Cognitive trajectories in schizophrenia: ISCTM working group summary (16th Oct 2018)

Chair: Phil Harvey
Acting co-chair: Kiri Granger

Topic summary:

The focus of this workshop is on baseline cognitive impairment and subsequent treatment response in schizophrenia.

- Are patients entering CIAS trials more likely than the overall population to have neuropsychological normality?
- Is this effect large enough to be concerned about?
- Does this reduce chances of seeing an improvement?
- Would we bias the data if we had an entry criterion?
- How would an entry criterion be developed

Group discussion:

Methods

- Whilst some patients enrolled in CIAS trials do perform with a 'clinically normal' range, should we really be excluding high performing patients who have suffered a cognitive decrement?
    - Not enough of an evidence base exists to exclude patients from a trial who may benefit from a pro-cognitive agent but it may be that higher cognitive performers at screening/baseline have less range to improve (or are less amenable to change) than those with poorer cognitive abilities
    - Compounds such as modafinil or amphetamine however, work for 'everyone' in terms of having a pro-cognitive effect – but does improvement in cognition vary by indication and by baseline cognitive performance? If so, what do these results look like? Is this effect limited to stimulants that are probably contraindicated for this population?
    - Other studies in this area do suggest that the higher the baseline score = smaller the change score
- Level of negative symptoms have been shown to predict treatment response in clinical trials: something we should consider further in CIAS trials?
- Should we stratify patients at randomisation to include more balanced proportions of high and low cognitive performers amongst treatment arms to aid identification of treatment responders?
    - Yes, but would need a much larger number of patients to stratify amongst treatment arms
    - Would impact on recruitment time and speed but provides an opportunity to understand degree of cognitive change depending on degree of impairment at screening/baseline
    - Help to define Go No-Go criteria for treatment success depending on level of impairment

- What variables/co-variates/endpoints do we need to consider in CIAS trial methodology?
    - Include level of pre-morbid cognitive function:
        - Has commonly been collected but is not easy to quantify
    - Time use scales to better inform functional outcome
        - This could be used as a covariate for level of cognitive activity
    - Age: this was a predictor in the Phase 2 trial with encenicline (Forum)
- Trial length considerations: e.g., How long would it take to see a change in function?
    - Can see a clinically relevant functional change in 12 weeks when pairing a pro-cognitive drug with CRT
    - Can we expect all cognitive domains impaired in schizophrenia to improve within a relatively short time frame e.g., executive function

Measurements

- MCCB composite is normed against healthy volunteer scores to create overall t score (it's a weighted score). Composite score as such, is worse than the individual test scores: could this be having an impact on results outcomes?
- Need to consider ceiling effects with cognitive tests and batteries. Look at array of different trials with different cognitive endpoints to asses any measurement issues
- Use of ADAS-Cog in Alzheimer's disease is not a sensitive measure of cognitive performance if AD is too mild or severe; it is most apt for moderate levels of AD. We could be dealing with a similar issue in schizophrenia where it is more difficult to detect change in mild or severe levels of cognitive impairment
- Considerations for future research: linking underlying biology to the target of the drug e.g., MMN as biomarker

Statistics

- Differences in cognitive performance at baseline could be considered in statistical analyses
    - Is post-treatment response based on baseline measures?
    - What would the benefit of a baseline stratification analysis be over using baseline as a co-variate in the treatment model?
    - A co-variates assumes a normal distribution of scores but a proportion of scores e.g., those in the upper performance band at baseline might change more/less than others. The effect and impact of this difference on treatment outcome will not be picked up with a co-variate
- Predicting placebo response: Change between screening and baseline predicts placebo response. Larger change, larger response ~ statistical consideration?
- Consider regression to the mean in placebo group
- Item response theory could be implemented to evaluate changes in scores

Regulatory

- Labelling is to ensure safe and effective use of the drug
- OK to analyse high/med/low performers separately but important to pre-specify as primary endpoints (not exploratory)

- Label would reflect the group of patients that demonstrated clinically relevant improvement by the agent e.g., moderate to severe levels of cognitive impairment
- If label is restricted to a certain threshold of cognitive impairment there wouldn't need to be an in-clinic tool to assess for that level of impairment in patients before the drug could be prescribed (i.e., HAM-D isn't used in-clinic to measure severity of depressive symptoms before a drug can be prescribed to patients experiencing symptoms of depression).

General conclusions:

- Majority agree patient stratification over pre-screening for level of cognitive impairment
- Baseline co-variates not suitable for determining differences in treatment response based on baseline score of cognitive performance
- Post-hoc analyses of previous negative CIAS trial data is needed

Next steps:

Review the available data pertaining to cognitive trajectories and treatment outcomes in recent clinical trials, to ascertain the potential need to modify the recommendations for inclusion / exclusion criteria (i.e., patient selection) or stratification for clinical trials in CIAS.

Kiri G to facilitate & set up call late November with those named in action points below to discuss progress re: obtaining data and plans for data analysis.

Re-group at next ISCTM in Feb 2019 to discuss and present findings to address questions raised.

Action points:

Post-hoc analysis of data to include: Forum Phase III (Steve Brannan); Abbvie Phase II (Kiri Granger to discuss with George Haig); analysis on cognitive training data (Phil Harvey); further analysis of BI Phase II (Kiri Granger & Michael Sand); other existing CIAS trial datasets (Rich Keefe).