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ORIGINAL INVESTIGATION

Dronabinol, a cannabinoid agonist, reduces hair pulling in trichotillomania: a pilot study

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Abstract
Rationale Trichotillomania is characterized by repetitive pulling causing noticeable hair loss. Pharmacological treatment data for trichotillomania are limited.
Objective Dronabinol appears to reduce the exocitotoxic damage caused by glutamate release in the striatum and offers promise in reducing compulsive behavior.
Methods Fourteen female subjects (mean age=33.3±8.9) with DSM-IV trichotillomania were enrolled in a 12-week open-label treatment study of dronabinol (dose ranging from 2.5–15 mg/day). The primary outcome measure was change from baseline to study endpoint on the Massachusetts General Hospital Hair Pulling Scale (MGH-HPS). In order to evaluate effects on cognition, subjects underwent pre- and post-treatment assessments using objective computerized neurocognitive tests. Data were collected from November 2009 to December 2010.
Results Twelve of the 14 subjects (85.7%) completed the 12-week study. MGH-HPS scores decreased from a mean of 16.5±4.4 at baseline to 8.7±5.5 at study endpoint (p= 0.001). Nine (64.3%) subjects were "responders" (i.e., ≥35% reduction on the MGH-HPS and "much or very much improved" Clinical Global Impression scale). The mean effective dose was 11.6±4.1 mg/day. The medication was well-tolerated, with no significant deleterious effects on cognition.
Conclusions This study, the first to examine a cannabinoid agonist in the treatment of trichotillomania, found that dronabinol demonstrated statistically significant reductions in trichotillomania symptoms, in the absence of negative cognitive effects. Pharmacological modulation of the cannabinoid system may prove useful in controlling a range of compulsive behaviors. Given the small sample and open-label design, however larger placebo-controlled studies incorporating cognitive measures are warranted.

Keywords Cannabinoid · Impulsivity · Cognition · CANTAB · CB1 · CB2

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Introduction

Trichotillomania is a disabling, under-recognized condition in which individuals repeatedly pull out hair, leading to noticeable hair loss (American Psychiatric Association 2000). Psychosocial problems are common among individuals with trichotillomania and include significantly reduced quality of life (Odlaug et al. 2010), reduced work productivity, and impaired social functioning (Christenson et al. 1991a, b; Woods et al. 2006a, b).

Currently, there are no FDA-approved pharmacological treatments for trichotillomania, despite almost two decades of research. Controlled clinical trials evaluating potential pharmacological interventions for trichotillomania have

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demonstrated that N-acetyl cysteine (Grant et al. 2009), olanzapine (Van Ameringen et al. 2010), and clomipramine (Swedo et al. 1993) all show some promise in reducing hair-pulling behavior. Similarly, psychosocial interventions, particularly cognitive behavioral therapy, have become established treatments for trichotillomania (Keuthen et al. 2011; Woods et al. 2006a, b; Diefenbach et al. 2006), but few individuals seek these treatments or can find trained therapists. Despite their promise, these treatments do not appear effective for all individuals with trichotillomania, and so additional options are needed.

A recent study using diffusion tensor imaging demonstrated that trichotillomania subjects exhibited significantly reduced fractional anisotropy in anterior cingulate, presupplementary motor area, and temporal cortices (Chamberlain et al. 2010a). These data suggest that the disorganization of white matter tracts in motor habit generation and suppression may underlie the pathophysiology of the disorder (Chamberlain et al. 2010a). Neurochemically, motor habits may rely partially on the endocannabinoid system. CB1 receptors are highly expressed in the basal ganglia nuclei, the hippocampus, cerebellum, and neocortex (Herkenham et al. 1990; Glass and Felder 1997) and are implicated in attenuating glutamatergic exocitotoxic damage by suppressing the neuronal release of glutamate via inhibition of calcium channels (Gerdeman et al. 2002; Marsicano et al. 2003; Khaspekov et al. 2004; Benito et al. 2007). The activation of CB1 receptors reduces glutamate release in the dorsal and ventral striatum [possibly through an interaction with brain-derived neurotrophic factor (de Chiara et al. 2010)], thereby modulating neurotransmission in the basal ganglia and mesolimbic reward system (van der Stelt and Di Marzo 2005). Stress-induced anxious behavior has been associated with the loss of CB1 receptor function in the striatum (Rossi et al. 2008).

