# Abstracts of the 3rd Symposium of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) and Deutsche Gesellschaft für Biologische Psychiatrie (DGBP)

## P1 Biomarker

### P1.1   Traumatic childhood experiences are related to higher hair cortisol in postpartum

**Authors**  Thorsten Mikoteit[1], Valerie S Falzberger[1], Sibil Tschudin[2], Irene Hoesli[2], Serge Brand[3], Martin Hatzinger[1]
**Institutes**  **1**  Psychiatric Services Solothurn, Switzerland; **2**  University Hospital Basel, Switzerland; **3**  Psychiatric University Clinics Basel, Switzerland
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**Introduction**  Childhood maltreatment (CM) can have a detrimental impact on later adult mental health, which could be mediated by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Findings of HPA axis dysregulation can be decreased or increased concentrations of cortisol or cortisone in hair samples. The aim of this study was to investigate if CM is related to findings of hair cortisol or cortisone in postpartum, and if such findings correlate with clinical outcome measures.

**Methods**  36 pregnant women (age (years), M = 33.3, SD = 4.4) were recruited in a psychosomatic out- patient clinic. At study entry (before 32nd week of gestation), traumatic childhood experiences were assessed with the Childhood Trauma Questionnaire Short Form (CTQ-SF). At 12 weeks postpartum, hair cortisol and hair cortisone corresponding to 3 months postpartum, perceived stress (PSS, PSI), depression (HAMD, EPDS), anxiety (STAI) and postpartum bonding (PBQ) were assessed.

**Results**  Traumatic childhood experiences of the mothers in general, and specifically physical neglect and abuse, were correlated with higher hair cortisol concentrations in postpartum (r = .512, p < .05). Except for a trend towards a positive relationship between hair cortisone and the Hamilton Depression Scale score (r = .434, p = .082), no correlation between the glucosteroids and perceived stress, depression, anxiety or postpartum bonding quality were found.

**Conclusion**  The pattern of results suggests that CM is associated with increased hair cortisol levels corresponding to increased HPA axis activity in postpartum period. This might indicate a dysregulation of HPA axis functioning and an increased vulnerability to stress related mental disorders in postpartum period.

**Conflict of interest**  None

### P1.2   Psychiatric syndromes associated with anti-neural autoantibodies differ in their affective psychopathology from those that are not

**Authors**  Insa M Grenzer[1], Aaron L Juhl[1], Dirk Fitzner[2], Jens Wiltfang[1], Niels Hansen[1]
**Institutes**  **1**  Department of Psychiatry and Psychotherapy, University Medical Centre Goettingen, Germany; **2**  Department of Neurology, University Medical Centre Goettingen, Germany
**DOI**  10.1055/s-0042-1757642

**Introduction**  Anti-neural autoantibodies are an important yet under-researched aspect in immunepsychiatry. Our primary aim is to investigate whether the psychopathology differs between anti-neural autoantibody-positive and -negative psychiatric syndromes. We will also investigate which type of psychiatric syndrome exists in psychiatric patients presenting neural autoantibodies compared to those psychiatric patients that do not.

**Methods**  We enrolled retrospectively a cohort of 154 psychiatric patients in the Department of Psychiatry and Psychotherapy, University Medical Centre Göttingen. All patients' psychopathology was assessed via the AMDP (Association for Methodology and Documentation in Psychiatry) guidelines, and anti-neural autoantibodies were determined in serum and/or cerebrospinal fluid (CSF). Psychiatric syndromes were specified in all patients. Fisher´s exact test was used for statistical analysis.

**Results**  We detected anti-neural autoantibodies (PsychAb + ) in the serum and/ or CSF of 36 of 154 psychiatric patients (23.4 %), whereas 118 of 154 (76.6 %) patients presented no neural autoantibodies (PsychAb-). Many more Psych-Ab-patients showed affective symptoms such as affective rigidity (45.8 %), blunted affect (33.1 %) and higher suicidality (15.3 %) than PsychAb + patients. The most frequent psychiatric syndromes did not differ between groups (psycho-organic syndrome: PsychAb + : 64 %, PsychAb-: 48 %; depressive syndrome: PsychAb + : 19 %, PsychAb-: 32 %).

**Conclusion**  Our results suggest that affective rigidity, blunted affect, and higher suicidality are more prevalent in PsychAb- than PsychAb + patients. Depressive syndromes per se are not more prevalent in PsychAb-patients. These encouraging findings make us eager to explore the psychopathology in Psych-Ab + patients in large-scale studies in which we plan to delineate subtypes of psychiatric syndromes more clearly. Such findings would have a strong impact on the diagnosis and therapy of autoantibody-associated psychiatric disease.

**Conflict of interest**  None

### P1.3   Investigation of axonal neurodegeneration in anti-neural autoantibody-associated psychiatric syndromes

**Authors**  Aaron L Juhl[1], Insas M Grenzer[1], Dirk Fitzner[2], Jens Wiltfang[1], Niels Hansen[1]
**Institutes**  **1**  Department of Psychiatry and Psychotherapy, University Medical Centre Goettingen, Germany; **2**  Department of Neurology, University Medical Centre Goettingen, Germany
**DOI**  10.1055/s-0042-1757643

**Introduction**  Although autoantibodies have such a strong impact in many different diseases and modern medicine, anti-neural autoantibodies (NAb) have attracted little attention from researchers in psychiatric diseases. Our primary goal is to discover whether neurodegenerative processes are enhanced in autoantibody-associated psychiatric syndromes compared to psychiatric syndromes whose patients reveal no autoantibodies. Our secondary aim is to

detect which psychiatric syndromes are more prevalent in antibody-positive than antibody-negative patients.

**Methods** We examined a cohort of 123 psychiatric patients in the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen from 2015 to 2020, screening them for degeneration markers and autoantibodies in serum and/or cerebrospinal fluid (CSF). They were divided into autoantibody-positive and autoantibody-negative groups; their neurodegenerative biomarkers were then compared via Mann-Whitney-U tests between groups. We assessed their psychopathology as psychiatric syndromes according to the AMPD (Association for Methodology and Documentation in Psychiatry) system.

**Results** We detected anti-neural autoantibodies in 22,8% of psychiatric patients and no autoantibodies in 77,2% of psychiatric patients. There were no differences in neurodegeneration biomarkers between groups (t-tau protein: p = 0.47; p-tau protein 181: p = 0.388; Aβ42: p = 0.986; Aβ40: p = 0.698 and Aβ42/Aß40 ratio: p=0.513). The most frequent psychiatric syndrome was psycho-organic; its occurrence did not differ between autoantibody-positive (64%) and autoantibody-negative psychiatric patients (57%). The second most frequent syndrome was depressive syndrome, which likewise revealed no group difference.

**Conclusion** Our results suggest that anti-neural autoantibodies are not directly involved in axonal- neurodegenerative processes. We can thus assume that major brain damage manifesting as axonal neurodegeneration is probably not present in most psychiatric patients presenting anti- neural autoantibodies. Because of its high diagnostic relevance, we will validate this assumption in prospective studies.

**Conflict of interest** None

## P1.4    Age-dependent sex differences in the association between cortisol concentrations and childhood trauma

**Authors** Johanna Klinger-König[1], Stefan Frenzel[2], Anna Hannemann[2], Katharina Wittfeld[1], Robin Bülow[3], Nele Friedrich[2], Matthias Nauck[2], Henry Völzke[4], Hans J Grabe[1]

**Institutes** **1** Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Germany; **2** Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Germany; **3** Institute of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Germany; **4** Institute for Community Medicine, University Medicine Greifswald, Germany

**Introduction** More severe childhood trauma was associated with lower basal cortisol concentrations. Nevertheless, basal cortisol concentrations vary between men and women. Interactions between the cortisol-inducing hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-pituitary-gonadal (HPG) axis were reported. As gonadal variations over the lifetime are stronger in women than in men, the present study aimed at investigating age- dependent associations between basal serum cortisol concentrations and childhood trauma in a sex-specific manner.

**Methods** Data of 2,595 participants of the Study of Health in Pomerania (SHIP) were analyzed. Single- sample serum cortisol concentrations were determined using the AVIDA CENTAUR XP. Childhood trauma was assessed via the Childhood Trauma Questionnaire. Magnetic resonance imaging was used to assess global cortical thickness. Age-dependent sex differences for the association between serum cortisol concentrations and childhood trauma were researched in moderation analyses. Sensitivity analyses were used to check the impact of serum sex hormone concentrations.

**Results** Cortisol concentrations varied with age in women (F = 20.26, p = 8.52e-13) but not in men (F = 1.90, p = .128). This association was diminished by childhood trauma (F = 5.28, p = .001). In men, no age-dependent association between cortisol concentrations and childhood trauma was found (F = .67, p = .571). Sex hormones did not influence any of the associations. Independent of age, inverse associations between cortisol concentrations and cortical thickness were observed in men (F = 6.65, p = 0.010). This association was independent of childhood trauma (F = 5.11, p = 0.024).

**Conclusion** Associations between basal cortisol concentrations and childhood trauma were age-dependent, particularly in women. This sex-specific age-dependency was not explained by sex hormones and thus an assumed interaction with the HPG axis. Nevertheless, the dynamic variance may offer the opportunity to reduce the negative long-term effects of childhood trauma via treatment.

**Conflict of interest** None

# P2    Electroconvulsive therapy

## P2.1    Age-dependent stimulus dose increase during an acute ECT series

**Authors** Jana Plemper, Sebastian Karl, Alexander Sartorius
**Institute** Clinic for Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim, Germany

**Introduction** The stimulation dose used in electroconvulsive therapy (ECT) is highly relevant for its efficacy as well as possible side effects. It is often determined by dose titration, in which the seizure threshold (ST) is established during the first treatment and suprathreshold stimulation is used in subsequent treatments. Prior studies have shown that the ST increases over the course of an ECT series. Clinical observation suggests this rise might be more pronounced in geriatric patients.

