ARTICLE

Double-Blind Placebo-Controlled Study of Memantine in Trichotillomania and Skin-Picking Disorder

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Objective: Trichotillomania and skin-picking disorder are underrecognized and often disabling conditions in which individuals repeatedly pull at their hair or pick at their skin, leading to noticeable hair loss or tissue damage. To date there is a severe paucity of evidence-based treatments for these conditions. In this study, the authors sought to determine whether memantine, a glutamate modulator, is more effective than placebo in reducing hair-pulling and skin-picking behavior.

Methods: One hundred adults with trichotillomania or skin-picking disorder (86 women; mean age, 31.4 years [SD=10.2]) were enrolled in a double-blind trial of memantine (dosing range, 10–20 mg/day) or placebo for 8 weeks. Participants were assessed with measures of pulling and picking severity. Outcomes were examined using a linear mixed-effects model. The prespecified primary outcome measure was treatment-related change on the NIMH Trichotillomania Symptom Severity Scale, modified to include skin picking.

Results: Compared with placebo, memantine treatment was associated with significant improvements in scores on the NIMH scale, Sheehan Disability Scale, and Clinical Global Impressions severity scale in terms of treatment-by-time interactions. At study endpoint, 60.5% of participants in the memantine group were "much or very much improved," compared with 8.3% in the placebo group (number needed to treat=1.9). Adverse events did not differ significantly between the treatment arms.

Conclusions: This study found that memantine treatment resulted in statistically significant reductions in hair pulling and skin-picking symptoms compared with placebo, with relatively high efficacy (based on number needed to treat), and was well tolerated. The glutamate system may prove to be a beneficial target in the treatment of compulsive behaviors.

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Trichotillomania (also known as hair-pulling disorder) and skin-picking disorder (also known as excoriation disorder) are characterized by repetitive behaviors that often result in noticeable cosmetic issues (e.g., alopecia, excoriations, scarring) as well as significant distress or functional impairment (1–3). Although prevalence rates of 1.7% for trichotillomania and 2.1% for skin-picking disorder suggest that these are not uncommon psychiatric disorders, they lack clearly identified treatments (4, 5). Behavioral therapy is generally regarded as the first-line treatment (controlled studies support the use of habit reversal or acceptance-enhanced behavior therapy) (6, 7), but trained therapists are difficult to find (8). In addition, there is no medication currently approved by the U.S. Food and Drug Administration (FDA) for these disorders (8), and pharmacological clinical trials focusing on these disorders are relatively uncommon (double-blind placebo-controlled studies support the use of olanzapine, *N*-acetylcysteine, or clomipramine but not the use of selective serotonin reuptake inhibitors) (7, 9).

Although regarded as separate disorders, accumulating research evidence supports the idea of classifying trichotillomania and skin-picking disorder under one category. Both behaviors are directed toward one's own body and focus on modifying parts of the body (hair or skin) (1, 3). Research further suggests that these two disorders share important similarities in terms of phenomenology and course of illness, as well as with respect to certain etiological, genetic, and maintaining factors (10, 11). In terms of neurobiology, studies using diffusion tensor imaging found that individuals with trichotillomania and skin-picking disorder both exhibited significantly reduced fractional anisotropy in the anterior cingulate, the pre-supplementary motor area, and the temporal cortices (12, 13). These data suggest that the disorganization of white matter tracts in motor habit generation and suppression may contribute to the pathophysiology of these

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disorders (12, 13). Neurochemically, motor habits and the intrusive urges that drive them may be at least partially driven by the glutamate system, and glutamatergic dysfunction has been implicated in the pathophysiology of compulsive or habitual behaviors (14–20). Furthermore, glutamate's role as a proposed mechanism in the pathophysiology of these disorders stems from animal data on compulsive grooming. The SAPAP3 knockout mouse, a model of grooming behaviors (SAPAPs are proteins that act between glutamate receptor–binding proteins and the cytoskeleton) (21), exhibits excessive self-grooming behaviors that appear to be somewhat analogous to hair pulling and skin picking. Memantine, which is FDA approved for moderate to severe Alzheimer's disease, is a glutamate receptor antagonist that targets excessive glutamatergic drive and may therefore offer unique benefits in reducing the excessive self-grooming seen in trichotillomania and skin-picking disorder (22–24).

