Introduction

• REACH2HD examined the safety and benefits of PBT2 on cognitive impairment, the major and untreatable source of disability in early HD.1,2
• Trails Making Test B (TMT-B), a validated measure of executive cognitive function and pre-specified clinical trial end point, improved among research participants assigned to PBT2 250 mg/day compared with placebo.1,3

Objectives

• Examine the relationship between TMT-B performance and bothersome cognitive complaints among Huntington Disease (HD) research participants in the phase 2 REACH2HD randomized-controlled trial of PBT2.

Methods

• The TMT-B and HD-PROP were administered to the 109 REACH2HD participants at baseline (BL), Week 12 (not shown), and Week 26 of experimental treatment (W26) randomly assigned to PBT2 250 mg/day (n=36), PBT2 100 mg/day (n=38), or placebo (n=35).
• Verbatim most bothersome HD-PROP problems were categorized independently, without knowledge of treatment assignment, into seven umbrella terms: 1) Thinking, 2) Motor, 3) Psychiatry, 4) Activities, 5) Somatic, 6) Family/Genetic, and 7) Other (Table 1).
• Change Scores of ‘Thinking Problems’ (CSTP) between BL and W26 were calculated for: 1) subjects who showed the greatest TMTB improvement (n=15) 2) subjects who showed the greatest TMTB worsening (n=15) 3) subjects who had no change in TMTB (n=17)

Table 1: Neuroscientist Coded Example Patient Responses

<table>
<thead>
<tr>
<th>Problem Code</th>
<th>Example Verbatim Reported Patient Thinking Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>The fact that I lose my memory...I worry about that. My memory is not what it used to be. I struggle with names of relatives, acquaintances. I think the lack of memory and forgetting to do things like taking my medications.</td>
</tr>
<tr>
<td>Attention</td>
<td>It's hard for me to concentrate...Concentration has grown much worse. Lack of focus.</td>
</tr>
<tr>
<td>Communication</td>
<td>Sometimes trying to explain something to someone I can't get my words out...I guess the short term communication connecting the dots etc...Sometimes when I want to say something to someone I can't get my thoughts out and it turns into an argument.</td>
</tr>
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</table>

Results

• Responder analysis shows
  1) Most people who improved on TMT-B were in the highest treatment group (PBT2 250 mg/day = 10, PBT2 100 mg/day = 3, placebo = 2, Figure 1).
  2) Those who worsened on TMT-B were comprised of PBT2 250 mg/day = 4, PBT2 100 mg/day = 6, placebo = 5 (Figure 2).
• Of the 15 subjects who exhibited the greatest improvement in TMTB, the two who reported improvement in CSTP were both assigned to PBT2 250 mg/day (Zero CSTP = 9, Negative CSTP = 4, Table 2).
• Of the 15 who exhibited the greatest worsening in TMTB, four had favorable CSTP: 3 PBT2 250 and 1 PBT2 100 (Zero CSTP = 10, Negative CSTP = 0, Table 3).
• Of the 17 subjects who had no change in TMTB, four had favorable CSTP: 1 PBT2 250, 2 PBT2 100 and 1 placebo (Zero CSTP = 12, Negative CSTP = 1, Table 4).
• Tables 2-4 display cognitive problems in red, Positive CSTP in dark yellow background, Zero CSTP in white, Negative CSTP in light yellow, and treatment group in corresponding shades of blue with Figure 1 and 2.

Table 2: The 15 greatest TMT-B worsening subjects (7.25 mean ± 2.31 sd sec, range 35-140 sec slower than baseline). BL TFC 9.1 mean ± 2.9 sd. BL TMT-B 130.5 mean ± 45.8 sd.

Table 3: The 15 greatest TMT-B worsening subjects (7.25 mean ± 2.31 sd sec, range 35-140 sec slower than baseline). BL TFC 9.1 mean ± 2.9 sd. BL TMT-B 130.5 mean ± 45.8 sd.

Table 4: The 17 no change TMT-B performance subjects. BL TFC 8.35 mean ± 1.8 sd. BL and W26 TMT-B 231.5 mean ± 34.9 sd.

HD-PROP Questions

• A study staff member asked each participant the following questions and recorded verbatim responses. Participants were allowed to report up to eight bothersome problems.
  1. What is the most bothersome problem of your Huntington disease?
  2. In what way does this problem bother you by affecting your every day functioning or ability to accomplish what needs to be done?
  3. How much (severely) does this problem bother you by limiting your functioning?
    • 1 = Not at all
    • 2 = Mildly (minimally or rarely)
    • 3 = Moderately (more often than not)
    • 4 = Severely (plenty or all of the time)

Conclusion

• Within positive, negative, and no change TMT-B performance groups, 90% of improvement in CSTP occurred among PBT2-treated subjects.
• HD-PROP may capture the subjects’ own experience of meaningful improvement in cognition, observed in the REACH2HD trial on formal testing.
• All positive CSTP reported zero W26 cognitive complaints, indicating absence of bothersome thinking problems.
• The higher dose of PBT2 (250 mg) may be more effective in treatment of subjects' cognitive complaints.

Future Directions

• Other analytic approaches may be useful such as Natural Language Processing (NLP) of responses.
• Further and wider implementation and pairing of participant, caregiver and clinician HD-PROP reports are essential to capture PROs and address cognition as an unmet need in HD

Acknowledgements & References

*References are available in the full article.