**Methods** Retrospectively, we analysed the stimulation dose during the first 20 ECT treatments in 472 patients undergoing ECT between January 2010 and March 2021 at the Central Institute of Mental Health Mannheim, Germany. The initial stimulation dose was determined by titration, involving known factors influencing the ST (e.g. age, medication). Adjustments were made in case of decreasing seizure quality or missing clinical response. The stimulation dose adjustments in relation to patients' age were assessed using ANOVA.

**Results** Stimulation dose increased significantly during the acute ECT course (mean initial stimulation dose: 12.88 ± 13.5 mC; at 10th ECT: 76.7 ± 41.9 mC). In a generalized least squares regression model, stimulation dose was significantly correlated with ECT treatment number, electrode placement, and the interaction between age and ECT treatment number. Dose increase was significantly more pronounced in geriatric patients compared to non-geriatric patients (F = 9.57; p= 0.002).

**Conclusion** Our results indicate that the seizure threshold in elderly patients is not only higher compared to younger patients at the beginning of ECT but might also increase more rapidly during the course of an ECT series. To ensure high efficacy throughout the course of treatment, attention should be paid to decreasing seizure quality, especially in geriatric patients, and dose adjustment should be considered.

**Conflict of interest** None

## P2.2    Caffeine augmentation in electroconvulsive therapy

**Authors** Else Schneider[1], Annette Brühl[2]
**Institutes** **1** Department of Psychiatry, Psychotherapy and Psychosomatics, University Clinic Zurich, Switzerland; **2** Psychiatric University Clinics, Basel, Switzerland

**Introduction** Electroconvulsive therapy (ECT) is considered the most effective treatment in psychiatry, with particular efficacy in the major psychoses. However, seizure threshold progressively rises during the course of ECT indicated by reduced seizure quality and length. Therefore, the applied charge is increased. However, charge is linked to cognitive side effects and therapists strive for lowest possible charge evoking a sufficient seizure. Proconvulsive augmentation using caffeine can prolong seizure length but might also evoke cardiac dysrhythmias.

**Methods** In the present study, we retrospectively investigated the effect of caffeine in 64 patients who underwent ECT treatment at the Psychiatric University Hospital Basel. 52 of these patients received caffeine intravenously in the course of the ECT treatment.

**Results** When we compared the seizure duration between patients who received caffeine and who did not, we found no significant differences in the seizure duration or in the postictal suppression index. However, comparing the seizure duration within patients (with/without caffeine) seizure duration with caffeine was increased while postictal suppression index was reduced. Peak heartrate during the seizure was significantly increased in patients who received caffeine but no cardiac arrhythmia were reported.

**Conclusion** Our results suggest that preictal caffeine augmentation is an effective way to increase the seizure duration and, thus, to enhance the efficacy of ECT treatment.

**Conflict of interest** None

## P2.3 Drawing new lines – Machine-learning guided response prediction and bio-signal analysis of ECT index series

**Authors** Max Kayser[1], Else Schneider[2], Niels Freundlieb[3], Maximilian Kiebs[1]
**Institutes** 1 University Clinic Bonn, Germany; 2 Department of Psychiatry, Psychotherapy and Psychosomatics, University Clinic Zurich, Switzerland; 3 GiB Stiftung e.V., Germany

**Introduction** The scientific understanding of electroconvulsive therapy (ECT) and its therapeutic procedures are largely based on pre-calculated EEG seizure parameters and pre-post treatment indices. Analysing data from the novel multicentric GENET research collaboration by implementing biosignal-analysis and artificial intelligence methods, we present new research opportunities to reach a better understanding of ECT's mechanisms of action. Presenting preliminary results, we will also discuss challenges which arise when handling multidimensional variable length as well as unbalanced panel-data.

**Methods** We present a data flow importing anonymized unbalanced ECT-treatment data and associated bio-signals (EEG, ECG, EMG) from a novel data-documentation tool directly into a python- based machine learning (ML) pipeline. This pipeline includes data-transformation into ML-suitable nested data structures by extracting features, reducing dimensionalities, and digitally analysing EEG seizures.

**Results** Using traditional EEG-based seizure quality indices and treatment parameters, treatment- response-prediction models showed significant differences in model performance depending on model parameters. Preliminary evidence also indicates that using existing python-libraries is helpful in reproducing the results of currently available ECT quality indices.

**Conclusion** The outlined methods will give a first impression of how machine learning approaches offer new research opportunities in ECT to potentially develop alternative seizure quality markers above and beyond the already existing ECT predictive parameters (e.g. PSI, ASEI, MSI.) using digital bio-signal analysis. This approach may allow us to improve clinical decision making and individualize treatments.

**Conflict of interest** None

## P2.4 POMC and NR3C1-1F DNA methylation in major depressive disorder and electroconvulsive therapy

**Authors** Hannah B Maier[1], Nicole Moschny[1], Franziska Eberle[1], Kirsten Jahn[1], Thorsten Folsche[1], Rasmus Schülke[1], Stefan Bleich[1], Helge Frieling[1], Alexandra Neyazi[2]
**Institutes** 1 Clinic for Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany; 2 Department of Psychiatry and Psychotherapy, Otto von Guericke University, Magdeburg, Germany

**Introduction** Patient-tailored treatment and precision medicine is still to be established in psychiatry. Adequate indicator for treatment prediction of response are still in urgent need. Major Depressive Disorder (MDD) is one of the most disabling diseases worldwide with 30.50 % of MDD patients failing to be in remission after several treatment attempts. Even with electroconvulsive therapy (ECT) remission rates fail to exceed 50 %. The stress response system, and its epigenetics, seem to play a role in MDD.

**Methods** We analyzed the DNA methylation (DNAm) of genes encoding the glucocorticoid receptor (NR3C1) and proopiomelanocortin (POMC) in a longitudinal fashion in peripheral blood mononuclear cells (PBMCs). For analysis, blood was taken before and after the first ( + 15 min) and last ECT from MDD patients (n = 31), as well as from matched unmedicated depressed controls (UDC; n = 19, baseline) and healthy controls (HC; n = 20, baseline). Depression severity was assessed using Montgomery – Åsberg Depression Rating Scale and Beck Depression Inventory.

**Results** Baseline DNAm in NR3C1 was significantly lower in UDC compared to both other groups (EMM ± SE): UDC $0.014 \pm 0.001$, ECT $0.027 \pm 0.001$, HC $0.024 \pm 0.001$; $p < 0.001$, whereas regarding POMC, ECT patients had the highest DNAm levels (ECT $0.269 \pm 0.011$, UDC $0.178 \pm 0.014$, HC: $0.159 \pm 0.013$; $p < 0.001$). At baseline, responders were less methylated compared to non-responders to ECT in NR3C1 ($p < 0.001$), whereas in POMC there was no difference detectable ($p = 0.720$). NR3C1 and POMC DNAm decreased after the first ECT (NR3C1: $p < 0.001$; POMC: $p = 0.002$). In NR3C1 the effect was mainly driven by non-responders.

**Conclusion** Our findings indicate that NR3C1 DNAm might play a role in the chronification of depression. POMC DNAm on the other hand might point towards a dysregulated HPA axis sensitive to ECT.

**Conflict of interest** HBM and RS took part in an educational event sponsored by Lianova. HF receives speaker´s honoraria and served as advisor for Recordati Pharma GmbH and Janssen-Cilag GmbH. AN received lecture fees from Novartis and Merck. NM, FE, KJ, TF, SB declare no conflict of interest.

## P2.5 A retrospective comparison of etomidate and methohexital as anesthetic agents for maintenance electroconvulsive therapy

**Authors** Vincent Millischer, Sibylle Pramhas, Isabell Wiedermann, Vincenz Eder, Hans-Georg Kress, Andrea Michalek-Sauberer, Dan Rujescu, Richard Frey, Pia Baldinger-Melich
**Institute** Department of General Psychiatry, Medical University, Vienna, Austria

**Introduction** Electroconvulsive therapy (ECT) is performed under general anesthesia and muscle relaxation. Ideally, the anesthetic agent should not compromise the quality of the ECT-induced seizure while providing rapid induction and recovery, as well as few side effects. It is still unclear which of the commonly used substances is best suited for ECT. The present retrospective study aimed at comparing etomidate and methohexital for maintenance ECT with regards to seizure quality, time to recovery and occurring side-effects.

**Methods** All maintenance ECT sessions performed between October 1st, 2014 and February 28th, 2022 were included in this retrospective analysis. Maintenance ECT was performed using the Thymatron System IV ECT device under anesthesia with either etomidate or methohexital plus succinylcholine. Electrode placement and electric charge corresponded to the settings used during the last ECT session of the index series. All ECT-related parameters, vital signs, pharmacological interventions and side effects were recorded and compared between groups.

**Results** 573 ECT sessions from 88 patients were included in this analysis (methohexital n = 458, etomidate n = 115). Seizure duration was significantly longer in the etomidate group ( + 12.8 seconds [95 %-CI:8.64-16.95]. The use of etomidate was associated with longer procedure duration ( + 6.51 minutes [95 %-CI:4.14-9.04), higher maximum postictal systolic blood pressure ( + 13.64

mmHg [95 %-CI:9.33-17.94], more frequent use of antihypertensives, benzodiazepines and clonidine for postictal agitation.

**Conclusion** In this retrospective, head-to-head comparison, etomidate turns out to be inferior to methohexital as anesthetic agents during maintenance ECT with regard to procedure duration and adverse events requiring pharmacological interventions. In line with previous findings use of etomidate seems to be associated to longer seizure duration, which is desirable from a psychiatric point of view; however, therapeutic response is not solely based on seizure duration and potential, favorable effects do not outweigh the clear disadvantages.

