

ABSTRACTS

SCANDINAVIAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

SCNP

60th Annual Meeting, 24 – 26 April, 2019
Gothenburg, Denmark



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ORAL PRESENTATIONS

PRESIDENT'S WELCOME

SCNP: 60 years of progress

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Background: At the XII meeting of the Nordic Psychiatric Congress in Copenhagen in 1958, the subcommittee on psychopharmacology had discussed the perspective of a Scandinavian Society of Psychopharmacology. Parallel with this initiative, the executive of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) contacted the Scandinavian colleagues about establishing a Scandinavian section of the CINP. It was the marked rise in psychotropic drugs in the 1950s (chlorpromazine and imipramine in Europe and the monoamine oxidase inhibitors in United States of America) that resulted in the birth of CINP in 1958.

Objectives: On 5 February 1960, the SCNP was established with Arvid Carlsson (Sweden) as the Founding President and Jørgen Ravn (Denmark) as the Founding Secretary. Other board members were Erik Jacobsen (Denmark) and David H. Ingvar (Sweden). Present at this meeting

Methods: One of the major goals for establishing the SCNP was the standardisation of clinical trials with psychotropic drugs in Scandinavia.

Results: The Presentation will highlight the history of the SCNP in the first 60 years

Conclusion: The role of SCNP in the future will be discussed

LECTURE 1

SCNP 2019 OPENING LECTURE

L1 Arvid Carlsson, 1923-2018

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Background: The field of neuropsychopharmacology is to a great extent based on the assumption that psychiatric and neurological disorders are to some extent manifestations of specific neurotransmitter abnormalities, and that symptom reduction may be obtained by drugs rectifying or compensating for these aberrations. The first robust support for the feasibility of this approach to the treatment of brain disorders, constituting a starting point for modern neuropsychopharmacology, can be dated back to 1957, when Arvid Carlsson and co-workers showed the motor activity-impairing effect of the parkinsonism-mimicking drug reserpine in rabbits to be associated with a depletion of brain dopamine levels, and that restoring these levels by administration of the dopamine precursor levodopa reinstates the ability to move in the animals. Being the first evidence for a transmitter role of dopamine in the brain, and paving the way for an effective treatment of Parkinson's disease, this was the discovery that many years later rendered Carlsson the Nobel Prize in medicine or physiology. However, unlike the many Nobel prize winners who are known primarily for one single major contribution, Carlsson made numerous pivotal discoveries also subsequent to his discovery of the transmitter role of dopamine, such as showing that antipsychotic drugs are dopamine receptor antagonists, and developing the first selective serotonin reuptake inhibitor. In this presentation, the contributions of Arvid Carlsson, who died at the age of 95 in June 2018, in the same month that his last paper was published, will be summarized and discussed.

SYMPOSIUM 1

SCNP FESTIVE COLLEGE SYMPOSIUM

S1.1 Psychopharmacological approaches to Bipolar Depression

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Abstract: Bipolar disorder (BD) is a common, chronic, severe, complex and costly group of recurrent psychiatric illness that can be devastating for the affected individual and their families. There is a significant clinical need for more effective and better tolerated drug treatments for BD. Depression accounts for the predominant burden associated with bipolar disorder. However, both the identification and management of bipolar depression are challenging, since bipolar depression differs little symptomatically from unipolar depression and responds poorly to traditional antidepressants, which may also induce a switch to mania and/or cause rapid cycling. Current treatment options for bipolar depression are limited and guidelines vary greatly in their recommendations, reflecting gaps and inconsistencies in the current evidence base. Moreover, some recommended options, such as quetiapine, although clearly efficacious, are associated with adverse cardiometabolic side effects, which may be detrimental to the long-term physical health and wellbeing of patients, increasing the likelihood of treatment non-adherence and relapse. More recent evidence for lurasidone and cariprazine suggests that it they may effectively manage patients' depressive symptoms. In addition, novel agents targeting alternative neurotransmitter pathways and inflammatory processes (such as ketamine, minocycline and N-acetyl cysteine) are emerging as promising potential options for the treatment of bipolar depression in the future.

S1.2 European College of Neuropsychopharmacology

Celso Arango

Madrid, Spain

Abstract not available.

SYMPOSIUM 2

SCNP YOUNG SCIENTIST SYMPOSIUM

The speakers in the SCNP Young Scientist Symposium are selected among the best abstracts submitted by young scientists.

The selection of the speakers was not finished at time of printing.

However, all abstracts can be found in the poster section, on page 11, as they are also presented as posters.

LECTURE 2

SCNP LECTURE

L2 Real world evidence on the pharmacological treatment of ADHD and SUD

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Background: Substance use disorders are major contributors to excess mortality among individuals with attention deficit hyperactivity disorder (ADHD), yet associations between pharmacological ADHD treatment and substance-related problems remain unclear.

Objectives: To investigate concurrent and long-term associations between ADHD medication treatment and substance-related events.

Methods: We followed two national cohorts of ADHD patients using data from Swedish national registers and commercial health care claims in the US. Within-individual analyses compared the risk of substance-related events during periods in which patients received prescribed ADHD medication relative to the risk during periods in which they did not.

Results: In both the Swedish and the US samples, relative to periods in which patients did not receive ADHD medication, ADHD patients had lower odds of concurrent substance-related events when receiving medication (odds ratios or hazard ratios ranged from 0.65 to 0.73). Moreover, ADHD patients had lower risk of substance-related events 3 years after medication (odds ratios or hazard ratios ranged from 0.69 to 0.84). Sensitivity analyses supported most findings but were less consistent for long-term associations among women.

Conclusion: These results provide evidence that ADHD medication is unlikely to increase the risk of substance-related problems in adolescence or adulthood. Rather, medication was associated with lower concurrent and long-term risk of substance-related events.

LECTURE 3

SCNP LECTURE

L3 Mental Health and Exercise

Lina Martinsson

Abstract not available

SYMPOSIUM 3

THE LEGACY OF ARVID CARLSSON I

S3.1 The dopamine hypotheses of schizophrenia

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Background: Background: The dopamine hypotheses of schizophrenia and antipsychotic drugs evolved during the 1960's, a few years after the discovery of dopamine in brain. In the 70's, the hypotheses

received strong support from radioligand binding studies in experimental animals and humans post mortem. Since then, the advent of Positron Emission Tomography has allowed for direct examination of the dopamine system in the living human brain.

Objectives: Objectives: To review the literature on studies applied to examine the dopamine system in patients with psychosis.

Methods: Methods: A large number of radioligands have been developed for PET-imaging of several markers of the dopamine system. Commonly used radioligands are [11C]SCH23390 and [11C]raclopride for the D1- and D2-dopamine receptor family (D1R and D2R), respectively, and [18F]F-DOPA for the presynaptic synthesis of dopamine.

Results: Results: Using PET it has not been possible to confirm early findings post mortem of markedly elevated D2R in the striatum, though a small increase cannot be excluded. Studies on the D1R has shown discrepant results whereas a presynaptic disturbance of the dopamine system is supported by clinical findings of elevated uptake of [18F]F-DOPA and increased release of dopamine following amphetamine challenges. The DA hypothesis of antipsychotic drug action has received strong support from consistent observations of high D2R occupancy (65 – 90%) in drug treated patients. An exception is the atypical antipsychotic clozapine for which the D2R occupancy is significantly lower.

Conclusion: Conclusions: PET-imaging of markers for the DA system points to a disturbance of the presynaptic dopaminergic neurons. The D2R is a common target for antipsychotic drugs.

S3.2 Immune activation is related to reduced GABAergic and enhanced dopaminergic transmission in first episode psychosis patients

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Background: Immune activation, reduced γ -Aminobutyric acid (GABA)-ergic activity as well as hyperactivity of the brain dopamine system are all, and independently, suggested to be part of the pathophysiology of schizophrenia. We recently reported decreased levels of cerebrospinal fluid (CSF) GABA in first-episode psychosis (FEP) patients. The

pro-inflammatory cytokine interleukin-18 (IL-18) as well as the chemokines monocyte chemoattractant protein-1 (MCP-1) and chitinase-3-like protein 1 (YKL-40) are all secreted by monocytes and macrophages peripherally, and by microglia in the central nervous system (CNS). FEP patients display elevated plasma levels of IL-18 and MCP-1, but thus far these markers have not been examined in relation to CSF levels of GABA and dopamine.

Objectives: The aim of the present study is to investigate the relationship between peripheral/central immune activation and CNS neurotransmission.

Methods: In the present study, CSF and plasma markers of immune activity (such as IL-18, MCP-1, YKL-40) as well as the neurotransmitter dopamine and its metabolites HVA and DOPAC were analyzed in 41 first episode psychosis (FEP) patients and 21 age- and sex-matched healthy volunteers by using electrochemiluminescence assays and high-performance liquid chromatography. Correlations between immune markers and neurotransmitters, including dopamine and its metabolites as well as CSF GABA levels were performed. Patients and healthy controls were enrolled within the Karolinska Schizophrenia Project, a multidisciplinary research consortium that investigates the pathophysiology of schizophrenia. Approximately half of the FEP patients were neuroleptic-naïve.

Results: Plasma levels of IL-18, MCP-1 and YKL-40 were increased in FEP patients compared to healthy controls (IL-18: 129.7 ± 9.23 pg/mL vs. 104 ± 6.69 pg/mL, $p=0.031$; MCP-1: 115.9 ± 6.97 pg/mL vs. 87.5 ± 4.87 pg/mL, $p=0.015$; YKL-40: 228.7 ± 15.56 ng/mL vs. 175.7 ± 10.08 ng/mL, $p=0.033$). IL-18 in CSF was below level of detection in all samples. The CSF levels of MCP-1 (317.8 ± 11.80 pg/mL, vs. 314.9 ± 30.01 pg/mL, $p=0.92$) and YKL-40 (811.6 ± 45.58 ng/mL vs. 721.1 ± 56.89 , $p=0.25$) did not differ significantly between FEP patients and healthy controls. In the CSF, dopamine levels were significantly increased (0.87 ± 0.2 μ M vs. 0.43 ± 0.09 μ M, $p=0.05$) in FEP patients compared to healthy controls. Significant correlations among patients were found between plasma IL-18 and CSF dopamine ($r=0.55$, $p=0.005$) and between plasma MCP-1 and CSF dopamine ($r=0.55$, $p=0.004$). CSF GABA was found to correlate with the dopamine metabolites HVA ($r=0.37$, $p=0.034$) and DOPAC ($r=0.50$, $p=0.001$) in patients. In healthy controls, correlations between CSF MCP-1 and CSF GABA ($r=0.63$, $p=0.002$) as well as between CSF GABA and CSF HVA ($r=0.69$, $p=0.001$) were found.

