are absent in later stages of the disease for both treatment-resistant and treatment-responsive patients. It is likely that neurodegenerative processes resulting from excitotoxicity due glutamatergic dysfunction are most impactful within the first few months from illness onset. Our data point to the urgent need to identify reliable biomarkers for the prediction of antipsychotic treatment-response and the development of novel interventions to address glutamatergic perturbations at the beginning of their illness.

**O7. Oral Session: Pharmacology**

**O7.1. MIDBRAIN DOPAMINE NEURON ACTIVITY CONTROLS THE EFFECTS OF REPEATED KETAMINE ON STRIATAL DOPAMINERGIC FUNCTION**

Michelle Kokkinou1, Oliver Howes2
1Medical Research Council, London Institute of Medical Sciences; 2Medical Research Council, London Institute of Medical Sciences; King’s College London

**Background:** Schizophrenia is a chronic debilitating disorder which affects about 21 million people worldwide (WHO 2017). Elevated pre-synaptic striatal dopamine synthesis capacity is a robust neurochemical alteration seen in patients with schizophrenia compared to controls, with a large effect size Cohen’s d=0.79 (Howes et al., 2012). Ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist induces psychotic-like symptoms in healthy human (Krystal et al., 1994, Stone et al., 2007) and exacerbates psychotic symptoms in patients with schizophrenia (Lahti et al., 1991). For these reasons, it has been used to model the neurochemical alterations seen in schizophrenia such as dopaminergic overactivity (Usun et al., 2013, Kokkinou et al., 2017). However, the effect of sub-chronic ketamine on dopamine synthesis capacity in vivo is not known. Here we investigated the effect of sub-chronic ketamine on striatal dopamine synthesis capacity in vivo using Positron Emission Tomography (PET) imaging and on locomotor activity in the mouse. Moreover, via a chemogenetics approach (Roth 2016) we explored the role of midbrain dopamine neuron activity in mediating ketamine-induced effects.

**Methods:** All procedures were conducted under licence in accordance with the UK Animals (Scientific Procedures) Act of 1986. Mice received a sub-anaesthetic dose of ketamine or an equivalent volume of saline for five consecutive days. Locomotor activity was assessed in the open field test. Moreover, mice received a dynamic 3,4-dihydroxy-6-[(18F]-fluoro-L-phenylalanine Positron Emission Tomography (PET) scan to assess striatal dopamine synthesis capacity in vivo. Data were analysed using an extended Patlak graphical analysis approach (Walker et al., 2013). Further midbrain dopamine neurons were transduced with an adenovirus-associated virus vector expressing Gi-coupled (hM4Di) inhibitory receptors under the control of the dopamine transporter (DAT) promoter in DATCre positive mice. Standard immunohistochemistry was used to label dopamine neurons and mCherry expression in dopamine neurons was confirmed using confocal microscopy. Two weeks following the stereotaxic injection of the viral construct, mice received clozapine N-oxide (CNO) to study the effects of inhibiting dopamine neuron firing on locomotor activity and striatal dopamine synthesis capacity in the sub-chronic ketamine model. Data were analysed by two-tailed independent samples t-tests, one-way ANOVA and repeated measures two-way ANOVA followed by Bonferroni post hoc tests where appropriate. p<0.05 was considered statistically significant.

**Results:** Sub-chronic ketamine treatment significantly increased striatal dopamine synthesis capacity (p<0.05, effect size=1.2) and induced locomotor sensitization (p=0.01). hM4Di-mCherry viral construct was successfully transduced in midbrain dopamine neurons with over 98% specificity. Chemogenetic inhibition of midbrain dopamine neurons prevented the ketamine-induced elevation in striatal dopamine synthesis capacity (p=0.05, effect size= 0.64) and locomotor sensitization (p<0.05).

**Discussion:** Our data show that sub-chronic ketamine results in the elevation in striatal dopamine synthesis capacity and locomotor sensitization and that these effects require midbrain dopamine neuron activation. Furthermore, our data are in support of the hypothesis that NMDA receptor hypofunction on GABAAergic interneurons leads to disinhibition of glutamatergic projections and subsequently increase in dopamine neuron activity and dopamine synthesis capacity in projection targets such as the striatum.

