

MEETING REPORT

CURRENT AND FUTURE PERSPECTIVES IN PSYCHIATRIC DRUG DISCOVERY

by Wendy Alderton, Eric Karran and Simon Ward

COGNITIVE ENHANCEMENT IN SCHIZOPHRENIA, DEPRESSION AND ADDICTION: PROSPECTS AND PITFALLS

Professor Trevor Robbins (Cambridge University, U.K.) gave the opening lecture of the meeting and set the scene for the current level of understanding in the field of cognitive enhancement, in particular highlighting opportunities for the future.¹ The importance of identifying agents to improve cognition was reinforced by a list of the disease states for which cognitive impairment is a key feature: Alzheimer's disease, Lewy body disease, fronto-temporal dementia, age-related cognitive impairment, Huntington's and Parkinson's diseases, acute brain injury, stroke, etc., schizophrenia, depression and bipolar disorder, posttraumatic stress disorder, sequelae of drug abuse, Korsakoff's psychosis, attention deficit hyperactivity disorder, phenylketonuria, autism, etc., anxiety states and obsessive-compulsive disorder. Prof. Robbins asserted that we would certainly see the emergence of new cognition enhancers over the coming years, while emphasizing the complexity of the underlying neurobiology and differences in pathways to the diseases listed above.

The translational relevance of preclinical models of cognition was questioned, and to improve on the clinical relevance, a number of techniques (e.g., functional magnetic resonance imaging, positron-emission tomography, voltammetry) were discussed which can be used to profile directly in humans and then back translate to learn what we should be modeling in animals. Furthermore, a number of these techniques give us

more precise information of the relevant brain regions involved.

One model was highlighted as an example of this process. The Visuo-spatial Paired Associates Learning (PAL) model in man has been shown to be sensitive to pro-dromal Alzheimer's disease, and has successfully been back-translated to the rodent using a touch screen method for cognitive testing of mice and rats which uses the same types of stimulus materials used in human subjects (objects and locations on a computer screen), and the same types of responses (responses directly to the stimuli on the screen).

Prof. Robbins also stressed the key nature of the cognitive impairment in schizophrenia and indicated its importance was recognized widely, citing the NIMH-MATRICES (National Institute of Mental Health Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative as proof. This project is focused on the seven domains of disturbed cognitive function (speed of processing; attention/vigilance; working memory; verbal learning and memory; visual learning and memory; reasoning and problem solving; and social cognition).

Ritalin (methylphenidate hydrochloride) was used as an example of medication which can lead to mixed benefit—increasing self-ordered spatial working memory and increasing efficiency of the dorso-lateral prefrontal cortical network² but impairing performance on an easy "Tower of London" task in practiced subjects.³ The effects of *Ritalin*, as well as modafinil, in models of extra-dimensional set shifting were also discussed^{4,5} as well as the potential for use of modafinil in medication for cocaine depend-

Highlights from the Society for Medicines Research Symposium, held March 12, 2009, at GlaxoSmithKline, Harlow, U.K.

SUMMARY

On March 12, 2009, the Society for Medicines Research held a 1-day meeting entitled Current and Future Perspectives in Psychiatric Drug Discovery at GlaxoSmithKline, Harlow, U.K. The meeting, organized by Wendy Alderton, Eric Karran and Simon Ward, brought together experts from industry and academia to review the current challenges in the treatment of depression, schizophrenia and addiction. Recent advances in the development of novel agents for the treatment of these diseases were also presented.

ence following some encouraging early clinical data.⁶

Prof. Robbins also highlighted the exciting potential of adenosine monophosphate acid (AMPA) receptor-positive allosteric modulators, and in particular data for CX-717 which showed that it potently enhances short-term memory and attention (matching-to-sample) performance in rhesus monkeys (and increases regional metabolism in the frontal and temporal lobes⁷) and has some initial positive clinical signals.

Prof. Robbins asserted that, in the future it was likely that therapeutics would need to be targeted carefully to the particular cognitive domains that were affected by the disease process, as it was likely that improvements in some cognitive domains may come at the expense of decrements in others.