**Conflict of interest** None

## P3 Experimental models

### P3.1 Influence of long-term citalopram treatment on the cognitive decline and pathology in a sporadic Alzheimer's disease mouse model

**Authors** Sören F Bock[1], Sofie China[1], Friederike Spandau[1], Jens Wiltfang[1, 2, 3], Nicola Beindorff[4], Yvonne Bouter[1]

**Institutes** 1 Department of Psychiatry and Psychotherapy, University Medical Centre Goettingen, Germany; 2 German Centre for Neurodegenerative Diseases, Goettingen, Germany; 3 Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Aveiro, Portugal; 4 Experimental Radionuclide Imaging Centre, Charité University Medicine, Berlin, Germany

**Introduction** Selective serotonin reuptake inhibitors are increasingly in the spotlight of Alzheimer's disease (AD) research. A long-term citalopram therapy has been shown to delay the progress from mild cognitive impairment to AD in depressive patients. Furthermore, citalopram reduced the amyloid-β load in a familial AD mouse model. We investigate the effects of citalopram on the behaviour deficits and AD's pathology in the Tg4-42 mouse model, which overexpresses neurotoxic Aβ4-42, a key player in Alzheimer's disease.

**Methods** Tg4-42 mice were treated daily for 6 months with 10 mg citalopram per kg body weight, starting at the age of 10 weeks. After this long-term therapy, the treated mice were compared to a control group in the Cross Maze Test and the Morris Water Maze Test to investigate learning and memory. An FDG-PET was conducted to investigate the metabolic brain activity and immunostainings were used to quantify the hippocampal Aβ load and neuroinflammation.

**Results** Long-term citalopram therapy in Tg4-42 mice led to an improved working memory and spatial reference memory in the behaviour tests. Additionally, the treated group showed a higher metabolic hippocampal activity in the FDG-PET. The immunostainings of the hippocampus revealed less intraneuronal Aβ4-42 and a decreased neuroinflammation in the citalopram treated group.

**Conclusion** Our findings demonstrate that a long-term citalopram treatment could be an effective treatment for AD.

**Conflict of interest** None

### P3.2 Effects of a citalopram treatment on the amyloid-β-pathology and behaviour in the 5xFAD Alzheimer mouse model

**Authors** Friederike Spandau[1], Steffen Pichlo[1], Nadine Curdt[1], Sören F Bock[1], Jens Wiltfang[1, 2, 3], Yvonne Bouter[1]

**Institutes** 1 Department of Psychiatry and Psychotherapy, University Medical Centre Goettingen, Germany; 2 German Centre for Neurodegenerative Diseases, Goettingen, Germany; 3 Institute of Biomedicine, Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

**Introduction** In recent years citalopram, a selective serotonin reuptake inhibitor, has become the focus of molecular research as a treatment for Alzheimer's disease (AD). It has been shown that citalopram was able to lower the concentration of Aβ in the cerebrospinal fluid in humans and caused a delayed progression of Mild Cognitive Impairment to AD in patients with depression. The purpose of our study was to investigate the effects of citalopram treatment on the pathology and memory deficits in the 5xFAD mouse model of familial AD. 5xFAD mice recapitulate many AD-related phenotypes and develop an aggressive and progressive plaque pathology as well as synaptic dysfunction and neuron loss.

**Methods** Mice were treated with citalopram in two consecutive studies. In the short-term trial mice received either 5 mg/kg, 10 mg/kg or 40 mg/kg body weight citalopram for 2 weeks, starting at the age of 10 weeks. Afterwards, the Aβ levels in the blood plasma of mice and immunohistochemical measurement of the Aβ plaque load in the brain were compared to a vehicle group. In the following long-term trial 10-week-old 5xFAD mice were treated with 10 mg/kg body weight citalopram for 6 months. To analyze the effects of a citalopram treatment on anxiety behaviour and memory skills, treated animals were compared to a control group in the Open Field Test, Elevated Plus Maze and Novel Object Recognition Test at the age of 8 months.

**Results** Short-term-treatment with citalopram significantly decreased the concentration of Aβ40 and Aβ42 in the blood plasma and led to a significantly lower Aβ plaque load in the hippocampus. Long-term-treatment with citalopram normalized the anxiety behaviour and locomotor activity in the Open Field test as well as in the Elevated Plus Maze. Additionally, citalopram improved the recognition memory of 5xFAD mice in the Novel Object Recognition test.

**Conclusion** The results of our study demonstrate that citalopram has a positive effect on several parameters of AD pathology in the 5xFAD mouse model and therefore appears as a possible treatment against AD in the future.

**Conflict of interest** None

### P3.3 Neutral sphingomyelinase is a major driver of sex-differences in depression and alcohol-abuse

**Authors** Christian Müller, Christiane Mühle, Tianye Jia, Erich Gulbins, Bernd Lenz, Gunter Schumann, Johannes Kornhuber, Liubov S Kalinichenko

**Institute** Department of Psychiatry and Psychotherapy, University Clinic Erlangen-Nuremberg, Erlangen, Germany

**Introduction** Sphingolipids, and particularly ceramides, are crucial components of biological membranes, which determine their integrity, functions, and dynamic plasticity. Here we hypothesized that naturally occurring variations in the activity of the enzyme neutral sphingomyelinase-2 (NSM), a key enzyme of ceramide synthesis, may be a common origin of the clinically highly relevant comorbidity trias of alcohol abuse, major depression and bone defects.

**Methods** Animal experiments were performed on female and male transgenic mice with reduced NSM activity (fro, fragilis ossium). Naïve fro mice were tested in a battery of behavioral tests or exposed to alcohol on the model of free-choice drinking. After alcohol drinking for at least 4 weeks, the behavioral status of mice, and changes in cellular and molecular parameters in the brain were evaluated. Plasma NSM activity is enhanced in patients with alcohol use disorder upon admission for treatment. Human association study data from 456,693 participants (56.0 % female) with complete genotype and behavioral data were drawn from the UK Biobank, a large cohort of United Kingdom residents aged 40–69 years. A genetic association analysis of numerous haplotypes of the SMPD3 gene, coding for NSM, with alcohol consumption, depression and anxiety, and bone density and related brain and bone-brain mechanisms was performed.

**Results** Animal studies revealed an essential contribution of the NSM to depression- and anxiety related behavior in mice, which was sex-dependent. Also the contribution to alcohol drinking was highly sex-dependent. This was mediated by a role of the NSM in brain development and monoaminergic signaling,

as well as in osteocalcin signaling from the bone system. These findings were confirmed in the human study, which found several associations between SMPD3 haplotypes and alcohol consumption, depression and anxiety, as well as with hippocampus size in humans. Also an association with bone mineralization was found in humans.

**Conclusion** We propose SMPD3 gene and its coded protein NSM as a joint base for the frequently comorbid symptom trias of alcohol addiction-depression/anxiety-osteoporosis. NSM mediates single disease symptoms as well as their reciprocal interaction along distinct brain pathways and by bone-derived osteocalcin signaling. Sex-specific targeting of NSM and osteocalcin may, thus, serve as a suitable treatment for the co-morbidity trias of alcohol addiction-depression/anxiety-osteoporosis.

**Conflict of interest** None

## P3.4    Caffeine influences Clock expression in study participants with an ADHD diagnosis

**Authors**  Denise Palm, Adriana Uzoni, Oliver Tucha, Johannes Thome, Frank Faltraco
**Institute**  Department of Psychiatry and Psychotherapy, University of Medicine Rostock, Rostock, Germany

**Introduction**  Attention deficit hyperactivity disorder (ADHD) is characterized by inattention and hyperactivity/impulsivity and is associated with alteration in circadian gene expression. Several studies reported an association between caffeine, sleep and attention. Thus, we investigate the influence of caffeine on the circadian gene expression in ADHD and healthy controls in a fibroblast model.

**Methods**  Human dermal fibroblasts (HDF) were obtained via skin biopsy from healthy volunteers without a neuropsychiatric disorder (4 men, 6 women; $45.90 \pm 14.23$ years, mean $\pm$ SD) and study participants diagnosed with ADHD (5 men, 5 women; $44.20 \pm 19.15$ years, mean $\pm$ SD). After ex vivo exposure to 2.5 mM caffeine and dexamethasone synchronization, the rhythmicity of circadian gene expression (Clock, Bmal1, Per1-3, Cry1) was analysed via qRT- PCR.

**Results**  Clock expression decreased in early hours ZT0–ZT8 (ZT4, $p = 0.010$) after synchronization, increased between ZT12–ZT16 and was significant higher at ZT20 ($p = 0.012$) and ZT24 ($p = 0.002$) in cultures from study participants with an ADHD diagnosis incubated with 2.5 mM caffeine compared to ADHD participants without caffeine incubation and healthy controls (with and without caffeine incubation).

**Conclusion**  Caffeine decreases Clock expression in early hours (ZT0–ZT8) after synchronization and increases clock expression between ZT20–ZT24 in fibroblasts of individuals with an ADHD diagnosis compared to healthy controls.

**Conflict of interest** None

## P3.5    Low glucose influences Clock expression in study participants with an ADHD diagnosis

**Authors**  Frank Faltraco, Denise Palm, Adriana Uzoni, Oliver Tucha, Johannes Thome
**Institute**  Department of Psychiatry and Psychotherapy, University Medicine Rostock, Rostock, Germany

**Introduction**  Hypoglycemia stimulates appetite and induces deterioration of cognitive function, e.g. attention. A key symptom of attention deficit hyperactivity disorder (ADHD) is – besides hyperactivity and/or impulsivity – inattention. Several studies reported about an association between glucose homeostasis and circadian rhythmicity. Thus, we investigate the influence of glucose on the expression of circadian genes in study participants with an ADHD diagnosis and healthy controls without a neuropsychiatric disorder in human dermal fibroblasts as in vitro model.