Conclusion: These findings are suggestive of increased immune activation concomitant with a reduced GABAergic and an enhanced dopaminergic tone in FEP patients. Stronger correlations between the immune markers, GABA as well as dopamine and its metabolites in FEP patients than in healthy controls suggest a pathophysiological signaling pathway that might be of relevance for schizophrenia. Analysis of these biomarkers in a larger cohort of FEP patients and healthy controls are needed before definitive conclusions can be drawn.

S3.3 Exploiting brain dopamine systems for development of new treatment modalities for alcohol use disorder

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Background: The Addiction Biology Unit has spent more than two decades of basic research to unravel ethanol's mesolimbic dopamine (DA) activating mechanisms with the aim to exploit these in the treatment of alcohol use disorder (AUD). This might be achieved by antagonistic or agonistic (substitution) treatments, or a combination of these. This work in rodents has led to the nAc-VTA-nAc neurocircuitry hypothesis of alcohol-induced DA activation, involving ethanol- and taurine-induced activation of glycine receptors in the nAc, and, secondary to this, acetylcholine-mediated activation of nicotinic receptors (nAChRs) in the VTA, resulting in increased DA neuronal firing and DA release in the nAc. We have shown that manipulations of both these receptor populations modulate alcohol intake in the rat. Recently, we and three other groups have translated part of these findings to humans by showing that the smoking cessation agent varenicline, a partial nAChRs agonist, reduces alcohol consumption in AUD with an effect size (Cohen's d , 0.35-0.45) approx. twice that of acamprosate and naltrexone. This effect may be produced partly by varenicline's blocking of ethanol's indirect activation of the mesolimbic DA system via nAChRs in the VTA (described above) and partly by varenicline slightly raising DA levels by itself. However,

varenicline's DA elevation is modest and we suggest that a further elevation by addition of the weak DA/noradrenaline reuptake inhibitor bupropion may boost this effect resulting in a combined effect size three times (0.6) that of approved therapies for AUD. Indeed, varenicline and bupropion produce additive effects when used for smoking cessation.

Objectives: To explore whether the combined administration of varenicline and bupropion produces additive effects on extracellular DA levels in rat nAc and on the alcohol deprivation effect (ADE) in male Wistar rats.

Methods: In vivo microdialysis followed by HPLC with electrochemical detection of DA in samples collected from the nAc of awake, freely moving male Wistar rats. Two-bottle free-choice test of intermittent ethanol or water followed by re-introduction of the alcohol bottle after an alcohol deprivation period of two weeks.

Results: In vivo microdialysis demonstrated an additive effect by systemic administration of varenicline and bupropion on DA output in the nAc. Varenicline slightly reduced the ADE whereas bupropion had no effect on its own. The combined administration of varenicline and bupropion abolished the ADE.

Conclusion: The present results obtained from animal models with high predictive values indicate that bupropion may enhance the alcohol intake reducing effect of varenicline and suggest that the mechanism may be an facilitation of varenicline's DA activating effect. We recently received substantial funding for a national, multicenter, randomized, placebo-controlled clinical trial examining the effects of varenicline and bupropion, alone or in combination, on alcohol consumption in AUD. The study has a parallel four-group design running over 13 weeks (study period: 2019-2021). Men and women (25-75 years) fulfilling at least four of the DSM-V criteria for AUD will be included. This will be the first study using a 100% specific biomarker for alcohol intake, phosphatidylethanol in blood (B-PEth), as one of two primary outcome variables, the other one being percentage of non-heavy drinking days, as estimated with TLFB. Recruitment is ongoing.

S3.4 The Monoamine Stabiliser (-)-OSU6162 - A Potential Novel Treatment Of Alcohol Use Disorders: Animal And Human Studies

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Background: Alcohol use disorder (AUD) is associated with a dysregulated dopamine system modulating e.g. reward, craving and impulsivity. The few currently available AUD medications have limited clinical efficacy and there is thus a crucial need for new more effective medications. The so-called "monoamine stabilizer" (-)-OSU6162 developed by late Nobel Laureate Arvid Carlsson is suggested to attenuate or stimulate dopamine functioning depending on the prevailing dopaminergic tone and thus might have potential as a novel AUD medication.

Objectives: To evaluate the potential of OSU6162 as a novel AUD medication using a combination of validated animal and human models of AUD.

Methods: The rodent behavioral models of chronic voluntary alcohol intake models key characteristics of a human AUD-profile including: (i) cycles of excessive alcohol intake and periods of abstinence, (ii) binge drinking and impulsive behavior (compulsive drinking and loss of control), (iii) alcohol seeking behavior (motivation and craving) and (iv) cue- and priming-induced reinstatement of alcohol seeking after protracted abstinence (relapse). These behavioral rodent models are used alone and in combination with in vivo microdialysis to investigate adaptations within the DA system during the progression of AUD. Finally, we evaluated the effects of OSU6162 on alcohol craving in a proof-of-concept placebo-controlled, double-blind, proof-of-concept human laboratory study in alcohol dependent patients.

Results: The results from the rodent studies showed that OSU6162 attenuated several alcohol-mediated behaviors including voluntary alcohol consumption, alcohol withdrawal symptoms, operant alcohol self-administration under progressive ratio schedule, and cue-induced reinstatement of alcohol seeking in rats that had voluntarily consumed alcohol for at least three months before treatment as well as improved impulse control in long-term drinking and alcohol-naive rats. In addition, the results indicated that OSU6162 attenuates alcohol-mediated behaviors by counteracting NAc dopamine deficits in long-term drinking rats. The results from the human-laboratory study showed the OSU6162, compared to placebo, significantly attenuated priming-induced craving and induced significantly lower subjective "liking" of the

consumed alcohol. Exploratory analyses showed that the effect of OSU6162 was more pronounced in individuals with higher level of baseline impulsivity.

Conclusion: Together with OSU6162's beneficial side-effect profile, the present preclinical and clinical results merits a larger placebo-controlled efficacy clinical trial to further investigate the potential of OSU6162 as a novel medication for AUD.

SYMPOSIUM 4

THE LEGACY OF ARVID CARLSSON II

S4.1 The future of Parkinson's disease treatment in the information technology age

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Declaration of interests: Remunerated advisor for Global Kinetics Inc. Board member Arvid Carlsson Research AB.

Background: Although it took 10 years to establish the clinical potential for levodopa in Parkinson's disease (PD) s after Arvid Carlsson demonstrated its effect in reserpinised animals, it is still the most effective symptomatic treatment in PD. Over time the pharmacodynamic profile of levodopa changes in individuals with PD. Adjusting treatment regimens to these gradual changes is a long standing challenge in which information technology using wearable sensors and artificial intelligence is starting to play a role.

Objectives: To discuss the role of objective treatment targets in PD in relation to current developments in the use of information technology for monitoring treatment response, and to describe recent efforts in improving levodopa administration.

Methods: Literature overview and presentation of own research involving phase I drug trial, clinical observation drug study, clinical descriptive prospective study and an interventional information study.

Results: The overview describes novel approaches to optimizing drug treatment of PD based on objective measurements. Evidence for the efficacy of objective outcome measures in PD management is evolving, but the first randomized study indicates that access to objective data does not change management or outcome. A need for objective targets in analogy with other diseases like diabetes mellitus is suggested. Interim data from the Infudopa project aiming at developing subcutaneous levodopa infusion therapy demonstrate the feasibility of this approach.

Conclusion: Despite PD being a movement disorder with measurable motor deficits, large scale objective data about outcome and complications resulting from dopaminergic treatment has been lacking. Current clinical treatment strategies are underachieving and could be enhanced by applying objective targets. Future treatment is likely to involve continuous subcutaneous levodopa infusion therapy.

S4.2 Clinical studies on modulation of L-dopa responses and novel dopamine stabilizers in PD

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Abstract: L-dopa is still the golden standard for the treatment of Parkinson's disease (PD). However, in advanced stages of PD, serotonergic terminals take up L-DOPA and convert it to dopamine. Abnormally released dopamine may participate in the development of L-DOPA-induced dyskinesias (LIDs). Using eltoprazine, we have examined whether simultaneous activation of 5-HT1A and 5-HT1B receptors counteracts L-DOPA-induced dyskinesias in patients with PD. In a double-blind, randomized, placebo-controlled and dose-finding phase I/IIa study we found that acute administration of eltoprazine caused a significant reduction of LIDs measured by the Clinical Dyskinesia Rating Scale and Rush Dyskinesia Rating Scale. Meanwhile, Unified Parkinson's Disease Rating Scale part III scores did not differ between the placebo and eltoprazine treatments. The most frequent adverse effects after eltoprazine were nausea and dizziness. It can be concluded that a single dose, oral treatment with eltoprazine has beneficial antidyskinetic effects without altering normal motor responses to L-DOPA.

Another approach to counteract LIDs is to stabilize dopamine neurotransmission. We have investigated

the effects of IRL790, a dopamine stabilizing compound primarily targeting the dopamine D3 receptor, for the treatment of LIDs. PD patients with peak-dose dyskinesia were randomized to placebo or IRL790 treatment (1:3 ratio) for 4 weeks. Adverse events were mostly reported during the titration phase of the trial. They were mainly central nervous system related and could be mitigated by dose adjustments. Assessments for motor function showed a numeric reduction in dyskinesia. It is concluded that IRL790 can be safely administered to patients with advanced PD. The results have guided the design of an ongoing phase 2 study.

