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 psychopathology 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 overvaluation 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
to be developed in close collaboration of academia, regulatory agencies and industry.

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Schulz C, Timm J, Cordes J, Gründer J, Mühlbauer B, Rüther E, Heinze M (2016) Patient-oriented randomisation: a new trial design applied in the NeSSy study. ClinTrials (in press)

S18: Recent Advances in Drug Dependence Genetics – Legal and Illegal

Chair: Joel Gelernter, USA
Co-Chair: Yeon Ho Joo, Republic of Korea

Speaker 1: Chih-Ken Chen, Taiwan
Title: Genetics of methamphetamine abuse and methamphetamine-induced psychosis
Abstract
Genetic studies on METH abuse and METH psychosis are influential in the fields of comorbidity of substance abuse, etiological models of schizophrenia, and the nosology of prolonged or chronic substance-induced psychosis. Most data of genetic markers associated with METH abuse or METH psychosis derived from Asian samples. Previous studies on Meth abuse and Meth psychosis have identified many potential genetic markers. However, most of the genetic associations are not replicated. Among few replicated genetic associations, BDNF rs6465 is concluded to be associated with METH dependence, whereas SOD2 gene is associated with METH psychosis. A genome-wide association studies (GWAS) of independent pooled DNA samples of METH users from Taiwan and Japan show that variants in the "METH dependence" genes are likely to alter cell adhesion, enzymatic functions, transcription, cell structure, as well as DNA, RNA, and/or protein handling or modification. The GWAS findings from individual DNA samples suggest shared genetic risk between Meth psychosis and schizophrenia.

Speaker 2: Kazutaka Ikeda, Japan
Genetic polymorphisms commonly associated with sensitivity to addictive substances
Kazutaka Ikeda1, Daisuke Nishizawa1, Ken-ichi Fukuda1,2, Masakazu Hayashida1,3, Susumu Higuchi1,4, Haruhiko Sugimura5, Ichiro Sora1,6,7
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Abstract
Sensitivity to addictive substance is well known to vary widely among individual subjects, which hampers effective prevention and treatment of addiction. Many genetic and environmental factors are involved in sensitivity to addictive substances including opioids, methamphetamine, alcohol, and nicotine. Interestingly, we recently found that several single nucleotide polymorphisms (SNPs) which are associated with sensitivity to an addictive substance are also associated with sensitivity to other addictive substances.

Firstly, we found that the rs2952768 SNP neighboring the CREB1 gene was strongly associated with the requirements for postoperative opioid analgesics after painful cosmetic surgery in a genome wide association study (GWAS), and consistent results were obtained in patients who underwent abdominal surgery. The SNP was also associated with vulnerability to severe drug dependence in patients with methamphetamine (METH) dependence, alcohol dependence, and eating disorders and a lower "Reward Dependence" score on a personality questionnaire in healthy subjects. These results demonstrate that the SNP affects both the efficacy of opioid analgesics and liability to severe substance dependence.

Secondly, we found that the nonsynonymous rs2653349 SNP (located on the gene that encodes orexin [hypocretin] receptor 2; Val308Ile) was associated with the Fagerström Test for Nicotine Dependence (FTND) score in a GWAS. This SNP was also associated with the initiation of METH use in patients with METH dependence.

Thirdly, we found that the rs2835859 SNP (located on gene that encodes G-protein-activated inwardly rectifying potassium (GIRK) channel 2 subunit) was associated with opioid analgesic sensitivity and the result was corroborated in further confirmatory study. Moreover, this SNP was also associated with susceptibility to nicotine dependence and successful smoking cessation. The results indicate that this SNP in the GIRK2 (KCNJ6) gene could serve as a marker that predicts sensitivity to analgesic and susceptibility to nicotine dependence.

These SNPs commonly associated with sensitivity to addictive substances suggest common mechanisms among vulnerabilities to addiction due to different addictive substances. Our findings may provide valuable information for the personalized prevention and treatment of addiction.

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