**Methods**  Human dermal fibroblasts (HDF) were obtained via skin biopsy from healthy volunteers without a neuropsychiatric disorder (4 men, 7 women; $51.36 \pm 16.93$ years, mean $\pm$ SD) and study participants diagnosed with ADHD (5 men, 5 women; $45.20 \pm 18.16$ years, mean $\pm$ SD). After cell starvation followed by incubation with 2 mM glucose and dexamethasone synchronization, the rhythmicity of circadian gene expression (Clock, Bmal1, Per1-3, Cry1) was analysed via qRT-PCR.

**Results**  Cell cultures from study participants with an ADHD diagnosis incubated with 2.0 mM glucose demonstrated less Clock expression at ZT8 ($p = 0.025$) and higher Clock expression at ZT24 ($p = 0.044$) compared to ADHD cultures with standard medium (5.6 mM glucose). Clock showed a phase-shift of approximately 16–24 hours. Between the two study groups (HC, ADHD), different expression levels of Per1 at ZT4 ($p = 0.002$), ZT16 ($p = 0.014$) and ZT28 ($p = 0.023$) were observed after exposure to 2 mM glucose.

**Conclusion**  Cell starvation and low glucose levels influence circadian rhythmicity, particularly gene expression, phase and period length of Clock in human dermal fibroblasts from participants with an ADHD diagnosis compared to healthy controls.

**Conflict of interest** None

## P3.6    Triiodothyronine: Strengthened evening preference in study participants with an ADHD diagnosis

**Authors**  Denise Palm, Adriana Uzoni, Oliver Tucha, Johannes Thome, Frank Faltraco
**Institute**  Department of Psychiatry and Psychotherapy, University Medicine Rostock, Rostock, Germany

**Introduction**  Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder associated with changes in thyroid-stimulating hormone (TSH) and free triiodothyronine (T3). Thyroid hormones are associated with diurnal rhythms and reported to modulate circadian gene expression in a tissue-specific manor. Thus, we investigate the influence of T3 on circadian gene expression in human dermal fibroblasts from study participants diagnosed with ADHD and healthy controls without a neuropsychiatric disorder.

**Methods**  Human dermal fibroblasts (HDF) were obtained via skin biopsy from healthy volunteers without a neuropsychiatric diagnosis (2 men, 8 women; $52.08 \pm 17.03$ years, mean $\pm$ SD) and study participants diagnosed with ADHD (5 men, 5 women; $44.60 \pm 18.63$ years, mean $\pm$ SD). After ex vivo exposure to 100 nM T3 and dexamethasone synchronization, the rhythmicity of circadian gene expression (Clock, Bmal1, Per1-3, Cry1) was analysed via qRT-PCR.

**Results**  T3 induced significant lower Bmal1 expression between ZT4–ZT24 (ZT8, $p = 0.013$; ZT12, $p = 0.034$) in cultures from ADHD participants. The expression levels of Cry1, Per1-3 after T3 incubation in the ADHD group were lower in the early hours (ZT0: Per3, $p = 0.010$; ZT4: Per1, $p = 0.016$; Per2, $p = 0.010$; ZT8: Cry1, $p = 0.008$; Per1, $p = 0.002$; Per2, $p = 0.034$) and higher in the late hours after synchronization (ZT16: Per1, $p = 0.038$; ZT20: Cry1, $p = 0.003$; ZT24: Cry1, $p = 0.003$; Per2, $p = 0.015$; Per3, $p = 0.050$; ZT28: Cry1, $p = 0.050$).

**Conclusion**  The results suggest that T3 has a stronger influence at circadian gene expression in fibroblasts from study participants with an ADHD diagnosis compared to volunteers without a neuropsychiatric disorder. The shift in circadian gene expression in human dermal fibroblasts from study participants with an ADHD diagnosis may strengthen evening preference in the ADHD group.

**Conflict of interest** None

## P3.7    Vitamin D: Adjustment of Per1 expression in study participants with an ADHD diagnosis

**Authors**  Frank Faltraco, Denise Palm, Adriana Uzoni, Oliver Tucha, Johannes Thome
**Institute**  Department of Psychiatry and Psychotherapy, University Medicine Rostock, Rostock, Germany

**Introduction** Several studies reported about an association between vitamin D, circadian rhythmicity and physiological mechanisms, e.g. sleep. The aim of this study was to investigate the circadian gene expression in primary human dermal fibroblast cultures (HDF) from study participants with an ADHD diagnosis and healthy controls without a neuropsychiatric disorder after exposure to vitamin D.

**Methods** Human dermal fibroblasts (HDF) were obtained via skin biopsy from healthy volunteers without a neuropsychiatric diagnosis (4 men, 5 women; 46.89 ± 19.02 years, mean ± SD) and study participants diagnosed with ADHD (8 men, 1 women; 38.44 ± 14.96 years, mean ± SD). After ex vivo exposure to 10 μM vitamin D and dexamethasone synchronization, the rhythmicity of circadian gene expression (Clock, Bmal1, Per1-3, Cry1) was analysed via qRT- PCR.

**Results** Per1 expression was significantly higher at ZT0 (p = 0.017) and significantly lower at ZT8 (p = 0.039) in cultures from ADHD participants incubated with 10 μM vitamin D compared to cultures from ADHD participants without vitamin D. Per1 expression in cultures from study participants with an ADHD diagnosis and incubated with 10 μM vitamin D showed a similar expression compared to HC without vitamin D. Per1 differed between HC and ADHD without vitamin D incubation at ZT8 (p = 0.021).

**Conclusion** Vitamin D influences circadian gene expression, particularly Per1. Vitamin D exposure results in an adjustment in Per1 expression in dermal fibroblasts from study participants diagnosed with ADHD compared to the control group (without vitamin D).

**Conflict of interest** None

## P4 Various

## P4.1 Functional connectivity analysis of locus coeruleus in patients with major depressive episode

**Authors** Anastasia Gaspert[1], Rasmus Schülke[1], Tabea Bätge[1], Thorsten Folsche[1], Nima Mahmoudi[2], Mike Wattjes[2], Christopher Sinke[1], Tillmann Krüger[1], Stefan Bleich[1], Alexandra Neyazi[1, 3], Helge Frieling[1], Hannah B Maier[1]

**Institutes** 1 Clinic for Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany; 2 Department of Diagnostic and Interventional Neuroradiology, Hannover Medical School, Hannover, Germany; 3 Department of Psychiatry and Psychotherapy, Otto von Guericke University, Magdeburg, Germany
**DOI** 10.1055/s-0042-1757657

**Introduction** Major Depressive Disorder (MDD) is one of the most prevalent psychiatric disorders (1). For better understanding of brain connectivity in MDD, we used resting-state functional magnetic resonance imaging (rs-fMRI) to measure the functional connectivity of the locus coeruleus (LC). The LC contributes to cognitive processes by controlling attention, decision making, and memory (2). Since depressed patients show an altered functional connectivity of various brain regions (3), we hypothesize an altered connectivity of the LC in patients with MDD compared to healthy controls.

**Methods** 36 patients with treatment-resistant MDD were included in our difficult-to-treat-depression registry study (NEKTOR). Furthermore, we recruited 23 healthy controls. Patients were diagnosed with MDD according to Structured Clinical Interview for Diagnostic (SCID) and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV). Severity of depression was assessed via Beck's Depression Inventory-II (BDI-II) and Montgomery-Åsberg Depression Rating Scale (MADRS). The rs-fMRI data was acquired on Siemens 3 T Skyra.

**Results** Compared to healthy controls, patients with treatment-resistant MDD showed decreased seed-based functional connectivity of the left LC to the left cerebellum (cluster-level inference, p = 0,001, FDR-corrected).

**Conclusion** The present study found, for the first time, a significant reduction in functional connectivity between the left LC and the ipsilateral cerebellum in patients with MDD compared with healthy controls. Our findings underline the significance of extracerebral network-alterations in unipolar depression [1–3].

**Conflict of interest** HBM and RS took part in an educational event sponsored by Livanova. HF received speaker's honararia and served as advisor for Recordati Pharma GmbH and Janssen-Cilag GmbH. AN received lecture fees from Novartis and Merck. SB, AG, TB declare no conflict of interest.

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## P4.2 Cortical and subcortical grey matter volume alterations in neuropsychiatric long-COVID syndrome episode

**Authors** Bianca Besteher, Tonia Rocktäschel, Marlene Machnik, Kathrin Finke, Philipp Reuken, Christian Gaser, Martin Walter
**Institute** Department of Psychiatry and Psychotherapy, University Clinic Jena, Jena, Germany
**DOI** 10.1055/s-0042-1757658

**Introduction** Neuropsychiatric symptoms are among the most common sequelae of long-COVID-19 and highly diminish the patient's quality of life. As accumulating evidence suggests an impact of survived SARS-CoV-2-infection on brain physiology, it appears necessary to further investigate brain structural changes in relation to clinical long-COVID symptoms. Understanding the pathogenic processes in neuropsychiatric long-COVID will be vital to identify targeted therapy and to ease the months long-lasting symptoms.

**Methods** The present cross-sectional study investigated 3T-MRI scans from long-COVID patients (n = 30) with neuropsychiatric symptoms, and healthy controls matched for age and gender (n = 20). Whole-brain comparison of grey matter volume (GMV) was conducted by voxel-based morphometry using the CAT12 software package. To determine whether changes in GMV are predicted by neuropsychiatric symptom burden and / or initial severity of symptoms of COVID-19 and time since onset of COVID-19, we performed multiple linear regression analysis.