We have also performed studies with another psychomotor stabilizer, IRL 752, against Parkinson Disease Dementia. IRL752 has the ability to increase synaptic availability of the neurotransmitters norepinephrine and dopamine in the frontal cortex. PD patients with cognitive impairments were randomized to placebo or IRL752 (1:3 ratio) in a double-blind, placebo controlled study that was run 9 centres in Sweden and one in Finland. IRL752 improves symptoms associated with executive functions and dementia in PD. Moreover, improvements on balance, falls and apathy were significant in patients treated with IRL752 but not in patients treated with placebo.

S.4.3 Depression/anxiety

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Abstract: For three decades, the selective serotonin reuptake inhibitors (SSRIs), the first of which was developed by Arvid Carlsson and co-workers, have been first line of treatment for depression and a variety of other psychiatry disorders, such as panic disorder, generalized anxiety disorder, obsessive compulsive disorder, social phobia and premenstrual dysphoric disorder. In this presentation, an overview of the history of these drugs, and that of their forerunner, the tricyclic antidepressant clomipramine, will be provided, including some comments on how these compounds have impacted both clinical psychiatry and our theoretical understanding of the role serotonin for the regulation of emotions. In addition, the recent questioning of the usefulness of the SSRIs will be commented and rebutted. Finally, the prospect of a future replacement of the SSRIs with superior drugs will be discussed.

S.4.4 Pioneers in Psychopharmacology - antidepressants

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Background: Major depression is a serious and debilitating disorder that ultimately can lead to suicide, with more than 300 million individuals estimated to suffer from depression, and the number of affected individuals increased by 18.4% from 2005 to 2015.

Objectives: More than 50 year ago, clinical introduction of the first two antidepressant drugs iproniazid and imipramine took place. Both compounds fundamental contributed to the development of psychiatry and pharmacological therapy, and marks the starting point for

Methods: In this area, Arvid Carlsson worked with the pharmaceutical company Astra AB during the 1970s and the 1980s, where he and colleagues were able to derive the first marketed selective serotonin reuptake inhibitor (SSRI), zimelidine, from brompheniramine. Although zimelidine was withdrawn from the market due to rare side-effects, it paved the way for new generations of very successful antidepressants, widely prescribed today.

Results: The presentation will highlight historical aspects and link this to current understanding of depression.

Conclusion: Without the work of Arvid Carlsson, the pharmacological options available today would be significantly more limited.

POSTEhRS

Poster 1

Identification of metabolomic biomarkers for antipsychotic treatment in first-episode psychosis patients

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Background: Schizophrenia is a devastating psychiatric disorder mainly characterized by psychosis in addition to a variety of cognitive deficits and negative symptoms such as flattened affect, anhedonia and depression. Patients with schizophrenia show great variations in symptomatic picture and severity and although many antipsychotic medications exist, their efficacy is most variable. The symptomatic heterogeneity of the disorder may reflect physiological and pathophysiological differences that may underlie the inconsistency in efficacy of antipsychotic medication. However, no biological tests or biomarkers exist to guide the choice of antipsychotic treatment. In recent years, metabolomics has proven valuable in identifying clinically relevant biomarkers for predicting and monitoring the efficacy of pharmacotherapeutic interventions, including treatments for depression and alcohol-dependence. In the Karolinska Schizophrenia Project we have a unique set of patients undergoing extensive clinical and physiological testing, including sampling of plasma and cerebrospinal fluid (CSF). Drug-naïve patients are recruited at their first psychotic episode and follow-up assessment is done after 1.5 years of treatment. In this study, we measured alterations in metabolites of these patients at baseline and follow-up to identify putative biomarkers associated with anti-psychotic treatment.

Objectives: The aim of this study was to identify metabolomic biomarkers in serum and CSF that may predict antipsychotic treatment response.

Methods: Large-scale, untargeted metabolomics analysis were performed using UPLC/ToF-MS. CSF

and serum samples of previously untreated first-episode psychosis patients were analyzed at baseline and at the 1.5-year follow-up assessment. In total 25 patients and 21 healthy controls were included.

Results: 216 metabolites were found to be significantly altered in patients at follow-up assessment compared to baseline and 20 of these were found similarly altered in both CSF and serum. Interestingly, the most significantly altered metabolites are related to growth factor signaling through epidermal growth factor, IRK, PI3K and insulin signaling. Furthermore, these metabolites are involved in inflammatory response, as they have a close relationship to tumor-necrosis factors.

Conclusion: In this study, we identify a putative catalog of metabolomics biomarkers that may be used as an objective measure to predict and monitor antipsychotic treatment response.

Poster 2

Acetylcholine mediates dopamine release via muscarinic acetylcholine receptors in rat nucleus accumbens, a potential participant for ethanol-mediated dopamine elevation

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Background: Alcohol use disorder is a serious medical condition, causing severe consequences for afflicted individuals and enormous costs for society. The pharmacological treatments available, is insufficient and the development of new, more effective drugs is crucial. In order to design effective pharmacological substances, a basic understanding in the mechanisms involved in the rewarding effect of ethanol is key. Within the nucleus accumbens (nAc), cholinergic interneurons (CIN) are present. These cells are few in numbers, however, research indicates an important role in mediating a dopamine (DA)-acetylcholine (ACh) homeostasis, vital for normal function. Thus, a defect in CIN have been suggested to be involved in diseases such as addiction.

Objectives: The aim of this project was to study the mechanisms involved in ethanol's dopamine releasing properties, especially focusing on the neurotransmitter ACh.

Methods: Physostigmine was administered locally in the nAc of rats via reversed in vivo microdialysis followed by addition of either scopolamine or mecamylamine. Further, ethanol following pretreatment of scopolamine or mecamylamine was administered using the same methodology. In the final dialysis experiment ethanol was administered locally in the nAc in rats with a selective lesion of CIN (anti-ChAT-saporine).

Results: Local administration of physostigmine induced a DA elevation within the nAc, suggesting that ACh alone can augment DA release. This DA increase was blocked by local pretreatment of scopolamine but not by mecamylamine, suggesting an ACh induced DA elevation mediated by muscarinic ACh-receptors and not by nicotinic ACh-receptors within the nAc. Local administration of ethanol increased DA, where scopolamine pretreatment was not able to prevent this elevation significantly. Following lesioning of CIN using anti-ChAT-saporine we found a significant reduction of CIN in toxin-treated animals as compared to sham-treated controls. No general neuronal loss was observed, confirming the specificity of the toxin, and a spatial specificity was confirmed as no cholinergic depletion in adjacent brain areas was detected. Preliminary results indicate a minor attenuation of DA elevation, following local administration of ethanol, in toxin-treated animals as compared to sham-treated controls.

Conclusion: ACh can augment DA release locally within the nAc via muscarinic ACh-receptors, an effect that may partially be involved in ethanol-mediated DA release. Further studies to investigate the role of ACh in ethanol-mediated DA elevation will be performed using the in vivo model of accumbal hypo-ACh signaling in in vivo microdialysis experiments.

Poster 3

Interplay between the immature Brain and Perinatal Inflammation in Autism

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Background and Objective: Autism Spectrum Disorders (ASD) are heterogeneous neurodevelopmental disorders with higher prevalence (4.5 times) among boys than girls. Considering the difficulties in understanding the etiology of ASD and the complexity of interactions between systemic immune responses and CNS, it is of fundamental importance to investigate how potentiation of early life inflammation may trigger symptoms of autism.

Methods: Male and female C57BL/6J pups received a single injection of lipopolysaccharide (LPS) (1mg/kg) or saline on postnatal day 5 (P5). This age in mice represents a critical brain developmental stage and is equivalent to preterm human infants. Behavioral testing (marbles test to examine repetitive behavior) was performed at age P45 followed by brain tissue collection for further analysis. One hippocampus per animal was sectioned and neurons from CA1.SR area of hippocampus on Golgi stained sections were analyzed to examine structural synaptic plasticity. Analysis was performed via 3D quantification of neuronal dendrites and spines using Imaris software.

Results: We found that perinatal inflammation was associated with significantly increased repetitive behavior in male and female mice 40 days after LPS injection. This was particularly evident in males ($p < 0.001$). Behavioral changes were accompanied by significantly increased complexity of apical and basal dendrites and spine density 40 days after LPS injection ($p < 0.01$; $p < 0.05$). Moreover, among different types of spines, the number of thin (immature spines) was significantly higher in LPS group compared with control group ($p < 0.05$).

Conclusion: Our results indicate that perinatal inflammation in preterm mice results in autistic-like behavior associated with abnormal arborization of neuronal dendrites and increased spine density in the hippocampus in adulthood. Therefore, neonatal anti-inflammatory treatment could be a possible strategy in preventing autism.

Poster 4**EFFECTS OF PATERNAL OBESITY ON OFFSPRING AUTISM-LIKE BEHAVIOR**

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Background: The prevalence of autism spectrum disorder (ASD) has increased drastically within the past decades. Epidemiologic studies have linked maternal obesity to the development of ASD mainly through intrauterine exposures. Recently, paternal BMI has also been implicated as a risk factor for ASD, and epigenetic inheritance (EI) has been suggested as one mode of risk transmission. EI reflects transmission of a phenotype to the next generation that is not carried by the DNA code itself but stem from environmental driven epigenetic modifications in gametes. Importantly, obesity has been shown to induce epigenetic alterations in spermatozoa. Thus, the stage for EI as a potential mechanism is set, which is in line with the heritable nature of ASD.

Objectives: This project aims to investigate the effect of paternal obesity on offspring behavior.

Methods: Five weeks old C57BL/6J male mice were fed either a high-fat diet (HFD) or control diet (n=15) for 10 weeks prior to mating. Initially, all offspring were weaned onto a normal chow diet. At 17 weeks of age, half of the offspring were further challenged with a HFD as an additional stressor. When the offspring were 21 weeks old, their behavior was examined in a battery of behavioral tests to assess autism-like behavior such as anxiety-level, repetitive behavior, and sociability.

Results: The sires fed a HFD showed increased body weight and decreased glucose tolerance compared to control fathers. The outcomes of the offspring behavioral tests as well as epigenetic changes in paternal spermatozoa are currently being evaluated.

Conclusion: Both positive and negative results will provide important information on the developmental effect of paternal obesity on the next generation's health.

