUC = .731  $p < .001$ ), and have significant discriminating efficacy which implied the smuggling in airports or customs.

#### **Conclusion**

Our findings showed that heroin's paths of transmission involve both online transaction and smuggling in airports or customs. New psychoactive substances, especially cathinones, mainly spread via Internet.

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## PTL394

### Parental involvement in the child's activities can contribute to cognitive development of preterm infants

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**Background:** According to the diathesis stress model preterm children are more susceptible to negative environmental influences. Parents' emotional distress had a greater effect on the cognitive and socioemotional outcomes of very preterm as compared with full-term children [Hadfield et al., 2017]. Researchers have underlined that postnatal depression is associated with infants' level of oxytocin, impairing their response to stress [Feldman & Eidelman, 2007]. It is important to know which are the features of parental behavior that can have positive effect on the development of preterm children.

**Methods:** 14 infants and their caregivers participated in this pilot research: 6 preterm (1 boy; mean corrected age 5.6 months) and 8 full-term (3 boys; mean age 5.5 months). 15min of parent-child interactions were recorded and coded through the Social interaction rating Scale (SIRS), which is composed of six items: level of affect, directiveness, initiation toward the child, maintenance of interaction, contingency, participation. The Beyeley Scales of Infant Development III were used to assess cognitive, speech, social-emotional development and adaptive behavior.

**Results:** Two-way ANOVA showed significant interaction between group and one item of SIRS (Participation) in Receptive communication scale ( $F=8.9$ ;  $p=0.015$ ) and Language scale ( $F=8.7$ ;  $p=0.016$ ). Parents' involvement in the child's activities has a more positive affect on language development in preterm infants.

**Conclusions:** It can be assumed that parental involvement in the child's activities as a positive environmental factor can contribute to cognitive development of preterm infants.

This work was supported by grant Russian Science Foundation №16-18-10371

## PTL395

### Psychological trauma suffered by the people of Kashmir through the eyes of cinema: a reappraisal

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#### **AIMS AND HYPOTHESIS:**

We aimed to investigate whether the Indian cinema has faithfully mirrored the emotional trauma suffered by the people of Kashmir in the last two decades? Our hypothesis is that the Indian films have merely managed to capture a slice of the whole spectrum of the emotional trauma suffered by the people of Kashmir. There is an urgent need for the film fraternity to be sensitized so that the world learns and understands the aspects related to mental health of the people of Kashmir.

#### **METHODS:**

16 Indian movies released during the last two decades which had Kashmir as their central theme were shortlisted and viewed by the team of two psychiatrists. The problems portrayed in these movies relating to emotional trauma suffered by the people of Kashmir, were identified and analyzed. Specific scenes from the movies included in the study were identified which portrayed different aspects of the emotional trauma in a sensitive and scientifically accurate way. The findings were then compared with the research carried out in this area till date.

#### **SUMMARY AND CONCLUSIONS:**

Kashmir presents a unique perspective to the mental health problems faced by people in the backdrop of terrorism and counter-terrorism operations. The emotional trauma suffered by the people of Kashmir has many faces ranging from acute stress reaction to Post traumatic stress disorder, and from psychotic illnesses to depression. Movies like "Yahaan", "Tahaan" and "Haider" have brought to the fore the emotional trauma of "half widows" and mothers the fate of whose sons is not known. The fear and uncertainty of the unknown has been brilliantly portrayed on the silver screen. The shock of losing a close family member in a bomb blast or some other act of violence has been portrayed quite well in this scene from "Yahaan" and another one from "Haider". The emotional trauma of daily life frequented by frisking by the security forces and identification parades has been brilliantly portrayed in one particular scene of "Haider"

The researches carried out till now have found out a general increase in the psychiatric morbidity in Kashmir. These include the emotional trauma associated with cordon and search operations carried out by the security forces, the trauma associated with frequent frisking by the security forces, the emotional distress of the "half widows",

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which refers to those women whose husbands' whereabouts are not known. They may have either joined the ranks of militants or have been arrested by the security forces.