**Results** Enlarged GMV in long-COVID patients was present in several clusters (p < 0.05, FWE- corr–ected) spanning fronto-temporal areas, insula, hippocampus, amygdala, basal ganglia, and thalamus in both hemispheres when compared to controls. Time since onset of COVID-19 was a significant regressor in three of these clusters (anatomically located in right inferior frontal gyrus, lateral and posterior orbital gyrus, anterior parts of the insula, left superior, middle and inferior temporal gyrus and left postcentral and precentral gyrus).

**Conclusion** Grey matter alterations in limbic and secondary olfactory areas are present in neuropsychiatric long-COVID patients. Some GMV alterations were inversely associated with time elapsed since acute COVID-19, suggesting higher GMV with shorter time since onset of COVID-19. Detection of associations between GMV and clinical symptoms might be difficult, because of heterogenous clinical presentation. Larger samples and longitudinal data in neuropsychiatric long-COVID patients are required to further clarify the mediating mechanisms between COVID-19 and GMV.

**Conflict of interest** None

## P4.3 ADHD and oligoantigenic diet – Feasibility, effectiveness and follow-up

**Authors** Greta Walz, Clarissa Karius, Lisei-Marie Brozat, Hans-Willi Clement, Reinhold Rauh, Christina Clement, Christian Fleischhaker
**Institute** Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University Clinic Freiburg, Freiburg, Germany
**DOI** 10.1055/s-0042-1757659

**Introduction** The influence of food on attention-deficit hyperactivity disorder (ADHD) was described as early as the early 20th century. The elimination of certain foods via an "oligoantigenic diet" has shown an improvement in typical ADHD symptoms in several studies. The present study examines the relationship between individual food intolerance and ADHD symptoms and shows its effectiveness in the long time.

**Methods** 28 children and adolescents with ADHD participated in an uncontrolled, open study on the oligoantigenic diet. Before and after a four weeks diet with hypoallergenic foods. Besides the primary outcome: ADHD rating scale, the quality of life was studied using the Inventar zur Erfassung der Lebensqualität (ILK), the Child Behaviour Checklist (CBCL/4-18) was used to study effects of the diet on other abnormalities. 21 of the 28 participants could be reached for a follow up.

**Results** 17 children (13 m/3 f) of the 28 participants showed improvements of their ADHD symptomatology according to the primary outcome, with improvements of more then 40 % change, so called responders, before and after diet. Of the 21 participants for the follow up, 3.5 ± 1 years after the diet, 14 were responders. Their ARS value was slightly lower then after diet, 10 of these 14 (70 %) were still without medication.

**Conclusion** Following an oligoantigenic diet, the symptoms in food-sensitive children suffering from ADHD are reduced. If the nutritional recommendation is implemented over the long term, an improvement can also be seen in some children after 3.5 years. The CBCL scores also show improvements in other behavioral problems. The quality of life improves among the responders both in the external assessment of the parents and in the self-assessment, especially in the categories of friends and alone.

**Conflict of interest** None

# P5 Neuropharmacology

## P5.1 Mineralocorticoid and glutamatergic NMDA receptor stimulation does not influence spatial learning and memory in depressed individuals and healthy control

**Authors** Michael Kaczmarczyk, Katja Wingenfeld, Jan Nowacki, Woo Ri Chae, Christian E Deuter, Dominique Piber, Christian Otte
**Institute** Department of Psychiatry and Psychotherapy, Charité University Medicine, Berlin, Germany
**DOI** 10.1055/s-0042-1757660

**Introduction** Major depressive disorder (MDD) is associated with cognitive impairments including spatial learning and memory. The hippocampus and the prefrontal cortex are brain areas, that have been associated with spatial performance. In both areas, mineralocorticoid receptors (MR) and glutamatergic N-methyl-D-aspartate receptors (NMDA-R) are highly expressed, and MDD has been associated with altered functioning of both receptors. By pharmacological stimulation, we examined the role of both receptors in spatial learning and memory in depressed and healthy participants

**Methods** We conducted a randomized, double-blind, placebo-controlled study with 116 depressed individuals (mean age: 34.7 ± 13.3 years; 78.4 % women) and 116 age-, sex-, education-matched healthy controls. To stimulate MRs we administered 0.4mg fludrocortisone and to stimulate NMDA-Rs we administered 250 mg D-cycloserine. All participants were randomly assigned to one treatment condition: 1) placebo; 2) MR stimulation; 3) NMDA-R stimulation;4) combined MR/NMDA-R stimu–lation. Spatial learning and memory were assessed using a virtual Morris Water Maze task.

**Results** Depressed and healthy individuals did not differ in sociodemographic variables (except for stable relationships, which were more common in the group of healthy controls). There was no difference between depressed individuals and healthy controls in spatial learning and memory. Separate or combined MR/NMDA-R stimulation did not influence spatial performance.

**Conclusion** In our sample of young and predominantly female participants, there was no effect of MDD on spatial performance. Moreover, there was no effect of separate or combined MR and NMDA- R stimulation. We therefore conclude, that both receptors might not play a pivotal role in spatial learning and memory.

**Conflict of interest** None

## P5.2 Processing and recall of safety- and threat cues: The influence of oxytocin and the menstrual cycle

**Authors** Fromut von Oertzen, Ekaterina Schneider, Maxim Fischer, Beate Ditzen, Monika Eckstein
**Institute** Institute of Medical Psychology, University Clinic Heidelberg, Heidelberg, Germany
**DOI** 10.1055/s-0042-1757661

**Introduction** Distinguishing adequately between safety and danger is necessary for survival. Safety cues are stimuli that have been initially and repeatedly associated with the absence of danger; a process called safety learning. Safety cues can have an anxiolytic effect. Fear learning, on the other hand, is modulated by the neuropeptide oxytocin. An interaction of oxytocin and sex hormones has been shown for social anxiety. Neuroendocrine mediators of safety learning are yet unclear.

**Methods** 99 healthy women participated either during the early follicular phase of the menstrual cycle or during/shortly after ovulation. In a double-blind randomized design, participants received a nasal spray containing either oxytocin or placebo. Participants were presented visual stimuli, consisting of social (faces) and non-social (houses) stimuli and in part paired with mild electric shocks. After the learning paradigm participants completed a questionnaire to rate their recall of the stimuli.

**Results** Statistical analyses revealed better recall of as well as discrimination between safety/ danger and neutral cues in the ovulating group when compared to the early follicular group. Participants in the early follicular stage showed better recall of social stimuli after oxytocin application. We therefore show an interaction of oxytocin and menstrual cycle regarding recall of social stimuli as well as an interaction of menstrual cycle and recall of stimuli of different valency.

**Conclusion** Our results show that oxytocin, a mediator in fear extinction, and the menstrual cycle influence the results of safety learning. This indicates an underlying correlation between safety learning and sex hormone plasma concentration, which should be addressed in further research. This dependence of the recall of both safety and danger signals on the menstrual cycle has implications for successful therapeutic alliance as well as for patients with deficits in safety signal perception.

**Conflict of interest** None

## P5.3 Interleukine-6 and high-sensitive CRP plasma levels and antidepressant response- A secondary analysis from the Early Medication Change (EMC) trial

**Authors** Kathrin M Kachel, Jan Engelmann, Jonas Kemper, Stefanie Wagner, André Tadic, Marianne Müller, Martin Schäfer, Klaus Lieb

Institute  Department of Psychiatry and Psychotherapy, University Medical Centre Mainz, Mainz, Germany
DOI  10.1055/s-0042-1757662

**Introduction**  Although the available pharmacological treatments of major depressive disorder (MDD) are well established, there is a great variability in patient´s individual response. Therefore, reliable predictors to guide treatment decisions are needed. Growing evidence in literature suggests alterations in IL-6 and hs-CRP levels in depression, but findings on antidepressant treatment response prediction are fare to be conclusive. Thus, our aim was to investigate the course of both parameters between later responders and non-responders to antidepressant treatment.

**Methods**  139 patients with a major depressive disorder who had participated in the EMC trial were included in the analysis. Patients were treated within a predefined antidepressant treatment algorithm for eight weeks. Depression severity was conducted weekly by HAMD17 and patients were selected based on their response after four weeks and stratified in responders (N = 79) and non-responders (N = 60). IL-6 and hsCRP plasma levels were measured at baseline, day14 und day 28.

**Results**  Mean age was 40.7 years, 58.9 % were women and mean HAMD17 sumscore was 22.1. In the total group, at baseline IL-6 levels were positively correlated to depression severity (p = 0.033), meaning that more severely depressed patients showed higher IL-6 levels. Responders and non-responders did not differ in hsCRP and IL-6 levels at baseline, day14, and day28, but there was a significant difference in hsCRP changes from baseline to day 14 between responders and non-responders (p = 0.017).

**Conclusion**  In conclusion, we confirmed earlier observation of increased IL-6 levels in severely depressed patients. In line with previous studies, in our sample IL-6 could not serve as a predictor for response to antidepressant treatment. The early change of hsCRP seems to be associated with later response and should therefore be confirmed in larger samples.

**Conflict of interest**  None

## P5.4    QTc interval alterations during antidepressant treatment with escitalopram and venlafaxine

**Authors**  Benedikt Figel, Jan Engelmann, Andreas Solheid, André Tadic, Christoph Hiemke, Klaus Lieb
**Institute**  Department of Psychiatry and Psychotherapy, University Medical Centre Mainz, Mainz, Germany
**DOI**  10.1055/s-0042-1757663

**Introduction**  Electrocardiographic alterations are rare but serious adverse drug reactions in antidepressant treatment. QTc interval prolongations are described for many antidepressants, although the current study situation is far from conclusive. Therefore, our aim was to investigate QTc interval alterations and its association to dosage and serum concentration of two commonly used antidepressants (escitalopram / high-dose venlafaxine).