Glutamatergic dysfunction has been implicated in the pathophysiology of trichotillomania (Grant et al. 2009; Bienvenu et al. 2009). Pharmacotherapies, such as dronabinol, that target excessive glutamatergic drive may, therefore, be expected to correct the underlying pathophysiology and symptoms of trichotillomania. We conducted an open-label study to examine the tolerability of dronabinol, a canabinoid agonist that contains delta-9-tetrahydrocannabinol (THC), in the treatment of trichotillomania.

In the USA, dronabinol is FDA-approved for the treatment of anorexia associated with weight loss in patients with AIDS and nausea and vomiting associated with cancer chemotherapy. In studies examining dronabinol for these indications, doses of up to 20 mg/day are associated with primarily central nervous system-related adverse events (for example, confusion, dizziness, euphoria, and somnolence) (Beal et al. 1995; Beal et al. 1997). These adverse events are generally mild to moderate in severity and generally reversible upon dose modification (Beal et al. 1995; Beal et al. 1997).

Preclinical studies have reported spatial working memory deficits in rats previously administered THC, which agonises CB1 and CB2 receptors (Realini et al. 2009). Long-term cannabis use in humans has been associated with deficits in domains such as memory, attention, executive function, and psychomotor speed (Jager and Ramsey 2008; Realini et al. 2009). Short-term dosing studies using double-blind placebo-controlled designs have reported deleterious effects of THC (the main psychoactive ingredient in cannabis) on these functions (e.g., Ramaekers et al. 2006, 2009; Ranganathan and D'Souza 2006; Hunault et al. 2009; Morrison et al. 2009; Dumont et al. 2011). However, it should be noted that the effects of psychoactive compounds on cognition are likely to depend on baseline function and therefore may differ (in magnitude and/or direction) between healthy volunteers and patient groups (Chamberlain and Sahakian 2007; Chamberlain et al. 2010b). For example, some studies suggest the beneficial effects of cannabis on aspects of cognition in schizophrenia (Rabin et al. 2011), in contrast to the majority of healthy volunteer studies.

We hypothesized that dronabinol would reduce compulsive hair-pulling behavior in individuals with trichotillomania. Since THC has been linked with cognitive deficits in some contexts as outlined above, as a secondary objective, we included neurocognitive tasks to evaluate the potential deleterious effects of treatment.

Methods

Subjects

Men and women aged 18 to 65 with a primary Diagnostic and Statistical Manual of Mental Disorder Fourth Edition (DSM-IV) diagnosis of trichotillomania were recruited by newspaper advertisements and referrals for medication treatment. All subjects met the DSM-IV criteria for current trichotillomania using the clinician-administered Trichotillomania Diagnostic Interview (Rothbaum and Ninan 1994). Because 17% of individuals with trichotillomania do not meet the DSM-IV criteria of either tension before or relief/gratification after pulling hair (Christenson and Mansueto 1999), this criterion was not required for study inclusion (all 14 subjects, however, met full DSM-IV criteria for trichotillomania). Women's participation required a negative beta-human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception. Exclusion criteria included: (1) unstable medical illness; (2) current pregnancy or lactation, or inadequate contraception in women of childbearing potential; (3) any thoughts of suicide; (4) lifetime history of bipolar disorder type I or II,

dementia, or any psychotic disorder; (5) current (past 3 months) substance abuse or dependence; and (6) previous treatment with dronabinol.

Subjects who were currently taking psychotropic medications were allowed into the study as long as the dose of medication had been stable for 3 months prior to study inclusion and there were no plans to modify the dose during the study duration. Similarly, subjects attending individual or group psychotherapy were allowed to participate if attendance had been ongoing weekly for at least 6 months prior to study entry. Subjects who changed the doses of medication or started therapy, based on their self-report, were discontinued from the study (changes in treatment were assessed at each study visit and no one was withdrawn due to this reason).