Given the potentially serious consequences associated with trichotillomania and skin-picking disorder (1–3), and given a likely role of the glutamate system in their pathophysiology, our aim in the present study was to examine the efficacy and safety of memantine compared with placebo in adults with trichotillomania or skin-picking disorder, using a double-blind, placebo-controlled design. We hypothesized that memantine would be more effective than placebo in reducing the symptoms of hair pulling and skin picking and in improving overall psychosocial functioning after 8 weeks of treatment.

METHODS

Participants

The study participants were men and women 18–65 years of age with a current primary DSM-5 diagnosis of trichotillomania or skin-picking disorder. Diagnoses were made using a validated structured clinical interview (see below) by a psychiatrist with extensive expertise in assessing and treating these conditions. Participants had to be pulling or picking daily for at least 15 minutes to be included in the study. Individuals were recruited through newspaper advertisements and referrals. Details of diagnostic procedures are provided below.

Exclusion criteria included unstable medical illness; history of seizures; lifetime bipolar disorder, dementia, or psychotic disorder; current (past 3 months) substance use disorder; current suicide risk; previous treatment with memantine; pregnancy or inadequate contraception in women of childbearing potential; and initiation of pharmacotherapy or psychotherapy within 3 months prior to study entry. Current use of psychotropic medications was allowed if the dosage had been stable for 3 months and there were no plans to modify it.

Data were collected from September 2021 to June 2022 at the University of Chicago. The Institutional Review Board for the Biological Sciences Division and University of Chicago Medical Center approved the study and the informed consent procedures. One investigator discussed potential risks of the study, as well as alternative treatments, with participants. After participants were given a complete description of the study and an opportunity to ask questions, they provided written informed consent. This study was carried out in accordance with the principles of the Declaration of Helsinki.

Study Design

Eligible participants were assigned to 8 weeks of double-blind treatment with memantine or placebo. The university's investigational pharmacy randomized all participants (block sizes of eight, using computer-generated randomization with no clinical information) to either memantine or matching placebo in a 1:1 ratio. All participants were seen every 2 weeks during the 8-week study period. Participants were started on memantine at 10 mg/day, and at week 2, the dosage was increased to 20 mg/day for the remaining 6 weeks. Placebo capsules were identical in appearance to the memantine capsules, and the number of capsules was increased at week 2, to maintain procedures identical with those of the active treatment arm. Participants and the research team were fully blinded to treatment condition. The dosage range for memantine was based on safety and efficacy data from studies using memantine (25, 26). Efficacy and safety measures were performed at each visit.

Steps taken to minimize risk of bias are summarized in Table S1 in the online supplement, using domains recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0 (chapter 8). The study was deemed to be at low risk of bias.

Screening Assessments

Demographic characteristics and clinical features of trichotillomania and skin picking were assessed with the Minnesota Impulse Disorders Interview (MIDI) (27). The MIDI includes DSM-5 diagnostic criteria for trichotillomania and skin-picking disorder as well as questions regarding their phenomenology. Psychiatric comorbidity was assessed using the Mini International Neuropsychiatric Interview (28). Racial/ethnic group was defined by participants, self-identifying their racial group based on a single open-ended question. Participants were also asked about their biological sex at birth and the gender that they currently identified as.

Efficacy Assessments

The study design, including the primary outcome measure, was preregistered at ClinicalTrials.gov. The primary outcome measure was change from baseline to week 8 in total symptom score on the NIMH Trichotillomania Symptom Severity Scale (29), which we modified for skin-picking disorder as there is not a common clinician-administered scale for both disorders. The NIMH scale is a 6-item scale (total score ranges from 0 to 20) comprising questions assessing pulling/picking frequency (past week and yesterday), urge intensity, subjective distress, and interference in daily activities. In the case of participants with both trichotillomania and skin-picking disorder, the questions pertain to both behaviors.