**Methods**  207 depressed patients were treated with escitalopram (SCT; 10mg on day 1 and 20mg from day 2 onwards) for four weeks and subsequently switched to venlafaxine and treated for another four weeks (VF; 75 mg on day 1, then increased up to 375 mg on day 4). Antidepressant serum levels were assessed weekly. Electrocardiograms were taken at baseline, day 28 and day 56. Known risk factors for QTc prolongation were considered for analysis.

**Results**  SCT did not significantly influence the QTc-interval, whereas high-dose VF resulted in a significant increase. We found no significant correlations between dosage or serum concentrations and QTc time. Changes into a critical QTc time range ( > 450ms for men and > 470 ms for women) were seen in 5 % of the patients treated with SCT and in 12 % treated with VF. These patients showed higher rates of cardiovascular comorbidities, cardiac comedication and a higher Body-Mass-Index.

**Conclusion**  In our sample of predominantly middle-aged patients, antidepressant treatment with VF showed a moderate influence on QTc time alterations, even under high doses and serum levels above the therapeutic serum range.

However, cardiovascular comorbidities seem to have a relevant influence on the extent of QTc prolongation and should therefore be considered in clinical practice.

**Conflict of interest**  None

## P5.5    Glycine and the ketamine model of schizophrenia: Modulating the N-methyl-D-aspartate receptor (NMDAR) offers new insights into the glutamate hypothesis of schizophrenia

**Authors**  Moritz Haaf[1], Stjepan Curic[1], Saskia Steinmann[1], Jonas Rauh[1], Christoph Mulert[2], Gregor Leicht[1]
**Institutes**  1  Department of Psychiatry and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; 2  Department of Psychiatry and Psychotherapy, Justus-Liebig University, Gießen, Germany
**DOI**  10.1055/s-0042-1757664

**Introduction**  Synchronized oscillating neural activity in the gamma frequency band (30–100 Hz) has a pivotal role in cognitive functions such as attention and perception. Humans with schizophrenia display differential alterations of resting-state (increases) and stimulus-evoked gamma oscillations (reductions). Interestingly, the application of the NMDAR antagonist ketamine induces comparable gamma alterations and schizophrenia-like symptoms in healthy volunteers. This disease model offers the opportunity to investigate the modulation of this excitatory-to-inhibitory imbalance through co-agonists of the NMDAR.

**Methods**  To test the hypothesis that glycine pretreatment will mitigate both, the schizophrenia-like psychopathology and neurophysiological alterations induced by ketamine, twenty-five healthy male participants were enrolled in this study. The study followed a double-blind (regarding pretreatment), randomized, counter-balanced, placebo-controlled design. The impact of glycine on ketamine-induced neurophysiological alterations was examined with 64-channel electroencephalography (EEG). The Positive and Negative Syndrome Scale (PANSS) was used to assess the psychopathological status.

**Results**  We observed significant alterations of the gamma activity and an increase in all PANSS scores following ketamine administration. Notably, higher schizophrenia-like negative symptoms scores were associated with larger reductions of the auditory-evoked gamma following the infusion of ketamine. Whilst glycine pretreatment did not mitigate ketamine-associated gamma increases at rest, it attenuated the reductions of the auditory-evoked gamma response. This glycine-mediated attenuation was largest in individuals displaying a clinically relevant reduction of negative symptoms.

**Conclusion**  In conclusion, our results point to a differential involvement of NMDARs in resting state as opposed to task-based gamma oscillogenesis. Further, we propose that the auditory-evoked gamma band response can be utilized as a potential biomarker for an impaired NMDAR function and associated negative symptoms in schizophrenia. This could provide the possibility to discern humans with schizophrenia affected by negative symptoms, who might respond to treatments targeting the glutamate system.

**Conflict of interest**  None

## P5.6    Neurological soft signs are increased in major depressive disorder irrespective of antidepressant treatment

**Authors**  Rasmus Schülke[1], Kyra Liepach[1], Anna L Brömstrup[1], Thorsten Folsche[1], Maximilian Deest[1], Stefan Bleich[1], Alexandra Neyazi[2], Helge Frieling[1], Hannah Maier[1]
**Institutes**  1  Clinic for Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany; 2  Department of Psychiatry and Psychotherapy, Otto von Guericke University, Magdeburg, Germany
**DOI**  10.1055/s-0042-1757665

**Introduction**  Neurological soft signs (NSS) – subtle abnormalities of sensory and motor functions – have previously been associated primarily with schizo-

phrenia and bipolar spectrum disorders. The significance of NSS in major depressive disorder (MDD), however, has remained unclear. In particular, the stability of NSS in relation to antidepressant treatment has never been investigated.

**Methods** NSS and depressive symptoms were assessed in chronically depressed, medicated MDD patients before (n = 23) and after (n = 18) a series of electroconvulsive therapy (ECT). In addition, NSS and depressive symptoms were assessed once in acutely depressed, unmedicated MDD patients (n = 16) and healthy controls (n = 20).

**Results** We found that both chronically depressed, medicated MDD patients and acutely depressed, unmedicated MDD patients showed more NSS than healthy controls. Overall, the degree of NSS in both patient groups did not differ. Across all groups, we also found moderate to large positive correlations of depressive symptoms with NSS, independent of age. Importantly, we found no change in NSS after on average eleven sessions of ECT.

**Conclusion** The manifestation of NSS in MDD seems to be independent of illness duration and antidepressant treatment. NSS in MDD may represent trait rather than state markers. From a clinical viewpoint, our findings corroborate the neurological safety of ECT.

**Conflict of interest** None

## P5.7 Clomethiazole for the treatment of alcohol withdrawal syndrome: A systematic review and metanalysis

**Authors** Martin Schäfer, Roussana Sabeva, Holger Cramer
**Institute** Department of Psychiatry, Psychotherapy, Psychosomatics and Addiction Medicine, Evangelical Clinics Essen-Mitte, Essen, Germany

**Introduction** The objective of this systematic review was to estimate the efficacy and safety of chlomethiazole for the treatment of alcohol withdrawal syndrome in patients with alcohol addiction.

**Methods** Electronic databases were searched through March 2022 for randomized prospective controlled trials (RCTs) investigating patients with alcohol dependence admitted and treated for alcohol withdrawal syndrome. Studies in any language were considered. Comperators were separated in two groups. Group A included chlordiazepoxide, alprazolam, GHB and carbamazepine with a proven own effect on alcohol withdrawal syndrome and Group B with bromocriptine, tiapride, trifluoperazine, clonidine and piracetame with effects only on specific symptoms of withdrawal syndrome.

**Results** 15 RCTs were included. Clomethiazole showed a significant better response if compared to placebo (OR 3,88; 95 % CI = 1.95 to 7.73; p = 0.0001) or to other substances in group B (OR 2.92; 95 % CI = 0.99 to 9.09; p = 0.06). No difference was found if compared to group A (OR 0.86; 95 % CI = 0.35 to 2.11; p = 0.74). Clomethiazole significantly reduced seizures during withdrawal treatment if compared to placebo (OR 0.12; 95 % CI = 0.02 to 0.84; p = 0.03).

**Conclusion** Clomethiazole has superior effects if compared to placebo regarding overall response and preventing seizures during withdrawal treatment. Response was also better if compared to other substances with effects only on specific symptoms of withdrawal syndrome. Based on the age of most trials with methodological deficiencies and the relatively low number of cases, data should be interpreted cautiously.

**Conflict of interest** None

## P5.8 Clomethiazole for insomnia in older adults: A systematic review and meta-analysis

**Authors** Marwa A Juburi, Holger Cramer, Martin Schäfer
**Institute** Department of Psychiatry, Psychotherapy, Psychosomatics and Addiction Medicine, Evangelical Clinics Essen-Mitte, Essen, Germany

**Introduction** The objective of this systematic review was to estimate the efficacy and safety of clomethiazole (also called chlormethiazole) in older adults experiencing insomnia (sleep disorder).

**Methods** A literature search was conducted where electronic databases were searched through December 2021. Manuscripts from Medline (through PubMed), Scopus, the Cochrane Library, PsycINFO, Ovid, ZB MED and PMC were reviewed and analyzed. Randomized controlled trials (RCTs) were eligible if they assessed the effects of clomethiazole on sleep duration, onset of sleep, quality of sleep, adverse events or drop-out rates compared to placebo and other drugs.

**Results** Eight RCTs with 424 patients were included. Clomethiazole significantly increased the duration of sleep when compared to placebo (SMD = 0.61; 95 % CI = 0.11 to 1.11) while no significant difference was seen compared to other drugs (SMD = −0.07; 95 % CI = −0.52 to 0.39). More patients receiving clomethiazole had adequate quality of sleep (OR = 1.44; 95 % CI = 1.04 to 1.98; P = 0.03) and also drop-out rates were significantly lower under clomethiazole treatment when compared to other drugs (OR = 0.51; 95 % CI = 0.26 to 0.99; P = 0.05).

**Conclusion** Our results demonstrate superior effects of clomethiazole on the duration of sleep and the quality of sleep in older adults with insomnia in combination with less drop-outs and hang-over effects in comparison to placebo and/or other drugs. Clomethiazole should be taken into account as alternative treatment in in older adults with severe insomnia.

**Conflict of interest** None

## P5.9 CYP2C19 and CYP2D6 genotyping in a cohort of patients with treatment-resistant depression

**Authors** Anton W Borchert[1], Hannah B Maier[1], Rasmus Schülke[1], Stefan Bleich[1], Alexandra Neyazi[2], Heike Weber[3], Maike Scherf-Clavel[3], Stefan Unterecker[3], Jürgen Deckert[3], Helge Frieling[1]
**Institutes** 1 Clinic for Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany; 2 Department of Psychiatry and Psychotherapy, Otto von Guericke University, Magdeburg, Germany; 3 Department of Psychiatry, Psychosomatics and Psychotherapy, University of Wuerzburg, Würzburg, Germany

**Introduction** The prevalence of treatment-resistant depression (TRD) can only be estimated, but it can be assumed that about 25 % of the initial treatment group meet the criteria for TRD (1). Since genetic polymorphisms of the corresponding genes of cytochrome P450 (CYP) isoenzymes CYP2C19 and CYP2D6 have been shown to influence the tolerability and efficacy and thus the therapeutic success of antidepressant pharmacotherapy (2), we aim to investigate the relationship between CYP polymorphisms and TRD in our study.

