nicotinic and muscarinic receptors have been shown in animal models to contribute to restoring cognitive function in various rodent models of CIAS while excessive D₂ receptor blockade has a negative influence on cognition.

Data from recent GWAS studies will be presented which demonstrate that the efficacy of atypical APDs to improve psychosis in schizophrenia is mediated by gene products that affect synaptic structure and function, e.g. neurexin and other synaptic adhesion gene products.

The synaptic mechanisms that are required for normal reality testing, rewarded behavior, and higher cognitive function may be impaired by too much or too little stimulation of all five DA receptors, certainly not just D₂ receptors. The atypical APDs are better able to achieve optimal stimulation of these receptors through a variety of mechanisms, many of which are serotonergic. D₂ receptor blockade is not necessary but sometimes sufficient which has led to long standing overevaluation of its importance. The heterogeneity in response to APDs may be related to genetic variations which govern the various ways in which synapses can be made to work effectively.

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Speaker 2: Jeff Lieberman, USA
Title: Ten years after the “effectiveness” studies - What have we learned?

Speaker 3: Wolfgang Fleischhacker, Austria
Title: Future directions in antipsychotic drug development
Abstract
Four main topics have shaped research and clinical practice in the past decade. These have dealt with: 1) Early intervention in the prediagnostic stage, i.e. the Attenuated Psychosis Syndrome; 2) Novel neurobiological treatment targets; 3) The introduction of alternative formulations; 4) Attempts to predict treatment response.

1) In a number of RCTs, researchers have investigated whether treating prodromal symptoms of schizophrenia helps to reduce the conversion risk to full-blown schizophrenia. Results are ambiguous and the discussion on whether or not an intervention at the stage is justified is ongoing.
2) Following the enhanced understanding of the pathophysiology of schizophrenia, also with respect to specific symptom domains, pharmacological targets beyond D₂ receptor antagonism have been explored. Much work and enthusiasm has revolved around nicotinergic and glutamatergic compounds, so far with mostly discouraging results.
3) Several new generation antipsychotics have become available as long-acting depot formulations. All of them have demonstrated a significant positive impact on relapse rates in placebo controlled studies. Whether these compounds also have advantages over first generation depots and/or oral antipsychotics is still debated and investigated.

Lastly, attempts from various perspectives, including genetics and neuroimaging, have investigated whether it is possible to predict treatment response and drug safety. Although some look promising, they have not yet reached a stage in which they can be applied to everyday clinical practice. What has become clear, though, is, that early non response predicts late non response, leading to the recommendation to switch antipsychotics much earlier than stated in most treatment guidelines.
This presentation will focus on topics 2) and 3).

Speaker 4: Gerhard Gründner, Germany
Title: The antipsychotic drug deadlock – causes and solutions
Abstract
It has been a matter of debate for more than a decade whether second-generation antipsychotics (SGAs) represent an advantage over first generation compounds (FGAs). Especially the “effectiveness” studies (CATIE, CUtLASS, EUFEST) could not unequivocally confirm the superiority of SGAs over FGAs. It has been even questioned whether there was any progress in schizophrenia drug treatment since the introduction of clozapine. We have recently demonstrated in the multicentre, randomised, double-blind “Neuroleptic Strategy Study” (NeSSy; Gründner et al., 2016) that quality of life was statistically and clinically significantly more improved with SGAs compared to FGAs, when selection of the antipsychotic was individualised for each specific patient. SGAs might represent a significant advantage in terms of quality of life, as judged by patients. Based on ratings of psychopathology by clinicians, however, SGAs did not differ significantly from FGAs. The randomised, placebo-controlled trial in parallel groups is considered the gold standard for the evaluation of novel pharmaceuticals (Stroup et al., 2006), although this trial design does not take into account the marked patient heterogeneity characterizing schizophrenia nor the profound disparity in the pharmacological profile of antipsychotics. We suggest that novel study-designs are needed to take into account marked patient heterogeneity and to allow for establishing individual clinical drug profiles (Schulz et al., 2016). In addition, current clinical endpoints completely ignore the patient perspective (social function, quality of life, subjective well-being), and they are usually obtained in short-term studies, which neglect long-term outcomes. The recent discussion about the potential negative effects of long-term antipsychotic treatment on brain structure and the finding that patients with less antipsychotic exposure might have better outcomes urge for the development of new study designs with very long observation periods and new patient-oriented outcomes. These new protocols have