(DA) neuron activity in the ventral tegmental area (VTA) in the methylazoxymethanol acetate (MAM) animal model of schizophrenia.

Methods: All experimental procedures were conducted according to NIH guidelines and were approved by University of Pittsburgh Institutional Animal Care and Use Committee. Sprague-Dawley pregnant dams were treated with MAM or saline on gestational day 17. Recordings of VTA dopamine neuron activity was performed on the male offspring at adulthood. The effects of four different drugs were evaluated: PNU282987 (full agonist), SSR180711 (partial agonist) NS1738 (type I positive allosteric modulator - PAM) and PNU120596 (PAM type II).

Results: Intravenous administration of alpha7 selective ligands did not induce a major change in the firing profile of spontaneously active DA neurons when dosed during dopamine neuron recording. PNU120596 increased in the number of active DA neurons found in the VTA of normal rats, their mean firing rate and percentage of spikes in bursts. In contrast, the full agonist PNU282987 and the partial agonist SSR180711 reduced the hyperdopaminergic tone in MAM rats, with a more prominent decrease in the number of DA neurons recorded in the lateral VTA. In order to investigate the drug site of action, both PNU282987 and SSR1800711 were infused into the ventral hippocampus (vHipp) and basolateral amygdala (BLA). After vHipp infusion, the alpha7 nAChR agonists significantly decreased the number of active DA neurons in MAM rats, with no significant impact in control rats. Once more, the effects were more robust in the lateral VTA. In contrast, the same drugs when infused directly into the BLA increased the number of spontaneously active DA neurons in the VTA of normal rats, but not in the MAM model.

Discussion: In summary, our results show that alpha7 nAChR positive modulators can affect midbrain dopaminergic neuronal activity in vivo in a state-dependent manner. Interestingly, alpha7 nAChR agonists counterbalanced the hyperdopaminergic state of MAM rats and this effect is partially mediated by their action in the vHipp. This effect is consistent with the potential use of alpha7 nAChR agonists for schizophrenia treatment and fits the current search for drugs able to control dopaminergic function acting in structures upstream from the dopamine receptor. The predominant inhibition of the lateral VTA points to a lower propensity to produce unwanted side effects in comparison to current employed antipsychotic agents. Our data show that drug effects can vary according to the basal level of activity of specific brain circuits and highlights the importance of using appropriated animal models to make inferences about potential therapeutic use of new neuropsychiatric drug candidates.

S234. ONE-YEAR OUTCOME AND USE OF CLOZAPINE IN FIRST-EPIsODE SCHIZOPHRENIA

Petros Drosos*1, Kolbjorn Bronnick2, Rune Kroken3, Inge Joa1, Jan Olav Johannessen3, Tor Ketil Larsen4
1Stavanger University Hospital; 2TIPS – Centre for Clinical Research in Psychosis, Stavanger University Hospital; 3Haukeland University Hospital, University of Bergen; 4University of Bergen

Background: The aim of this study is to examine the one-year outcome in a cohort of patients with a first-episode core schizophrenia diagnosis (schizophrenia, schizophreniform psychosis, schizoaffective disorder) and the use of clozapine in the non-remitted patients at one-year control.

Methods: The population studied is the patients who were included with a first-episode psychosis in the TIPS project in the period 01.01.2002-31.12.2010 and had a core schizophrenia diagnosis. We divided the patients into two groups according to their remission status at one-year follow up and compared their main characteristics. We then performed a digital search in the hospital’s journal of the non-remitted group for the words “clozapine” and “leponex”.

Results: Out of the 78 patients with first-episode core schizophrenia diagnosis included in the TIPS project during the examined period, 53 were continuously psychotic at one-year follow up. The one-year remission rate for our sample was therefore 32%. All of the non-remitted patients during the first year could be eligible for clozapine, but clozapine was considered to only 3 of them (5.7 %) and only two of them were offered clozapine. The mean number of periods with antipsychotic treatment in this group was four (4).

Discussion: The findings in our study show firstly a surprisingly low one-year remission rate for first-episode schizophrenia (32 %). This is much lower than what corresponding studies of the last years show. Our results also prove the underutilization of clozapine in non-remitted patients with a
first-episode core schizophrenia diagnosis. Therefore, the clinicians did not follow the recommended guidelines for the treatment of schizophrenia. The possible reasons for this low use of clozapine will be discussed, but it was not possible to verify them as there was not found any relevant information in the patients’ files.

S235. MAINTENANCE TREATMENT WITH ANTIPSYCHOTIC DRUGS IN SCHIZOPHRENIA – SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS
Johannes Schneider-Thoma*, 1, Stefan Leucht 1
1 Klinikum rechts der Isar, Technical University of Munich

Background: Antipsychotic drugs are the mainstay of the maintenance treatment of schizophrenia and they are known to prevent psychotic relapse as compared to placebo. Nevertheless, insufficient efficacy and reoccurrence of psychotic symptoms (relapse) are frequent phenomena. Furthermore, side effects of antipsychotic drugs can be very unpleasant and even dangerous, particularly, when drugs are applied over a long time. Nowadays, many different antipsychotic substances are available and they can be used in oral or long-acting-injectable applications. However, the comparative efficacy of the different drugs in preventing relapse as well as the efficacy in specific domains of the disease (such as positive and negative symptoms) over the long term is only know in parts. Also concerning side effects it is not clear for a lot of drugs which substance should be preferred over another. The novel method of network-meta-analysis provides the possibility to use indirect evidence to compare drugs for which no direct comparison is available. Moreover, hierarchies of drugs can be created with this method, that show which drug is the best, second best, and so on, for individual outcomes.