Poster 5**Latent toxoplasmosis and psychiatric symptoms – A role of tryptophan metabolism?**

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Background: *Toxoplasma gondii* (TOX) is a common parasite which infects approximately one third of the human population. In recent years, it has been suggested that latent toxoplasmosis may be a risk factor for the development of mental disorders, particularly schizophrenia and anxiety. With regards to depression the results have been varied.

Objectives: The main objective of this study was to examine subpopulations from the Danish PRISME and GENDEP populations for TOX IgG antibodies. These consisted of: a group with symptoms of anxiety, a group suffering from burnout syndrome, as well as two different subpopulations with depression of differing severity. The secondary objective of this study was to examine whether tryptophan metabolism was altered in TOX-positive subjects within each subpopulation.

Methods: Subjects from the Danish 2007 PRISME study were included in the study of anxiety, burnout and depression. The population included a control group (n=156), a group with anxiety symptoms (n=106), a burnout group (n=53) or mild-moderate depression (n=88). Furthermore, 56 subjects suffering from moderate-severe depression were included in the study. Serum samples were tested for IgG antibodies to TOX using ELISA. Measurements of tryptophan and -metabolites were performed by LC-MS/MS.

Results: Our results show that the anxiety and burnout populations were more likely to be TOX IgG seropositive. Furthermore, we find that the moderate-

severe but not mild-moderate depressive subpopulation were associated with TOX seropositivity, suggesting a possible role of symptom severity. Additionally, we found that TOX positive subjects in the anxiety and burnout subpopulations had altered tryptophan metabolism. This relationship did not exist in the mild-moderate depressive subpopulation.

Conclusion: These results suggest that TOX seropositivity may be related to anxiety, burnout and potentially to severity of depression. We furthermore show that the psychiatric symptoms could be associated with an altered tryptophan metabolism.

Poster 6

Effects of Sex and Neonatal Inflammation on Glia-vascular Interface of Hippocampus

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Background and objective: Increasing evidence conceptualizes associations of prenatal inflammation with neurodevelopmental disorders. Importantly, we have recently found that an immune challenge by LPS during the neonatal period can have distinct behavioural effects in a gender-dependent manner. Accordingly, we aimed to investigate the effect of neonatal inflammation on the gliovascular unit of hippocampus in male and female mice.

Method and Material: Male and female C57BL/6J pups received a single injection of lipopolysaccharides (LPS) (1mg/kg) or saline on postnatal day 5 (P5), animals were sacrificed after seven days (P12) and brains were collected for further analysis. Brains were cut into 40 µm thick coronal sections. Molecular layer of dentate gyrus (MDG) was selected for the morphological investigations due to the anatomical proximity to granular cell layer (GCL) as the layer

with high rate of neurogenesis. Morphological quantification of hippocampal fibrillary glial acid protein (GFAP) positive astrocytes was performed by using stereological methods in combination with 3-D image analysis. The structure of gliovascular unit was examined by measuring length of the CD31 positive and length of ensheathed aquaporin-4 (AQP4) positive blood vessels separately applying global spatial sampling method. AQP4 was used to examine the coverage of hippocampal blood vessels by astrocyte endfeet.

Results: Vascular analysis revealed significantly higher length of CD31 positive and AQP4 positive vessels in the male saline group compared with female saline group ($p < 0.05$). Coverage of vessels by astrocytic endfeet (as determined by AQP4+/CD31+ vessels) was higher in females (83%) than in males (59%) in saline treated groups. LPS, induced significant reduction in length of both CD31 and AQP4 positive vessels in males ($p < 0.05$); in contrast there was a significant increase in female pups ($p < 0.05$).

Morphological estimation of GFAP positive astrocytes in the hippocampus showed significant enhancement in the length and number of astrocytic branches one week following LPS injection in male and female mice ($p < 0.05$). Moreover, sholl analysis revealed significant increase of astrocytic arborization 10 µm away from the cell soma in both male and female mice one week following LPS injection ($p < 0.05$).

Conclusion: We propose that neonatal inflammation could induce susceptibility to neurodevelopmental disorders through modification of hippocampal gliovascular interface in a sex-dependent manner.

Poster 7

Systemic administration of glycine reduces voluntary ethanol intake and preference in male Wistar rats

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Background: Alcohol use disorder (AUD) is a major contributor to global disease burden, resulting not only in a significant economical toll on public

resources, but also a great deal of human suffering. The exact effects of ethanol on the brain are not fully understood, but previous studies suggest that the accumbal glycine receptors are involved in mediating the accumbal dopamine elevation observed after ethanol exposure. This makes the glycine receptor a valuable potential target for future ADU treatments.

Objectives: The aim of this study was to investigate the effect of systemic administration of the glycine transporter inhibitor sarcosine or glycine on voluntary ethanol intake in rats.

Methods: In the first set of experiments, male Wistar rats were equipped with microdialysis probes in the nucleus accumbens (nAc) and 48 h later treated with either sarcosine (6, 10 or 20 mg/kg, ip) or glycine (200, 400 or 800 mg/kg, ip), during continuous probe perfusion with ringer solution. The samples were analysed for dopamine and glycine, and the results were used to establish a dose for the second set of experiment. In the second set a new cohort of animals were exposed to an intermittent ethanol consumption schedule, with access to ethanol 24 h sessions three days of the week, for seven weeks (screening period). During the experimental period, the animals had access to ethanol and water for 2.5 h daily, with no access to water between the sessions. This period consisted of five baseline days, and seven days of treatment (sarcosine 10 mg/kg, 400 mg/kg, or vehicle, ip).

Results: Systemic administration of glycine significantly increased nAc dopamine and glycine levels in the microdialysis experiment. Sarcosine did not significantly increase dopamine or glycine compared to vehicle. We found that animals treated with glycine significantly reduced their ethanol intake during the first week of treatment, compared to the vehicle group. During the first week, these animals increased their water intake, resulting in an unaltered total fluid intake. Sarcosine had no significant effect on the ethanol intake during the seven days of treatment, compared to vehicle.

Conclusion: The data presented here suggests that treatment with glycine significantly decreases both ethanol consumption and preference in the rat. This supports the role of the glycine receptor as a potential target for treatment of alcohol dependence. In the future, modulation of glycine receptors in the nAc could be utilised in developing new and more effective treatments of AUD and addiction.

Poster 8

Altered tryptophan metabolism in female FSL rats, a genetic model of depression

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Background: Depression is a devastating and highly prevalent disease worldwide. Several different lines of research in depression demonstrate impaired metabolism of tryptophan resulting in altered levels of downstream products of the serotonin and the kynurenine pathways. Depression is more than twice as common in women than in men. Remarkably, preclinical research in depression rarely include female subjects or characterize effects of their estrous cycle. Therefore, we investigated the effects of the natural estrous cycle on depression-like behavior and tryptophan metabolism in a genetic rat model of depression.

Objectives: Our primary objective was to investigate the effect of the estrous cycle on behavioral despair in the forced swim test (FST). Our secondary aim was to characterize tryptophan metabolism in brain and blood from this model.

Methods: Adult (12-20 weeks) female Flinders Sensitive Line (FSL) rats were compared to the control, Flinders Resistant Line (FRL) rats. The estrous cycle was monitored daily for at least 2 consecutive cycles and rats were subjected to an open field test and the forced swim test (FST). 13 tryptophan metabolites were measured in plasma and whole brain using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with primarily ¹³C/¹⁵N isotopologues as internal standards.

Results: Female FSL rats showed depression-like behavior and had an increased level of the potential neurotoxin, 3-hydroxykynurenine, whereas levels of anthranilic acid and the serotonin precursor, 5-hydroxytryptophan were decreased. In plasma, anthranilate, picolinate and quinolinate concentrations were lower compared to FRL rats. There was no impact of the estrous cycle on any of the outcomes.

Conclusion: Overall, the female FSL rat is an interesting preclinical model with estrous cycle-independent, depression-like behavior in the FST and

with altered tryptophan metabolism. However, our study does not support a role for the female gonadal hormones in depression.

Poster 9

Effect of 5-HT₆ receptor manipulations on stress-induced defecation in rat: possible relevance for the treatment of irritable bowel syndrome

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Background: The importance of serotonin, and primarily the role of 5-HT₃ and 5-HT₄ receptors, for the regulation of gastrointestinal functioning, has since long been discussed. However, studies on the possible involvement of 5-HT₆ receptors, which are almost exclusively expressed in the brain, in this context are sparse.

Objectives: To explore the possible influence of 5-HT₆ receptors on conditioned fear stress (CFS)-induced defecation as a model of irritable bowel syndrome (IBS).

Methods: Three experiments using the same experimental design were performed. Rats were subjected to contextual fear-conditioning where electric foot-shocks served as unconditioned stimuli. The rats were tested one week later, and i.p. injections of drug or saline were giving one hour prior to testing. The effect of drug treatment on CFS-induced defecation was measured as the number of fecal boli produced by each rat during testing. In addition, context-conditioned freezing was evaluated as a measure of anxiety. The effects of three different 5-HT₆ receptor antagonists (SB-399885, SB-271046 and SB-258585) and one 5-HT₆ receptor agonist (WAY-208466) were evaluated.

Results: None of the drugs tested induced a significant effect on freezing. The 5-HT₆ receptor antagonists SB-399885, SB-271046 and SB-258585 all reduced stress-induced defecation. The 5-HT₆ receptor agonist, WAY-208466, displayed no significant effect on defecation in either fear-conditioned or non-shocked animals.

Conclusion: The marked reduction in stress-induced defecation obtained by three different 5-HT₆ receptor antagonists suggests that this might be a potential new treatment strategy for IBS. There was no general

effect on fear (or anxiety) manifested as freezing, which indicate that the effect is not secondary to stress reduction. As 5-HT₆ receptors appear to be expressed almost exclusively in the brain, we however assume the effect to be centrally mediated. Since administration of WAY-208466 did not enhance defecation, enhanced 5-HT₆ receptor activity is not sufficient to elicit defecation.