**O7.2. BREAKTHROUGH ON ANTIPSYCHOTIC MAINTENANCE MEDICATION IN A CLINICAL COHORT**

Jose Rubio1, Christoph Correll2, Anil Malhotra2, Majnu John2, John Kane1
1Northwell Health; 2Zucker Hillside Hospital

**Background:** Antipsychotic drugs are effective in reducing the severity of psychotic symptoms both in the short and long term, and in reducing risk of relapse. However, some patients may develop a relapse of their psychotic symptoms despite continued antipsychotic treatment. Arguably, this phenomenon would be best studied in patients treated with long-acting injectable (LAI) formulations, where the dates of exposure can be confirmed, removing the potential confounder of non-adherence. The characterization of this phenomenon can add important knowledge about the intrinsic efficacy of antipsychotic drugs, potential mechanisms involved in the decrease of their efficacy, and the underlying pathophysiology of psychosis that is not modulated via primarily dopaminergic mechanisms. Despite the implications of this clinical phenomenon, research on breakthrough on antipsychotic maintenance medication (BAMM) in models not confounded by non-adherence has been limited. To date, little is known about the incidence and predictors of BAMM in clinical populations.

**Methods:** We extracted data from a cohort of individuals with a psychotic disorder who were initiated on their first LAI treatment between 2010 and 2015 in the injection clinic at The Zucker Hillside Hospital (New York, USA). We defined BAMM as hospitalization during the period of continuous treatment with LAI, which we used as the primary outcome. LAI treatment was considered continuous for each treatment episode if it was administered following the manufacturer’s recommendations for the first 2 months, and until there was a delay in the administration that would have required additional oral supplementation according to the manufacturer instructions (typically >1.5 times the scheduled interval of administration).

We measured the cumulative incidence and time to BAMM in individuals with continuous LAI administration, and conducted univariate and multivariate analyses of covariates.

**Results:** A total of 291 episodes of continuous treatment were observed. Of those, 44 (15.1%) led to hospitalization despite continuous treatment with a LAI antipsychotic. The median time to hospitalization was 204.5 days. In the multivariate analysis, the number of hospitalizations prior to onset of LAI treatment (5 vs 2, OR=2.75; 95%CI=1.60–4.72) and time since last hospitalization (4 vs 24.8 weeks, OR 0.70; 95%CI=0.53–0.91) were significantly associated with greater odds of hospitalization during continuous antipsychotic treatment. Individuals who were hospitalized despite continuous treatment were more likely to subsequently be treated with clozapine or ECT (18.2% vs 0, OR=4.93; 95%CI=1.25–19.40). We conducted a multivariate Cox regression analysis for time to hospitalization and a sensitivity analysis comparing BAMM with individuals that completed 2 years of continuous treatment without being hospitalized and the results were consistent.

**Discussion:** In a clinical cohort, a meaningful proportion of patients with a psychotic disorder treated with LAIs were hospitalized, despite confirmed continuous treatment. The median time to this event occurred about 7 months after onset of LAI treatment, suggesting that these patients had been stable and had reached steady state antipsychotic levels prior to hospitalization. Patients with a more active illness at the time of initiation of LAI treatment were more likely to relapse. These data suggest that more
comprehensive investigation of Bamm is feasible; and therefore research focused on this unique group of individuals may provide novel insights into the pathophysiology of psychosis and into the mechanism of action of antipsychotic drugs.

O7.3. DOSE-RESPONSE META-ANALYSIS TO IDENTIFY THE OPTIMUM AND EQUIVALENT DOSES OF ANTIPSYCHOTIC DRUGS FOR SCHIZOPHRENIA

Stefan Leucht*1, Alessio Crippa2, Nicola Orsini3, John Davis1
1Technical University of Munich; 2Karolinska Institutet; 3University of Illinois at Chicago

Background: It is important to better understand the optimum doses and equivalent doses of antipsychotic drugs. Several methods to understand these relationships have been published, but all these methods have weaknesses. In this paper we present a dose-response meta-analysis which theoretically is the most appropriate method for this purpose.

Methods: We identified all double-blind, placebo-controlled, studies that compared at least two fixed doses of second-generation antipsychotic drugs or haloperidol in people with acute schizophrenia or with predominant negative symptoms. For this purpose, we searched multiple electronic databases, the website of the FDA, and the clinical trial database clinicaltrials.gov. The method applied was dose response meta-analyses with a spline model. The outcome was the reduction of the PANSS or BPRS total score from baseline or for negative symptoms - a negative symptom scale. With this method we identified 95% effective doses (these have also been called “near-to-maximum” doses). We applied linear splines to examine whether the dose-response curves had already reached a plateau. Moreover, the identified dose-response relationships of each drug were used to derive risperidone equivalent doses.

Results: We identified 67 randomized-controlled trials that were eligible. The following 1mg risperidone equivalent doses were identified: amisulpride 86.6mg/day, aripiprazole 1.9mg/day, asenapine 2.4mg, brexpiprazole 0.56mg clozapine 91mg, haloperidol 1.01mg, iloperidone 3.2mg, lurasidone 23.5mg, olanzapine 2.4mg, paliperidone 13.4mg, quetiapine 77mg, risperidone 1mg, sertindole 3.6mg, ziprasidone 30mg.