Fourteen individuals (14 women; mean age=33.3±8.9) with trichotillomania were started on dronabinol. The 14 subjects as a whole reported age of trichotillomania onset of 10.9 (±4.6) years [range 21–48]. Although many subjects had multiple triggers, the most common triggers of actual pulling were: feel of the hair (e.g., coarse, kinky, out-of-place hairs) (50%; n=7), stress (50%; n=7), and downtime/boredom (35.7%; n=5). The majority of subjects (n=8; 57.1%) pulled from multiple sites: eight (57.1%) pulled from their heads, seven (50%) from the eyebrows, two (14.3%) from their eyelashes, and one (7.1%) from the pubic area.

Although individuals with current bipolar, psychotic and substance use disorders were excluded, eight (57.1%) of enrolled subjects reported at least one current comorbid disorder: eight (50%) had major depressive disorder; five (35.7%) had an anxiety disorder (generalized anxiety disorder or post-traumatic stress disorder), and one (7.1%) had binge-eating disorder. Of the 14 subjects, two (14.3%) had an ongoing psychotherapy, and six (42.9%) were taking a stable dose of psychotropic medication. Of the six subjects taking medication, all had been on stable doses for at least 6 months: six were taking an antidepressant medication and one (7.1%) was taking an anxiolytic.

The institutional review board for the University of Minnesota approved the study and the informed consent. One investigator discussed potential risks of the study, as well as alternative treatments, with the subjects. After complete description of the study, subjects provided written informed consent. This study was carried out in accordance with the Declaration of Helsinki. Data were collected from November 2009 until December 2010.

Study design

After screening, eligible subjects were assigned to 12 weeks of open-label dronabinol. Subjects were started on 2.5 mg/day for 3 weeks. At week 3, the dose was increased to 5 mg/day for the next 3 weeks of the study. At week 6, the dose was increased to 10 mg/day and then to 15 mg/day at week 9 unless clinical improvement (i.e., cessation of all hair pulling for the entire three-week period as assessed by the investigator) was attained at a lower dose. Dose range selection was based on safety and efficacy data from studies using dronabinol in Tourette's syndrome (Müller-Vahl et al. 1998; Müller-Vahl et al. 2002).

Assessments

The subjects were evaluated at entry into the study using the Trichotillomania Diagnostic Interview, a reliable and valid diagnostic instrument using criteria for DSM-IV trichotillomania (Rothbaum and Ninan 1994). Demographics and clinical features of trichotillomania were assessed with a semi-structured interview. Psychiatric comorbidity was assessed using the Structured Clinical Interview for DSM-IV (First et al. 1995). Medical history, physical examination, and routine laboratory testing were obtained. Hair-pulling style and triggers were assessed using the Milwaukee Inventory for Styles of Trichotillomania-Adult Version (Flessner et al. 2008).

Subjects were seen every 3 weeks for 12 weeks. The primary outcome measure was the Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) (Keuthen et al. 1995). The MGH-HPS is a seven-item, self-report scale that rates urges to pull hair, actual amount of pulling, perceived control over behavior, and distress associated with hair pulling over the past 7 days. Analysis of the MGH-HPS has demonstrated two separate factors with acceptable reliability for both: "severity" and "resistance and control" (Keuthen et al. 2007).

Secondary measures that were used at each study visit included:

NIMH Trichotillomania Severity Scale (NIMH-TSS) (Swedo et al. 1989). The NIMH scale is a five-item, clinician-administered scale that rates hair-pulling symptoms during the past week. The items assess pulling frequency (both on the previous day and during the past week), urge intensity, urge resistance, subjective distress, and interference with daily activities. Four items are rated from 0 (none) to 5 (most severe) and the final item is rated from 0 to 4. A total score is calculated by summing all the item scores. The NIMH-TSS has demonstrated sensitivity to changes in symptom severity (Swedo et al. 1989; Tolin et al. 2007).

Clinical Global Impression-Severity and Improvement (CGI) (Guy 1976). The CGI consists of a reliable and valid seven-item Likert scale used to assess severity and improvement in clinical symptoms. The CGI severity scale was used at each visit and ranges from 1="not ill at all" to 7="among the most extremely ill."

The CGI improvement scale was used at each follow-up visit and ranges from 1="very much improved" to 7="very much worse."