The problems faced by the people anywhere in the world caught between the militants on one side and the security forces on the other, are likely to be similar. We intend to extend our study to these parts of the world and examine the portrayal of the emotional trauma by the media.

## PTL396

### Chronic unpredictable stress induces adaptation in inducible nitric oxide (iNos) knockout mice

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**Aim:** We investigate the participation of the inducible isoform of nitric oxide synthase (iNOS) in the behavioral consequences of chronic stress. **Methods:** we submitted Wild type (W.T) and iNOS Knock-out (K.O.) mice to 21 consecutive days of Chronic Unpredictable Stress (CUS). Control group were left undisturbed in their home cages. On the 20<sup>th</sup> day of stress, animals were submitted to the open field test (OFT). On the next day, mice were food deprived for at least 20 hours. On the 22<sup>nd</sup> day, animals were submitted to the novelty suppressed feeding test (NSF) to analyze anxiety-like behaviors. **Results:** iNOS K.O. explored less the OF than the WT, CUS prevented this effect. Regarding the NSF, non-stressed iNOS K.O. mice exhibited an anxiogenic-like effect that was also observed in the stressed groups (WT and iNOS K.O.), as demonstrated by their increased latency to feed in a new environment. **Conclusion:** Our results suggest that iNOS seems to modulate anxiety-like a phenotype not influenced by previous stressful experience.

## PTL397

### Maternal Nicotine's Effects on Learning and Memory in Adolescent Mice

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Maternal nicotine exposure influences over 314,000 adolescents per year in the United States alone. This accounts for over \$100 million dollars in healthcare costs associated with maternal tobacco smoking during pregnancy. The long-term consequences of maternal tobacco exposure in offspring are related to hyperactivity, learning, memory and addictive disorders. The basic mechanisms mediating these effects are unknown.

Out of the 8000-plus constituents in tobacco smoke, nicotine is considered the primary psychoactive component mediating the long-term consequences of maternal tobacco exposure in offspring. Binding to a range of nicotinic acetylcholine receptors (nAChRs) (alpha1-10, beta1-4, encoded by the *Chrna1-10* and *Chrbn1-4* genes), nicotine can modulate the release of neurotransmitters to influence long-term neurobehavioral alterations in offspring. We have recently discovered that alpha2 nAChRs are necessary and sufficient for nicotinic-facilitation of synaptic and behavioral plasticity in adolescent rodents<sup>1</sup>. These receptors are expressed in distinct regions of the brain, including the oriens lacunosum-moleculare GABAergic interneurons within the CA1 hippocampus<sup>2</sup>.

**The objective of our current studies** delineates whether the deletion of *Chrna2* subunit eliminates the long-term cognitive effects of maternal nicotine exposure on learning and memory in adolescent offspring<sup>3</sup>. **The methods used in our current studies include:** (i) wild type and genetically modified alpha2 nAChR null-mutant (*Chrna2*<sup>KO</sup>) mice<sup>4</sup> and (ii) a learning and memory behavioral assay called pre-exposure dependent contextual fear conditioning<sup>1</sup>. **Our results** demonstrate that maternal nicotine exposure delays extinction learning in adolescent wild type mice, which is abolished in *Chrna2*<sup>KO</sup> mice. These effects are not influenced by sensory, locomotor or anxiety-related behaviors. **In conclusion**, the findings provide evidence for a distinct molecular genetic target underlying the learning and memory effects of maternal nicotine exposure in adolescent offspring.

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## PTL398

### Vildagliptin prevents insulin resistance induced Cognitive Impairments in rat

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Consumption of high-fat diets (HFD) is a risk factor for insulin resistance and diabetes mellitus. It has been shown that HFD consumption has a central impact on cognition and memory. Vildagliptin has anti-inflammatory and anti-apoptotic effects. Therefore, the purpose of this study was to evaluate the effects of vildagliptin on brain function in insulin resistant rats.