Discussion: From a conceptual point of view, dose-response meta-analysis is the most appropriate method to identify maximally effective doses and equivalent doses. The results of this meta-analysis will be compared with other published methods to define dose-response, in particular the minimum-effect dose method, the classical mean dose method, the daily-defined-doses (DDD) method and expert consensus methods. The results of this analysis are likely to provide information with impact for treatment decisions.

O7.4. SYSTEMATIC REVIEW, META-ANALYSIS AND META-REGRESSION OF PREDICTORS OF PLACEBO RESPONSE IN ACUTE SCHIZOPHRENIA

Claudia Leuchtm,1 Anna Chaimani2, Stefan Leucht1
1Technical University of Munich; 2Paris Descartes University

Background: The drug-placebo differences (“effect sizes”) in acute phase, randomised, double-blind trials have become smaller and smaller over the decades. In a recent meta-regression analysis, it had been shown that the degree of placebo response is the strongest predictor of drug-placebo differences. Thus, the open question now was what the predictors of placebo response are.

Methods: Placebo-controlled, randomised, double-blind trials that compared any licensed antipsychotic drug with placebo were searched in multiple electronic databases, the website of the Food and Drug Administration and the clinical trial database ClinicalTrials.gov. The mean change from baseline of the PANSS or the BPRS total score from baseline to endpoint in the placebo-groups was extracted from each identified trial. The outcome was the degree of placebo response measured by the BPRS or PANSS change from baseline to endpoint. 24 patient-, and study design related parameters were analysed as potential predictors of placebo response in univariate and multivariate meta-regression analyses.

Results: Of 167 included RCTs 99 provided the necessary data. In univariate analyses more recent publication year, larger sample size (total number of participants and sites), use of PANSS rather than the BPRS, studies conducted outside the US or mixed, shorter wash-out phases and shorter study duration, lower participant mean age and lower mean duration of illness were associated with higher placebo-response.

Discussion: This meta-regression included approximately two times more studies than previous attempts to solve this issue and it is therefore the to date by far largest analysis of this kind. Multiple potential moderators of placebo response were identified. Importantly, these moderators of placebo response were not identical with those identified in a previous analysis as significant moderators of drug-placebo differences in the same dataset. Thus, different factors appear to play a role in this complex area.

References:
1. Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, Samara M, Rabaiali M, Bächer S, Cipriani A, Geddes JR, Salanti G, Davis JM. Sixty Years of Placebo-Controlled Antipsychotic Drug Trials in Acute Schizophrenia: SystematicReview, Bayesian Meta-Analysis, and Meta-Regression of Efficacy Predictors. Am J Psychiatry. 2017;174(10):927–942.

O7.5. LONG-TERM SAFETY AND TOLERABILITY OF BREXIPRAZOLE IN PATIENTS WITH SCHIZOPHRENIA

Mika Hakala*1, Mette Gislum1, Aleksandar Skuban1, Stine Meehan1
1H. Lundbeck A/S; 2Otsuka Pharmaceutical Development & Commercialization, Inc.

Background: Long-term maintenance treatment is recommended to control the symptoms of schizophrenia; therefore, safety monitoring for longer than the period required to treat an acute exacerbation is warranted. The aim of the present study (Lighthouse extension; NCT01810783) was to assess the long-term safety and tolerability of open-label treatment with brexiprazole (flexible dose 1–4 mg/day) in adult patients with schizophrenia. Brexiprazole is a serotonin-dopamine activity modulator that acts as a partial agonist at the serotoninin-5-HT1A and dopamine D2 receptors, and as an antagonist at the 5-HT2A and noradrenaline α1B/2C receptors, all with subnanomolar potency. Brexiprazole is approved in the US as adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and in the US, Australia and Canada as monotherapy for treatment of schizophrenia.

Methods: Patients rolled over into this 52-week open-label study from a randomized, double-blind, placebo-controlled, active referenced, Phase 3 study (Lighthouse; NCT01810380). The primary endpoint was safety and tolerability. Efficacy was assessed as an exploratory endpoint using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions – Severity of illness (CGI-S) and Improvement (CGI-I) scales, and the Personal and Social Performance (PSP) scale. Changes from baseline were analyzed using a mixed model repeated measurements (MMRM) approach.

Results: 210 patients were enrolled, and 101 (48.3%) completed the study. The mean and mean modal doses of brexiprazole were 3.07mg/day and 3.10mg/day, respectively; at last visit, 50% of the patients received 4mg/day. Among patients who took ≥1 dose of brexiprazole, the incidence of discontinuation due to treatment-emergent adverse events (TEAEs) was 17.2%. TEAEs with an incidence of ≥5.0% were schizophrenia