Sheehan Disability Scale (SDS) (Sheehan 1983). The SDS is a three-item, reliable, and valid self-report scale that assesses functioning in three areas of life: work, social, or leisure activities, and home and family life. Scores on the SDS range from 0 to 30.

Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959). The HAM-A is a reliable and valid, clinician-administered, 14-item scale that provides an overall measure of global anxiety.

Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960). The HAM-D is a valid and reliable, 17-item, clinician-administered rating scale assessing severity of depressive symptoms.

A secondary measure used only at baseline and study endpoint was the Quality of Life Inventory (QOLI) (Frisch et al. 1993). The QOLI is a valid and reliable 16-item self-administered rating scale that assesses life domains such as health, work, recreation, friendships, love relationships, home, self-esteem, and standard of living.

Cognitive assessments

Subjects undertook paradigms from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition Limited 2006) at study entry and end of participation. Tests were selected on the basis of domains known to be affected by THC (see Introduction) and established sensitivity to sedative and other deleterious effects of certain compounds as well as on the basis of what is known of the neurobiology of trichotillomania. (see e.g., Chamberlain et al. 2010b).

Intradimensional/extradimensional set shift task (IDED) The IDED task includes aspects of rule learning and behavioral flexibility, and was derived from the Wisconsin Card Sort Test (Lezak et al. 2004). There are nine stages to the task requiring different components of set acquisition, reversal, and flexibility.

Stop-signal test The Stop-signal test is a well-validated task quantifying the ability to suppress impulsive responses (Logan et al. 1984; Aron et al. 2004). This task provides a sensitive estimate of the time taken by the subject's brain to stop a prepotent response, referred to as the 'Stop-signal reaction time'.

Cambridge gamble task (CGT) The CGT fractionates the aspects of decision-making and has been shown to be sensitive to lesions of the orbitofrontal and insular cortices (Manes et al. 2002; Clark et al. 2008; Clark 2010). Primary outcome measures are the overall proportion of points gambled and the overall proportion of rational decisions made.

Rapid visual information-processing task (RVIP) On RVIP, volunteers view a series of single digit numbers appearing in a box on-screen, 1/s, and attempt to monitor for the occurrence of specific 'target' sequences (such as a '2' followed by a '4' followed by a '6'). The primary outcome measures are A' (a measure of the ability to detect targets), B' (a measure of the tendency to hit the button pad irrespective of whether or not a target was actually present), and latency (to respond).

Spatial working memory task (SWM) The SWM is based on foraging behavior in animals (Owen et al. 1996). Several boxes are presented on-screen, and volunteers attempt to locate tokens that have been hidden behind the boxes. The key outcome measures include the total number of errors (inappropriately returning to boxes that previously yielded tokens) and strategy scores (lower score equates to superior strategy use).

Safety assessments

Safety assessments at each visit included evaluations of sitting blood pressure, heart rate, and weight. Adverse effects were documented and included time of onset and resolution, severity, action taken, and outcome. Common side effects of dronabinol include feeling 'high', sedated, and light-headed.

Data analysis

In all analyses, it was decided a priori that only subjects who returned for one visit after starting medication would be included ($n=14$) (in fact, all 14 subjects who started the study returned for at least one follow-up visit). Primary analysis used a last observation carried forward approach. Variables that were collected at baseline and final visit (including cognitive variables) were analyzed using a paired t test or the nonparametric Wilcoxon test. The nonparametric Cochran Q test was used to analyze the binary responder variable. The remaining variables were analyzed using a repeated measures general linear model (GLM) analysis with polynomial contrasts across the repeated visits. The GLM analyses used the Greenhouse–Geisser correction (fractional degrees of freedom) when there was a significant Mauchly sphericity test. This being a pilot study, all tests of hypotheses used a significance level of 0.05.

Results

Subject characteristics

Demographics and clinical characteristics of the subjects at baseline are presented (Table 1). Baseline trichotillomania scores on both the MGH-HPS and the NIMH-TSS were consistent with severity scores seen in other studies of trichotillomania (Dougherty et al. 2006; Grant et al. 2009). Twelve (85.7%) of 14 subjects completed the 12-week trial. All 14 subjects were available for at least two ratings following the baseline assessment with final data points for the two subjects who failed to complete the study occurring at week 6 and week 9, respectively. These two individuals withdrew due to inabilities to comply with the study schedule.