The secondary outcome measures of interest included the Massachusetts General Hospital Hairpulling Scale (MGH-HPS).

The MGH-HPS is a 7-item self-report scale that rates frequency and intensity of urges to pull hair, frequency of hair pulling and attempts to resist pulling, ability to control the urges and the pulling, and distress over the past week on a severity scale from 0 to 4 for each item (total score ranges from 0 to 28, with higher scores reflecting greater illness severity) (30). Because of the lack of an identical scale for skin-picking disorder, we modified the wording of the MGH-HPS to include skin-picking behavior (using the same seven items and scoring) to keep the outcome measurements consistent across the disorders. In cases where participants had both disorders, they were asked to combine their behaviors when answering the questions. Thus, if one condition improved but the other did not, the answers would reflect the condition that did not improve. We refer to this modified instrument as the MGH scale.

The Clinical Global Impressions improvement scale (CGI-I) (31) was used to rate changes in symptoms of trichotillomania and skin picking, taking into account the participant's report about behavior, observations of the excoriated lesions or alopecia, and the self-report measures.

The Sheehan Disability Scale (SDS) (32) is a three-item self-report scale that assesses functioning in work, social or leisure activities, and home and family life.

The Hamilton Anxiety Rating Scale (HAM-A) (33) and Hamilton Depression Rating Scale (HAM-D) (34) were used to assess anxiety and depressive symptoms, respectively.

Safety Assessments

Safety assessment at each visit included the evaluation of suicidality using the Columbia–Suicide Severity Rating Scale (C-SSRS) (35). Adverse events were documented at each visit and included time of onset and resolution, severity, action taken, and outcome.

Data Analysis

All data analyses were conducted by a statistical company that was independent of the study team (Professional Data Analysts GBC, Minneapolis), while the study team remained blinded to drug conditions. The data analysis plan was agreed on with the independent company prior to database lock and prior to unblinding. Key baseline demographic and clinical characteristics were analyzed (age, gender, education, employment status, and baseline severity measures), comparing the treatment groups (with trichotillomania and skin-picking disorder combined) using chi-square tests (or Fisher's exact tests if expected cell sizes were <5) and two-sample t tests for all enrolled participants and for those who completed the study. Descriptive statistics were calculated for all variables of interest (means and standard deviations for continuous variables and frequencies and proportions for categorical variables). Distributions of outcomes were assessed for normality, and missing data were reviewed. Participants who were lost to follow-up and those who had missing data at week 8 were excluded from the analyses.

Change from baseline to week 8 in continuous primary and secondary outcomes were assessed using paired t tests within each group (placebo, memantine) for all participants (trichotillomania and skin-picking disorder combined). Two-sample t tests were used to compare the change from baseline to week 8 between the placebo and memantine groups where sample sizes allowed. For secondary categorical outcomes (CGI-I score), the proportions of participants with a CGI-I score of 1 or 2 (very much improved or much improved) were compared using Fisher's exact test (expected cell sizes are <5) between the placebo and memantine groups.

A linear mixed-effects regression model was used with primary or secondary variables as the dependent variable. Independent variables included terms for treatment group, study visit, and treatment-by-visit interaction. Imputation was not undertaken for missing visit data. Correlation between visits for the same participant were modeled using an autoregressive correlation. Residuals and model fit were examined. Type III tests of fixed effects (F tests) and t tests for each coefficient parameter were performed. The effect of interest was the treatment-by-visit interaction, specifically the change between groups from baseline to visit 8. Age and diagnosis were considered as predictors in the model; model fit statistics (Akaike information criterion, Bayesian information criterion) with and without these variables were compared, and the model with the better fit was selected.

If primary analyses were significant, follow-up analyses were conducted including investigation into which week was significant and whether response differed by diagnosis (trichotillomania vs. skin-picking disorder). Additionally, post hoc analysis was undertaken to address whether antidepressant status affected the NIMH scale total score using Mann-Whitney U tests within treatment groups.

