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ABSTRACT

Methodological Question Being Addressed: Can taking into account diurnal variation in cognitive functioning help to enhance signal detection in clinical trials of pro-cognitive agents for schizophrenia?

Introduction. Circadian rhythms exert changes in cognitive functioning over the course of the day. Patients with schizophrenia are known to have profoundly disturbed circadian rhythms that can affect their cognitive functioning. Diurnal variations in cognitive functioning were analyzed by examining the impact of time of day on baseline composite MATRICS Consensus Cognitive Battery (MCCB) scores. Next, post hoc exploratory analyses were conducted in two Phase 2 clinical trials to examine whether taking into account consistency in the timing of neurocognitive administrations between the baseline and endpoint visits could affect signal detection.

Methods. For the diurnal variation analyses, 1,971 baseline MCCB assessments administered in the U.S. were aggregated across 8 separate schizophrenia clinical trials. The assessments were divided into five 2-hour time intervals based on the start-time of the assessments (varying from 8:00 am to 5:59 pm) and then analyzed for differences by time interval. Next, Phase 2 schizophrenia clinical trials were used to explore the impact of diurnal variation on neurocognitive signal detection. We separated subjects into those with consistent (+1hr) versus inconsistent (-1hr) timing of neurocognitive battery administrations between their baseline and endpoint visits, and then compared the subgroups.

Results. Time of day exerted a significant effect on baseline composite MCCB scores (p<.001), with highest scores occurring in the 8am-10am interval and lowest scores in the 10am-12pm interval. Follow-up contrasts with Bonferroni correction for 10 multiple comparisons revealed significant differences among the 10am-12pm time period as compared to both the 8-10am (p=.001) and 12-2pm (p=.001) periods. The 10am-12pm time period also yielded higher scores than the 2-4pm period, although not statistically significant using the Bonferroni correction (p=.09).

Conclusions. Cognitive functioning varies and flows over the course of the day. Maintaining consistency in the time of day of neurocognitive administrations between visits can help to enhance signal detection in clinical trials of pro-cognitive therapies.

INTRODUCTION

Circadian rhythms exert changes in cognitive functioning over the course of the day.² Patients with schizophrenia are known to have profoundly disturbed circadian rhythms that can affect their cognitive functioning. Diurnal variations in cognitive functioning were analyzed to determine whether accounting for time of day effects could enhance signal detection in clinical trials of pro-cognitive therapies.

METHODS

For the diurnal variation analyses, 1,971 baseline MCCB assessments conducted in the U.S. were aggregated across 8 separate schizophrenia clinical trials:

- Assessments were divided into 2-hour time intervals based on their start-time (varying from 8:00am to 5:59pm) and then analyzed for differences by time interval.
- Next, two Phase 2 schizophrenia clinical trials were used to explore the impact of diurnal variation on pro-cognitive signal detection.
- We separated subjects into those with consistent (+1hr) versus inconsistent (-1hr) timing of neurocognitive battery administrations between their baseline and endpoint visits, and then compared the subgroups.

RESULTS

Impact of Consistent vs. Inconsistent Timing of Neurocognitive Assessments on Signal Detection

<table>
<thead>
<tr>
<th>Therapy (Battery)</th>
<th>Grouping</th>
<th>LUM Change [SE from Baseline]</th>
<th>High-Dose vs. PBO</th>
<th>High-Dose vs. Active Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add-On (MCCB)</td>
<td>All Subjects (n=139)</td>
<td>2.9 [1.1]</td>
<td>0.5 [0.4]</td>
<td>0.0 [0.2]</td>
</tr>
<tr>
<td></td>
<td>Consistent (n=139)</td>
<td>2.8 [1.0]</td>
<td>0.7 [0.6]</td>
<td>0.0 [0.2]</td>
</tr>
<tr>
<td></td>
<td>Inconsistent (n=139)</td>
<td>2.6 [1.0]</td>
<td>0.5 [0.4]</td>
<td>0.0 [0.2]</td>
</tr>
</tbody>
</table>

Broad-Spectrum Therapy: BACS Test Changes from Baseline to Day 42

CONCLUSION

Maintaining consistency in the time of day of neurocognitive administrations between visits can help to enhance signal detection in clinical trials of pro-cognitive therapies.

References


Author Disclosures

M. Hufford is an employee of NeuroCog Trials, Inc. Y. G. Davis is a part-time employee of NeuroCog Trials, Inc. M. Gaweł, N. Dgetluck, and D. Hill are employees of EnVivo Pharmaceuticals. A. Rappaport is an employee of BiolaLewie. R. Keefe currently or in the past 2 years has received investigational-research funding support from the National Institute of Mental Health; Allon, Asta-Zeneca, Glass/SmithKline; Novartis, Psychogenics; Department of Veterans’ Affairs; Research Foundation for Mental Illness; Inc., and the Singapore National Medical Research Council. He currently or in the past 2 years has received honoraria, served as a consultant, or advisory board member for Alkpli, Allerion, Asta-Zeneca, BiolaLewie, Biogen, Cato Research, Cogstate, Cogenics, Daiichi Sankyo, Shire, Solvay, Sutentosis, Teckers, and Wyeth. D. Keefe receives royalties from the BACS testing battery and the MATRICS Battery (BACS Symbol Coding). He is also a shareholder in NeuroCog Trials, Inc., Durham NC. R. Keefe is also a professor at Duke University, Durham, NC.