Early-Phase Drug Development Strategies to Inform Decision-Making in the Viability of Novel CNS Compounds for Schizophrenia

Introduction

Schizophrenia is a severely debilitating psychiatric disorder consisting of positive and negative symptoms, cognitive impairment and social dysfunction, impacting about 1% of the general population. The currently marketed antipsychotics are effective primarily against positive symptoms (e.g.: hallucinations), while the second generation antipsychotics (SGAs) have modest clinical benefit on negative symptoms (e.g: anhedonia) and weaker effects on cognitive deficits. Therefore, in addition to novel treatments that improve the overall symptomatology in schizophrenia, whether as add-on or monotherapy, there is currently particular focus on drug development to treat negative symptoms and cognitive impairment. While numerous potential drug candidates representing myriad novel mechanisms have advanced from the preclinical stages, many have failed in early phase or later phase (Ph2 or Ph3) trials due to either toxicity or lack of efficacy on primary clinical endpoints (i.e. change in PANSS score). The failures of novel antipsychotics beyond second generation type therapies for schizophrenia illustrate challenges in translating the effect of these new chemical entities on preclinical models of schizophrenia into pharmacodynamic (PD) endpoints in humans during early phase trials, predictive of antipsychotic efficacy. Proper selection and utilisation of pharmacodynamic “tools” may therefore increase success of novel antipsychotics through the drug development pathway.

CNS “Toolkit” Informing Decision-making in Early Phase Trials

The need to improve and accelerate the success of drug development in schizophrenia has resulted in the increased utilisation of novel pharmacodynamic methodologies that may readily translate from preclinical models to patients, and provide informative data predictive of clinical efficacy. The incorporation of pharmacodynamic biomarkers, including the use of patients earlier in Ph1 trials may provide useful strategies to predict antipsychotic efficacy during later proof-of-concept (POC) trials. Traditional Phase 1 (Ph1) studies typically involve single (SAD) and multiple-ascending dose (MAD) trials in healthy volunteer subjects in order to establish safety and to identify the maximally tolerated dose (MTD) that may be reflective of the predicted clinically effective dose in the affected population.

While many Ph1 studies use healthy volunteers to establish dose-limiting tolerability, the inclusion of schizophrenic patients directly into the Ph1 programme may aid in dose-finding studies as data has shown that schizophrenic patients exhibit a higher tolerance of D2-dopamine antagonists compared to healthy volunteers. Similarly, the inclusion of pharmacodynamic biomarkers, which include those such as biochemical, imaging, electroencephalography (EEG) and cognitive assessments, employed during Ph1 studies constitute a “toolkit” that may aid in informing decision-making on the course of a compound’s future development. By selecting among available mechanistic and possible state- or trait-related biomarkers (extrapolated from preclinical studies), such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) imaging, quantitative EEG (qEEG) and cognitive and behavioural measures, and by considering patient enrichment or stratification strategies in Ph2 trials, critical information related to the “3 pillars” of compound survival (i.e. determination of drug exposure, target occupancy and functional modulation), can be efficiently obtained, potentially improving the success of these antipsychotic agents in later phase trials. Typically, multiple assessments are combined into the same pharmacodynamic trial to provide corroborative confirmation of target engagement and modulation of relevant mechanisms of action which are believed to be relevant in the treatment of a disease or specific target symptom. An additional challenge in the application of a ‘toolkit’ approach is to determine the ‘level of evidence’ deemed sufficient to move forward, or to “kill the development plan”. In general, early development trials relying on a single ‘toolkit biomarker’ would not be sufficient to end a development programme. An illustrative ‘development plan’ for the early development of new therapy for the Cognitive Impairment Associated with Schizophrenia (CIAS) is portrayed in Figure 1. The role of “toolkit” strategies to inform antipsychotic drug development is described below and illustrated in Table 1.

Figure 1: Illustrative “accelerated” development “Go/No-Go” plan of an add-on treatment CIAS programme run by a contract research organisation (CRO).
Table 1: CNS “toolkit” strategies employed in early phase antipsychotic trials

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Healthy volunteers</th>
<th>Schizophrenic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG (pEEG)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ERP</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>PSG</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Imaging (fMRI, PET)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive testing</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Psychiatric rating scales</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>CSF (biomarkers)</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Drug-induced reflux</td>
<td>-</td>
<td>+</td>
</tr>
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</table>

Legend: HNVs, healthy normal volunteers; SAD, single ascending dose; MAD, multiple ascending dose; MTD, maximum tolerated dose; AE, adverse events; DDI, drug-drug interactions; POC, proof-of-concept; PSG, polysomnography; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; PK, pharmacokinetic; PD, pharmacodynamic.

