Verbatim Patient Reported Outcomes and Trails Making Test B (TMTB) performance in the REACH2HD Trial

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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 performance and pre-specified clinical trial end point, improved among research participants assigned to PBT2 250 mg/day compared with placebo.[1,3]

• Huntington Disease Patient Reported Outcome of Problem (HD-PROP) captures bothersome problem verbatim descriptions reported by individual patients.

Objective: 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 - 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: Neuropsychologist Coded Example Patient Responses

Problem Code	Example Verbatim Reported Patient Thinking Problems
Memory	"The fact that I lose my memory - I worry about that." "My memory is not what I would like it to be. I struggle with names of relatives, acquaintances." "I think the lack of memory and forgetting to do things like taking my medications."
Attention	"It's hard for me to concentrate." "Concentration has gotten much worse." "Lack of focus." "Distractibility."
Communication	"Sometimes trying to explain something to someone I can't get the 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."

Results

• Responder analysis shows
1) Most people who improved on TMT-B were in the higher treatment group (PBT2 250mg/day =10, PBT2 100mg/day = 3, placebo = 2, Figure 1).

2) Those who worsened on TMT-B were comprised of PBT2 250mg/day = 4, PBT2 100mg/day = 6, placebo = 5 (Figure 2).

• Of the 15 subjects who exhibited the greatest improvement in TMTB, the two who reported improvement in CTSP were both assigned to PBT2 250 mg/day (Zero CSTP = 9, Negative CSTP = 4, Table 2).

Figure 1: Treatment assignments for the 15 subjects who showed the greatest improvement in TMT-B performance

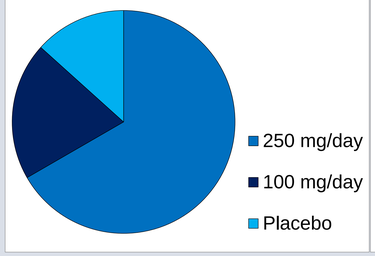
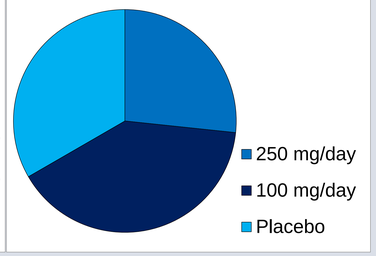


Figure 2: Treatment assignments for the 15 subjects who showed the the greatest worsening in TMT-B performance



• 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: 15 subjects who showed the greatest improvement in TMT-B performance (-43.7 mean ± 20.4 sd secs, range 24-105 sec faster than baseline). BL TFC 9.6 mean ± 2.6 sd. BL TMT-B 158 mean ± 61.2 sd.

Best	BL TFC	BL TMT-B	Δ in TMT-B	Problems at BL	Problems at W26	CSTP	Treatment
1	13	215	-105	Future	Attention	-1	PBT 100
2	9	102	-57	Mood Speed	Perception	0	PBT 250
3	8	240	-56	Drive Family	Drive Speed	0	PBT 100
4	6	240	-54	Depend/Memory/Family Mood Walk/Drive	Reading Attention	-1	PBT 250
5	7	240	-48	Memory Swallow Irritate	Decline Clumsy Cognition	0	PBT 250
6	12	110	-45	Clumsy Communication	No Cure Family Balance/Movement	1	PBT 250
7	9	129	-42	Movement	Movement Process	-1	Placebo
8	7	167	-41	Memory Fatigue	Cognition	0	PBT 250
9	6	219	-39	Work/Social	Social	0	PBT 250
10	12	118	-34	Fatigue Balance Communication	Balance Attention Memory	-1	PBT 250
11	9	106	-32	Cognition Balance Irritate Family	Decline Work Behave Memory	0	PBT 250
12	9	190	-31	Nothing Balance	Balance	0	Placebo
13	11	138	-25	Drive Irritate/Work Walk/Function Movement	Drive Irritate Movement/Perception Loss Enjoy/Balance Motor	0	PBT 250
14	13	92	-23	Future	Nothing	0	PBT 100
15	13	64	-23	Memory Balance Cognition	Balance	2	PBT 250

Table 3: The 15 greatest TMT-B worsening subjects (72.1 mean ± 25.3 sd secs, range 35-140 sec slower than baseline). BL TFC 9.1 mean ± 2.0 sd. BL TMT-B 130.5 mean ± 45.8 sd.

Worst	BL TFC	BL TMT-B	Δ in TMT-B	Problems at BL	Problems at W26	CSTP	Treatment
1	10	93	147	Anxiety Attention	Attention	0	PBT 100
2	12	151	89	Clumsy	No Cure	0	PBT 250
3	7	156	84	Family Loss Enjoy Weight	Movement Cooking Balance	0	PBT 100
4	7	67	83	Movement Comprehension	Movement Memory Death	0	PBT 100
5	9	161	79	Genetic	Nothing	0	Placebo
6	11	124	72	Mood Movement Swallow	Nothing	0	Placebo
7	8	79	70	Memory Drive Family/Future	Irritation Weight	1	PBT 100
8	6	171	69	Cognition	Attention	0	Placebo
9	12	66	67	Confusion Mood	Confusion Mood	0	Placebo
10	7	112	66	Speech Walk Memory	Speech Movement Future	1	PBT 100
11	11	139	64	Movement Speech	Speech Movement	0	Placebo
12	11	183	57	Fatigue Cognition Physical	Future	1	PBT 250
13	8	185	55	Dependence Attention Work/Money	Driving	1	PBT 250
14	9	195	45	Write Speech Memory Sick	Movement Memory Writing	0	PBT 100
15	8	75	35	Work Movement Memory/Attention	Movement Speech Balance	2	PBT 250

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.

No Change	BL TFC	BL TMT-B	Δ in TMT-B	Problems at BL	Problems at W26	CSTP	Treatment
1	9	240	0	Cognition Communication Writing Communication Planning	Nothing	4	PBT 100
2	10	240	0	Movement Cognition Memory	Movement Drive Balance	2	Placebo
3	8	240	0	Motor Memory Motor	Memory Movement Speech	0	PBT 100
4	8	240	0	Speech Cognition Movement Writing	Decisiveness Memory	-1	Placebo
5	7	240	0	Tremor Perception	Movement	0	PBT 250
6	8	240	0	Driving Social	Loss Enjoy Driving Dependence Loss Enjoy	0	Placebo
7	6	240	0	Balance Speech Communication Movement	Loss Enjoy Communication	0	PBT 100
8	7	240	0	Cognition Travelling Decline Loss Enjoy Family	Driving	1	PBT 250
9	12	240	0	Movement Future Meds	Driving Movement	0	PBT 250
10	8	240	0	Anxiety Balance Sleep Don't Know	Walking	0	Placebo
11	12	96	0	Sick	Future	0	Placebo
12	8	240	0	Movement Memory Balance Movement Balance	Memory	1	Placebo
13	6	240	0	Balance Speech Memory	Memory	1	PBT 100
14	10	240	0	Movement Memory	Movement	1	PBT 100
15	7	240	0	Cooking Dependence Movement Incontinence	Dependence Speech	0	Placebo
16	8	240	0	Sick Meds Dependence	Sick Housework Meds	0	PBT 100
17	8	240	0	Working Driving Loss Enjoy Speed	Function Showering Driving	0	Placebo

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 (250mg) 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.[4]

• 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

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