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Randomized Controlled Trial of Atomoxetine for Cognitive Dysfunction in Early Huntington Disease

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Abstract

Background—Cognitive symptoms are associated with functional disability in Huntington disease; yet, few controlled trials have examined cognitive treatments that could improve patient independence and quality of life. Atomoxetine is a norepinephrine reuptake inhibitor approved for treatment of attention-deficit/hyperactivity disorder.

Methods—Twenty participants with mild Huntington disease who complained of inattention were randomized to receive atomoxetine (80 mg/d) or placebo in a 10-week double-blind crossover study. Primary outcome measures were self-reported attention and attention and executive neuropsychological composite scores. Secondary outcomes were psychiatric and motor symptom scores.

Results—The rate of reported adverse effects while on atomoxetine was 56% (vs 35% on placebo), which most commonly included dry mouth (39%), loss of appetite (22%), insomnia (22%), and dizziness (17%). There were no serious adverse events related to atomoxetine. There were statistically significant, although mild, increases in heart rate and diastolic blood pressure on atomoxetine, consistent with other studies and not requiring medical referral. There were no significant improvements while on atomoxetine compared with placebo on primary outcomes. However, there was evidence of significant placebo effects on self-reported attention and psychiatric functions. There were no group differences on the Unified Huntington's Disease Rating total motor score.

Conclusions—Atomoxetine demonstrated no advantages over placebo for primary or secondary outcomes. Although atomoxetine was not effective at improving attention at this dose, its safety and tolerability were similar to other studies.

Keywords

Huntington disease; randomized controlled trial; neuropsychological assessment; clinical trials

Huntington disease (HD) is an autosomal-dominant neurodegenerative disorder caused by an unstable expansion of CAG repeats in the IT15 gene that causes motor, cognitive, and psychiatric symptoms.1 Although motor symptoms remain at the forefront of the diagnosis,

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recent research has indicated that subclinical cognitive and psychiatric symptoms may be detectable years before diagnostic criteria are met and are highly associated with functional disability.2–8 However, very few controlled trials have been conducted, targeting the cognitive features of HD.

Patients with prediagnosed conditions and early symptoms show cognitive deficits that implicate a frontostriatal dysfunction,2,3,9 including deficient attention and executive functions (eg, attentional and conceptual set shifting and verbal fluency). Neuropathologic studies in attention-deficit/hyperactivity disorder (ADHD) have also reported disruptions in frontostriatal circuits.10,11 Palliative therapies have successfully improved attention and executive functions in children and adults with ADHD. Given that both HD and ADHD produce cognitive impairments in attention and executive functions (albeit with some important differences because HD is a neurodegenerative disorder and ADHD is largely stable over time),12 we hypothesized that a medication with proven efficacy for ADHD,13–19 atomoxetine, would be effective in patients with early HD.

Atomoxetine is a nonstimulant norepinephrine reuptake inhibitor. A recent open-label trial of atomoxetine in Parkinson disease demonstrated improved performance on self-reported executive dysfunction.20 We conducted a randomized, placebo-controlled, double-blind crossover study to evaluate the safety and efficacy of atomoxetine to improve attention and executive functions in adults with mild HD.

METHODS

Participants

Participants were recruited using advertisements and through the University of Iowa Huntington Disease Registry. Twenty adult male and female participants with diagnosed HD (test positive for HD gene expansion or family history positive for the presence of characteristic motor abnormalities diagnosed as HD by an independent neurologist) were included. Inclusion criteria also required mild disease severity (stage 1 or 2 on the Shoulson and Fahn Scale 21) and self-reported complaints of decreased attention (ie, participant answering positively that he/she has experienced a change in thinking that included attention or aspects of executive functions) but an otherwise minimal functional impairment as assessed by the Unified Huntington's Disease Rating Scale (UHDRS) and Total Functional Capacity Scale. Exclusion criteria were age older than 60 years, hypertension, tachycardia, cardiovascular or cerebrovascular disease, use of a monoamine oxidase inhibitor in the past 14 days, pregnancy or lactation, head injury with loss of consciousness longer than 5 minutes, neurological disorder or insult other than HD, learning disability or other medical conditions that were likely to affect cognitive function, history of ADHD symptoms in childhood, and current substance abuse.