SAS, version 9.4 (SAS Institute, Cary, N.C.) was used for analysis. The significance threshold was set at a p value of 0.05.

The sample size was calculated for the primary endpoint of change from randomization. For 80% power to compare the change from randomization, assuming a true effect size of 0.5 between the memantine group and the placebo group, 30 participants with either trichotillomania or skin picking (or both) were needed in each treatment group, based on a two-group t test at the 0.05 level of significance.

RESULTS

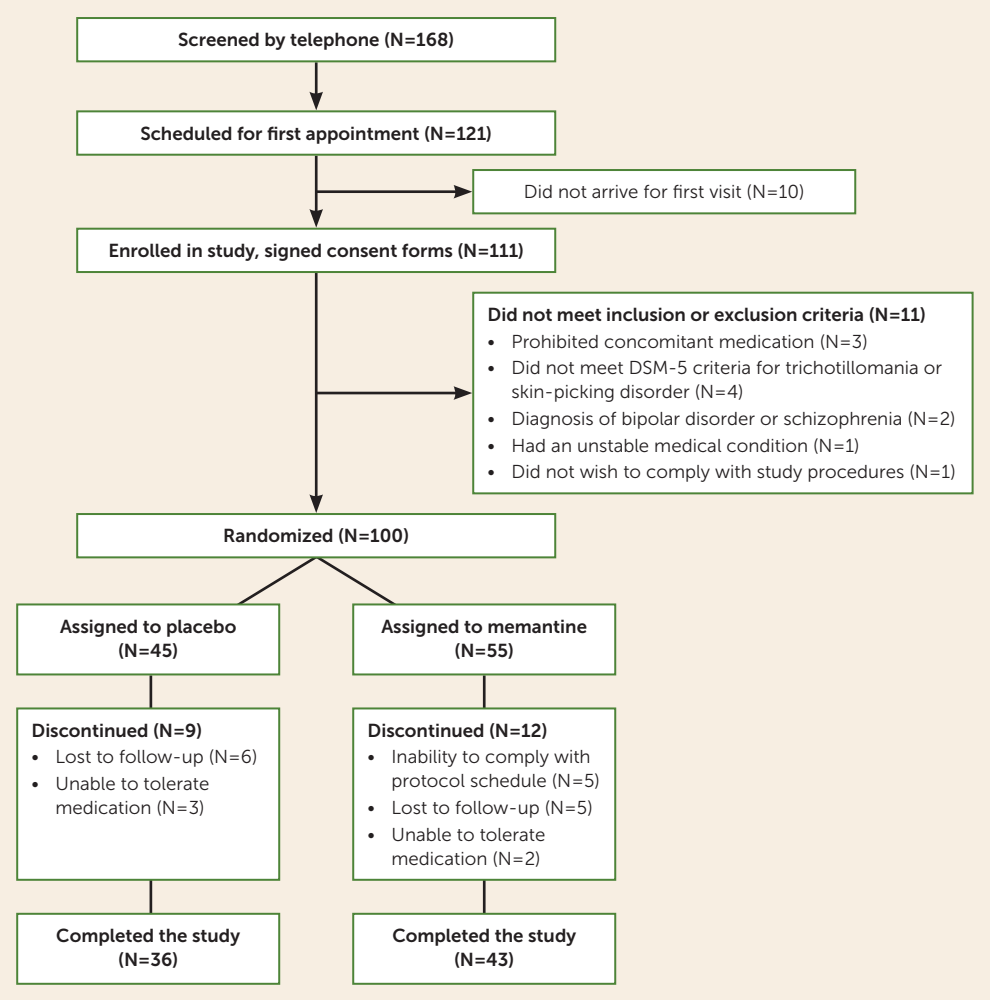
Participant Characteristics

Of 168 individuals screened, 100 (86 women; mean age, 31.4 years [SD=10.2]) with trichotillomania (N=53), skin-picking disorder (N=43), or both (N=4) were randomized: 55 to the memantine group and 45 to the placebo group (Figure 1). The distribution of those with trichotillomania, skin-picking disorder, or both was similar between the treatment and placebo groups (roughly 50%, 45%, and 5%, respectively).

