Enhancing clinical trial success for pro-cognitive drugs in schizophrenia
Despite best efforts, no drugs have been approved for the amelioration of cognitive deficits in schizophrenia: are compounds ineffective or are trial designs the limiting factor?

In this ebook, we discuss the primary methodological challenges faced in the design of pro-cognitive drug trials, and present some potential solutions to overcome them, including:

- Recruitment
- Trial design
- Outcome measures
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Schizophrenia typically develops during late adolescence and early adulthood and is characterised by the presence of positive, negative and cognitive symptoms. Whilst positive symptoms such as hallucinations and delusions are the most recognisable hallmark of the disorder, negative and cognitive symptoms are most closely associated with poor social and functional outcome.

Current antipsychotic medications are reasonably effective at treating the positive (psychotic) symptoms but only minimally remediate (if at all) negative and cognitive symptoms. As such, many patients continue to exhibit marked and persistent impairments in social and occupational functioning and experience poor quality of life (Velthorst et al., 2017).

This functional disability is associated with substantial costs, both to patients and their carers as well as the wider community (Rössler et al., 2005).

In England alone, the societal cost of schizophrenia is estimated to be around £11.8 billion a year, with more than half of this accounted for by loss of productivity, such as unemployment (Schizophrenia Commission, 2012).
Cognitive impairment is a key issue in schizophrenia

Cognitive impairment is a core feature of schizophrenia, with deficits frequently observed on both neurocognitive measures (e.g., processing speed, memory and executive function), as well as social cognitive tasks (e.g., being able to accurately interpret emotions of others or their mental states).

Meta-analyses suggest patients with schizophrenia perform, on average, one standard deviation below healthy control group means on cognitive tasks. However, performance within a neuropsychologically ‘normal’ range, or deficits exceeding 1.5 standard deviations below a normative mean, are also not uncommon (Fioravanti et al., 2012; Savla et al., 2013).

Over the past decade, studies have consistently demonstrated that cognitive impairment is among the strongest determinants of social and occupational functioning in people with schizophrenia (Fett et al., 2011; Green et al., 2015), indicating that these deficits represent an important unmet target for therapeutic intervention.

Advances in this area are likely to hold direct, real-world benefits for patients and their families, while also reducing the financial burden of the disorder on society.
Barriers in pro-cognitive drug trials

Despite considerable efforts by pharmaceutical companies, there are currently no drugs that have been approved for the amelioration of cognitive deficits in schizophrenia.

Participant selection and recruitment, trial design and the sensitivity of outcome measures are all important considerations and potential areas for improvement in this research area.

A series of drugs have demonstrated early promise, only to have failed at the later stages of development. It remains unclear whether this has been due to the nature of the compounds, sub-optimal trial methodology or both.

Tackling the issues

Here we will discuss some of the potential limitations of existing pro-cognitive drug trials in schizophrenia, as well as some ideas for solutions. The primary questions for consideration are as follows:

• Are we recruiting the right patients?
• Are we using the most appropriate trial designs?
• Are we using the most sensitive outcome measures?
Schizophrenia is a heterogeneous disorder, associated with varied clinical and cognitive profiles among patients.

Cognitive performance is relatively independent from the severity of psychosis, emphasising the need to assess and treat these factors as distinct domains. Nevertheless, patients are predominantly recruited into clinical trials on the basis of an established diagnosis (DSM-5) and psychosis severity (Positive and Negative Syndrome Scale; PANSS), neither of which is indicative of cognitive ability. This presents a potential problem for pro-cognitive drug trials in this population as there is a risk of:

1. Some patients having minimal cognitive impairment or performance within a healthy normative range.

2. Bias in patient inclusion, possibly towards including those patients who are ‘higher functioning’ as these patients are typically easier to recruit.
Why screen for cognitive dysfunction?

Though the majority of patients with schizophrenia exhibit some general cognitive dysfunction compared to antecedent expectations, such as premorbid intelligence, up to a quarter display cognitive performance in the ‘normal’ range (Fanning et al., 2012; Heinrichs et al., 2017).

**Inclusion of those patients without a clinically relevant deficit in cognitive performance has the potential to inflate baseline scores,** and reduce scope to see an improvement between drug and placebo groups.

This suggests a possible need to screen prospective participants in order to identify those with a cognitive deficit. This can be done established from a relevant pre-specified domain(s), based on the hypothesised mechanism of action of the study drug.

To put this theory into context, in a trial of a compound intended to improve memory it is unlikely that you will see considerable gains in memory performance among patients whose task performance at baseline is in the normal range.

The use of cognitive screening measures to identify patients with relevant deficits for inclusion into pro-cognitive drug trials has the potential to increase the likelihood of identifying a positive signal from the compound.

**An alternative approach could be to include all patients in a trial, but to stratify the sample to ensure an equal representation of cognitively impaired and cognitively ‘normal’ individuals among the trial arms.** Pre-planned analysis can be run to assess performance differences between ‘high’ and ‘low’ performers, with different go/no-criteria for each to determine drug success. This represents a possible risk management strategy, particularly for later phase trials where risk of failure can be high.
Are any drug developers currently using a pre-screen?