Procedures

The study was approved by the University of Iowa Institutional Review Board, and all participants provided written informed consent. Participants were screened before baseline for the presence of attentional problems through interview, medical status (including safety laboratories and electrocardiogram), and history for inclusion/exclusion criteria. The study design consisted of a randomized (1:1), placebo-controlled, double-blind crossover study with a 4-week treatment period in each arm and a 2-week washout between arms (total, 10 weeks). The length of treatment has varied in previous atomoxetine studies from 3 to 11 weeks. Spencer et al 14 were able to show efficacy on a cognitive test after 3 weeks. Because this was a pilot crossover study, a treatment period toward the shorter end of the range was most cost-effective and most likely to maximize subject participation and

retention, so 4 weeks was chosen. Dose has also varied from a beginning dose of 40 to 60 mg, with later increases to 80 to 120 mg in past studies. To improve atomoxetine tolerability, a divided dosage of 20 mg twice a day (total, 40 mg/d) was administered for 1 week then increased to 40 mg twice a day (total, 80 mg/d) for the remainder of the active treatment phase. Matching placebo was administered in the same dosing schedule. Participants added the atomoxetine or placebo to their existing medication regimens. Participants were evaluated on cognitive and other outcome measures at 4 time points: baseline, after the first treatment phase (4 weeks), after washout (6 weeks), and after the second treatment phase (10 weeks).

Outcome Measures

To monitor safety, vital signs, health checks, and assessment for adverse effects were performed at every visit. Cognition was evaluated with a detailed battery of tests targeting attention and executive functions including the Trail-Making Test, Wechsler Adult Intelligence Scale III Digit Symbol and Letter-Number Sequencing Subtests, computerized simple-choice reaction time and working memory subtests, Stroop Color and Word Test, and verbal fluency test (Controlled Oral Word Association Test). The Wide Range Achievement Test 3: Reading Subtest was given at baseline only as a premorbid IQ estimate. The Conners' Adult ADHD Rating Scale (CAARS)22 is one of the most frequently used self-rating measures in the adult ADHD literature and was given as a self-report measure of attention. Psychiatric symptoms were evaluated with the Symptom Checklist-90-Revised (SCL-90-R). Although changes in motor symptoms were not hypothesized, the UHDRS 23 motor examination was administered at every visit for monitoring purposes.

Statistical Analysis

The primary and secondary measures were analyzed using a series of analyses of covariance controlling for age. The results were screened for model violations (eg, outliers). Preliminary analyses assured no treatment order effects by examining block by treatment interactions. The primary outcomes were changed from baseline in each treatment arm (atomoxetine or placebo) in CAARS score (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, ADHD symptoms total score) and 2 cognitive composite summary scores (calculated as the mean z score across tests using the study sample for standardization). The attention composite included letter-number sequencing, trails A, symbol digit, 2-back, and choice reaction time. The executive composite included trails B, Stroop, and verbal fluency. Secondary measures included individual the SCL-90-R Global Severity Index and the UHDRS total motor score.

RESULTS

Twenty participants were randomized (women-men, 14:6). Concomitant medications were stable throughout the study and included antidepressants (70% of the sample), anxiolytics (20%), antipsychotics (20%), supplements (eg, CoQ-10; 40%), sleep aids (15%), and medications prescribed for chorea (eg, tetrabenazine; 25%). Compliance with study medication was high (99% for the 40-mg dose and 94% for the 80-mg dose). The clinical characteristics of the sample were reflective of early-stage HD. The mean (SD) age of the participants was 46.2 (10.3) years (range, 19–60 years), and they generally had some college education (mean [SD], 14.2 [1.5]). The mean (SD) UHDRS total motor score was 27.8 (13.4), and the mean (SD) Total Functional Capacity Scale score was 10.5 (2.3). According to the UHDRS Independence Scale, 14 of 20 participants had lower than 100% independence scores, suggesting some mild functional impairment. The sample had a mean estimated premorbid IQ (mean [SD] Wide Range Achievement Test 3 Reading standard score, 95.2 [9.3]). In contrast, the mean standardized scores on the 5 UHDRS cognitive

measures at baseline (before randomization) were all between 1 and 2 SDs below the mean, indicating mild cognitive impairment (symbol digit, 69.1; verbal fluency, 75.4; Stroop word, 72.1; Stroop color, 74.2; and Stroop interference, 80.7).

