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Results of the Citalopram to Enhance Cognition in Huntington Disease Trial

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Abstract

Objective—Evaluate citalopram for executive functioning in HD.

Design—Randomized, double-blind, placebo-controlled.

Patients—Thirty-three adults with HD, cognitive complaints and no depression (Hamilton Depression Rating Scale ≤12).

Intervention—Citalopram 20 mg or placebo [7 visits, 20 weeks], with practice and placebo run-ins.

Primary Outcome—Change in executive functioning.

Results—Intent to treat analysis controlling for practice effects comparing visits 1–2 to 5–6 for citalopram vs. placebo. There were no significant benefits on the executive function composite (treatment-placebo mean difference −0.167 95% CI (−0.361 to 0.028), p=.092). Citalopram participants showed improved clinician-rated depression symptoms on the HAM-D (t=−2.02, p=0.05). There were no group differences on motor ratings, self-reported executive functions, psychiatric symptoms or functional status.

Conclusion—No evidence that short-term treatment with citalopram improved executive functions in HD. Despite excluding patients with active depression, participants on citalopram showed improved mood, raising the possibility of efficacy for subsyndromal depression in HD.

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Keywords

Huntington disease; neuropsychological assessment; cognitive disorders/dementia; clinical trial

Introduction

Prior therapeutic trials in Huntington disease (HD) have focused on reduction of motor impairments. But while motor symptoms remain at the forefront of diagnosis, research has indicated that cognitive and psychiatric symptoms are detectable years before diagnosis [1–3] and are most strongly associated with functional disability [4]. “Executive” impairment is an early cognitive manifestation of HD that implicates frontal-striatal circuitry [5–8] including aspects of attention, conceptual set shifting and verbal fluency. Reduced levels of serotonin have been found in animal and human HD studies [9–11] [12–15]. Treatment trials with selective serotonin reuptake inhibitors (SSRI) have shown improved symptoms in HD mice [13] [16], yet only one randomized controlled trial (RCT) using an SSRI (fluoxetine) in adults with HD has been conducted [17]. The current trial is the first RCT in HD with the primary endpoint of improved executive function.

Methods

Thirty-four adults with HD were seen at University of Iowa, University of Rochester, or Mayo Clinic Scottsdale. All participants were diagnosed with HD by a neurologist independent from the study, or had positive genetic test for the HD gene expansion with at least some motor abnormalities on the Unified Huntington’s Disease Rating Scale (UHDRS) motor exam (i.e., Diagnostic Confidence Level ≥ 1). Participants demonstrated evidence of cognitive decline secondary to HD at screening on 2 out of 3 UHDRS cognitive measures by scoring at least 1 standard deviation below average (based on published normative data) and/or self-reported complaints of poor cognition. Participants could not have significant depression, a Hamilton Depression Rating Scale score >12 or have taken an SSRI 14 days prior to study drug. Medications known to affect cognition were excluded. Inclusion criteria required mild disease severity defined as premanifest, stage 1 or 2 on the Shoulson & Fahn Scale [18].

Procedure

All procedures were approved by individual sites’ Institutional Review Boards. Written consent was obtained. A 1:1 allocation, placebo-controlled RCT with a cognitive test practice run-in and a single-blind placebo run-in before randomization was used. Thus, participants completed cognitive testing at screening and the first three visits before taking the study drug in an effort to minimize practice effects (i.e., intrasubject “noise”). Participants and staff were blinded to treatment assignment. Cognitive tests were administered at six visits: Screening, week 0 (baseline), week 2 (Visit 1=placebo run-in), week 4 (Visit 2=randomization), week 16 (Visit 5), and week 19 (Visit 6). All participants received placebo at Visit 1 and either 20 mg citalopram or matching placebo at Visit 2. Study medication was added to existing medication regimens. Concomitant medications largely involved preventative supplements (i.e., co-enzyme Q10, vitamins, creatine) and medications for chronic conditions (e.g., allergies, hypertension). Dosing compliance was reconciled at every visit with pill counts.

Measures

The primary outcome was a composite scale of executive functioning. All subjects were evaluated using the UHDRS, including a brief cognitive, neurological, and psychiatric exam,

and assessment of functional skills. A neurologist or trained motor rater scored participants' individual motor signs yielding the Total Motor Score (TMS). The Total Functional Capacity (TFC) score [18] is derived from participant/companion report and quantifies ability to perform basic and instrumental activities of daily living. A categorical classification of disease severity is based on TFC, grouped into 5 stages, with lower stage indicating better functioning (e.g., TFC scores between 13 and 11 = stage 1 HD). Psychiatric symptoms are assessed in 11 domains (e.g., anxiety, depression).