To get a better idea as to whether any commercial companies running pro-cognitive drug trials are using a pre-screen, a systematic search was conducted on www.ClinicalTrials.gov for all protocols associated with cognition in schizophrenia from 2000 to mid-2017 (N = 614).

44.8% of the 614 clinical trials employed inclusion or exclusion criteria to eliminate subjects who demonstrated severe cognitive deficits.

- Screening out the low performers but not acknowledging the impact of including high performers in the sample.

Only 48 (7.8%) employed inclusion or exclusion criteria to establish the presence of a cognitive deficit.

- Higher functioning individuals are typically easier to recruit, which might introduce bias into the recruited sample.

These findings indicate that pre-screening for cognitive impairment in pro-cognitive drug trials for schizophrenia has, to date, not been considered a requirement. However, with increasing understanding of schizophrenia, and recent publications of trial data (e.g., Granger et al., 2018), the time has come to re-evaluate patient selection for cognition in schizophrenia trials.
Targeted patient recruitment

There is a growing international recognition of the importance for stratified medicine and precision psychiatry: the idea that certain individuals within a broad diagnostic grouping may benefit more from different forms of treatment.

To date, trials of pro-cognitive drugs in people with schizophrenia have largely adopted a ‘one size fits all’ approach, with little consideration for exactly which individuals are most likely to be responsive to particular treatments.

This area remains in its relative infancy; though secondary analyses of existing trials may help to provide a data-driven approach to the identification of individuals who are most likely to benefit from particular compounds, which could then be further explored in future trials.

Future pro-cognitive drug trials in schizophrenia may consider primarily selecting patients for treatment on the basis of their specific profile of cognitive dysfunction.
Case study: Exploring participant-level trajectories of cognitive performance in patients with schizophrenia

To explore participant-level trajectories of cognitive performance, with the aim of picking up cognitive heterogeneity within the sample, post-hoc analyses were performed on existing trial data (Granger et al., 2018). The existing data was gained from 463 patients with schizophrenia enrolled in a randomized, double-blind, placebo-controlled, phase II, pro-cognitive drug trial, conducted by Boehringer Ingelheim.

All the patients completed the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the MATRICS Consensus Cognitive Battery (MCCB), at 4 separate time points:
The patients with schizophrenia who were sampled showed substantial variability in cognitive performance. Furthermore, a substantial subsample of patients (approximately 25%) showed neuropsychologically ‘normal’ cognitive performance.

The study results suggested that patients who exhibited impaired performance on CANTAB PAL at screening had the potential to improve in cognitive performance across the time-points, as illustrated in the figure below.

Figure 1. (A) Individual and (B) Mean PAL total errors adjusted (PALTEA) scores for participants plotted over 4 testing sessions colour coded by PALTEA scores at screening visit. Lower scores indicate better performance. Orange lines specify individuals who scored less than 10 errors at screening: high scorers. Whilst blue lines specify individuals who scored more than 10 errors at screening: low scorers.

This finding brings into question whether the inclusion of unimpaired patients in pro-cognitive drug trials minimizes the chance to detect the efficacy of a compound.
In the search for a compound to target cognitive deficits in schizophrenia, at present, it is difficult to parse the effectiveness of the compound from the limitations of the trial design. Here we will discuss potential ways to improve pro-cognitive drug trials in schizophrenia, moving towards a more robust, consistent methodology in this area.

Include a familiarisation session

Use a familiarisation session at screening to reduce test anxiety, and for subjects to become comfortable with the cognitive tests and the test environment. The greatest change as a result of practice effects is seen universally across cognitive test batteries between the first and second exposure to those tasks. A familiarisation session at screening allows for more stable cognitive performance once dosing begins, enhancing the ability to detect pro-cognitive effects by reducing unnecessary placebo increase.

Take care with the duration of testing protocols

Lengthy testing protocols can cause fatigue and confound results, decreasing the signal-to-noise ratio. This should be an important consideration when selecting a suitable cognitive assessment battery.
Use consistent assessment timings

Psychiatric disorders, including schizophrenia, are associated with atypical circadian rhythms (Wulff, Gatti, Wettstein, & Foster, 2010). As a result, the time-of-day when an assessment takes place can be an important consideration. As is maintaining consistency in these timings across assessments.

Consider the effects of subject age

Younger adults, who have been affected by schizophrenia for fewer years, are expected to show the best outcomes following cognitive remediation (Corbera, Wexler, Poltorak, Thime, & Kurtz, 2017). Furthermore, younger participants have more brain plasticity and are also less likely to have cognitive impairment due to other illnesses (such as MCI). Consequently, variance in the efficacy of pro-cognitive interventions may vary depending upon the age of the cohort, as well as clinical symptom profiles.
Future directions: Digitise clinical trials

To date, studies have adopted conventional trial designs; conducting a baseline assessment, randomising patients to a treatment or placebo arm then conducting further assessments at the mid- and end-points of the trial and at a longer term follow-up time point.

Incorporating more frequent cognitive assessments based on less resource-intensive monitoring, for example using smartphones, wearable devices or web-based testing may optimise the identification of compound efficacy on cognitive performance as well as on clinical symptoms.