Methods: We are conducting a network-meta-analysis of randomized controlled trials (RCT) in patients with schizophrenia or schizoaffective disorder. To identify eligible studies, we searched the register of the Cochrane Schizophrenia group, the most comprehensive database of clinical trials in schizophrenia. RCTs comparing antipsychotic drugs with each other or placebo are included. We focus hereby on the clinically most important newer and older antipsychotic drugs – as identified by a survey of international schizophrenia experts. The primary outcome is patients with a psychotic relapse at any time. Relapse at specific time-points as well as several other efficacy and tolerability parameters will be evaluated as additional outcomes. We include only trials of at least 3 months in duration, conducted with patients in a stable state of the disorder. Special attention is paid to the question if populations of different studies are comparable. This is of particular importance for network-meta-analysis because this method is based on the assumption of transitivity, i.e. that each patient in the analysis would have been in principle eligible for each study in the network.

Results: All so called second-generation antipsychotic drugs as well as several first-generation antipsychotics (list provided on the poster) were identified as clinically important drugs. A systematic literature search including the generic names of these drugs as well as search terms for maintenance treatment and stable condition found 3562 references. Screening of title and abstracts resulted in 1188 references referring to potentially eligible studies. In the ongoing full-text-screening and cross-referencing process 136 included studies are identified so far (complete search results presented on the poster). More detailed assessments of study characteristics are warranted to decide which studies are eligible to be included in the network-meta-analysis, i.e. to fulfill the transitivity criteria from a clinical point of view.

Discussion: Studies examining antipsychotic drugs for maintenance treatment differ in inclusion criteria for participants, in criteria for stable condition and also in criteria for psychotic relapse. Therefore, some official maintenance studies may not be eligible for network-meta-analysis. However, other studies, focusing not on maintenance but on other outcomes, may fulfill the transitivity criteria. The resulting problems for conducting network-meta-analysis as well as the reasoning for inclusion and exclusion of studies will be discussed.

S236. IS MAINTENANCE TREATMENT NEEDED WHEN THE FIRST EPISODE OF PSYCHOSIS IS NOT DUE TO SCHIZOPHRENIA?
Gbolahan Odejayi* 1, Robert Zipursky† 1
† McMaster University

Background: Debate continues about how long maintenance treatment should be continued following a first episode of psychosis (FEP). Resolving this question requires an understanding of the risk of recurrence which would be expected to vary as a function of the underlying cause of the psychosis. The range of diagnoses that may present as a FEP include schizophrenia and related schizophrenia spectrum disorders, bipolar mania, bipolar and unipolar depression, substance-induced psychosis, and unspecified psychotic disorders. The majority of FEP patients will receive the diagnosis of schizophrenia or bipolar disorder for which the 1-year risk of illness recurrence is estimated at 77% and 41%, respectively. We reviewed the literature in order to estimate the risk of relapse and the risk of developing a primary psychotic disorder following a FEP due to other diagnoses.

Methods: We conducted a primary literature review using Medline and PubMed. We included the following search terms: first episode, relapse, recurrence, depression with psychosis, psychotic depression, mania with psychosis, substance induced psychosis and psychosis. We included prospective and retrospective studies including those that involved medication discontinuation or naturalistic follow-up to determine the risk of recurrence following a FEP. We also reviewed the literature to determine the likelihood that FEP with these diagnoses would transition to a primary psychotic disorder (schizophrenia spectrum disorder or major mood disorder) for which published rates of recurrence would apply.

Results: Two studies were identified which reported on the recurrence rate following a first episode of psychotic depression. Recurrence rates ranged from 27% at eight months to 80.6% at a mean of 32 months. An additional study found that following a first episode of psychotic depression, 29.9% and 14.3% of patients were diagnosed with schizophrenia and bipolar disorder, respectively, at 10-year follow-up. The risk of developing a primary psychotic disorder following a first episode of substance-induced psychosis has been investigated in three studies which reported rates of conversion to a primary psychotic disorder of 25% at one year, 25% at 10 years and 32% at 20 years. The risk of developing a primary psychotic disorder following a cannabis-induced psychosis has been investigated in three studies which reported rates of conversion of 44.5% at three years, 46% at eight years, and 47.4% at 20 years. Patients with a first episode of unspecified psychosis have been reported in a single study to have a 73.7% risk of developing a primary psychotic disorder at 10 year follow-up.

Discussion: The risk of illness recurrence following a FEP not initially diagnosed as a schizophrenia spectrum or bipolar disorder was found to vary by both initial diagnosis and by follow-up duration. Psychotic depression, substance-induced psychosis and other unspecified psychosis were all associated with either substantial risks of illness recurrence or development of a primary psychotic disorder. The risk of illness recurrence following medication discontinuation has not been established for these disorders as many of these studies included patients whether they were on or off of their prescribed medications. Clinical recommendation should be informed by future research on recurrence rates with and without maintenance medication for the different causes of FEP. In the meantime, patients with a FEP and their family members should be fully informed about the risk of illness recurrence and development of a primary psychotic disorder when considering any trial of medication discontinuation.