Efficacy results

Scores on the MGH-HPS decreased from a mean of 16.5 ±4.4 at baseline to 8.7±5.5 (p=0.001) at the end of 12 weeks (Table 2). Nine (64.3%) subjects met criteria as treatment responders (≥35% reduction on the MGH-HPS and CGI improvement score of 1 or 2) at the end of the study [definition of responder as previously used in treatment studies (Dougherty et al. 2006; Keuthen et al. 2011)]. The mean effective dose of dronabinol was 11.6± 4.1 mg/day. Neither physiological nor psychological tolerance was witnessed in the study. No withdrawal symptoms upon dronabinol discontinuation were experienced by the two subjects who discontinued treatment early in the study or by those subjects who completed all visits.

Responders and non-responders did not differ significantly on baseline characteristics (including cognitive performance) (all p>0.10). Responders and non-responders had the same baseline rates of other psychotropic medication use (21.4% in each group). No baseline trichotillomania, psychiatric, or functional variable was significantly associated with the non-treatment responsive group.

Of the nine subjects classified as treatment responders (≥35% reduction on the MGH-HPS and CGI Improvement score of 1 or 2 at study endpoint), three (33.3%) responded at 2.5 mg/day, two (22.2%) responded at 5 mg/day, two (22.2%) responded at 10 mg/day, and two (22.2%) responded at 15 mg/day. All three of the non-responders who completed the study were titrated up to 15 mg/day.

Table 1 Demographic and clinical characteristics of individuals with trichotillomania

	Subjects (n=14)
Age	
Mean (±SD) (range), years	33.29 (8.86) [21–48]
Female, *n* (%)	14 (100)
Race/ethnicity, *n* (%)	
Caucasian	14 (100)
Marital status, *n* (%)	
Single	5 (35.7)
Married	8 (57.1)
Widowed/separated/divorced	1 (7.2)
Education, *n* (%)	
High school grad or less	1 (7.2)
At least some college	13 (92.8)
Unemployed, *n* (%)	1 (7.2)
Age of trichotillomania onset, years	10.86 (4.57)
Trichophagia, *n* (%) of subjects endorsing behavior	6 (42.9)
MGH-HPS total score	16.5 (4.38)
MGH-HPS Factor 1 scale (items 1, 2, 4, 7)	8.93 (3.15)
MGH-HPS Factor 2 scale (items 3, 5, 6)	7.57 (1.91)
NIMH Trichotillomania Severity Scale, total score	11.21 (3.75)
MIST-A Focused Pulling scale (items 4–6,8–11, 13–15)	42.86 (12.09)
MIST-A Automatic (Habit) Pulling scale (items 1–3, 7, 12)	19.93 (8.72)
Clinical Global Impression (CGI) Severity Scale	4.21 (0.58)
Previously sought treatment for trichotillomania	12 (85.7)
Any current psychiatric comorbidity, *n* (%)	8 (57.1)

All variables are mean (±SD) (range) unless otherwise indicated. Comorbid disorders did not include bipolar disorder or psychotic disorders as these were exclusion criteria

MGH-HPS Massachusetts General Hospital Hair-Pulling Scale, *MIST-A* Milwaukee Inventory for Styles of TTM-Adult Version, *Mgh-Hps Factor 1 scale* severity scale, *Mgh-Hps Factor 2 scale* resistance and control scale

Table 2 Changes on primary and secondary non-cognitive measures in trichotillomania subjects treated with dronabinol