Furthermore, such technologies also present convenient methods for tracking symptoms and side-effects in real-time, so that potential drug-interactions may be better understood. Methodologies which employ digital technologies hold the potential to revolutionise pro-cognitive trials in schizophrenia, as well as many other therapeutic areas.
Case study: High-compliance for wearable devices in major depressive disorder

A six-week observational study, as presented at the 2017 CNS Summit, was conducted by Takeda and Cambridge Cognition to assess the feasibility, accuracy and acceptability of delivering daily assessments of cognition and mood in 30 patients with major depressive disorder (MDD). The daily assessments were delivered by an Apple Watch.

The study found that near-patient testing using wearable devices was feasible and well-tolerated by patients with depression, and excellent compliance (94.6% overall) was achieved. Furthermore, good correspondence was seen between data obtained from the watch and full-length patient reported outcomes and cognitive measurement.

These findings present wearables as an avenue with distinct potential for high-frequency, near-patient testing.
Successful pro-cognitive drug trials in schizophrenia are predicated on recruiting the most appropriate patients, and employing carefully considered trial designs.

These factors create the necessary environment to facilitate identification of pro-cognitive drug signals. However, outcome measures must be sufficiently sensitive to these potentially subtle effects in order to convincingly support any pro-cognitive claims.

Case study: Outcome measure sensitivity determines whether a drug is effective

A recent study conducted by Lees et al. (2017) is a classic example of how a pro-cognitive drug can be considered both effective and ineffective, depending upon the sensitivity of the outcome measure.

The study investigated why Modafinil, a known cognitive enhancer for healthy adults (Turner et al., 2003), has an inconsistent history of pro-cognitive effects in schizophrenia (Lees et al., 2017).

A central hypothesis for this inconsistency was outcome measure sensitivity. This hypothesis was tested by comparing how 46 adults with schizophrenia performed on two different cognitive test batteries, following Modafinil administration.

Sensitivity to the pro-cognitive effects of Modafinil, in schizophrenia, was compared for the MATRICS Consensus Cognitive Battery (MCCB) and the Cambridge Neuropsychological Test Automated Battery (CANTAB).
Co-primary end points in pro-cognitive drug trials

The United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommend that compounds with the potential to exert a pro-cognitive effect should be accompanied by measureable improvements in real-world functioning.

This has led to the development of several instruments specifically for use in this population that seek to capture the subjective experience and impact of cognitive dysfunction on daily living for use as co-primary (cognitive, functional) endpoints in clinical trials.

A co-primary endpoint means that in order for a trial to be deemed successful, significant improvements must be seen in both cognitive performance and functional outcomes.
Whilst this ebook has focused on some of the issues with pro-cognitive drug trials in the context of schizophrenia, these recommendations are equally applicable to a range of serious mental illnesses.

**Major depressive disorder, bipolar disorder, and anxiety disorders are all associated with the presence of psychiatric symptoms** (which can generally be improved with existing treatment) and cognitive dysfunction (which currently cannot).

Both symptom severity and the degree of cognitive impairment are also recognised as important and independent drivers of functional disability trans-diagnostically and consistently with that observed among patients with psychosis. As we know, functional disability can present significant financial and societal costs (Rössler et al., 2005).

**As such, the successful remediation of cognitive deficits holds potential benefits for a number of adversely affected individuals.** Indeed, social cognitive dysfunction (for example) is a transdiagnostic issue, as shown in a meta-analysis of 31 disorders by Cotter and colleagues in 2018.
Figure 2.
Theory of mind effect size estimates and corresponding 95% confidence intervals showed that performance was worse across almost all clinical conditions, compared to healthy controls (Cotter et al., 2018).
Cognitive impairment associated with schizophrenia (CIAS) is detrimental for patients both socially and occupationally, which has wider ramifications for the societal cost of the disorder. Despite the significant burden that CIAS poses, and considerable efforts from pharmaceutical companies, this major therapeutic need remains unmet.

In this ebook we have argued that clinical trials in CIAS have typically been run in the same way for the last few decades and with a drug yet to see the market for CIAS, it’s time to revise and optimise our trial methodology in the hope to discover a successful treatment for this debilitating disorder.

Our top three recommendations to enhance pro-cognitive drug trial success are as follows:

1. Recruit the right patients
   - Pre-screen based on cognitive impairment
   - Stratify patients into ‘high’ and ‘low’ performers at screening

2. Smart study designs
   - Include a familiarisation session for cognitive tests
   - Consider the effects of subject age
   - Use consistent assessment timings
   - Take care with the duration of testing protocols

3. Individual endpoints appropriate for MOA
   - Use sufficiently sensitive outcome measures
   - Carefully consider functional outcome measures to accompany cognition
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UK Headquarters
Cambridge Cognition
Tunbridge Court
Bottisham
Cambridge
CB25 9TU, UK

info@camcog.com
+44 (0)1223 810 700

US Headquarters
Cambridge Cognition
Cambridge Innovation Center
One Broadway
Cambridge
MA, 02142

info@camcog.com
+1 617 859 6499

www.cambridgecognition.com