Poster 10

Disrupted Sensory Gating in first-episode psychosis

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Background: Impaired sensory motor gating, commonly measured as disrupted prepulse inhibition (PPI) of the acoustic startle response has widely been observed in subjects with psychotic disease. However, most PPI studies published so far involve patients with long illness duration and different drug treatment. Relatively few studies have investigated untreated patients at their first episode of psychotic symptoms.

Objectives: The aim of this study is to investigate PPI in antipsychotic-naïve first episode psychosis (FEP) patients.

Methods: PPI in an acoustic startle paradigm (30, 60, 120, 1000 -msec interstimulus intervals), startle reactivity and habituation were assessed in 50 FEP patients (34 male, 16 female) and compared with 35 age and gender-match healthy controls subjects (18 male, 17 female). Mean age of patients was 28.3 years (SEM 0.9) and 27.0 years (SEM 1.1) for controls. Treatment with antipsychotics was not allowed more than 30 days and 25 out of 50 patients received antipsychotic treatment with a mean treatment time of 13 days (SEM 2).

Results: PPI was significantly reduced in FEP patients at ISI30. Antipsychotic treatment did not affect the response as there were no differences in PPI between those receiving antipsychotic medication and those not. Neither did we observe any difference in PPI when comparing male and female FEP or any

difference in habituation between FEP and healthy controls.

Conclusion: The present study suggest that acute pharmacological treatment does not reverse reduction in PPI in FEP patients. We therefore suggest that PPI could be considered a phenomenon of default sensory information processing not primarily affected by the acuteness of the disease but instead more of a robust marker of the pathology of psychosis.

Poster 11

Impact of baseline severity on the effects of selective serotonin reuptake inhibitors in depression: an item-based patient-level post hoc analysis

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Background: Reports claiming that antidepressants are effective only in severe depression have exerted a major impact on treatment guidelines. Since these reports have usually been based on a questioned measure of improvement, i.e. the sum score of the Hamilton Depression Rating Scale (HDRS-17-sum), and been trial- rather than patient-based, their validity may however be questioned.

Objectives: To assess the effect of selective serotonin reuptake inhibitors (SSRIs) on different HDRS-17-based measures of improvement in patients with differing baseline depressive severity.

Methods: Patient-level (n=8262), post hoc analyses of industry-sponsored, placebo-controlled and HDRS-based trials assessing the efficacy of citalopram, paroxetine or sertraline in adult depression using multiple HDRS-17 based measures of response: i) HDRS-17-sum, ii) the depressed mood item, iii) the sum of six core symptoms of depression (HDRS-6-sum) and iv) the sum of all items not included in HDRS-6 (non-HDRS-6-sum). In addition, effect sizes for all different HDRS-17 items were assessed, as was the commonness of all items at baseline, in cases defined as non-severe or severe, respectively.

Results: There was no difference in efficacy between non-severe and severe cases with respect to reduction in depressed mood and other core symptoms of depression. A significant positive association between severity and efficacy was however found after exclusion of rare extreme values, but driven entirely by a more pronounced response to non-core symptoms in cases defined as severe. Non-core symptoms but not core symptoms being much more severe and prevalent in severe than in non-severe cases may partly explain this outcome.

Conclusion: The use of a measure of response (HDRS-17) which includes a number of non-core symptoms that are often rated low or zero at baseline in cases defined as non-severe may have impacted the outcome of previous meta-analyses suggesting SSRIs to be ineffective in non-severe cases. With respect to the alleviation of core symptoms of depression, SSRIs appear as effective in cases defined as non-severe as in those defined as severe.

Poster 12

The Hamilton Depression Rating Scale Measures Side Effects and Therefore Underestimates the Antidepressant Effect of SSRIs and SNRIs

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Background: Selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are some of the most commonly prescribed drugs in the treatment of major depression. Among the side effects frequently reported in relation to the use of SSRIs and SNRIs are insomnia, sweating, nausea, constipation, diarrhea, loss of appetite, ejaculation difficulties, anorgasmia, loss of libido and weight loss. As the 17-item Hamilton Depression Rating Scale (HDRS-17) includes three items pertaining to sleep difficulties (items 4-6), one for non-specific markers of somatic anxiety (item 11), one for gastrointestinal symptoms (item 12), one for sexual dysfunction (item 14) and one for weight loss (item 16), there is reason to believe that side effects of SSRIs and SNRIs may be mistaken for depressive

symptoms when using the sum score of the HDRS-17 as outcome measure in clinical trials, as well as in clinical practice. If true, such a measurement bias would lead to an underestimation of the actual antidepressant efficacy of the SSRIs and SNRIs.

Objectives: To assess whether the HDRS-17 is biased against selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) due to the HDRS-17 items that may reflect common antidepressant side effects.

Methods: The data used for this study comes from 13 acute-phase trials of duloxetine that were either placebo-controlled or placebo- and actively controlled (SSRIs). Two authors went through all individual adverse events reported by at least 0.5% of patients in each treatment group (placebo, duloxetine, SSRI) and classified these into five side-effect groups (SE-groups): sleep-, somatic anxiety-, gastrointestinal-, sexual- and weight loss-related side effects. As the main purpose of this analysis is to see whether adverse events influence HDRS-17 ratings, the primary analyses were conducted on the observed cases population so as to not confound the effects of adverse events with time under treatment. Patients were stratified according to the total severity of pertinent side-effects that they had reported at the endpoint visit.

Results: Total side-effect severity was higher for the active treatment groups, and was inversely related to endpoint HDRS-17 scores for all treatments. This association appeared to be specific in such a way that patients with side-effects related to, e.g., sleep had higher endpoint scores on the HDRS-17 sleep items than patients without sleep-related side effects, but had comparable endpoint scores with respect to unrelated items such as depressed mood or the sum of the six core items included in the HDRS-6 subscale (depressed mood, guilt, work and interests, psychomotor retardation, psychic anxiety, and general somatic symptoms). Similar patterns were seen for side effects related to somatic anxiety, gastrointestinal symptoms, sexual symptoms and weight loss.

Conclusion: The HDRS appears negatively biased against SSRIs and SNRIs due to the inclusion of items that may reflect the common side effects of these drugs. The inclusion of these items in studies and meta-analyses has likely resulted in an underestimation of the efficacy of antidepressants.

Poster 13

The role of immune factors involved in severe mental disorders - involvement of brain or body?

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Background: Numerous studies show alterations in the immune system in severe mental disorders. It remains elusive whether these changes are the result of primary immune dysfunction contributing to mental illness, or are secondary and are associated with comorbidity.

Objectives: We aimed to investigate the immune system in brain and body by examining immune markers, cognitive performance, brain volumes and cardiovascular risk factors.

Methods: The studies were carried out at the Norwegian Center for Mental Health Research (NORMENT), and we collaborated with the Lieber Institute in the USA. We used large samples (n up to 1667) and multidisciplinary methods including plasma protein assessments, gene expression analyses, brain imaging, cognitive testing, as well as clinical assessment. We also measured gene expression in the brain.

Results: We identified altered cytokine levels (sTNFR1, sTNFR2, TNF, IL-1Ra, sIL-2R, sCD-14 and ALCAM) and gene expression (lower TNF and increased ADAM17 mRNA) in peripheral blood in severe mental disorders. These results remained significant after controlling for cardiovascular risk factors. sTNFR1 and IL-1Ra remained elevated after 1 year follow-up. Increased TNF pathway cytokines were associated with lower cognitive performance.

Conclusion: We show low grade pro-inflammatory state in SCZ and BD that persists after 1 year follow-up indicating a trait phenomenon. This may be a primary immune dysfunction as the results remain significant after controlling for confounders. However, it is unlikely to be generalized to all immune cells as circulating white blood cells show decreased expression. An imbalance in the immune system could be relevant for cognition.

Poster 14**The Norwegian Prednisolone in Early Psychosis Study: putting immune findings in schizophrenia to the clinical test**Erik Johnsen

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Background: Accumulating evidence from several lines of research implicates immunological and inflammatory mechanisms in the patho-aetiology of schizophrenia. Clinical trials investigating the efficacy of various low potency anti-inflammatory agents have however revealed equivocal results regarding symptom relief in psychotic disorders.

Objectives: The primary objective of the trial is to investigate whether prednisolone, a potent anti-inflammatory agent, improves symptom severity as compared to placebo when given in addition to antipsychotic medication to patients with early-stage psychotic disorders. Secondary objectives include investigations of improvement of cognitive functioning, negative symptoms, and general functioning.

Methods: A total of 90 men and women, aged 18-70 years, and diagnosed with schizophrenia, schizoaffective or schizophreniform disorder (DSM-IV 295.*) or psychosis NOS (not otherwise specified) (298.9), will be included in the trial. The time interval between the diagnosis of psychosis and study entry should not exceed seven years. Participants will be randomized 1:1 to either prednisolone or placebo daily for a period of 6 weeks. During the treatment period, patients will be assessed weekly, and then 6 and 12 months after the end of treatment to evaluate symptom severity, cognition, global functioning and immune parameters. MRI scans will be conducted before initiation of treatment, and then repeated twice.

Results: The trial is currently recruiting participants in the cities of Bergen, Stavanger, and Trondheim, Norway.

Conclusion: The results of the study may strengthen the case for immune-modulatory treatment and encourage further research in this direction.

Poster 15**Biomarkers of depression – focusing on non-coding RNAs**Erik Kaadt¹, Birgitte Mumm¹, Sanne Andersen¹, Christian Damgaard² and Betina Elfving¹¹Translational Neuropsychiatry Unit, Aarhus University, Denmark²Institute for Molecular Biology and Genetics, Aarhus University, Denmarkerik.kaadt@clin.au.dk

Background: The current diagnosis of depression relies on the assessment of the symptomatic profile, which is obtained through direct interview with the patient. As symptoms between multiple psychiatric disorders are partly overlapping, the current diagnosis has been determined to be inaccurate. It is therefore of great clinical importance to identify objective biomarkers of depression that can aid the diagnosis. Recently, it has been shown that a list of 38 microRNAs (miRNAs) exhibit dysregulation in the dermal fibroblasts of human depressed subjects compared to controls.