**Methods** We analyzed a cohort of the Northern German Electroconvulsive Therapy Outcome Registry (TRD patients n = 109; unmedicated depressed controls [UDK] n = 29; healthy controls n = 41). DNA isolation and CYP genotyping was carried out by the Therapeutic Drug Monitoring Laboratory of the University Hospital Würzburg. To describe the CYP alleles the consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC) were applied (3). To assess the severity of depression, BDI-II and MADRS were used.

**Results** Except for a single diplotype (CYP2D6 3N * 1/ * 4 or * 10/ * 4 or * 39/ * 4 or * 4/ * 46), that differed in distribution between the three groups (p < 0.001, diplotype accumulated in the UDK group), there were no statistical differences in diplotype frequencies between groups. When the frequencies of CYP2C19 and CYP2D6 phenotypes (poor, intermediate, normal, rapid, ultrarapid metabolizer) were analyzed between the three groups, no statistical differences were observed (CYP2C19: p = 0.58; CYP2D6: p = 0.766).

**Conclusion** We could not verify our hypothesis, that there is a clustering of non-normal metabolizers in the TRD group on the basis of our data. Nor did we find any evidence that specific CYP phenotypes might act as a risk factor for the development of TRD. Because the proportion of normal metabolizers does not exceed 60 % (CYP2C19) or 45 % (CYP2D6) in any of the groups, genotyping can

be assumed to be of high clinical relevance in patients receiving antidepressant medication [1–3].

**Conflict of interest** None

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## P5.10 Major depressive episodes with high rapid eye movement density do not respond better to rapid eye movement sleep suppressive antidepressants than to others

**Authors** Thorsten Mikoteit[1, 2], Kim M Probst[1, 2], Marek Adamczyk[3], Marcel A Zeising[3], Axel Steiger[3], Martin Hatzinger[1, 2]
**Institutes** 1 Psychiatric Services of Solothurn, Solothurn, Switzerland; 2 Department of Medicine, University of Basel, Basel, Switzerland; 3 Max Planck Institute of Psychiatry, Munich, Germany
**DOI** 10.1055/s-0042-1757669

**Introduction** Increased rapid eye movement (REM) density, i.e. a high frequency of rapid eye movements in REM-sleep, has been acknowledged as a feature of major depressive disorders [1]. As antidepressants differ in their ability to modify REM-sleep, the aim of this study was to investigate whether REM-density at baseline would be predictive for treatment outcome, and whether REM-sleep suppressive antidepressants would be more effective in patients with high REM-density than other antidepressants.

**Methods** Thirty-four patients with major depressive episode were enrolled in the study (age M = 42.88 ± SD = 13.54 years, 53 % women). We compared a group with high REM-density vs. a group with low REM-density (N = 17 vs.17). Antidepressants were classified into REM sleep- suppressing antidepressants and REM sleep-non-suppressing antidepressants according to [2]. Severity of Depression was assessed with the HAMD at week 1(t1), week 2(t2) and week 4(t3). Response was defined as a ≥ 50 % reduction of baseline HAMD score at t3.

**Results** Concerning the course of treatment, patients with high REM-density did not differ from patients with low REM-density (ANOVA: time x group: p = .10, η2 = .069). Descriptively, at week 2 patients with low REM-density were better off (Hedges g = .58, p < .10), which means, that these patients had an more rapid improvement. In subjets with high REM density, REM sleep suppressing antidepressants had no advantage to non-suppressive antidepressant (response rates: 64.7 % vs. 66.7 %).

**Conclusion** These results suggest that patients with high REM-density do not have a different treatment course than patients with low REM-density. Furthermore, the application of a REM-sleep suppressive antidepressant does not seem to yield a better treatment outcome, than the application of a non-REM-sleep suppressive antidepressant.

**Conflict of interest** None

## P6 Therapeutic drug treatment

## P6.1 Therapeutic reference range for aripiprazole revised: A systematic review and combined analysis

**Authors** Xenia Hart[1], Christoph Hiemke[2], Hans-Willi Clement[3], Andreas Conca[4], Luzie Eichentopf[1], Frank Faltraco[5], Vincenco Florio[4], Jessica Grüner[3], Ursula Havemann-Reinecke[6], Xenija Lense[1], Michael Paulzen[7], Thomas Riemer[8], Georgios Schoretsanitis[9], Gerhard Gründer[1]
**Institutes** 1 Department of Molecular Imaging, Central Institute of Mental Health, Mannheim, Germany; 2 Department of Psychiatry and Psychotherapy, University Medical Centre Mainz, Mainz, Germany; 3 Department of Child and Adolescent Psychiatry, Psychotherapy and Psychosomatics, University Clinic Freiburg, Freiburg, Germany; 4 Sanitario di Bolzano, Servizio Psichiatrico del Comprensorio, Bolzano, Italy; 5 Department of Psychiatry and Psychotherapy, University Medicine Rostock, Germany; 6 Department of Psychiatry and Psychotherapy, University Medical Centre Goettingen, Göttingen, Germany; 7 Department of Psychiatry, Psychotherapy and Psychosomatics, Alexianer Hospital, Aachen, Germany; 8 Institute of Clinical Pharmacology and Toxicology, Charité University Medicine, Berlin, Germany; 9 Department of Psychiatry, Psychotherapy and Psychosomatics, University Clinic Zurich, Switzerland
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**Introduction** 500 ng/mL for the sum of aripiprazole + active metabolite). The range(s) might be transferable to aripiprazole's long-acting injectable (LAI) formulation. Here we present a prototypical meta-analysis of the relationships between BLs of aripiprazole (ARI), its target engagement in the human brain, and clinical effects and side effects.

**Methods** We performed a systematic literature review followed by a qualitative and quantitative analysis of the literature to identify a target range for oral and injectable aripiprazole formulations. Studies in humans were selected without restriction to diagnosis. Population-based concentration ranges were computed and pharmacokinetic influences investigated. 54 study cohorts (51 articles) met the eligibility criteria.

**Results** 29 studies report blood level after oral and 16 after injectable formulations. 13 and 10 of them reported clinical or side effect assessments. Conflicting evidence for a relation between concentration and efficacy or side effects exists resulting in a grading as low and absent. The mean aripiprazole concentration across 17 studies (N = 3,778) is 230.2 ng/mL. PET studies report quite consistent values of 90 % receptor occupancy above 89-110 ng/mL.

**Conclusion** When treated under flexible doses, 50 % of patients with schizophrenia and related disorders had drug concentrations within a range of 120-273 ng/ml (N = 3,373). Several LAI studies have demonstrated concentrations within the current recommended range for oral ARI. We suggest a therapeutic reference range of 120-270 ng/ml and 180-370 ng/ml, respectively, for ARI and its active moiety (AM) for the treatment of schizophrenia (SCZ) and related disorders.

**Conflict of interest** None

## P6.2 Therapeutic drug monitoring of venlafaxine in real-world patients: Dose, concentration and therapeutic efficacy

**Authors** Nathalie Wendler, Xenia Hart, Xenija Lense, Gerhard Gründer
**Institute** Department of Molecular Imaging, Central Institute of Mental Health, Mannheim, Germany
**DOI** 10.1055/s-0042-1757671

**Introduction** Venlafaxine (VEN) is an antidepressant prescribed for major depression, anxiety and panic disorders. The currently recommended reference range for VEN is 100–400 ng/ml, referring to the sum of VEN and its active metabolite O-desmethylvenlafaxine (ODV). High interindividual variability of

VEN and ODV presents a challenge for an effective and safe pharmacotherapy. Therapeutic Drug Monitoring (TDM) is an affordable tool for optimizing outcomes in daily clinical practice.

**Methods** One level per patient, the most current level, measured in steady state, was used. Additional data included information on age, sex, vital signs, comedication, addictive substances, liver- and kidney function, adverse drug reactions (ADR) and additional therapies. Dose-adjusted serum concentrations were computed to assess pharmacokinetic variability of VEN and ODV. TDM data of patients for whom treatment efficacy was assumed by VEN treatment at the time of discharge were compared to patients with medication switch.

**Results** VEN and ODV concentrations were derived from patients at the Central Institute of Mental Health, for whom drug level measurement was requested under the treatment with VEN within the time period of 2014 to 2018. A total of 1808 drug level measurements from about 800 patients were assessed. Steady state levels were available for about 75 % of these patients. Concentration results will be presented at the conference.

**Conclusion** A high interindividual variability is expected in patients treated with VEN. Most patients are treated with concomitant medication potentially interfering with VEN and ODV metabolism. TDM is a valuable tool to address these issues.

**Conflict of interest** None

## P6.3 Serious adverse drug reactions to antipsychotics in children and adolescents with multiple disabilities: Avoidability and potential cost savings by therapeutic drug monitoring

**Authors** Stefanie Fekete[1], Tim Güntzel[1], Karin Egberts[1], Julia Geissler[1], Antje Neubert[2], Manfred Gerlach[1], Marcel Romanos[1], Regina Taurines[1]
**Institutes** 1 Department of Child and Adolescents Psychiatry, Psychosomatics and Psychotherapy, University of Wuerzburg, Wuerzburg, Germany; 2 Department of Experimental and Clinical Pharmacology and Toxicology, Friedrich Alexander University Erlangen-Nuernberg, Erlangen, Germany

**Introduction** Children and adolescents with multiple disabilities and mental disorders (CAMD) are frequently treated with antipsychotic drugs. However, CAMD are particularly susceptible to serious adverse drug reactions (sADRs). This retrospective study examined the frequency of sADRs to antipsychotics in CAMD. It furthermore explores the potential preventability of these sADRs through therapeutic drug monitoring (TDM), as well as the potential socio-economic benefits of TDM.