The UHDRS includes phonemic fluency (The Controlled Oral Word Association Test),[19] Symbol Digit Modalities,[20] and Stroop Color and Word Test [21], measuring speed, attention and executive functions. The executive composite included six tests: the three UHDRS tests above (Stroop Interference condition), with the Trail Making Test (TMT) part B [22], Letter-Number Sequencing (complex attention/working memory) from the Wechsler Adult Intelligence Scale – III[23] and Semantic Fluency [24]. Estimated premorbid intellect was calculated using the Wide Range Achievement Test-IV (WRAT-IV; [25]) Reading Subtest, a commonly used estimate of general intelligence (Smith-Seemiller, Franzen, Burgess, & Prieto, 1997). Alternate test forms were used.

The Conners' Adult ADHD Rating Scale (CAARS)[26] is a self-report attention questionnaire that has shown sensitivity to improvement in prior trials [30]. The Hamilton Depression Rating Scale (HAM-D) [27] is a clinician-rated scale of severity of depressive symptoms. The Neuropsychiatric Inventory (NPI)[28] is a widely used measure of neuropsychiatric symptoms associated with cognitive disorders.

Statistical Analysis

t tests were used for continuous comparisons and chi-square (or Fisher exact) tests for categorical comparisons. Intent to treat analysis was performed using a mixed effect linear model with random subject intercepts and a predefined two-tailed linear treatment contrast. The primary test was for a difference in change from visits 1 & 2 to 5 & 6 for citalopram vs. placebo. We used a Kenward-Roger correction of degrees of freedom in the t statistic [29

Results

Participants

Thirty-six individuals were screened and 33 participants randomized between 5/2007 and 4/2011. Descriptive statistics are provided in Table 1. There were no significant differences in baseline clinical or demographic characteristics between treatment groups.

Efficacy

Prespecified primary outcomes measure: change in executive composite score. Z scores (patient mean minus mean/standard deviation based on published test norms) were obtained for each test and averaged (equally weighted), yielding an overall average executive functioning score. There were no significant benefits on executive function for citalopram compared to placebo [citalopram-placebo mean difference = −0.167, p=.092 95% CI (−0.361 to 0.028)]. Change scores in the individual treatment arms revealed no significant change in the citalopram group (p = 0.94) but did show a significant change for the placebo group (t=2.41, p=0.02). Those treated with citalopram (completer analysis) showed marginally improved depression symptoms on the HAM-D (mean difference −2.5, t=−2.02, p=0.05 95% CI (−5.04 to 0.04). There were no group differences on motor ratings, psychiatric symptoms or functional status. However, there was a group difference on self-reported executive functions, with placebo participants reporting greater self-reported attention compared to citalopram (CAARS Index citalopram – placebo mean difference =

1.94 (0.87), t(df=30) =2.23, p=0.03). Exploratory analyses examining individual cognitive tests, including memory tests, and controlling for processing speed where applicable (i.e., TMTB-TMTA and Stroop Interference-Color) all failed to show a benefit of citalopram. When 9 subjects who had milder HD signs (DCL 1 or 2) were excluded, results did not change.

Safety and Tolerability

There were no group differences in vital signs (heart rate, blood pressure), weight change or adverse events between citalopram and placebo . Three serious adverse events (1 on citalopram, 2 on placebo), all of which were worsening depression with suicidal ideation, were reported. Reported side effects did not differ between groups and included: constipation, dry mouth, dizziness, headache, ejaculation disorder, and insomnia.

Discussion

There was no evidence that short-term treatment with citalopram improved executive functions in HD. Although citalopram treatment has not been examined before in HD, there is evidence of functional improvement in Parkinson's disease after 8 weeks of citalopram [30]. Statistical power was limited in this study but confidence intervals indicate conclusions are unlikely to change in a similar future trial with more subjects. Although the primary treatment effect difference between citalopram and placebo might be considered "marginally" significant (p = .09), the direction of the difference suggested less improvement in the citalopram group.

Given the encouraging HD animal model studies using SSRI treatment, there is great interest in the potential benefit of this class of medication to human patients. This study improved upon the methodological shortcomings in previous human SSRI trials in HD. In three of the four published trials, the sample sizes were one or two subjects, with mainly psychiatric or behavioral outcomes. [31], [32] In the only placebo-controlled SSRI study in HD [17] using fluoxetine, the sample size was similar to the current study with 23 completers. There was no significant benefit of the drug on measures of functional capacity, neurological or cognitive scales. There was a trend of worsened performance in the placebo group on one executive measure of cognition (Digit Symbol) with a moderate effect size of 0.54. The current study adds to the fluoxetine trial, in that the depression exclusion was stricter, concomitant use of benzodiazepines was not allowed, sociodemographic variables were balanced across treatment arms, and cognitive screening at study entry more selectively identified patients with executive dysfunction. Additional methodological strengths of the current study included minimizing practice effects by using three testings prior to drug administration to attempt to wash out practice-related improvement, and the use of repeated measures analyses to control for intra-subject variability across multiple sessions, both of which improved the power to detect change in this limited sample study. Unfortunately, there were no indications that citalopram improved cognition in this sample, either on the composite score or any of the individual executive function or memory tests.