The 100 randomized participants reported a mean onset age of 12.6 years (SD=8.1) for hair pulling or skin picking. The majority (N=55; 55.0%) pulled or picked from multiple sites. Few participants had prior pharmacological treatment for

trichotillomania or skin picking: four (4.0%) had a previous trial of *N*-acetylcysteine and two (2.0%) had a trial of naltrexone. Thirty-four (61.8%) participants in the memantine group had at least one co-occurring disorder: 22 (40.0%) had major depressive disorder, 21 (38.2%) had an anxiety disorder, five (9.1%) had posttraumatic stress disorder (PTSD), two (3.6%) had obsessive-compulsive disorder, one (1.8%) had body dysmorphic disorder, and one (1.8%) had a tic disorder. Among participants in the placebo group, 27 (60.0%) had at least one co-occurring disorder: 15 (33.3%) had major depressive disorder, 12 (26.7%) had an anxiety disorder, four (8.9%) had obsessive-compulsive disorder, three (6.7%) had PTSD, and two (4.4%) had tic disorders. Rates of comorbidity in the groups did not differ significantly.

FIGURE 1. CONSORT flow diagram for a placebo-controlled trial of memantine in the treatment of trichotillomania and skin-picking disorder



Twelve participants in the placebo group (26.7%) had ongoing psychotherapy: two had cognitive-behavioral therapy (CBT) focusing on mood, anxiety, and pulling/picking behavior, which had been ongoing for over 6 months each, and 10 had general supportive psychotherapy for issues other than pulling/picking. In the memantine group, 15 participants (27.3%) had ongoing psychotherapy: three had CBT for anxiety and picking/pulling for over 1 year, and 12 had general supportive therapy for issues other than picking/pulling. Rates of psychotherapy did not differ significantly between treatment groups. Approximately 44% of both groups were taking a therapeutic dosage of an antidepressant (in all cases the antidepressant was being used for depressive or anxiety symptoms), and these rates did not differ significantly between groups ($p>0.999$).

Table 1 summarizes demographic and clinical characteristics for all randomized participants and for those who completed the study. Baseline hair pulling and skin picking scores were reflective of moderate severity, and overall baseline psychosocial dysfunction was mild to moderate. Randomized participants and those who completed the study showed similar results, indicating that those who dropped out were not biasing the sample on these variables.

Dropout rates were similar between study groups. Of the 45 participants randomized to the placebo group, 36 completed the study (80%). Of the 55 participants randomized to the memantine group, 43 completed the study (78%) (Figure 1). An attrition rate of approximately 20% is in keeping with many pharmacological trials in obsessive-compulsive spectrum disorders (19%–29%) (18, 36–38). For the two participants who were assigned to the memantine group and withdrew from the study because of medication side effects, in both cases it was dizziness that led to treatment discontinuation.

Efficacy Results

In the comparisons of change from baseline to week 8 in the severity measures in the memantine and placebo groups separately, the unadjusted average change in the memantine group was statistically significantly different from the unadjusted average change in the placebo group on four measures: NIMH scale total score (group unadjusted average, −6.98 [SD=3.65] vs. −1.19 [SD=2.80]; t=7.78, df=77, $p<0.0001$), SDS score (−5.73 [SD=5.76] vs. −1.66 [SD=7.25];

TABLE 1. Baseline demographic and clinical characteristics of participants in a placebo-controlled trial of memantine in the treatment of trichotillomania and skin-picking disorder[a]