	Baseline	Week 3	Week 6	Week 9	Week 12 (or study endpoint)	Statistic	*df*	*p* value
MGH-HPS total score	16.50 (4.38)	12.14 (6.43)	11.71 (5.05)	10.93 (4.81)	8.71 (5.48)	8.423a	2.52, 32.766	0.001[a]
MGH-HPS Factor 1 scale (total score)	8.93 (3.15)	6.71 (3.71)	6.07 (3.03)	5.86 (3.035)	4.57 (3.11)	7.869a	2.193, 28.508	0.001[b]
MGH-HPS Factor 2 scale (total score)	7.57 (1.91)	5.43 (3.52)	5.64 (2.74)	5.07 (2.37)	4.14 (2.69)	5.783a	4, 52	0.001[c]
Responder, *n* (%) (35% improvement from visit 1 MGH-HPS total score and CGI improvement score of 1 or 2)		4 (28.6)	4 (28.6)	6 (42.9)	9 (64.3)	5.743q	3	0.125
NIMH Trichotillomania Severity Scale, total score	11.21 (3.75)	7.82 (6.20)	8.21 (4.61)	5.57 (3.92)	4.36 (4.11)	9.588a	2.234, 29.037	<0.001[d]
Hamilton Anxiety Rating Scale	4.64 (3.52)	3.71 (2.81)	3.00 (2.83)	3.21 (2.08)	3.43 (2.03)	2.362a	4, 52	0.065
Hamilton Depression Rating Scale	5.07 (3.63)	4.07 (3.39)	3.29 (2.40)	3.00 (2.08)	3.57 (2.95)	3.657a	4, 52	0.011[e]
Sheehan Disability Scale—total score	9.36 (6.37)	6.79 (6.12)	6.14 (5.52)	4.79 (4.12)	4.43 (4.47)	9.234a	2.216, 28.813	0.001[f]
Clinical Global Impression—severity	4.21 (0.58)	3.29 (1.27)	3.21 (1.19)	2.79 (0.98)	2.21 (1.05)	12.573a	4.52	<0.001[g]
Clinical Global Impression—improvement		2.93 (1.38)	2.50 (1.16)	2.29 (1.07)	1.79 (0.7)	4.521a	3, 39	0.008[h]
Quality of life inventory *T* score	45 (14.09)				45.14 (15.35)	−0.077t	13	0.940

Last observation carried forward. All values shown as mean±SD, unless otherwise indicated. Logistic regressions were run for responders dependent variable

Statistic: *t* *t* test, *a* F statistic from GLM repeated measures, *w* Wilcoxon test *q* Cochran's Q; *p* value: *Linear* linear component across visits, *Quadratic* quadratic component across visits; *MGH-HPS* Massachusetts General Hospital Hair Pulling Scale, *MGH-HPS Factor 1 scale* severity scale, *MGH-HPS Factor 2 scale* resistance and control scale, *NA* not applicable, *CGI* Clinical Global Impression, *NIMH* National Institute of Mental Health

Significance of polynomial contrasts:

[a] Linear=0.002; quadratic=0.332; cubic=0.049; order 4=0.456

[b] Linear=0.004; quadratic=0.298; cubic=0.049; order 4=0.882

[c] Linear=0.002; quadratic=0.455; cubic=0.104; order 4=0.298

[d] Linear=0.001; quadratic=0.687; cubic=0.349; order 4=0.010

[e] Linear=0.007; quadratic=0.063; cubic=0.657; order 4=0.982

[f] Linear=0.002; quadratic=0.062; cubic=0.603; order 4=0.193

[g] Linear=<0.001; quadratic=0.658; cubic=0.116; order 4=0.296

[h] Linear=0.011; quadratic=0.869; cubic=0.523

All variables had a significant (improving) linear trend in the curve for mean scores over visits. Variables that were collected at all time points had a significant quadratic component (curvature in the line connecting mean scores over visits) (Table 2). On cognitive tasks, there were no significant effects of drug treatment on the primary outcome variables (Table 3).

The incidence and severity of adverse experiences were consistent with prior studies (Müller-Vahl et al. 1998) and no unexpected experiences were reported (Table 4). Most adverse experiences were of mild to moderate intensity, and all adverse events resolved without sequelae. Mean weight for the group decreased from 168.57±29.19 pounds at baseline to 165.36±26.42 pounds (p=0.762) at the end of the treatment period.