CNS Imaging (functional MRI)

Functional magnetic resonance imaging (fMRI) may offer another tool to understand how newly-developed compounds alter neural circuitry and functional connectivity in the CNS. This neural activity is indirectly measured by regional changes in blood-oxygen level dependent signal (BOLD), which is the most commonly used fMRI technique. Neural activity in response to specific, reproducible and well-characterised stimuli can serve as a “fingerprint” of specific function for disease state or drug action. Unlike other imaging modalities (i.e. PET), fMRI allows for a more global measure of target engagement since it does not rely on radioligands developed for specific predetermined receptor sites with adequate drug concentrations. Preclinical fMRI data may also reveal neural processing (both conscious and subconscious) that is more sensitive than behavioural assays, since it does not rely on motor-driven behavioural outcomes.

Translating this circuit-based approach into early phase trials may also reveal connectivity patterns that are indicative of off-target side-effects like sedation (intralaminar nuclei of the thalamus and cortical regions) or nausea and emesis (nucleus tractus solitarius of brainstem).

Some issues with fMRI have been uncertain reproducibility and test-retest reliability consistency, which is classically evaluated with mathematical variance determination, adverse events profiling and pharmacodynamic signals potentially predicting efficacy.

Cognitive Testing

Neurocognitive impairments in a number of functional domains are core features associated with schizophrenia. These include deficits in memory, attention, processing speed, working memory, executive function and social functioning. The severity of cognitive impairment in schizophrenic patients has been associated with poor treatment outcomes and risk of relapse, while imaging studies have demonstrated functional and structural abnormalities associated with impairment in specific domains. Recognizing the clinical and societal importance of these cognitive impairments in schizophrenic patients, key opinion leaders from academia, industry and government developed guidelines for the design of clinical trials and recommended domain-specific cognitive assessment batteries (i.e. MATRICS Consensus Cognitive Battery, MCCB) for evaluation of novel therapeutics on cognitive function.

Early clinical trials with second-generation antipsychotics (SGAs) suggested beneficial effects in cognition, however, results from the NIH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) demonstrated modest improvements in cognitive outcomes with SGAs, but no statistically significant differences between treatments when compared to first-generation antipsychotics (FGAs). These findings have led many antipsychotic drug development programmes to explore detection of changes in domain-specific cognitive function during early phase studies.

While cognitive batteries such as the MCCB are considered...
the gold standard for FDA registration trials for antipsychotics (ex. Ph3 trials), the employment of cognitive assessments during early phase studies can provide useful information related to domain-specific cognitive outcomes. First, during a first-in-human (FiH) study, utilisation of simple cognitive tests can be used as safety assessments informing potential effects on cognition or mood, particularly for compounds exhibiting CNS penetration. These may include simple tasks of motor function (reaction time task), attention (digit-symbol substitution), working memory (n-back) or executive function (Stroop task). These tasks can serve to identify clinically meaningful CNS effects that may limit subsequent development. Secondly, while Ph1 studies are not traditionally powered to demonstrate a statistically significant effect of treatment vs. placebo, these assessments can provide metrics that will inform statistical decisions regarding cognitive changes in subsequent Ph2 POC trials. Additionally, for cognitive domains demonstrating a treatment trend, examination of PK/PD relationships can be performed to characterise dose-exposure effects informing later phase dose selections for outcome measures.

Selection of a particular cognitive battery during Ph1 studies should be tailored to the pharmacologic mechanism and modified neurological circuits underlying the behavioural effects identified from preclinical studies. Consideration of the types and extent of changes in specific cognitive domains from single and multiple-dose studies in preclinical models can aid in determining translatable cognitive assessments in similar FiH trials. For example, single-dose improvements in a number of specific cognitive domains have been reported in both health volunteers and in patients receiving procognitive drugs. Another important consideration is the availability of normative data from the specific cognitive battery, whereby data from individual treatment effects can be compared. In addition, data obtained from PK or exploratory PD studies can be used to support dose-finding studies predictive of clinical efficacy when transitioning from healthy normal volunteers to schizophrenic patients. For example, data from the CATIE trial showed that antipsychotic doses predictive of >80% D2 receptor occupancy, based upon plasma concentrations using population PK modelling, increased the risk of cognitive impairment and predicted performance on vigilance tasks.

Although beyond the scope of this article, the assessment of cognition or function in patients receiving novel therapies is probably best assessed under a stimulating environment encompassing “cognitive loading”. Moreover, an important new frontier of drug development is to combine cognitive remediation or cognitive behavioural therapies with cognitive-enhancing drugs or with cerebral spinal fluid (CSF) or plasma biomarkers. For example, plasma-based biomarkers such as brain-derived neurotrophic factor (BDNF) changes as a result of cognitive remediation programmes for patients with schizophrenia suggest that the pharmacodynamic and biomarker approaches discussed in this article are applicable to non-drug interventions as well.