Limitations of our design could include underdosing, too short a treatment period, and lack of sensitivity of measures. Also, although we screened participants to include those with cognitive dysfunction prior to entry, it is possible that those with less cognitive impairment may have dampened findings. An exploratory analysis, however, did not find a drug signal in the group with higher disease-related signs. It is also unclear whether CAG repeat length variability, which was slightly higher in the citalopram group, may affect drug response. However, the fact that two human RCTs have been negative certainly casts doubt on the potential clinical benefit of SSRIs for cognitive improvements.

RCT research examining treatment for psychiatric features of HD with any medication is almost nonexistent. This study represents one of only a few using a psychiatric medication and is the first to show the safety and tolerability of citalopram in HD. Although this study was not designed to determine efficacy of citalopram on symptoms of depression, there was some evidence that citalopram may be beneficial for mood in HD patients without clinical levels of depression. This finding warrants further study as mood is the primary psychiatric manifestation in HD and an important contributor to functional status and quality of life. Nevertheless, the efficacy of antidepressants in non-HD patients with mild depression is questionable [33] and RCTs are needed to determine whether patients with HD respond to SSRIs.

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Table

Baseline Demographics and Change in Primary and Secondary Outcome Variables Between Baseline and Visits 5/6

Demographics	**Citalopram**		**Placebo**		
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**P value**
Age in Years	47.33 (14.61)	22–71	45.13 (13.59)	22–62	0.67
Education in Years	14.76 (2.91)	10–20	15.0 (1.75)	12–18	0.78
CAG length	43.62 (8.01)	38–69	43.92 (3.92)	36–50	0.91
HAM-D Composite Score [a]	4.06 (2.99)	0–12	2.94 (1.95)	1–8	0.21
WRAT-4 Standard Score[b]	92.0 (11.54)	62–111	93.63 (7.53)	82–108	0.64
UHDRS Total Motor Score [a] Range 0–124	25.59 (17.96)	5–53	28.13 (19.03)	2–70	0.70
Total Functional Capacity [b] Range 0–13	11.29 (2.05)	7–13	10.69 (2.44)	7–13	0.44
Diagnostic Confidence Level [a] Range 0–4	3.18 (1.13)	1–4	3.0 (1.32)	1–4 58% DCL = 4	0.68
Sex (% male)	53%		56%		
	Citalopram Least Squares Mean ± Standard Error	**Placebo** Least Squares Mean ± Standard Error	**Estimated Treatment Difference** Mean ± Standard Error	**95% Confidence Interval** for Citalopram minus Placebo	**P Value**
Primary outcome variable	n=16	n=15			
Executive Composite [c]	0.005 ± 0.067	0.172 ± 0.071	−0.167 ± 0.09	−0.361, 0.028	0.092
Secondary outcome variables					
Hamilton Rating Scale for Depression (HAM D)	−0.67 ± 0.76	1.23 ± 0.89	−1.90 ± 1.17	−4.30, 0.50	0.12
HAM D completers analysis[d]	−1.0 ± 0.85	1.50 ± 0.9	−2.50 ± 1.23	−5.04, 0.04	0.05
Neuropsychiatric Inventory Total Score	−3.13 ± 3.59	−1.41 ± 1.19	−1.72 ± 3.78	−10.85, 7.40	0.66
UHDRS Total Functional Capacity	−0.54 ± 0.46	−0.06 ± 0.50	−0.48 ± 0.68	−1.87, 0.91	0.49
UHDRS Total Motor Score	−0.71 ± 1.24	1.56 ± 2.66	−2.27 ± 2.93	−8.37, 3.83	0.45
Conners Adult ADHD Rating Scale Index Score[e]	0.68 ± 0.62	−1.06 ± 0.63	1.75 ± 0.88	−0.06, 3.56	0.06

[a] higher scores indicate greater impairment

[b] lower scores indicate greater impairment Mean changes and treatment effects (citalopram – placebo) estimated using a repeated measures analysis model

[c] excluded two baseline placebo measurements due to incomplete data

[d] citalopram n=14, placebo n=14 for this analysis

[e] completers analysis significant at p=0.03 (citalopram n=14, placebo n=14)