36 rats were randomly allocated into three groups: Group I (control group) received normal diet, Group II received HFD during 10 weeks as well as Streptozotocin (35mg/kg S.C.) and Group III received HFD, Streptozotocin and Vildagliptin (3mg/kg, P.O. for 3 weeks). Learning and memory was evaluated by measuring elapsed time in target quadrant and latency time to find target box in Barnes test. Finally, after killing animals, their brain (hippocampus) was isolated and their BDNF were examined.

The results demonstrated that diabetes decreased elapsed time in target quadrant and increased latency time in Barnes maze test, whereas vildagliptin (3mg/kg, P.O. for 3 weeks) increased elapsed time in target quadrant and decreased latency time. Moreover, there was significant decrease in BDNF in HFD fed rats. Also, significant increase was observed in brain BDNF in HFD fed rats receiving vildagliptin.

We showed that vildagliptin improves cognitive performances by increasing BDNF and antioxidant agents. However, further investigations should be undertaken to clarify the exact mechanism of interaction between HFD and cognitive impairments.

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## PTL400

### Comparison of antipsychotic action of positive allosteric modulators of muscarinic M1, M4 and M5 receptors

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Schizophrenia is a complex mental disorder characterized by the prevalence of positive, negative and cognitive symptoms. As current pharmacotherapy is not fully efficient in treating negative and cognitive symptoms, there is a need to characterize new targets for novel antipsychotics.

Recent data suggests that acetylcholine could also be involved in schizophrenia pathology. A clinical trial involving xanomeline, a non-selective muscarinic agonist, proved that modulation of muscarinic receptors could be beneficial, as an antipsychotic effect has been noted in those studies. Unfortunately, the trial was discontinued due to gastrointestinal side effects, possibly because of xanomeline's action on M2 and M3 muscarinic receptors.

Thus, our studies focused on characterizing the antipsychotic action of muscarinic M1, M4 and M5 receptors, using selective positive allosteric modulators (PAM) (VU0357017, VU0152100 and VU0238429, respectively).

In order to investigate the action of the aforementioned PAMs, several behavioral tests were carried out. DOI-induced head twitches were used to model positive symptoms, the social interaction test modeled negative symptoms, the novel object recognition test assessed the

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cognitive functions and the rotarod test was used to determine the side effects. Male CD-1 mice were used in the study.

All of the muscarinic PAMs used in the study significantly decreased the number of DOI-induced head twitches. Moreover, VU0357017, VU0152100 and VU0238429 reversed the MK-801-induced impairment in novel object recognition test. Modulation of M4, but not M1 or M5 receptors, resulted in a reversal of the MK-801-induced deficit in both the duration and number of social episodes. None of the tested compounds produced motor impairment.

Our results suggest that modulation of muscarinic receptors could be beneficial in treating schizophrenia symptoms. Clearly, modulation of M4 receptors provided a different profile of action than modulation of M1 or M5 receptors, as VU0152100 was effective in all of the tests modeling symptoms of schizophrenia. However, different modes of actions might be of use in targeted pharmacotherapy.

Supported by NCN grant no OPUS 2015/17/B/NZ7/02984 (J.Wierońska)

## PTL401

### Effects of the antipsychotics haloperidol, clozapine, and aripiprazole on the dendritic spine

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Three types of antipsychotics, typical (e.g. haloperidol), atypical (e.g. clozapine), and dopamine partial agonist (e.g. aripiprazole), are administered for treatment of schizophrenia. These antipsychotics have different efficacy and side-effect profiles. We investigated whether aripiprazole, clozapine, and haloperidol differentially regulate the dendritic spine through the AKT-GSK-3 beta cascade. We followed the 'Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions'. Dissociated cortical neurons from Sprague-Dawley rats were prepared and cultured for 28 days. Aripiprazole, clozapine, or haloperidol was administered to the rat cortical neurons. The levels of PSD95 protein and AKT-GSK-3 beta cascade-related proteins were investigated by Western blot. The number of spines and PSD95 puncta were investigated by immunofluorescence cell staining. Aripiprazole (1  $\mu$ M or 10  $\mu$ M) and clozapine (1  $\mu$ M) increased the levels of PSD95 protein, the number of spines, phosphorylated Akt Thr308 and Ser473, and phosphorylated GSK-3 beta Ser9. On the