Safety and Tolerability

There were no serious adverse events related to atomoxetine. Compared with the 35% on placebo, 56% of the participants on atomoxetine reported adverse effects. The most commonly reported adverse effects while on atomoxetine were dry mouth (39%), loss of appetite (22%), insomnia (22%), and dizziness (17%). The following were also reported by 11% of the sample while on atomoxetine: weight loss, headache, nausea, urinary trouble, and constipation. There were statistically significant, mild increases in heart rate (mean of 9 beats/min) and diastolic blood pressure (mean of 5 mm Hg) on atomoxetine, consistent with other studies and not requiring medical referral. Two participants withdrew from the study; one was withdrawn by the study physician at the end of the placebo arm (arm 1) because of an elevated creatinine level of 1.8 mg/dL (this participant was also taking creatine, 1 g twice a day), and the other withdrew voluntarily for personal reasons midway through the atomoxetine arm (arm 2). One participant taking 10 g of creatine twice a day had a moderately elevated creatinine level (1.6 mg/dL) while on atomoxetine and was advised to discontinue creatine supplementation during the study.

Efficacy

Regarding the primary outcome measures of self-reported attention (CAARS score) and objective executive and attention composite scores, there were no significant improvements while on atomoxetine compared with placebo (Table 1). On the CAARS, participants taking atomoxetine improved by 0.65 points more than the placebo group, but both groups improved from baseline by 2 to 3 points, suggesting a placebo effect. Similarly, there was a significant improvement in global psychiatric functioning under both treatment conditions, further supporting some placebo effect. There were no group differences on the UHDRS total motor score.

DISCUSSION

Functional disability is highly associated with cognitive decline, and controlled trials targeting cognition in HD are subsequently needed. The current study represents one of very few randomized placebo-controlled studies in this area. A previous randomized controlled trial of donepezil failed to show an effect on cognition.24 Two recent trials of memantine have been reported, but these were both open-label trials.25,26 Neither showed a cognitive benefit, but both studies demonstrated a delay of motor symptoms. The results of this pilot trial demonstrate no significant benefit of atomoxetine on cognitive, psychiatric, or motor functions in early HD. There were small but significant improvements in self-reported attention and psychiatric ratings while on atomoxetine, but an analogous improvement was observed on placebo. Evidence of a noteworthy placebo effect on self-reported attention and psychiatric ratings underscores the need for placebo-controlled versus open-label studies when self-report measures are used. A recent 8-week open-label trial of atomoxetine in Parkinson disease demonstrated improvements in self-reported executive and attention functions but failed to show improvements on objective neuropsychological tests,27 similar to the results of the current study.

The current study design (ie, a crossover study) conveys some limitations but was well suited for a pilot single-center trial in a rare population where subject recruitment is limited. We attempted to obviate possible carryover effects by designing the trial with an adequate washout period. However, we cannot rule out possible carryover effects on some tasks. In

addition, the sample size limited the power to detect small treatment changes. It is possible that the treatment duration was too brief to see the full effect of the medication in this sample. As noted previously, one previous study demonstrated a positive effect after 3 weeks, but other efficacy studies have used a longer treatment period 13,14 and have indicated that the positive effect of atomoxetine continues to build up to 10 weeks. Our measures may have also limited our ability to detect changes. Recent research has shown that clinician-rated measures were more sensitive to atomoxetine improvements than subject-report measures.28 This effect may be further compounded in patients with HD who often show a lack of insight to cognitive changes. Unfortunately, we did not have any cognitive or functional clinician-rated measures in this trial (only motor ratings). In addition, the CAARS has not been previously reported in patients with HD. Finally, we recruited participants who had early-stage HD and relatively minor cognitive impairment at baseline, which may have limited the range of possible improvement from the drug.

Although atomoxetine was generally well tolerated, there were mild but common adverse effects that may be problematic in HD, such as dizziness and loss of appetite. Reported adverse events with atomoxetine occurred with comparable frequency to other published studies,13,27 and important to HD, there was no worsening of motor symptoms during treatment with atomoxetine. We thus found no evidence of clinical worsening in any HD symptom domain with atomoxetine, although the general adverse effect profile may compel careful clinical consideration before use in this population. Although our current study does not suggest any benefit of atomoxetine, further study using a parallel design and possibly a longer treatment period is needed to definitively assess the effectiveness of atomoxetine in treating executive dysfunction in patients with mild HD.

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REFERENCES

1. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993; 72:971–983. [PubMed: 8458085]
2. Campodonico JR, Aylward E, Codori AM, et al. When does Huntington's disease begin? J Int Neuropsychol Soc. 1998; 4:467–473.
3. Lawrence AD, Hodges JR, Rosser AE, et al. Evidence for specific cognitive deficits in preclinical Huntington's disease. Brain. 1998; 121(Pt 7):1329–1341.
4. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. Huntington Study Group. Neurology. 2000; 54:452–458.
5. Paulsen JS, Zhao H, Stout JC, et al. Clinical markers of early disease in persons near onset of Huntington's disease. Neurology. 2001; 57:658–662.
6. Hamilton JM, Salmon DP, Corey-Bloom J, et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry. 2003; 74:120–122.
7. Nehl C, Paulsen JS. Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. J Nerv Ment Dis. 2004; 192:72–74. [PubMed: 14718780]
8. Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. J Neurol Neurosurg Psychiatry. 2008; 79:874–880.
9. Beglinger LJ, Nopoulos PC, Jorge RE, et al. White matter volume and cognitive dysfunction in early Huntington's disease. Cogn Behav Neurol. 2005; 18:102–107.