Characteristic	All Randomized Participants					Completers Only				
	Placebo Group (N=45)		Memantine Group (N=55)			Placebo Group (N=36)		Memantine Group (N=43)		
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
Age (years)	32.82	11.46	30.25	9.08	0.214	33.47	12.16	30.19	9.59	0.183
	N	%	N	%	p	N	%	N	%	p
Gender					0.380					0.338
Female	33	73.3	47	85.5		26	72.2	37	86.1	
Male	9	20.0	6	10.9		8	22.2	5	11.6	
Another gender	3	6.7	2	3.6		2	5.6	1	2.3	
Education					0.211					0.182
Some college or less	11	24.4	21	38.2		9	25.0	18	41.9	
College degree or higher	34	75.6	34	61.8		27	75.0	25	58.1	
Employment					0.121					0.284
Full-time	29	64.4	27	49.1		23	63.9	21	48.8	
Part-time	6	13.3	15	27.3		5	13.9	11	25.6	
Student	5	11.1	11	20.0		4	11.1	9	20.9	
Unemployed	4	8.9	2	3.6		3	8.3	2	4.7	
Retired	1	2.2	0	0.0		1	2.8	0	0	
Diagnosis					0.466					0.728
Trichotillomania	24	53.3	29	52.7		19	52.8	22	51.2	
Skin-picking disorder	18	40.0	25	45.5		15	41.7	20	46.5	
Both	3	6.7	1	1.8		2	5.6	1	2.3	
Taking therapeutic dosage of antidepressant	20	44.4	24	43.6	0.999	17	47.2	19	44.2	0.966
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
Baseline severity measures										
NIMH scale	12.02	3.30	12.67	3.21	0.325	12.36	3.33	12.56	3.23	0.791
MGH scale	19.57	3.52	19.30	4.41	0.741	19.78	3.33	19.36	3.65	0.599
Sheehan Disability Scale	9.43	7.75	10.23	7.19	0.602	9.50	7.92	10.21	7.18	0.677
HAM-A	5.20	5.67	6.89	5.55	0.137	5.42	6.06	7.47	5.60	0.123
HAM-D	4.29	3.80	5.87	4.12	0.052	4.50	4.10	6.36	4.18	0.052

[a] The p values in the table are for Fisher's exact tests or two-sample t tests. HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; MGH scale=Massachusetts General Hospital Hairpulling Scale, modified to include skin picking; NIMH scale=NIMH Trichotillomania Symptom Severity Scale, modified to include skin picking.

t=2.65, df=70, p=0.0101), HAM-A score (−3.88 [SD=4.89] vs. −1.42 [SD=5.20]; t=2.17, df=77, p=0.0331), and MGH scale total score (−6.95 [SD=4.20] vs. −3.09 [SD=4.43]; t=3.80, df=70, p=0.0003). For total change on the NIMH scale, the effect size (Hedges' g) was 1.76.

A linear mixed-effects regression model was used with each of the four significant outcome variables as the dependent variable (NIMH scale, SDS, HAM-A, and MGH scale) (Table 2). The variables age and diagnosis were tested in the models, although they did not improve model fit and therefore were removed. It can also be seen in Table 2 that effects of age and diagnosis were not statistically significant when they were included in the initial model.

For the primary outcome variable, NIMH scale total score, the memantine group experienced change from baseline to week 2, followed by a steady decline in score to week 8. The placebo group saw a minimal decline from baseline to week 2, and no additional change over the following 6 weeks. Statistical differences between groups emerged at week 4 (Figure 2).

On MGH scale total score (the self-report measure), the memantine group experienced steady decline until week 6, and the placebo group had a slight decline from baseline to week 2 and then remained stable. There were statistical differences between groups starting in week 4 (Figure 3).

On the SDS, the memantine group experienced a decrease in score each week from baseline to week 6, with a slight increase in week 8. The placebo group saw a decline from baseline to week 2, with no additional change (see Table S2 in the online supplement).

On the HAM-A, both groups experienced improvement from baseline to week 2, and then scores remained fairly steady throughout the remaining visits (see Table S2 in the online supplement).