other hand, haloperidol (1  $\mu$ M or 10  $\mu$ M) or an inappropriate concentration of clozapine (10  $\mu$ M) decreased them. A GSK inhibitor also increased the levels of PSD-95 protein and caused the same morphology. Aripiprazole, clozapine, and haloperidol differentially regulate the dendritic spine, and this effect may occur through the AKT-GSK-3 beta cascade. Selection and appropriate dose of these antipsychotics may be important for the protection of dendritic spines in patients with schizophrenia.

## PTL402

### Nicotine Gateway Effects Enhance Adolescent Alcohol Intake and Preference in Mice

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**Introduction:** Adolescence represents a vulnerable period of development where nicotine and alcohol are often co-used. Adolescent versus adult nicotine exposure is consistently reported to enhance later substance use in humans and animals, i.e. nicotine's gateway effects.

**The objective of our current proposal** tests whether adolescent versus adult nicotine exposure enhances alcohol intake and preference in C57BL/6J mice.

**We use the behavioral methods of** Drinking-in-the-Dark (DID) and the two-bottle choice preference task to measure alcohol intake and preference. We pretreat animals with low-dose nicotine (2x 0.5 mg/kg/s.c./day) or vehicle for 7-days followed by assessing alcohol intake and preference post a 7-day washout.

**Results:** Adolescents exhibit enhanced overall fluid intake versus adults. Adolescents and adults exhibit increased alcohol versus water intake over time. Further, nicotine-pretreated adolescents illustrate quicker acquisition of alcohol intake versus adults or water drinking groups. While both adolescent and adult mice illustrate preference for alcohol, nicotine pretreated adolescents versus adults had a greater preference for alcohol intake in alcohol experienced mice. The findings are not confounded by changes in blood alcohol levels.

**Conclusions:** Data provide support for nicotine's gateway effects on adolescent alcohol intake and preference in mice. The results have important public health implications, given the growing use of e-cigarettes in the adolescent human population.

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## PTL403

### **Altered rostromedial tegmental activation and behavioural response to chronic ethanol exposure in a preclinical model of depression-addiction comorbidity**

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Depression substantially increases risk for addiction, for which comorbidities often impede successful treatment. To elucidate neurobehavioural correlates of addiction-depression comorbidity, we examined depressive/anxiety-like behaviour and ethanol consumption in a diathesis(risk)-stress model. We tested the response of the rostromedial tegmental nucleus (RMTg) to ethanol since it is known to mediate impact of aversive stimuli on dopamine and serotonin activity, implicated in addiction and depression. We reproduced diathesis-like liability in rats by employing an olfactory bulbectomy (OBX) procedure that conferred a sensitized response to novelty without necessarily producing depressive/anxiety-like phenotypes in a sucrose preference test and in the novelty-suppressed feeding test. In OBX animals, we found that long-term (44 days) but not short-term (22 days) ethanol exposure results in an anxiolytic-like behaviour despite profound anhedonia-like reactivity, an effect associated with indices of increased behavioural sensitivity to ethanol (increased intake and motor response). Sham and OBX animals showed divergent activational responses of the RMTg to ethanol as indicated by glucose utilization (biosensor) measurements. In particular, sham animals displayed lower initial peak-trough amplitudes and maintained a biphasic, negative-positive glucose signal profile, suggesting lower basal RMTg activity. OBX animals had greater peak-trough amplitudes followed by a stable decrease in signal, suggesting high basal RMTg activity. Moreover, OBX powerfully attenuated the correlational strength between RMTg activation and comorbidity scores for depression and ethanol sensitivity, indicating a drastic narrowing of the dynamic range in RMTg activation. Altogether, these provide first demonstration for the use of OBX in bestowing a diathesis-like risk for depression-addiction comorbidity that can be unraveled by the stress of subsequent ethanol withdrawal. The consequent comorbidity was associated with marked alterations in RMTg response to ethanol. This highlights a role for RMTg in mediating increased concurrence of symptoms under

comorbid conditions and potentially offers a therapeutic target for the effective treatment of comorbid disorders.