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COGNITION IN ANIMALS: MEASUREMENT AND APPLICATION TO NEUROSCIENCE DRUG DISCOVERY FOR SCHIZOPHRENIA

Dr. Mark Tricklebank (Lilly, U.K.) described Lilly's strategy to develop approaches to address the cognitive impairments associated with schizophrenia. Prediction of efficacy against the cognitive symptoms of schizophrenia requires development of translational assays of cognitive processes and ways of impairing those cognitive processes in clinically relevant models. Lilly has developed a battery of rodent behavioral tests to model three of the cognitive domains as follows:

- Attention and speed of processing: 5 choice serial reaction test, psychomotor vigilance task;
- Executive function: reversal learning, stop signal reaction time and set shift tests;
- Learning and memory: object preference, Y maze, paired associative learning.

The delayed matching to position and Quad Cog test (discrimination learning, reversal, extinction and consolidation) are applicable across all domains. Before the undertaking of the tests above, a dose is selected where no motor impairment is observed based on the results in sleep EEG architecture, motor activity and a VI30 (variable interval operant responding) tests.

The methods for achieving perturbation of the normal state to model schizophrenia in rodents were reviewed and included the acute or chronic dosing of amphetamine or *N*-methyl-D-aspartate (NMDA) antagonists, environmental conditions such as social isolation, neurodevelopmental models such as neonatal hippocampal ablation, and transgenic models. The speaker illustrated that NMDA antagonists are not behaviorally equivalent, possibly due to subtype specificity for NR2A versus NR2B, by comparing the differing and contrasting profiles of a range of NMDA antagonists in cognitive tests. It was suggested that chronic phenylcyclydine (PCP) dosing may give more selective cognitive impairment, but the relevance of this to the effects of ketamine in humans was questioned. MAM E17 was highlighted as a promising new model of schizophrenia.⁸ This neonatal development model, in which rat brain cellular proliferation is inter-

rupted with methylazoxymethanol during late gestation at embryonic day 17, gives similar anatomical changes to those described in schizophrenic patients. The model is able to reproduce some fundamental features of schizophrenia with respect to both phenomenology and temporal pattern of the onset of symptoms and deficits. Increased sensitivity to NMDA antagonists, impaired cognitive flexibility and social interaction deficits are observed. Furthermore, set shifting is impaired in both reversal and extra-dimensional tests, in contrast to the effects of PCP. Finally, the promise of oxygen sensing was described as a surrogate for functional magnetic resonance imaging. [O₂] response can be used to measure neuronal activation revealing sensitivity to psychotropics. The correlation of [O₂] response in freely moving rats in rewarded cue operational tasks and in fear response to extinction of conditioned freezing is being investigated. Convergent validation of these approaches will achieve a preclinical model relevant for schizophrenia.

DEVELOPMENT OF A NEUROLOGY AND PSYCHIATRY IMAGING TOOLBOX

Dr. Ian Wilson (GE Healthcare, U.K.) picked up a number of themes presented earlier by Prof. Robbins concerning the failure of preclinical models to translate to the clinical setting. Dr. Wilson again highlighted the benefits of reverse pharmacology in which study of the human state can lead on to discoveries of how to model in animals—and in particular, how to take advantage of imaging techniques (PET/SPECT) to understand the distribution of the relevant pharmacological target. However, the accusation was made that the use of imaging tools is typically too late and we should focus on improving target validation studies in patients at the inception of a drug discovery program. To assist this, microdosing (administration of 1/100th of calculated pharmacological dose and total dose ≤ 100 µg) was mentioned as an attractive approach requiring a truncated preclinical toxicology package to progress imaging agents into the clinic. Dr. Wilson highlighted a number of imaging agents that have been developed by a number of groups which can be viewed as a toolbox for use in psychiatric research.