**Methods** Routine clinical data from all patients treated at a specialized psychiatric clinic for CAMD between 2017 and 2018 were retrospectively examined. Data on the occurrence of sADRs (definition according to European Medicines Agency), their causality with antipsychotics as well as their preventability (Schumock criteria) was extracted from the patient file. Furthermore, the prolongation of the hospital stay due to sADRs was calculated as well as the cost savings.

**Results** 102 CAMD who were administered at least one antipsychotic drug during inpatient treatment were identified. In 22 (21.6 %) of these patients, sADRs with a possible causal relationship with the antipsychotic treatment were documented. Eleven sADRs (50 %) could potentially have been prevented through TDM. Mitigating sADRs through TDM likely would have prevented prolonged hospital stays and thus conferred considerable savings for health insurance companies.

**Conclusion** The routine implementation of TDM is urgently recommended for antipsychotic treatment in CAMD to increase drug therapy safety.

**Conflict of interest** None

## P6.4 Bariatric surgery: impact on oral aripiprazole and fluoxetine bioavailability – A clinical case

**Authors** Maxim Kuzin[1], Georgios Schoretsanitis[2], Markus Götschi[1], Fabian Gardin[1], Wolfram Kawohl[1], Franziskos Xepapadakos[1]
**Institutes** 1 Private Psychiatric Hospital and Academic Teaching Hospital of the University of Zurich, Oetwil am See, Switzerland; 2 Department of Psychiatry, Psychotherapy and Psychosomatics, University Clinic Zurich, Switzerland

**Introduction** Bioavailability alterations for pharmacological agents following bariatric operations have been previously reported, although they may vary based on the medication. Here we report the post- bariatric impact of the Roux-en-Y gastric bypass (RYGB) on the bioavailability of aripiprazole using therapeutic drug monitoring (TDM).

**Methods** TDM was performed in a female inpatient that had received a RYGB in 2014 and was treated with aripiprazole (15 mg/d) and fluoxetine (80 mg/d, dispersible tablet). A switch to the liquid form of aripiprazole was made as a part of therapy optimization.

**Results** During intake of pills, we assessed subtherapeutic concentrations of aripiprazole (mean 71.8 ng/mL), but supratherapeutic concentration of fluoxetine (fluoxetine + norfluoxetine: 746 (368.4 + 377.6) ng/mL). Switching to aripiprazole on a syrup basis under the same daily aripiprazole dosage led four days later to an increase in serum-concentration by 61.6 % (116.6 ng/mL), representing an increase of the concentration to dose ratio (C/D) of aripiprazole from the initial range of 4.5-5.1 to 7.8 (ng/mL/mg).

**Conclusion** A reduction of the daily dosage of aripiprazole up to 50 % is recommended under simultaneous prescription of CYP2D6 inhibitors, e.g. fluoxetine. The low C/D of aripiprazole despite the inhibiting effects of fluoxetine may be due to post-RYGB malabsorption. This hypothesis is further supported by variations of the measured serum concentrations, depending on the mode of drug delivery. This case underlines the importance of TDM in dose selection to enhance safety and efficacy outcomes.

**Conflict of interest** MK received travel grants from Sunovion Pharmaceutical (Basel, Switzerland) and Otsuka Pharmaceutical (Glattbrugg, Switzerland). He also received a travel grant, particapted and obtained a grant at speaker board of Lundbeck (Zurich, Switzerland).

## P6.5 Dose-corrected serum concentrations of antidepressant drugs in patients of a gerontopsychiatric day care unit – Dependence on renal function and multimorbidity?

**Authors** Sibylle Reber, Maike Scherf-Clavel, Jürgen Deckert, Stefan Unterecker, Alexandra S Herr
**Institute** Department of Psychiatry, Psychosomatics and Psychotherapy, University of Wuerzburg, Würzburg, Germany

**Introduction** The geriatric patient is prone to develop chronic diseases. Mental disorders, especially the geriatric depression is challenging considering the diagnostic process as well as the treatment because of the age-related changes in pharmacokinetics and pharmacodynamics. The present study aimed to examine the effect of multimorbidity (≥ 5 somatic diseases), respectively chronic kidney disease, on the dose-corrected serum concentration of antidepressants in geriatric patients.

**Methods** In this retrospective, naturalistic study the data of 153 patients, predominantly diagnosed with affective disorders, of a psychogeriatric day-care unit, with an antidepressant pharmacotherapy with mirtazapine (n = 76), venlafaxine (n = 47), escitalopram (n = 22) and sertraline (n = 22) from September 2014 to June 2016 were included. Multimorbid patients were compared to non- multimorbid patients regarding dose-corrected serum concentration by Mann-Whitney-U tests. Spearman's Rho correlation was used to evaluate the

association between renal impairment (GFR) and dose-corrected serum concentration.

**Results** The dose-corrected serum concentration of the active moiety of venlafaxine was significantly higher in multimorbid patients (Mann-Whitney-U test; p = 0.027), whereas it was not in patients treated with mirtazapine. Patients with decreasing renal function showed significant higher dose- corrected serum concentrations of venlafaxine (r = -0,535, p < 0.001) as well as the active moiety of venlafaxine (r = -0,334, p = 0.023) and sertraline (r = -0,553, p = 0.015). Renal function impairment had no significant influence on the serum concentration of mirtazapine and escitalopram.

**Conclusion** Multimorbidity is associated with higher dose-corrected serum concentrations in patients treated with venlafaxine and renal function impairment is associated with higher dose-corrected serum concentrations in patients treated with venlafaxine as well as in those treated with sertraline. Therefore, the therapeutic references range for multimorbid, geriatric patients should be re-evaluated in larger studies, especially with longitudinal study designs.

**Conflict of interest** None

## P6.6    Comparative study of suggested reference values and observed distributions in daily routine of a medical laboratory

**Authors** Xenia Hart[1], Gerhard Gründer[1], Gabriela Zurek[2], Andreas Sputtek[2]
**Institutes** 1 Department of Molecular Imaging, Central Institute of Mental Health, Mannheim, Germany; 2 MVZ Medizinisches Labor Bremen GmbH, Bremen, Germany

**Introduction** The Consensus Guidelines of the TDM-AGNP working group contains a comprehensive list of therapeutic reference ranges, often derived from clinical trials with strict predefined inclusion criteria [1]. The goal of this study is to analyze whether these ranges are reflected in routine patient care using samples from a medical laboratory.

**Methods** The drugs analyzed include aripiprazole (N = 9,640), olanzapine (N = 6,074), venlafaxine (N = 6,291) plus desmethylvenlafaxine (N = 3,512), and lithium (N = 9,640). Anonymized data was extracted from the routine archive, plotted as frequency histograms and data distributions were fitted. The observed distribution was compared with the published reference ranges.

**Results** Aripiprazole, olanzapine, and venlafaxine blood levels followed a lognormal distribution, whereas lithium blood levels were best described by a loglogistic curve. Frequency of samples in relation to current reference ranges varied widely across the four substances: 19.7-25.8 % of values were lying below and 1.8-14.6 % of values above the current ranges.

**Conclusion** Interquartile ranges of all substances were located within the lower-left of the current reference ranges. Of note, the lower quartiles (25th) for lithium, aripiprazole, and olanzapine corresponded well with the lower values of the published reference ranges.

**Conflict of interest** None

## P6.7    Positive association between norfluoxetine serum concentration and prolonged QTc intervals in children and adolescents

**Authors** Wiebke Warrings, Karin Egberts, Regina Taurines, Julia Geissler, Marcel Romanos, Stefanie Fekete
**Institute** Department of Child and Adolescents Psychiatry, Psychosomatics and Psychotherapy, University of Wuerzburg, Wuerzburg, Germany

**Introduction** Fluoxetine is frequently used to treat depression and other psychiatric disorders in children and adolescents. However, fluoxetine has known cardiac side effects such as QTc prolongation. This retrospective study is the first to examine the association between the daily dose, serum concentrations of fluoxetine and of its active metabolite, norfluoxetine, with the QTc interval in minors.

**Methods** TDM routine data and electrocardiogram (ECG) with focus on the ECG based corrected QT intervals (QTc; calculated with Bazett's and Fidericia's formula) were retrospectively extracted and analyzed from patient files from 2016 to 2019 in the Department of Child and Adolescent Psychiatry at the University Hospital Würzburg.

**Results** 130 patients (70 % female, mean (SD) age 14.8 ($\pm$ 1.6) years) were included. Seven patients (5.4 %) displayed QTc prolongation (> 450msec). Norfluoxetine concentrations correlated positively with QTc duration (Bazett: r = 0.18, p = 0.02; Fidericia: r = 0.13, p = 0.07), whereas fluoxetine dose (Bazett: r = 0.04, p = 0.34; Fidericia: r = 0.04, p = 0.32) and fluoxetine concentrations (Bazett: r = 0.06, p = 0.26; Fidericia: r = 0.06; p = 0.27) did not. No severe cardiac adverse drug reactions e.g. Torsade de Pointes (TdP), cardiac arrhythmia, were observed.

**Conclusion** This study supports evidence on the safety of fluoxetine in children and adolescents with regard to cardiac adverse effects. However, due to the potential influence of norfluoxetine serum concentrations on QTc and the potential risk of serious ADRs, in addition to ECG surveillance also TDM is recommended. Determination of the metabolizer phenotype of fluoxetine to norfluoxetine could further enhance the safety of fluoxetine treatment for children and adolescents.

**Conflict of interest** None

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