## PTL404

### **The antidepressant-like behavioural and neuroplastic effects of stress controllability training are mediated by cortical endocannabinoid-CB1 receptor signaling**

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Affective disorders such as major depression can be exacerbated by a perceived lack of control over stressors, a phenomenon that is linked to perturbed prefrontal-raphe and hippocampal neurotransmission. Conversely, cognitive-behavioural remediation ameliorates mood-related symptoms by enhancing behavioural control. We developed a rodent model of cognitive remediation based on a modified Morris water maze (with vs. without an escape platform) in mice. Animals were first exposed to at least six weeks of chronic mild stress (CMS), then were submitted to behavioural control training (BCT), where BCT+ animals were repeatedly allowed to learn to evade swim stress, while BCT- were subjected to inescapable swim stress. CMS-exposed animals exhibited depressive-like behaviours in the sucrose consumption, fruit loops and forced swim tests, as well as anxiety-like reactivity in the novelty-suppressed feeding test. CMS also increased plasma corticosterone levels and decreased plasma levels of brain-derived neurotrophic factor. The CMS-induced behavioural deficits were reversed by 10 days but not by 3 days of BCT in CMS-exposed animals (BCT+), an effect that was not observed in CMS-exposed BCT- animals. The therapeutic-like effects of BCT was nullified by administration of the cannabinoid CB1 receptor antagonist AM251 and recapitulated by the endocannabinoid enhancer URB597. We recorded long-term potentiation (LTP) in the dentate gyrus, and found that CMS disrupted LTP, and this impairment was rescued by BCT. This rescuing effect was abrogated by AM251. Electrophysiological recordings of prefrontocortical and raphe neuronal activity after CMS and BCT (BCT+ vs. BCT-), as well as assessment of CMS and BCT-induced changes in CB1 receptor density and fatty acid amide hydrolase (FAAH) expression are under way.

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## PTL405

### Combination of an epigenetic modulator and a transcription regulator of a differentially-methylated pathway reverses PTSD in a rat model: A novel approach to PTSD treatment.

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**Objective:** Post-traumatic stress disorder (PTSD) is a severe psychiatric disorder that may develop in survivors of a traumatic event<sup>1</sup>. PTSD is characterized by dysfunctional regulation of the central stress response. Additionally, recent data show changes in hedonia—the ability to experience reward—in PTSD patients<sup>2</sup>. A dominant brain region associated with hedonia is the nucleus accumbens (NAc), which is linked to reduce reward responsivity in PTSD patients<sup>2–5</sup>. Here we show the role of DNA methylation – a critical epigenetic mechanism that programs gene expression<sup>6,7</sup>—in the NAc of PTSD animal model. **Methods:** We used an established PTSD-rat-model<sup>8,9</sup>, which mimics PTSD symptoms after exposure to trauma (controls were not exposed to the trauma) and its reminders. This model enables identification of trauma susceptibility and resilience. For DNA methylation detection we performed a genome-wide targeted bisulfite sequencing of functional genomic regions, which was followed by a site-specific differential methylation computational analysis. **Results:** DNA methylation analysis revealed overall hypomethylation of different CpG sites in susceptible animals, which was correlated with the reduction in expression of the DNA methyltransferase (*DNMT3A*). Since disease-related epigenetic changes involve different gene pathways, rather than single candidate genes, we looked for a pathway that may be involved in PTSD via an analysis of the unbiased methylation data. We identified enrichment in an endogenous pathway in-which a key receptor was downregulated in the susceptible group (receptor name is confidential due to an ongoing patent application). Intra-NAc injection of lentiviruses that overexpress either *DNMT3A* or the candidate receptor reversed PTSD-like behaviors. To translate our results into a potential pharmacological therapeutic strategy, we tested the systemic effect of the global methyl donor S-Adenosyl-Methionine, for supplementing DNA methylation, and an agonist of the candidate receptor. We found that combined treatment reversed PTSD-like behaviors.

