Background: Fast-spiking, parvalbumin-positive GABAergic interneurons in corticolimbic circuits modulate the synchronous firing of pyramidal neurons to enhance gamma-frequency oscillations which are thought to underpin cognitive function. Increasing evidence from post-mortem studies and animal models suggest that reduced activity of this class of interneuron may contribute to schizophrenia. Kv3 potassium channels are specifically expressed on PV interneurons and contribute to the rapid firing and transmitter release that is required to synchronize cortical networks. We have shown that positive modulation of Kv3 channels with a novel drug, AUT00206 can enhance the activity of PV interneurons and rescue cognitive function in animal models. Clinical evaluation of the potential of AUT00206 to treat schizophrenia includes assessment of the ability of the drug to modulate relevant neural circuitry and neurocognitive function, first in healthy volunteers (Phase 1a), and subsequently in patients (Phase 1b).

Methods: The phase 1a clinical trial evaluated safety, tolerability and the pharmacokinetics of AUT00206 versus placebo in healthy male subjects aged between 18–45 years. Potential effect of the drug on cognitive performance was also evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB) and potential effect on neural circuitry was assessed from measurement of auditory-evoked potentials, including the mismatch negativity (MMN) response. A phase 1b proof of principal study is currently underway to establish whether AUT00206 administered for 28 days to patients within 5 years of a schizophrenia diagnosis can positively impact a relevant biomarker of the disease. Twenty-four patients (aged 18–50 years) with clinically and medically stable schizophrenia are being enrolled to receive either AUT00206 (16 subjects) or matching placebo (8 subjects). The primary objective is to assess the pharmacokinetics, safety and tolerability of the compound with secondary outcome assessing the effect of AUT00206 on MMN, with an exploratory endpoint of CANTAB at baseline and after drug treatment.

Results: The phase 1a results support the cognitive safety of AUT00206 in healthy male volunteers across all cognitive domains known to be impaired in patients with schizophrenia and show preliminary evidence for a potential positive effect of AUT00206 800mg BID on sustained attention (CANTAB RVP; Rapid Visual Information Processing task). We also identified a possible effect of AUT00206 on reduction in latency of frequency deviant MMN. An interim blinded review of baseline data for the on-going phase 1b trial (N=14/24 schizophrenia patients) suggests a range of cognitive performance in patients at baseline, with MMN data at baseline in the phase 1b trial in line with expectation for patients with schizophrenia.

Conclusions: Phase 1a study results support the cognitive safety, and potential efficacy, of AUT00206, a potent and selective modulator of Kv3.1 and Kv3.2 voltage-gated potassium channels in healthy volunteers using schizophrenia-relevant cognitive tests. The intermix analysis of the phase 1b CANTAB data, an exploratory endpoint, in about 2/3 of the intended sample support previous findings that patients with schizophrenia are heterogeneous. In light of this finding, we will explore the data for correlations between baseline cognitive performance and treatment outcome.

33. SIRS ETHICS COMMITTEE SYMPOSIUM: PREVENTION OF PSYCHOSIS: WHEN AND HOW? THE ETHICAL PERSPECTIVE

Steve Marder
Semel Institute for Neuroscience

The Ethics Committee is proposing a special symposium at the SIRS meetings that will focus on ethical challenges in early intervention research. Each of the presentations will address the challenges inherent in trying to prevent an illness when there is uncertainty as to the individual's true risk. Talks by Drs. Weiser, McGorry, and Perkins will discuss prevention in individuals who fulfill criteria for the at risk or prodromal state. The issue has been discussed in the past and was the subject of a special issue of Schizophrenia Research in 2001. Dr. McGorry will discuss how data from nearly two decades has shaped this area and suggested modifications of prior guidance. Dr. Weiser will discuss the importance of improving our ability to identify individuals who are truly at risk for developing schizophrenia. Dr. Perkins will discuss the relative effectiveness and risk of pharmacological and psychosocial interventions for prodromal symptoms and the ethical issues in selecting interventions. The session will also address challenges in studies of primary prevention. Dr. Freedman will discuss recent studies of a prenatal strategy for preventing schizophrenia and the ethical challenges faced in the design of perinatal interventions. Dr. Carpenter will discuss each of the presentations and will highlight the state of the field.

33.1 ETHICAL ISSUES IN EARLY INTERVENTION

Patrick McGorry1, Barnaby Nelson2, Alison Yung*1
1Orygen Youth Health Research Centre; 2Orygen, The National Centre of Excellence in Youth Mental Health

Background: A number of ethical issues arise in relation to medical research and to the early diagnosis of potentially serious illnesses in medicine. While these apply in a similar way in psychiatry, additional issues have been raised by an ethicist and some critics. These related to stigma and a lack of consensus regarding the nature and course of mental disorders. When the early intervention field was gaining momentum in the late 1990s, these issues were examined in depth. Since then the evidence base has grown, the stance of critics altered and an expansion to a transdiagnostic perspective and a youth mental health paradigm indicate that another look at the issues is warranted.

Methods: Historical review and analysis.

Results: The same considerations as apply to research and treatment in mainstream medicine apply to psychosis, and mental disorders. Potential additional considerations that might increase harm can be addressed through reform of cultures of care, user participation plus advocacy and education targeted at discrimination and stigma.

Conclusions: Ethical issues are crucial in influencing the conduct of research and clinical care.

33.2 EARLY INTERVENTION FOR SCHIZOPHREНИA: THE RISK-BENEFIT RATIO OF ANTIPSYCHOTIC TREATMENT IN THE PRODROMAL PHASE

Mark Weiser*1
1Sheba Medical Center at Tel Hashomer

Background: In schizophrenia, once psychosis and negative symptoms have manifested, most patients will suffer from persistent illness and declining social and vocational functioning; hence prevention has been contemplated for many years. In the early 1990s, the perception that second-generation antipsychotics improved the risk-benefit ratio of antipsychotic treatment was the impetus for investigators to attempt to treat the illness before the appearance of full-blown psychosis.

Methods: In order to identify these future patients, diagnostic criteria for this prodromal phase of the illness were developed, and initial results indicated that 40% of patients who met these criteria transitioned to full-blown psychosis within a year. However, as time went by the rates of transition from prodrome to schizophrenia dropped and are currently under 10% after one year. The reasons for this are unknown and might include publicity and increased awareness leading to earlier referrals, and increased exposure of putative prodromal patients to pharmacological and psychosocial interventions. These data are further confounded by the finding that that attenuated psychotic symptoms are quite frequent in the nontreatment-seeking general population, and about 10% of persons in the community endorse having attenuated, but generally transient positive symptoms, and a person with attenuated...