EEG and PSG Methodology

The neuronal pathways responsible for generating the electroencephalography (EEG) signals are similar between species due to similarities in anatomical and functional organisation of the CNS, allowing the use of EEG methodology as an easily translatable pharmacodynamic biomarker between preclinical models and humans. Numerous EEG studies have been conducted in schizophrenic patients demonstrating deficits in EEG frequency band power (ex: decreased gamma and increased delta band power), synchronous activity and in event-related potentials (ERP). For example, auditory evoked potentials; P50, P300 response), measures of sensory gating that have similarly been identified in preclinical models of schizophrenia. During Ph1 studies, EEG/ERP paradigms can be applied to either single- or multiple-dose studies with healthy volunteers or in patients as traditional safety measures of epileptic potential or electrophysiologic measures predictive of clinical effect. EEG measurements, especially when combined with PK sampling, allow the characterisation of PK/PD relationships of centrally acting drugs and can aid in discerning treatment-emergent adverse effects or procognitive effects of antipsychotic compounds. For example, gamma frequency changes with non-selective NMDA antagonism or specific NR2A antagonists have been identified using qEEG in preclinical rodent models of schizophrenia, and have been shown to correlate with cognitive dysfunction in schizophrenic patients.

The use of EEG/ERP methodology has been performed during single-dose studies of antipsychotics in healthy normal volunteers. For example, single-dose administration of olanzapine to healthy controls produced increases in theta band activity associated with treatment-emergent somnolence, although no changes in P300 component were seen compared to placebo. Risperidone in conjunction with a novel 5-HT6 antagonist administered to healthy controls resulted in an increased EEG alpha and beta frequency. Similar to methods involving reversal of scopolamine or ketamine-induced deficits in cognition utilised in preclinical studies for screening antipsychotic compounds, clinical pharmacology trials utilising these compounds have been shown to induce similar deficits in EEG band activity and ERP, and may be reversed by traditional and novel mechanism antipsychotic compounds.

In addition to EEG, polysomnography (PSG) studies have documented a number of sleep EEG abnormalities in patients with schizophrenia that have been associated with cognitive impairment and diminished quality of life. The most common sleep abnormality - a decrease in slow-wave sleep (SWS) - has been correlated with deficits in consolidation of procedural and declarative learning. Many currently available antipsychotics improve sleep abnormalities in schizophrenia via 5-HT2A blockade. For example, the SGA olanzapine, a potent 5-HT2A antagonist, has been reported to increase SWS and was positively correlated with an increase in verbal memory consolidation. Thus, the use of PSG in Ph1 studies may serve as a useful biomarker for novel treatments for schizophrenia capable of inducing changes in SWS reflective of positive changes in cognition. Conversely, drugs that are procognitive and increase arousal could readily delay sleep onset, and reduce sleep efficiency. Given the close inter-relationship between normal physiologic sleep and cognitive function, characterisation of a drug’s effects on PSG can play a role in the go/no-go decision process.

In addition to PSG studies, physiologic characterisation of...
the sedative effects of CNS active compounds can be performed using methods such as the multiple sleep latency test (MSLT), a technique measuring the speed at which a person falls asleep during the day (and is observed repeatedly over time, since subjects are not permitted to remain asleep). When coupled with various psychometric tests assessing attention, concentration and psychomotor processing, a robust model for sleepiness and sedative effects on cognitive function, typically as a function of concentration time course over the dosing interval, can be built. Sedation is one of the primary adverse events associated with many CNS active compounds, and early characterisation of the severity of these effects is an important tolerability assessment in early phase studies.

These methods can be employed during Ph1 studies to examine electrophysiologic changes characteristic of procognitive or CNS sedative/sleep disruptive effects that may worsen cognition or primary symptomatology. Electrophysiologic techniques offer non-invasive strategies to directly also measure temporal pharmacokinetic and pharmacodynamic relationships between drug exposure and its effect on CNS physiology.

Conclusions and Recommendations

While Phase 1 trials often focus on the safety and tolerability of an investigational agent, novel methodological strategies should be employed during this “learn” phase of drug development to improve PK/PD knowledge and support the three pillars of drug development that can inform key decisions related to a compound’s subsequent development plan. Novel strategies including the addition of imaging, cognitive testing and EEG/PSG in Ph1 can provide information regarding CNS penetration, extent of exposure and target engagement, and provide surrogate signals related to cognitive improvement that can inform subsequent dose selections in later Ph2 studies. Although significant challenges exist in developing and translating these strategies from preclinical models of schizophrenia to humans, as well as from healthy volunteers to patients with schizophrenia, the wider use of these early phase methodological approaches will aid in our identification, understanding, and validation of pharmacodynamic biomarkers. It is hoped that these approaches will increase the efficiency (cost and speed) of drug development by more accurately nominating candidates for global development that have a greater likelihood of successful progression to regulatory approval and to meaningful improvement in the lives of our patients with schizophrenia.

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translational include the identification of novel drug targets and the
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