Discussion

This pilot study, the first to examine a cannabinoid agonist in the treatment of trichotillomania, found that trichotillomania symptoms improved significantly in a majority (64.3%) of subjects. The current study is also the first to explore the effects of dronabinol treatment on specific cognitive functions, assessed with the CANTAB. It was found that there were no significant effects of treatment on

Table 3 Dronabinol produced no significant deleterious effects on cognition in trichotillomania subjects

	Pre-mean (SD)	Post-mean (SD)	*t*	*p* value
CGT quality of decision-making	0.96±0.04	0.96±0.05	1.000	0.336
CGT proportion of points gambled	0.56±0.09	0.59±0.12	1.000	0.336
IDED total errors (adjusted)	28.64±39.03	18.15±17.61	1.143	0.274
SST SSRT, ms	176.07±48.23	180.3±51.2	−0.391	0.703
SST median "go trial" reaction time, ms	508.15±145.53	458.58±164.58	1.832	0.090
RVIP A'	0.92±0.03	0.93±0.04	−1.349	0.207
RVIP B'	0.92±0.07	0.94±0.08	−0.899	0.390
RVIP mean response latency	437.65±122.76	383.49±98.09	1.230	0.247
SWM total errors	22.31±11.83	21.25±17.07	0.105	0.918
SWM strategy scores	32.69±4.15	32.42±3.68	0.135	0.895
OTS problems solved in minute moves	16.77±3.68	16.67±3.31	0.085	0.934

Statistic: *t* *t* test, *CGT* Cambridge Gamble Task, *IDED* Intra/Extradimensional Set Shift Task, *SST* Stop Signal Task, *RVIP* Rapid Visual Information Processing Task, *SWM* Spatial Working Memory, *OTS* One Touch Stockings (of Cambridge)

any of the cognitive measures examined. These findings suggest that pharmacological modulation of the cannabinoid system with dronabinol may reduce the compulsive motoric aspect of trichotillomania, in the absence of deleterious cognitive effects that have been reported with certain pharmacological agents affecting the cannabinoid system.

Subjects experienced a mean improvement of 50% reduction on the primary outcome measure (i.e., MGH-HPS), and a responder rate of 64.3% (i.e., ≥35% on the MGH-HPS and "much" or "very much" improved on the CGI by study endpoint). Although open-label studies have notoriously high response rates, when we compare our results to previous open-label studies, we find that the percentage of responders in this study compares favorably to that seen in previous open-label pharmacotherapy trials of trichotillomania using antidepressants (39% to 67%) (Stein et al. 1997; Gadde et al. 2007; Ninan et al. 1998). In fact, our definition of "responder" mirrors the most restrictive definition of this term used in previous studies (Dougherty et al. 2006; Keuthen et al. 2011). Of course previous open-label studies of fluoxetine in trichotillomania demonstrated promising response rates (50% to 67%) (Koran et al. 1992; Winchel et al. 1992) which were not confirmed by double-blind, placebo-controlled studies (Christenson et al. 1991a, b; Streichenwein and Thornby 1995) and so these promising results must be viewed cautiously.

The promising results of dronabinol in this study lend support to the hypothesis that pharmacological manipulation

Table 4 Adverse events associated with dronabinol

	Pooled trial data from studies of subjects with AIDS-related anorexia and chemotherapy-related nausea[a]	Trichotillomania study participants (*n*=14)			
Adverse event	Dose range (5–20 mg/day)	2.5 mg/day (*n*=14)	5 mg/day (*n*=13)	10 mg/day (*n*=12)	15 mg/day (*n*=7)
Light-headed/dizzy	3–10%	2 (14.3%)	1 (7.7%)	1 (8.3%)	–
"High" (i.e., easy laughing, elation, and heightened awareness)	8–24%	–	1 (7.7%)	2 (16.7%)	–
Sedation	3–10%	1 (7.7%)	1 (7.7%)	–	–
Dry mouth	Frequency not specified	–	1 (7.7%)	1 (7.7%)	–
Constipation	Frequency not specified	–	1 (7.7%)	–	–
Headache	<1%	–	–	1 (7.7%)	–
Nausea/vomiting	3–10%	–	1 (7.7%)	–	–
Abdominal pain	3–10%	–	–	–	–
Paranoia	3–10%	–	–	–	–
Any side effect	Frequency not specified	3 (21.4%)	6 (46.2%)	5 (41.7%)	0