**Conclusions:** These data strongly support the involvement of epigenetic mechanisms in PTSD. In addition, our study points to a novel therapeutic approach for PTSD, which is potentially translatable to humans.

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## PTL406

### D-neuron hypothesis: A new clue for central nervous system medicinal chemistry

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**Introduction:** Relationship between pathophysiology of mental disorders and trace amines, such as beta-phenylethylamine, or tyramine has long been described from early in 1970's. D-neuron (trace amine neuron) system was described by Jeager *et al.* in 1983 in rat central nervous system. The author specified human D-neuron system, and examined D-neuron neuropathology of neuropsychiatric illnesses to discover novel treatments.



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**Methods:** Immunohistochemistry by using antibodies against monoamine-synthesizing enzymes and postmortem brains of controls, patients with schizophrenia obtained by legal and pathological autopsy (registered cases of national hospital research resource network (RRN)) were used. Available references were used to establish pathophysiological hypothesis.

**Results:** I specified anatomical subgroups of mammalian D-neurons into 18 groups from D1 (spinal cord) to D18 (cerebral cortices) in a caudorostral order. D-neurons could not be detected in monkey striatum, whereas, D-neuron system was developed in human forebrain. In postmortem brains of patients with schizophrenia, D-neurons were reduced in D15 and D16 (Ikemoto et al., 2003). Newly established "D-cell hypothesis of schizophrenia" (Ikemoto, 2012, 2016), a pivotal theory to link neural stem cell dysfunction hypothesis to dopamine hypothesis, explained mesolimbic hyperdopaminergia and disease progression of schizophrenia (Kippin et al., 2005), showing a novel direction in medicinal chemistry, trace amine-associated receptor 1 (TAAR1) as a target receptor (Revel et al., 2013). Domestically developed SEP-363856, a TAAR1 partial agonist, was preceded to a phase 2 clinical trial in foreign countries.

**Conclusion:** D-neuron research has a potential to further build novel therapeutic strategies of neuropsychiatric illnesses, including addiction, mood disorders, and narcolepsy. Regenerative medicine, such as D-neuron transplantation would be available in future.

## PTL407

### Is TAAR1 prospective target receptor for narcolepsy?

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Recent studies have shown that trace amine-associated receptor, 1 (TAAR1) is related to pathogenesis of hypersomnia, narcolepsy. D-neurons are ligand neurons of TAAR1. Lack of D-neurons in the nucleus accumbens (Acc, D16) of post-mortem brains of schizophrenia, and TAAR1 stimulation decrease in the Acc has been regarded as the cause of mesolimbic dopamine (DA) hyperactivity. D-neurons are located in mammalian brains from spinal cord (D1) to cerebral cortices (D18) in caudorostral order. Though the suprachiasmatic nucleus (SCN, D13) contained D-neurons, the role of D13 D-neuron in sleep-wake-cycle (SWC) has not yet been clarified. Interestingly, TAAR1, expressed in pancreatic  $\beta$  cells, has been shown to be related with etiology of diabetes mellitus, obesity, and metabolic syndrome. TAAR1 pathology may explain not only hypersomnia of narcolepsy, similar to hypoactivity of

orexin system, but also etiology of obesity frequently seen in patients with narcolepsy. Monoamine oxidase, type B (MAOB) inhibitors suppress trace amine (TA) degradation, and prescribed for the treatment of hypersomnia. Daytime hypersomnia and nocturnal insomnia has usually been observed from the early stage of schizophrenia, presumably due to dysfunction of subventricular neural stem cells (NSC) and D-neurons in D15-D16. Stimulation of D-neuron activity, trace amine increase, and TAAR1 stimulation increase in the central nervous system and some peripheral organs, may improve the symptoms of narcolepsy. Detailed analysis should be done by using animal models, and brain imaging studies of TAAR1 in patients of narcolepsy and controls.

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