CLINICAL PERSPECTIVE: NEW THERAPEUTIC APPROACHES FOR TREATING DEPRESSION

Dr. Pierandrea Muglia (GlaxoSmithKline, Italy) considered the unmet medical need for depression. Major depression is a common and debilitating condition with a prevalence somewhere in the region of 5–10% in the adult population, although much higher estimates have been published. Core symptoms include depressed mood, reduced ability to experience pleasure, irritability, sleep disturbances and cognitive impairment. Major depressive disorder (MDD) is frequently associated with comorbidities—up to 80% of patients with MDD have other conditions. Frequently, a major depressive episode follows a psychosocial stressor, such as the death of a close relative. The average age of onset is the late 20s, but the disorder can be triggered at any age. The first demonstration of antidepressant activity was with imipramine in the late 1950s, and since that time a number of agents have successfully been shown in placebo-controlled trials to show efficacy. The mainstays of therapeutic intervention are the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, sertraline and citalopram, although newer agents that are dual serotonin and noradrenaline reuptake inhibitors (venlafaxine, duloxetine) are also available.

The extent of the unmet medical need was highlighted during the National Institute of Mental Health 6-year, multisite controlled trial of outpatients with MDD called Sequenced Treatment Alternatives to Relieve Depression (STAR*D). This study enrolled nearly 4000 patients across the United States to compare commonly used antidepressant drugs using inclusion criteria that were reflective of real clinical practice. Patients were initially treated with citalopram, but if treatment was unsuccessful they were offered a further three treatment options (levels) with different agents or using augmentation strategies.⁹ The remission rates for each treatment level were 33% for level 1, 31% for level 2, 14% for level 3 and 15% for level 4. The cumulative remission rate after four treatments was 67%. However, relapse rates were high: 33%, 47%, 43% and 50% for each treatment level. Thus, with current therapies a substantial proportion of patients do not

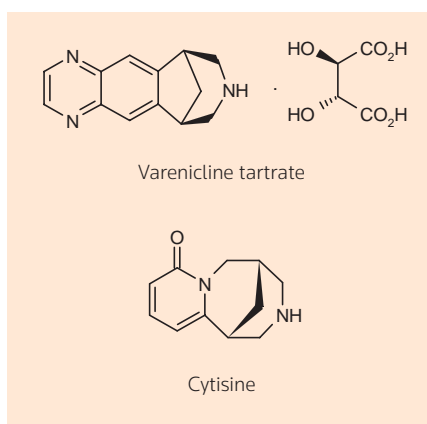
respond and many responders ultimately relapse.

The underlying pathology for MDD is poorly understood and the plastic changes that presumably underpin the efficacy mediated by the current therapeutic approaches are also obscure. There is undeniably a significant genetic component that predisposes to MDD, of the order of 40%, but single genes of high effect have not been identified. Current hypotheses for the etiology of MDD implicate deficiencies in brain-derived neurotrophic factor (BDNF). Life stressors are known to predispose to MDD, and interestingly increased cortisol levels reduce BDNF production. Thus, the hypothalamic–pituitary axis features prominently in the research into MDD, as does neuroimmune interaction.¹⁰ In terms of neuronal circuitry, Dr. Muglia suggested that fear and affective processing, reward and hedonic responses, and cognitive and emotion control are areas of significant interest. One result of a clinical experiment in 7 patients that has increased interest in the glutamatergic neurotransmitter system has been the observation that a 40-minute infusion of ketamine, a noncompetitive NMDA antagonist, produced profound, sustained relief in MDD patients.¹¹

Finally, Dr. Muglia touched upon the difficulty in performing clinical studies to assess antidepressant efficacy. The subjective nature of the clinical rating and how the scale reflects the symptomatology might contribute to the large number of failed trials: both those where new therapeutics fail to show efficacy but also where the active comparator does not separate from the placebo group.