10. Casey BJ, Castellanos FX, Giedd JN, et al. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 1997; 36:374–383.
11. Heilman KM, Voeller KK, Nadeau SE. A possible pathophysiologic substrate of attention deficit hyperactivity disorder. J Child Neurol. 1991; 6(suppl):S76–S81.
12. Hervey AS, Epstein JN, Curry JF. Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. Neuropsychology. 2004; 18:485–503. [PubMed: 15291727]
13. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry. 2003; 53:112–120.
14. Spencer T, Biederman J, Wilens T, et al. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. Am J Psychiatry. 1998; 155:693–695.
15. Adler L, Dietrich A, Reimherr FW, et al. Safety and tolerability of once versus twice daily atomoxetine in adults with ADHD. Ann Clin Psychiatry. 2006; 18:107–113. [PubMed: 16754416]
16. Adler LA, Spencer T, Brown TE, et al. Once-daily atomoxetine for adult attention-deficit/ hyperactivity disorder: a 6-month, double-blind trial. J Clin Psychopharmacol. 2009; 29:44–50. [PubMed: 19142107]
17. Adler LA, Spencer TJ, Williams DW, et al. Long-term, open-label safety and efficacy of atomoxetine in adults with ADHD: final report of a 4-year study. J Atten Disord. 2008; 12:248–253. [PubMed: 18448861]
18. Chamberlain SR, Del Campo N, Dowson J, et al. Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. Biol Psychiatry. 2007; 62:977–984.
19. Faraone SV, Biederman J, Spencer T, et al. Atomoxetine and Stroop task performance in adult attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2005; 15:664–670. [PubMed: 16190797]
20. Marsh L, Biglan K, Gerstenhaber M, et al. Atomoxetine for the treatment of executive dysfunction in Parkinson's disease: a pilot open-label study. Mov Disord. 2009; 24:277–282.
21. Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology. 1979; 29:1–3. [PubMed: 154626]
22. Conners, C. Conners' Adult ADHD Rating Scales (CAARS). North Tonawanda, NY: Multi-Health Systems; 1999.
23. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord. 1996; 11:136–142.
24. Cubo E, Shannon KM, Tracy D, et al. Effect of donepezil on motor and cognitive function in Huntington disease. Neurology. 2006; 67:1268–1271. [PubMed: 17030764]
25. Beister A, Kraus P, Kuhn W, et al. The N-methyl-d-aspartate antagonist memantine retards progression of Huntington's disease. J Neural Transm Suppl. 2004:117–122. [PubMed: 15354397]
26. Ondo WG, Mejia NI, Hunter CB. A pilot study of the clinical efficacy and safety of memantine for Huntington's disease. Parkinsonism Relat Disord. 2007; 13:453–454.
27. Solomon AC, Stout JC, Weaver M, et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. Mov Disord. 2008; 23:1830–1836.
28. Adler LA, Faraone SV, Spencer TJ, et al. The reliability and validity of self- and investigator ratings of ADHD in adults. J Atten Disord. 2008; 11:711–719.

Table 1

Pretreatment and Posttreatment Change Scores on Primary and Secondary Outcome Variables in Atomoxetine and Placebo Treatment Conditions

Outcome	Atomoxetine, Mean (SE)	*P*	Placebo, Mean (SE)	*P*	Difference	*P* Difference
CAARS ADHD total score	−2.88 (1.1)	0.02	−2.24 (1.1)	0.05	−0.65 (1.3)	0.63
Attention composite score	−0.13 (0.07)	0.07	0.02 (0.06)	0.73	−0.15 (0.08)	0.09
Executive composite score	−1.68 (1.4)	0.26	−2.94 (1.4)	0.04	1.26 (1.7)	0.46
SCL-90-R GSI	−4.20 (1.9)	0.04	−4.64 (1.8)	0.02	0.44 (2.2)	0.84
UHDRS total motor score	0.42 (1.8)	0.82	−0.35 (1.7)	0.84	0.77 (2.5)	0.76

Lower scores represent better performance on all variables except the attention and executive composite scores.
GSI Indicates Global Severity Index.