Objectives: To validate and specify the 38 miRNA alterations from the human study, we investigated their dysregulation in the skin from four distinct rat models of depression to identify overlaps. Furthermore, we investigated their dysregulation in both skin, dermal fibroblasts, blood, and brain to identify communication between compartments.

Methods: Establishment of fibroblast cultures. miRNA extraction, cDNA synthesis, real-time qPCR, and statistical analysis.

Results: 15 distinct miRNA-dysregulations were re-identified in the skin of the four rat models and 3 miRNAs overlapped between the models. The majority of the 15 miRNAs could be linked through their matched mRNA-targets, which indicate coordinated suppression of relevant depression targets. We found minimal overlap between compartments, which indicate a complex, non-linear communication between brain, blood, and skin.

Conclusion: We re-identified multiple miRNAs from the human study that were dysregulated in depressive-like rat models. This overlap could indicate that these specific miRNAs are correlated to the depressive phenotype. Furthermore, we also identified multiple mRNA targets for the dysregulated miRNAs that has been experimentally linked to depression.

Poster 16**Nicotinic modulation of neurotransmission in rodent dorsolateral striatum, an area of importance for habitual and compulsive drug-seeking behavior**

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Background: Nicotine use is a chronic and relapsing brain disorder, causing suffering to the individual and its environment. Smoking is a leading risk factor for cardiovascular and lung disease and cancer, and, although it is known that tobacco use is the leading preventable cause of death worldwide, most who try to quit relapse. Available interventions are limited, and it is thus of importance to find new effective treatment approaches for nicotine addiction. We have previously shown that nicotine depresses neurotransmission in dorsolateral striatum (DLS), a key brain region for both motor- and reward systems. DLS is highly involved in mediating several reward-related behaviors, and has been linked to the transition from recreational to compulsive/habitual drug use (addiction). How nicotine induces changes in DLS neurotransmission in only partly understood, and determining pathological changes in cellular mechanisms induced by nicotine is essential for developing novel interventions for nicotine addiction and relapse.

Objectives: The aim of this project was to characterize nicotine-induced cellular mechanisms in DLS that are suggested to drive escalated nicotine intake and compulsive drug-taking behavior.

Methods: The main method for studying the acute effects of nicotine on neurotransmission was in vitro electrophysiological field potential recordings performed on Wistar rats and mice with a genetic deletion of the $\alpha 7$ subunit of the nicotinic acetylcholine receptor (nAChR). Electrophysiology was combined with DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), and immunotoxin-mediated cell-targeting, in order to outline the involvement of astrocytes and cholinergic interneurons in neuronal communication and the nicotinic modulation of neural activity.

Results: Nicotine reduced excitatory inputs onto dorsal striatal neurons via $\alpha 7$ and $\alpha 4\beta 2$ containing nAChR, which may be co-expressed on astrocytes and cholinergic interneurons. Further supporting this finding, we found that the depressant effect of nicotine remained in $\alpha 7$ knock-out mice, and that combined inhibition of $\alpha 4\beta 2$ nAChRs was required to fully block the effect. Selective inhibition of astrocytes using the DREADD's technology indicated no involvement of astrocytes in mediating these effects. However, preliminary data from electrophysiological recordings shows that ablation of acetylcholinergic interneurons partially block the depressant effect by nicotine.

Conclusion: We have further established that nicotine depresses striatal neurotransmission through activation of both the $\alpha 7$ and $\alpha 4\beta 2$ nAChR's. There are no previous reports of $\alpha 4\beta 2$ nAChR on glutamatergic terminals and we suggest that other cell types are involved as well. Our preliminary results suggest that cholinergic interneurons, which may express both the $\alpha 7$ and $\alpha 4\beta 2$ nAChR's, are important regulators of nicotine-induced effects on striatal neurotransmission. We now continue with experiments to clarify and conclude the involvement of cholinergic interneurons in the nicotine-induced depression of excitatory inputs on dorsal striatal neurons.

Poster 17**SSRI doses in Swedish primary care**

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Background: Selective serotonin reuptake inhibitors (SSRIs) are since long first-line treatment for depression. In Sweden, 70% of all SSRIs are prescribed from primary care centres (1). While prescription rates are provided in the public domain by the National Board of Health and Welfare, it remains unknown what dosages are commonly used, as this information is only available in free-text form in the Swedish Prescribed Drug Register (SPDR).

Objectives: The aim of this study was to analyse SSRI doses and to compare these to dose-response data from clinical trials (2,3).

Methods: An algorithm aimed to extract dose information from the free-text description given in the

SPDR was developed and evaluated on 1000 randomly selected cases. Data from the administrative regional healthcare database in Region Västra Götaland (VEGA) were used to identify individuals with depression (ICD F32-34, F38-39) in primary care that had not obtained any psychiatric diagnoses in specialised care according to the National Board of Welfare's patient register. Data were linked with the SPDR to obtain information about prescriptions for individuals that collected an SSRI at least twice. Only the highest prescribed dose was considered. The study period was from July 1 2005 to July 1 2017.

Results: The algorithm correctly assessed 99.4% of all prescriptions with readable instructions. The population consisted of 78304 individuals. 81% of individuals prescribed citalopram never received a dose that is optimal as judged by data from clinical trials (i.e. ≥ 40 mg/day). For escitalopram, this number was 67% (≥ 20 mg/day), for sertraline it was 58% (≥ 100 mg/day), for paroxetine it was 3% (≥ 20 mg/day) and for fluoxetine it was 1% (≥ 20 mg/day). Less than 3% of all subjects received supra-therapeutic doses.

Conclusion: In primary care in Sweden, three of the SSRIs, citalopram, escitalopram and sertraline, are usually prescribed at doses below the optimal ones.

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Poster 18

5-HT_{2A} receptor antagonism unmasks an anxiolytic effect of acute SSRI administration in a contextual fear paradigm

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Background: Selective serotonin reuptake inhibitors (SSRI) may both inhibit and exacerbate anxiety-like behaviour in various animal models. While the mechanisms behind these apparently dual effects 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 setting.

Objectives: In these experiments, the importance of the 5-HT_{2A} and 5-HT_{2C} receptor subtypes, respectively, on the effect of acute SSRI on contextual fear was evaluated.

Methods: Rats were administered an SSRI, escitalopram (5 mg/kg), with or without pretreatment with the 5-HT_{2C} receptor antagonist SB242084 (0.3 or 1 mg/kg), or the 5-HT_{2A} receptor antagonist MDL100907 (0.01, 0.1 or 0.3 mg/kg), before contextual conditioned freezing, measured as complete immobility, was tested.

Results: Neither SB242084 or escitalopram, nor the combination of the two treatments altered immobility. While neither escitalopram nor MDL100907 caused any immobility-reducing effect when administered per se, the combination of escitalopram and MDL100907 resulted in a marked reduction in immobility ($p < 0.001$ vs saline).

Conclusion: These results suggest that 5-HT_{2A} receptor activation counteracts a fear-reducing effect of acute SSRI administration.

Poster 19

Functional implications of oxytocin receptor expression patterns in the human brain across the lifespan

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Background: The neuropeptide oxytocin has attracted considerable interest for its role in social behavior and its potential for the treatment of psychiatric illnesses characterised by social

dysfunction. However, the distribution of oxytocin receptors in the human brain, and the functional significance of expression patterns, are poorly understood.

Objectives: Our aim was to characterise gene expression patterns of the oxytocin receptor (OXTR) gene across the lifespan and the association of these expression patterns with cognitive states in adulthood, to better understand the functional relevance of the oxytocin signalling system.

Methods: OXTR mRNA expression values were identified from post-mortem brain samples across the lifespan using the Brainspan and Allen Human Brain Atlas databases. Voxel-by-voxel gene expression values were calculated from the adult post-mortem samples, which provided high spatial resolution. Voxel-by-voxel OXTR maps were correlated against 20,736 generated maps of protein coding genes, to identify the strongest gene expression pattern associations. Mental state correlates of oxytocin receptor expression were identified by performing a large-scale meta-analysis of 14,371 fMRI studies, using the NeuroSynth platform.

Results: Whole-brain oxytocin receptor expression was significantly enriched in early childhood ($p < .05$). In adulthood, OXTR was enriched in subcortical and olfactory regions ($p < .05$) and highly co-expressed with several dopaminergic and muscarinic acetylcholine genes ($p < .001$). OXTR expression patterns were most strongly correlated with the brain expression patterns of genes associated with metabolic regulation. The OXTR expression map corresponded with the brain activity patterns associated with social, anticipatory, appetitive, and aversive cognitive states ($p < .001$).

Conclusion: OXTR enrichment in early childhood compared to the rest of the lifespan suggests that oxytocin signalling plays a particularly important role in this critical developmental period. While OXTR expression patterns in adulthood were associated with social cognitive states, which is consistent with prior work, our results point to a more complex role in human behaviour. The data also suggests that oxytocin signalling is critically involved in metabolic regulation. Altogether, our results illustrate the sophisticated nature of oxytocin signalling in the human brain, which may help guide future therapeutic interventions with intranasal oxytocin.

Poster 20

Effect of chronic escitalopram on serotonergic and immune-related genes in hippocampus in a genetic rodent model of depression

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Background: None of the current theories e.g. of serotonin dysfunction provide sufficient explanations for the nature of depression. There is growing evidence pointing towards a role of inflammation in depression; anti-inflammatory treatment has been shown to be effective in at least a subgroup of depressed patients, and antidepressant treatment has been shown to influence the expression of cytokines.

Objectives: In the present study we investigated the effect of chronic escitalopram treatment on central expression levels of the serotonergic and immune-related genes *Bdnf*, *C3*, *Htr2a*, *Il18*, *Il1b*, *Il4*, *Il6*, *Mmp9*, *Nfkb*, *S100a10*, *S100b*, *Timp1* and *Tnf* in a genetic model of depression, the Flinders Sensitive line (FSL) and its control, the Flinders Resistant line (FRL).