SMOKING CESSATION: VARENICLINE, AN $\alpha_4\beta_2$ PARTIAL AGONIST

Dr. Brian O'Neill (Pfizer, U.S.A.) presented the discovery of varenicline. This compound is a partial agonist at the nicotinic $\alpha_4\beta_2$ receptor. The nicotinic receptors are part of the cholinergic system. The nicotinic receptors are ligand (acetylcholine) gated cation-permeable channels that are formed from a family of subunits into pentameric structures. The nicotinic receptor family consists of 17 homologous genes (16 in mammals) encoding nicotinic receptor subunits named $\alpha 1$ – 10 , $\beta 1$ – 4 , γ , δ and ϵ . Thus, there is the potential for bewildering complexity in the formation of different nicotinic acetylcholine



receptors (nAChR) to mediate a wide range of physiological functions. The receptors can be simplistically divided into the “muscle” type and “neuronal type”. Neuronal nAChRs are generated from $\alpha 2$ – 10 and $\beta 2$ – 4 subunits and the most abundant brain receptors are $\alpha_4\beta_2$ and $\alpha 7$ nAChRs. The nAChR receptor family plays, by virtue of their presynaptic location, an important role in the fine tuning of other neurotransmitter systems. Thus, nAChR modulation plays an important role in the control of the ventral tegmental area dopaminergic pathway to the nucleus accumbens (NA); this pathway is heavily involved in reward and addiction behaviors.

Dr. O'Neill outlined the scope of the medical need: smoking is the leading cause of preventable death in the United States currently, with 435,000 deaths per annum being ascribed to smoking-related diseases (figures for the year 2000). The data from transgenic mice that have had components of the $\alpha_4\beta_2$ receptor knocked out were consistent with the view that this receptor played a critical role in nicotine-induced dopamine release in the NA.

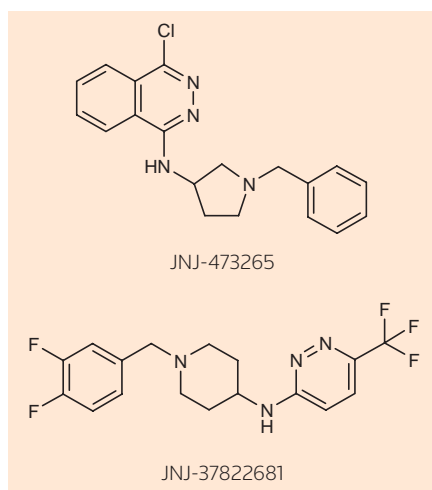
The objective of the drug discovery effort was to find partial agonists for the $\alpha_4\beta_2$ receptor. Pharmacologically, these would be expected to act as nicotine antagonists during smoking to reduce addiction reinforcement when nicotine levels are high, and act to ameliorate craving during abstinence. The *in vitro* tests used to develop the structure activity relationship included binding assays against the common neuronal and muscle receptors ($\alpha_4\beta_2$, $\alpha_3\beta_4$, α_7 and $\alpha_1\beta\gamma\delta$) followed by functional cell-based assays to find partial agonists in the range of 30–80% of nicotine's efficacy. In order to assess *in*

vivo activity, tests were developed to measure dopamine turnover in the NA, as were drug discrimination assays to assess pharmacological similarity to nicotine and self-administration assays to determine addictive potential.

The chemistry starting point for the drug discovery effort was (–)-cytisine, a natural product, that was first isolated in 1894. After total synthesis, it was found that the cytisine was a functional partial agonist *in vivo* and, furthermore, that simple bromination substituents were able to increase *in vivo* potency by 100-fold in the dopamine turnover *in vivo* assay. After considerable structure-activity relationship (SAR) development, however, the cytisine analogue chemistry was halted due to unacceptable toxicity of the compounds, although the SAR knowledge was valuable in directing the 3,5 bicyclic aryl piperidine series of compounds that ultimately led to the now-marketed product, varenicline tartrate. Varenicline has 0.1 nM binding affinity for the $\alpha_4\beta_2$ receptor, with 285, 870 and 2600 nM affinities versus $\alpha_3\beta_4$, α_7 and $\alpha_1\beta\gamma\delta$, respectively. The compound is a partial agonist *in vivo* (34% of nicotine's efficacy), and at a 5.6 mg/kg s.c. dose acts as an antagonist versus 1 mg/kg nicotine in an *in vivo* dopamine turnover model. In summary, this was an excellent example of innovative drug discovery to provide a new therapeutic modality for an unmet medical need.