At week 8, three of 36 (8.3%) placebo participants had a CGI-I score of much or very much improved (i.e., were responders), compared with 26 of 43 (60.5%) in the memantine group (Fisher's exact test, p<0.0001). Based on rates of response, the absolute "risk reduction" was 52.2%, and therefore the number needed to

TABLE 2. Efficacy outcome regression results, reported as mean memantine-placebo differences[a]

	Dependent Variable											
	NIMH Scale Score			Sheehan Disability Scale Score			HAM-A Score			MGH Scale Score		
Analysis	F[b]	SE	p	F[b]	SE	p	F[b]	SE	p	F[b]	SE	p
Study visit[c]			<0.001			<0.001			<0.001			<0.001
Week 2	−1.63*	0.70		−2.15†	1.11		5.11†	0.65		−2.18*	0.93	
Week 4	−1.45*	0.69		−0.82	1.08		−1.37†	0.78		−2.18*	0.92	
Week 6	−1.13†	0.66		−0.72	1.05		−1.37*	0.76		−2.79**	0.91	
Week 8	−1.11†	0.57		−1.49†	0.87		−1.59*	0.73		−3.06**	0.78	
Treatment group randomization[d]			<0.001			0.026			0.526			<0.001
Memantine	0.46	0.74		1.01	1.31		2.00	0.88	<0.1	−0.17	0.94	
Study visit-by-group interaction[e]			<0.001			<0.001			0.045			<0.001
Week 2, memantine group	−3.48**	0.97		−1.40	1.58		−1.49	1.10		−2.66*	1.29	
Week 4, memantine group	−4.11**	0.95		−5.21**	1.52		−2.12*	1.06		−5.01**	1.28	
Week 6, memantine group	−5.46**	0.90		−6.42**	1.43		−1.64	1.00		−4.87**	1.24	
Week 8, memantine group	−5.94**	0.77		−4.57**	1.19		−2.49**	0.84		−3.88**	1.07	
Intercept	12.21	0.54		9.37	0.97		5.11	0.65		19.47	0.70	
Covariance												
Autoregressive 1	0.58	0.04		0.70	0.04		0.65	0.04		0.52	0.04	
Residual	13.94	1.20		44.61	4.52		20.46	1.93		22.63	1.90	
Initial model fit statistics[f]												
Age	0.00		0.974	1.58		0.212	0.52		0.473	0.04		0.839
Diagnosis	0.18		0.672	1.84		0.178	2.36		0.128	0.25		0.619

[a] HAM-A=Hamilton Anxiety Rating Scale; MGH scale=Massachusetts General Hospital Hairpulling Scale, modified to include skin picking; NIMH scale=NIMH Trichotillomania Symptom Severity Scale, modified to include skin picking.
[b] Type III F test.
[c] Reference is baseline.
[d] Reference is the placebo group.
[e] Reference is the placebo group at baseline.
[f] Includes the terms in the preceding entries, plus age and diagnosis (trichotillomania or skin-picking disorder). For the F values, df's are 1,95 or 1,96.
†p<0.1. *p<0.05. **p<0.01.

treat was 1.9. In terms of complete symptom remission rates, six participants in the memantine group (10.9%) stopped pulling/picking completely by the end of the trial, whereas only one (2.2%) of the participants in the placebo group achieved complete symptom remission.

To address whether antidepressant status affected NIMH scale total score (since 20 participants in the placebo group and 24 in the memantine group were on a stable antidepressant regimen at study entry and during the study), we conducted post hoc Mann-Whitney U tests within treatment groups. The unadjusted mean total change in NIMH scale did not differ significantly between those taking and not taking antidepressants in either the placebo group (−0.71 [SD=2.89] vs. −1.63 [SD=2.71]; U=336.5, z=0.688, p=0.4960) or the memantine group (−7.26 [SD=2.86] vs. −6.75 [SD=4.21]; U=403, z=−0.356, p=0.7233).

To address whether memantine was effective for cases of greater symptom severity, we performed a preliminary analysis of those participants who had scores ≥16 on the NIMH scale (indicative of severe illness) at baseline. Of the 18 participants in this more severe category, none of the 10 participants in the placebo group were regarded as responders based on CGI-I score, whereas six of the eight participants (75.0%) in the memantine group were responders (Fisher's exact test, p<0.001).