[a] http://www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-emc0004-04.pdf and http://www.merckmanuals.com/professional/lexicomp/dronabinol.html

of the cannabinoid system (via its probable effects on the glutamate and dopamine system) may target the core symptoms of compulsive behaviors. There are high densities of cannabinoid receptors in the basal ganglia and hippocampus indicating a putative functional role of cannabinoids in movement and behavior. A study of 17 subjects with Tourette's syndrome who used marijuana found that 14 (82%) reported a reduction or remission of motor tics and a reduction in premonitory urges and co-occurring obsessive compulsive disorder (OCD) symptoms (Müller-Vahl et al. 1998). The authors speculated that cannabinoids influenced dopaminergic processes and therefore regulated motor activity (Herkenham et al. 1990; Mailleux and Vanderhaeghen 1992). A follow-up randomized, cross-over trial of delta-9-THC in 12 patients with Tourette's syndrome further supported the initial examination as both tics and OCD symptoms improved (Müller-Vahl et al. 2002).

Although dronabinol may be a promising treatment for trichotillomania, prior pharmacological studies in trichotillomania have shown that particular treatments have not been effective for all individuals. These prior results may reflect the heterogeneity of individuals with trichotillomania and how this heterogeneity may necessitate individually tailored treatment approaches. It is possible that individuals with trichotillomania and motor impulsivity may respond preferentially to dronabinol. While this notion remains speculative and requires additional studies to examine its appropriateness, one future direction for the treatment of trichotillomania may be to better define cognitive subtypes of trichotillomania to guide pharmacological treatment selection.

This study represents, to our knowledge, the first trial of a cannabinoid agonist in trichotillomania that has included objective cognitive measures. Nonetheless, there exist several important limitations. The study was open-label, and it is possible that patient and clinician bias may have influenced the results. There may have been positive responses not attributable to drug such as positive effects of regular clinician contact and/or subjects feeling obliged to meet the expectations of the research. Even the natural waxing and waning course of trichotillomania may explain some of the benefit seen with medication. Trichotillomania is a chronic disease that may require long-term therapy. By design, this study did not assess treatment effects beyond a 12-week treatment period. It is possible that a longer course of treatment could result in continued and even greater reductions in symptoms. Alternatively, dronabinol's therapeutic effects in trichotillomania might not endure beyond 12 weeks. We enrolled subjects seeking pharmacological treatment, not psychotherapy. Therefore, these results may not generalize to the larger population of people with trichotillomania. Fewer exclusionary criteria in this study (e.g., most current Axis I disorders were not grounds for exclusion), however, suggest that this sample may generalize to a large population of individuals with trichotillomania. Subjects taking stable doses of psychotropic medications were enrolled and these medications might have affected treatment outcome. Given that there was no differential treatment response based on whether or not a subject was taking other psychotropic medications, the evidence suggests that positive outcome is not likely due to dronabinol augmenting another agent. Finally, with respect to the neurocognitive measures, the sample size may have limited power to detect deleterious or positive effects of active treatment on cognition, and we assessed cognition at baseline and at the end of the trial only. Given that negative effects of THC on cognition have been described following both acute dosing and longer-term use, future studies should measure cognition not only at the end of treatment but also at initiation, e.g., following the first dose.

This investigation suggests that dronabinol may be effective in the acute treatment of trichotillomania by improving motor impulsivity. As effective treatments for trichotillomania emerge, it becomes increasingly important that physicians and mental health care providers screen for trichotillomania to provide timely treatment. Given the open-label design of the study and the small number of subjects participating, however, the interpretation of the efficacy results of this study is limited. Additionally, in the USA, dronabinol is a schedule 3 controlled substance and is potentially habit forming [although this aspect of dronabinol has been questioned (Calhoun et al. 1998)]. This type of medication, therefore, needs to be used cautiously in those with histories of substance addiction. It also raises ethical implications of using a potentially habit-forming medication to treat a non-life-threatening disorder. The choice to use dronabinol therefore needs to be examined in light of the severity of illness and the risks versus benefits of this type of medication. This study may support the future development of non-habit-forming medications that target the cannabinoid system in clinical disorders associated with repetitive motoric habits.

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