A FAST TRACK TO ATYPICALITY—THE DISCOVERY OF JNJ-37822681 FOR THE TREATMENT OF SCHIZOPHRENIA

Dr. Gregor MacDonald (Johnson & Johnson, Belgium) presented J&J's program which led to the development of JNJ-37822681, a fast-associating dopamine D_2 antagonist, for the treatment of schizophrenia. Schizophrenia affects 1% of the adult population, a prevalence that is twofold higher than that of Alzheimer's disease and costs the U.S. health authorities USD 46.1 billion a year in patient care. The disease manifests itself as a combination of positive symptoms (hallucinations, delusions, thought disorder), negative symptoms (decline in emotional response, speech and motivation) and cognitive dysfunction. Current treatments, the typical antipsychotics and second-generation antipsychotics, have efficacy against the positive symptoms but have major side



effects including hyperprolactinemia and weight gain. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study examined the comparative effectiveness of current antipsychotic treatments for individuals with chronic schizophrenia.¹² The study revealed high discontinuation rates due to lack of efficacy or intolerable side effects highlighting the clinical need for new medications. The “fast-off D_2 ” theory¹³ hypothesizes that antagonists with fast dissociation rates from the D_2 receptor will be efficacious but may allow for low incidence of D_2 -mediated side effects such as hyperprolactinemia and extrapyramidal signs and symptoms. The program at J&J sought to discover a compound with moderate D_2 affinity with a fast dissociation profile and no affinity for histamine H_1 , serotonin 5-HT_{2C} or adrenergic α_1 or β_2 receptors to avoid off-target side effects. An indirect in vitro filtration assay with [³H]-spiperone was used to assay D_2 antagonists and define leads that dissociated from D_2 faster than clozapine. Four lead series were initially investigated. The hit JNJ-473265 was the subject of an extensive lead optimization, resulting in JNJ-37822681 by overcoming problems of potent hERG and CYP450 2D6 inhibition.

JNJ-37822681 has a moderate D_2 affinity (pIC_{50} 6.3) and dissociates as fast as clozapine and faster than haloperidol, risperidone and paliperidone. The compound is highly selective with $pIC_{50} < 5$ for H_1 , 5-HT_{2C} or α_1 receptors and no significant interactions in a CEREP screen at 10 μ M. The hERG activity was reduced to moderate (56% inhibition at 3 μ M) and the $pIC_{50} = 5.3$ for CYP450 2D6. JNJ-37822681 shows high

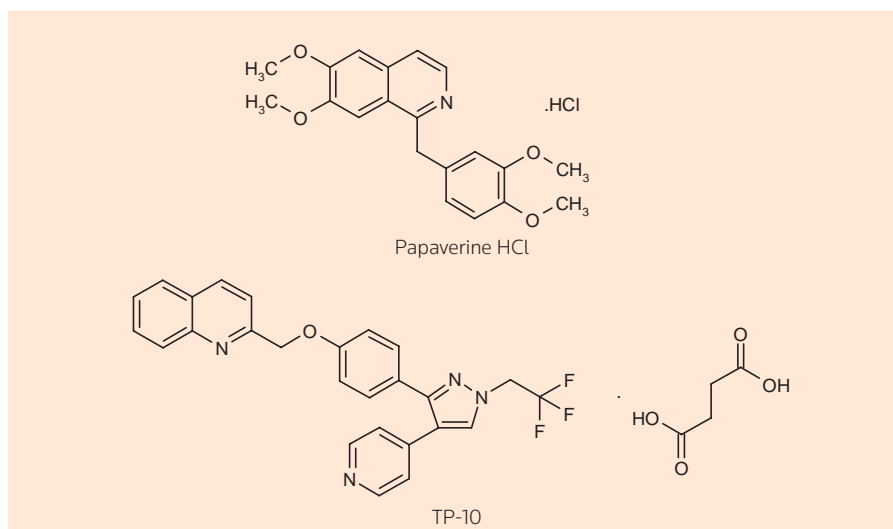
occupancy of D_2 receptors, measured in vivo and ex vivo ($ED_{50} = 0.39$ mg/kg). The compound has an ED_{50} of 0.26 mg/kg by subcutaneous dosing with a similar efficacy to olanzapine in an apomorphine challenge model in the rat. The safety margin of > 30 was defined in a crossed leg test for catalepsy and measuring prolactin release liability in rat. JNJ-37822681 has a good in vivo profile with high oral bioavailability in multiple species and is currently in phase IIb trials for schizophrenia.