Methods: Animals were randomly assigned to four groups ($n=8-10$ per group): FRL control, FRL escitalopram, FSL control and FSL escitalopram. Animals in the escitalopram groups received escitalopram p.o. in food pellets (aiming at an administered escitalopram dose of approximately 25 to 30 mg/kg rat weight/day). After four weeks of treatment all animals were sacrificed, their brains dissected and mRNA levels analyzed in amygdala, hippocampus, prefrontal cortex, hypothalamus, raphe and striatum were measured using quantitative real time PCR.

Results: We found significant differences in mRNA levels comparing FSL with FRL animals for *Il18*, *Il1b*, *Nfkb*, *S100a10* and *S100b*. Escitalopram treatment significantly lowered mRNA levels of *Htr2a* and *S100b* in amygdala and hypothalamus in FRL and FSL rats.

Conclusion: The results in this study indicate the involvement of immune-related genes in behavioural differences of the FSL depression rat model. Our findings furthermore support a role of S100B as well as the serotonergic receptor 5-HT_{2A} in the mechanisms underlying antidepressant action.

Poster 21

CHRONIC ORAL G115 REDUCES IMMOBILITY IN THE FORCED SWIM TEST WITHOUT ALTERING BDNF SIGNALING OR HIPPOCAMPAL NEUROGENESIS

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Background: Current drug therapies for depression often show a lack of efficacy or troublesome side effects so many patients are turning to natural products. Panax ginseng has long been used for depression in traditional Asian medicine. Purified ginsenosides are reported to reduce depressive behaviours in animal models; an effect that often correlates with increases in depression-induced reductions in BDNF signaling and neurogenesis. These data imply a causal relationship that has not yet been established.

Objectives: To determine if chronic consumption of the ginsenoside mixture G115 would alter depressive-like behaviours, BDNF signaling and neurogenesis in normal (non-depressed) rats.

Methods: Male CD rats (225-250 g; N=30) were acclimated over 3 days to voluntarily consume a 10% sucrose solution within a predetermined time. Rats that met criterion were then randomly assigned to either control (n=13) or G115 (n=14) groups and fed either G115 in sucrose, or vehicle, twice daily for 14 days plus 4 testing days. Rats were then tested in an open field (OF), elevated plus maze (EPM), Forced swim pre-test and Forced Swim Test (FST) on successive days. After euthanasia brain tissue was dissected and either flash frozen for Western blot analysis of BDNF and TrkB expression or formalin fixed for dual immunohistochemistry of doublecortin (DCX) and NeuN. All experiments were conducted and analysed experimenter-blind. Behaviours were

scored from remotely acquired video recordings. Data were imported into SPSS (v.23) and compared between groups using Student's t-test.

Results: Rats chronically consuming G115 had significantly reduced immobility time and increased latency to immobility with a corresponding increase in both struggling and swimming time in the FST. No significant differences between groups were found in measures of locomotor (OF) or anxiety (OF; EPM) behaviour eliminating these as confounding factors. BDNF and TrkB expression in prefrontal cortex and hippocampus was not different between groups, nor were DCX positive cell counts in hippocampal regions.

Conclusion: We conclude that oral G115 reduces depressive-like behaviours in rats that is not causally related to changes in either BDNF signaling or hippocampal neurogenesis.

Poster 22

Confirmation of a reduced Picolinic Acid / Quinolinic Acid ratio in the cerebrospinal fluid of suicide attempters

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Background: The kynurenine pathway of tryptophan degradation produces several neuroactive metabolites, such as kynurenic acid (KYNA), quinolinic acid (QUIN) and picolinic acid (PIC). KYNA and QUIN are directly involved in glutamatergic neurotransmission since KYNA is an antagonist and QUIN is an agonist of the N-methyl-D-aspartate (NMDA) receptor. PIC has neuroprotective properties. Recently, we showed that the PIC/QUIN ratio is reduced in the cerebrospinal fluid (CSF) and plasma of suicide attempters.

Objectives: To investigate that PIC/QUIN ratio is reduced in the CSF of a small cohort of suicide attempters and healthy controls.

Methods: 1. Lumbar puncture: Lumbar puncture was performed in the morning between 8.00 - 11:00 after fasting from midnight and bed resting. CSF was obtained between lumbar vertebrae IV and V, using a protocol well standardized. The CSF collected was directly aliquoted and stored in -80 degrees C. 2.

LC/MS: Samples of cerebrospinal fluid were analyzed by Ultra performance liquid chromatography – tandem mass spectrometer. 3. Statistics: The statistical analysis were performed using GraphPad Prism 8 for Mac. Non-parametrical test (Mann-Whitney) was used to compare KYNA, QUIN, PIC levels and the PIC/QUIN ratio between healthy controls and suicide attempters.

Results: We found that the PIC/QUIN ratio is decreased in the CSF of suicidal attempters (n=12) compared to healthy controls (n=13) (p=0.02). CSF levels of KYNA, QUIN and PIC did not differ between healthy controls (KYNA: 1.3±0.3 nM; QUIN: 26.4±2.4 nM; PIC: 16.3±1.1 nM) and suicide attempters (KYNA: 1.3±0.5; QUIN: 29.8±1.9; PIC: 14.4±2.7 nM; p=0.73; p=0.23; p=0.15).

Conclusion: In a small cohort, we confirm that the ratio PIC / QUIN is decreased in the CSF of suicide attempters.

Poster 23

Mechanisms by which ethanol increases extracellular taurine levels in the rat nucleus accumbens

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Background: Alcohol use disorder (AUD) produces numerous health and social problems as well as tremendous costs for the society. Alcohol activates the mesolimbic dopamine system and increases dopamine levels in the nucleus accumbens (nAc), an effect associated with positive reinforcement. However, the exact mechanisms by which this occurs are not fully understood. We have shown that an extracellular increase of the endogenous amino acid taurine is required for ethanol-induced dopamine release, and hypothesize that taurine, which may work as an osmotic regulator, is released to re-equilibrate

the osmotic pressure. Supporting this theory we have previously shown that inhibition of cell swelling, or manipulation of extracellular osmolarity, antagonizes ethanol-induced taurine and dopamine release in the nAc.

Objectives: The aim was to determine if the ethanol-induced elevation of extracellular taurine in the nAc involves astrocytes or neurons, and if taurine release might be mediated via volume regulated anion channels (VRACs).

Methods: In vivo microdialysis in awake freely moving Wistar rats was used to measure the effects of ethanol following pre-treatment with the action potential inhibitor tetrodotoxin (TTX), the glial metabolic inactivator fluorocitrate or the VRAC antagonist DCPIB. We also utilized the DREADDs technology to chemogenetically target astrocytes in vivo. In this latter set of experiments, rats were transfected with astrocyte-specific activating or inactivating DREADDs in the nAc, and pretreated with the DREADD-ligand clozapine-N-oxide (CNO) prior to ethanol. Accumbal taurine- and dopamine levels were monitored in all experiments.

Results: Taurine levels after ethanol administration were not influenced by local perfusion with TTX, whereas the increase of dopamine was blocked. Preliminary data show that local perfusion with fluorocitrate decreases the ethanol-induced taurine and dopamine release. Furthermore, local perfusion with DCPIB blocked the ethanol-induced taurine release and partially blocked the dopamine release.

Conclusion: We conclude that the ethanol-induced increase of extracellular taurine in the nAc derives from astrocytes and that taurine is likely released by VRACs.

Poster 24

Caffeine and taurine produces additive effects on ethanol-induced locomotion in mice

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Background: The consumption of alcohol mixed with energy drinks has become a growing trend during the last decade. However, there are reports showing that this mix is associated with risks, such as increased probability of binge drinking, alcohol-related harm and development of alcohol use disorder. What ingredients in the energy drinks that are responsible for these increased risks, and the mechanisms of action underlying the effects, are not clear. Caffeine has been suggested to be the major pharmacological active ingredient in energy drinks. However, another common ingredient, previously associated with the dopamine elevating properties of ethanol, is the endogenous amino acid taurine. Ethanol increases extracellular levels of taurine and we have previously proposed that this increase of taurine is required for ethanol-induced accumbal dopamine release. Therefore, the role of taurine as a pharmacological active ingredient in energy drinks and its interaction with ethanol and caffeine should be further investigated.

Objectives: We aimed to investigate the combination of caffeine and taurine on ethanol-induced locomotor activity in the naïve and caffeine experienced animal.

Methods: Locomotor activity in drug-naïve male NMRI mice, a dopamine dependent behavior, following systemic administration (i.p.) of ethanol (0, 1.75, 2.5, 3.25 g/kg), caffeine (0, 1, 5, 15, 30 mg/kg) or taurine (0, 30, 60, 300, 600 mg/kg) alone or in combination was determined. A new set of drug-naïve mice were administrated caffeine (15 mg/kg) or vehicle for eighteen days in an intermittent treatment design (a total of eleven injections). Locomotor activity was measured on the first and last day of this treatment period. On day nineteen, were animals administrated (i.p.) the combination of ethanol (0, 2.5 g/kg), caffeine (0, 15 mg/kg) and taurine (0, 300 mg/kg) and locomotor activity was monitored.

Results: We found that caffeine but not taurine increased the locomotor stimulatory effect of ethanol. We also found that co-administration of caffeine and taurine further enhanced the locomotor response to a moderate dose of ethanol, an effect that remains in the caffeine experienced animal.

Conclusion: We conclude that co-administration of caffeine and taurine as well as caffeine alone increase ethanol-induced locomotion in mice. Based on the present study we suggest that joint systemic administration of caffeine and taurine enhances centrally mediated dopamine dependent effects of

ethanol, a phenomenon that needs to be further investigated in depth.

Poster 25

Opioid System Plays A Role In Cognitive Processes And Depression

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Background: The endogenous opioid system can affect emotions and modulate cognitive processing such as perception, attention, memory and learning. Furthermore, it is well established that cognitive functions can be affected by mood level. Therefore, negative cognitive affective bias (CAB) recognizes as a hallmark of depression. Investigating the mechanism behind this behavior could reach to a novel approach in depression research and development of novel antidepressants by altering CABs positively. Recently, affective bias test (ABT) have been validated in rodent animal models.

Objectives: The aim of this study is to investigate the role of kappa opioid receptors (KOR) in CAB.