PDE10 INHIBITORS FOR PSYCHIATRIC DISORDERS

Dr. Frank Menniti (Pfizer, U.S.A.) described a program aimed at developing selective phosphodiesterase (PDE) 10A inhibitors for the treatment of schizophrenia. PDE10A has been shown by localization studies to have the most restricted distribution of all the known PDE families, with the PDE10A messenger RNA (mRNA) expressed only in the brain and testes. PDE10A is highly expressed in striatal medium spiny neurons (MSN), which is the major input site of the basal ganglia circuit. A disruption of corticostriatal signaling is believed to underlie the psychotic symptoms and contribute to many of the cognitive deficits associated with schizophrenia. This presentation described the characterization of the PDE10-mediated activity in MSNs by pharmacological inhibition of PDE10 and genetic deletion of the enzyme in mice. Driven by crystallography, a medicinal chemistry program produced the PDE10A inhibitor TP-10,

which is potent (IC_{50} 0.2 nM) with 2500-fold selectivity against other PDE enzymes when compared to the literature standard papaverine (IC_{50} 17 nM), and has a very short exposure half-life.

Selective PDE10A inhibitors such as TP-10 give balanced activation of direct and indirect striatal output pathways as indicated by induction of mRNA for both substance P and enkephalin. The PDE10 knockout mouse was less sensitive to PCP in a stimulated locomotor assay. TP-10 has a similar profile to D_2 receptor blockade in preclinical rodent assays predictive of antipsychotic efficacy, such as conditioned avoidance responding. TP-10 also reduces spontaneous locomotor activity and the stimulant response to both amphetamine and NMDA antagonists. These results are indicative of effects on the indirect striatal output pathway while the variable catalepsy also observed is indicative of effects on the direct striatal output pathway. Therefore, it was hypothesized that PDE10 inhibitors will suppress psychosis and improve the cognitive symptoms in schizophrenic patients. This hypothesis is now being tested clinically. In phase I trials, a PDE10A inhibitor was well tolerated with low pharmacokinetic variability and a $t_{1/2}$ of 14 hours. No anhedonia was observed but a side effect profile of sedation and dystonia was seen. The agent is currently in phase II trials and the outcome is awaited. PDE10 inhibitors may also have utility in the treatment of related disorders of basal ganglia function such as Huntington's disease.



CONCLUSIONS

This well-attended meeting reviewed the current challenges in the treatment of depression, schizophrenia and addiction and in producing predictive preclinical models in which to assess novel treatments. It is clear that despite having a range of therapeutic options, there is still a significant unmet medical need. For schizophrenia, the response rates to current medication are still too low, and the side effect burden, especially iatrogenic weight gain, is a significant issue in clinical practice. In particular, negative symptoms and cognitive impairment, especially of executive function, remain poorly treated. In depression it is a similar picture, although the barriers to clinical success are further compounded by very high placebo rates in control groups that have led to a number of failed studies.

For neuropsychiatry in general, the field is still struggling to put in place robust preclinical models that have high predictive, construct and face validity to the human conditions. The problems of trying to model human cognitive processes were also clear. Also, the issue of patient segmentation will become an increasingly important element to the field. Different patients may have different types of cognitive impairment, and a therapeutic mechanism that is appropriate for treating certain cognitive domains may be appropriate for some patients but not others.

In summary, while significant progress has been made to develop medicines for these debilitating diseases, there is still a long way

to go before the needs of patients are fully met.

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