Methods: Female Sprague Dawley rats learnt in ABT two independent substrate-reward associations during discrimination learning sessions under vehicle or treatment conditions. Through the preference test, the two previously rewarded substrates were presented together and the rats preferences tested over 30 trials. Affective bias of corticosterone (CORT) and the KOR agonist U50,488, expressed as % choice bias, was measured. Subsequently, we tested the effect of DIPPA as KOR antagonist on CORT-induced negative bias in this paradigm.

Results: Both U50,488 and CORT significantly reduced choice bias in the ABT. In addition, DIPPA completely eliminated CORT-induced negative affect.

Conclusion: We conclude that KOR plays an important role in CAB. Our data support that KOR can be a therapeutic target in depression by modulating cognitive functions and mood level. Opioid peptides may influence the hypothalamic-pituitary-adrenal (HPA) axis and therefore modulate CAB.

Poster 26**Endocrine-linked metabolic mechanisms of antipsychotics**

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Background: Antipsychotic drugs represent a cornerstone in the treatment of severe mental disorders like schizophrenia and bipolar disorders, but the drug group is associated with a wide range of side effects. The prevalence of metabolic syndrome, overweight and type 2 diabetes mellitus is increased in this patient group, and use of second generation antipsychotics in particular has been found to induce metabolic alterations. However, the drug impact on thyroid function and the underlying mechanisms inducing type 2 diabetes mellitus are not fully known.

Objectives: The aim of this project was to investigate the overall burden of side effects associated with use of antipsychotics in a large, naturalistic sample of patients with severe mental disorders, with special focus on thyroid function disturbance and association with adipokine levels and insulin resistance.

Methods: Patients (N=1345) with severe mental disorders between 18 and 65 years of age from the Oslo-area underwent thorough diagnostic and clinical investigations including assessments of pharmacological data and drug side effects. Blood samples were collected for measurements of free thyroxin (fT4), thyroid-stimulating hormone (TSH), glucose, insulin and adipokine levels. Statistical analyses were performed investigating associations with use of antipsychotics in general and selected agents used in monotherapy while controlling for possible confounding factors.

Results: More than 75% of antipsychotics-users reported side effects of their treatment with polypharmacy and female sex representing risk factors, and there were significant associations with neurologic and sexual side effects, sedation and weight gain. Levels of fT4 were negatively associated with use of antipsychotics in general ($p=0.001$), as well as use of quetiapine ($p=0.003$) and olanzapine ($p=0.018$) in monotherapy. Also, fT4 levels were negatively associated with reported weight gain ($p=0.004$). Further, there was a significant direct effect from use of antipsychotics on calculated insulin

resistance both without ($p=0.007$) and with ($p=0.013$) adjustment for BMI. Also, there was a significant mediating effect on insulin resistance via altered adipokine levels from use of antipsychotics in general as well as use of olanzapine ($p<0.001$) and aripiprazole ($p<0.001$) in monotherapy.

Conclusion: Use of antipsychotics is associated with a wide range of side effects including disturbance of endocrine systems. Clinicians should be aware that thyroid function may be affected, and that insulin resistance associated with antipsychotics may develop independently of BMI.

Poster 27**The GABAA Receptor Positive Allosteric Modulators Brexanolone and SAGE-217 in the Treatment of Mood Disorders: Results from Recent Placebo-controlled Studies**

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Background: Background: Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and acts through synaptic and extrasynaptic GABAA receptors (GABAARs) to mediate phasic and tonic inhibition. Dysregulation of GABAergic signaling, including altered expression levels of GABA and GABAARs or aberrations in functionally-linked stress pathways (i.e. the hypothalamic-pituitary-adrenal axis), is thought to be associated with certain mood disorders, such as postpartum depression (PPD) and major depressive disorder (MDD). Positive allosteric modulators (PAMs) of GABAARs may offer a novel mechanism of action for exploration as potential PPD and MDD therapeutics.

Objectives: Objective: To assess the efficacy and tolerability of the investigational positive allosteric modulators (PAMs) of GABAARs, brexanolone iv (BRX) and oral SAGE-217 as potential treatments for

postpartum depression (PPD) and major depressive disorder (MDD) respectively.

Methods: Methods: In three double-blind, randomized, placebo-controlled studies of women diagnosed with moderate to severe PPD [17-item Hamilton Rating Scale for Depression (HAM-D) ≥ 26 in Studies A/B; HAM-D score 20-25 in Study C], patients were treated with 60-hour infusions of placebo or BRX 90 $\mu\text{g}/\text{kg}/\text{hour}$ (BRX90) or BRX 60 $\mu\text{g}/\text{kg}/\text{hour}$ (BRX60, Study B only). A pivotal, double-blind, randomized, PBO-controlled study (NCT03000530) evaluated the efficacy and safety of SAGE-217 in 89 subjects (N=45 SAGE-217, N=44 PBO) with moderate to severe MDD (HAM-D total score ≥ 22). Subjects received an evening dose of study drug for 14 days.

Results: Results: Brexanolone iv: In a pooled analysis, 102, 38, and 107 patients were treated with BRX90, BRX60, and placebo, respectively. At Hour 60 (primary endpoint), significantly greater least square mean (LSM) HAM-D reductions were achieved with BRX90 (-17.0) and BRX60 (-19.1) vs. placebo (-12.8; $p < 0.001$ for both). Significant differences from placebo were seen as early as Hour 24 ($p = 0.001$ for both BRX90 and BRX60) and maintained through Day 30 (BRX90, $p = 0.021$; BRX60, $p = 0.003$). The most common adverse events ($\geq 10\%$) with BRX were headache, dizziness, and somnolence. SAGE-217: At Day 15 (primary endpoint), the SAGE-217 group showed a significantly greater LSM reduction from baseline in HAM-D total score versus the placebo group (-17.4 versus -10.3; $p < 0.0001$). These significant differences from placebo were observed as early as Day 2 (-5.5 versus -3.9; unadjusted 95% CI for treatment difference -4.3 to -0.3) and were maintained through Day 28 (-15.6 versus -11.9; unadjusted 95% CI for treatment difference -7.6 to -0.5). Common AEs ($\geq 5\%$) in the SAGE-217 group included headache, dizziness, nausea, and somnolence.

Conclusion: Conclusion: Brexanolone iv and SAGE-217 developmental programs are examples of novel GABAAR PAMs that showed, in the above studies, rapid and sustained (over the study period) reductions in depressive symptoms. Their presumed mechanism of action as positive allosteric modulators of GABA_A receptors is a novel approach in the development of therapeutic agents for mood disorders.

Poster 28

CSF levels of synapse markers in first-episode patients with schizophrenia

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Background: Schizophrenia is one of the most severe mental disorder that affects thoughts, cognition, and behavior. The prevalence of the disease is about one percent. The pathophysiology of the disease is still relatively unknown in spite of the many efforts made by genetic, biochemical and brain imaging approaches. Recent reports suggest that increased synaptic pruning is associated with schizophrenia. The presynaptic protein synaptosomal-associated protein (SNAP-25) is a core compartment in the SNARE complex, and together with synaptotagmin-1 (SYT1) the compound acts a functional unit of the neurotransmitter exocytotic machinery and may reflect a synaptic loss in neurodegenerative states. According to postmortem studies patients with schizophrenia express a low expression of SNAP-25.

Objectives: The aim of the present study was to analyze cerebrospinal fluid (CSF) concentrations of SNAP-25, SYT1 and neurogranin, another biomarker for synaptic loss, in 44 first-episode psychosis (FEP) patients and 21 healthy controls.

Methods: SNAP-25, SYT1 and neurogranin was analyzed with mass spectrometry

Results: We found no difference in the analyzed synapse markers between FEP patients and healthy controls. However, there was a trend towards a decrease of all three markers in FEP patients. Further, in FEP patients antipsychotic treatment or smoking was associated with lower ($\beta = -0.323$, $p=0.040$) or higher ($\beta = 0.317$, $p=0.040$) CSF concentration of neurogranin, respectively

Conclusion: The present findings that FEP patients show a trend towards a decrease in SNAP-25, SYT1, and neurogranin is in accordance with previous post-mortem studies. Further studies are required to investigate the role of synaptic degradation in the pathophysiology of schizophrenia.

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The GABAA Receptor Positive Allosteric Modulators Brexanolone and SAGE-217 in the Treatment of Mood Disorders: Results from Recent Placebo-controlled Studies

Poster 28

CSF levels of synapse markers in first-episode patients with schizophrenia

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ABOUT SCNP

At the XII meeting of the Nordic Psychiatric Congress in Copenhagen in 1958, the sub-committee on psychopharmacology had discussed the perspective of a Scandinavian Society of Psychopharmacology. Parallel with this initiative, the executive of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) contacted the Scandinavian colleagues about establishing a Scandinavian section of the CINP. It was the marked rise in psychotropic drugs in the 1950s (chlorpromazine and imipramine in Europe and the monoamine oxidase inhibitors in United States of America) that resulted in the birth of CINP in 1958.

On 5 February 1960, the SCNP was established with Arvid Carlsson (Sweden) as the Founding President and Jørgen Ravn (Denmark) as the Founding Secretary. Other board members were Erik Jacobsen (Denmark) and David H. Ingvar (Sweden). Present at this meeting were also (among others) Odd Lingjærde (Norway), Gunnar Lundqvist (Sweden), Carl-Gerhard Gottfries (Sweden), Asser Stenbäck (Finland), and Mogens Schou (Denmark) while Paul Kielholz from Switzerland was one of the guests from the Continent.

One of the major goals for establishing the SCNP was the standardisation of clinical trials with psychotropic drugs in Scandinavia.

The 1961 meeting was the first ordinary congress of the College. The board was elected at this meeting by the general assembly with Gunnar Lundqvist (Sweden) as the

President and Jørgen Ravn (Denmark) as the Secretary. The other members of the board were Arvid Carlsson (Sweden), Erik Jacobsen (Denmark), and Tollak Sirnes (Norway). Since then, the SCNP has held annual congresses. Until 2009, the scientific contributions were all published in the Nordic Journal of Psychiatry. Starting in 2013, the abstracts from the SCNP congresses were published in *Acta Neuropsychiatrica*, the official journal of the SCNP.