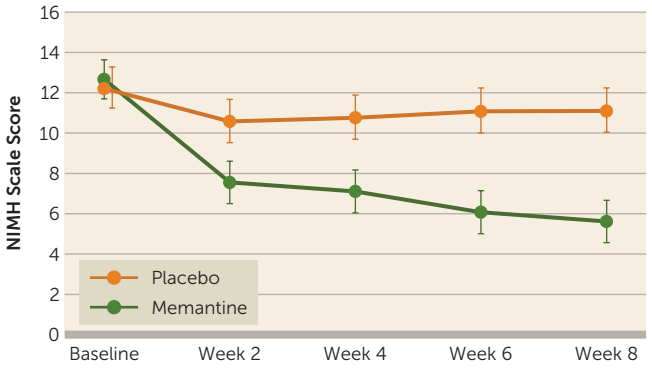
Safety and Tolerability

There were no serious adverse experiences among participants assigned to memantine or placebo. The few adverse experiences were of mild intensity and did not differ significantly between groups (except in two cases in the memantine group, where dizziness led to treatment discontinuation). The most common adverse experiences were fatigue/drowsiness, gastrointestinal issues (nausea, constipation), and dizziness, which were experienced, respectively, by 11.1%, 8.9%, and 6.7% of those on placebo and by 9.1%, 5.5%, and 7.3% of those on memantine. None of the participants experienced any level of suicidality during the study, as reflected by the C-SSRS.

DISCUSSION

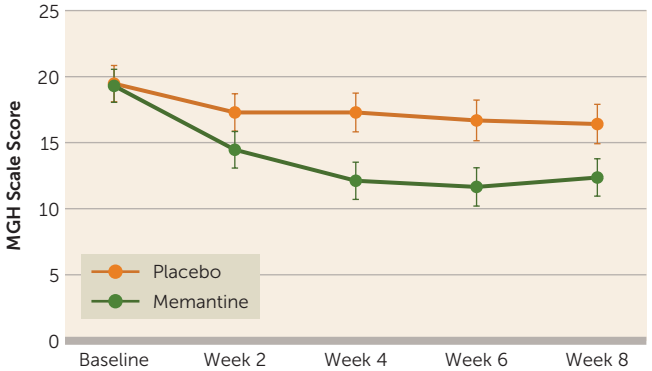
The results of this double-blind randomized clinical trial indicate that memantine was safe and more effective than placebo (number needed to treat=1.9) for treatment of both trichotillomania and skin-picking disorder. The efficacy of

FIGURE 2. Change in NIMH scale score over time with memantine and placebo[a]



[a] Statistically significant differences between groups emerged at week 4 and continued through week 8. NIMH scale=NIMH Trichotillomania Symptom Severity Scale, modified to include skin picking.

FIGURE 3. Change in MGH self-report scale total score over time with memantine and placebo[a]



[a] Statistically significant differences between groups emerged at week 4 and continued through week 8. MGH scale=Massachusetts General Hospital Hairpulling Scale, modified to include skin picking.

memantine in this study lends support to the hypothesis that pharmacological manipulation of the glutamate system may target core symptoms of these compulsive behaviors. Based on the results of this study, memantine constitutes a promising treatment option for trichotillomania and skin-picking disorder—conditions that have a relative paucity of evidence-based pharmacological intervention options.

The beneficial effects of memantine in trichotillomania and skin picking are interesting in light of a possible role for the glutamate system in repetitive compulsive behaviors more broadly (14–20). Previous work indicated that a different glutamate modulator, *N*-acetylcysteine (NAC), showed efficacy compared with placebo in trichotillomania and in skin-picking disorder (17, 18). Memantine has also shown some promise in the treatment of obsessive-compulsive disorder (OCD) when used as augmentation to first-line interventions (39). The beneficial effects of memantine in the present study, however, appear to be directly on the pulling and picking behavior and not due to comorbid OCD, as only two participants in the memantine group had this comorbidity. In future work, it would be informative to consider whether memantine and NAC have similar or different neurobiological effects (or even synergistic effects) in these disorders.

The effect size (Hedges' g) for memantine in this study was 1.76. When we compare the effect size of this study to other treatments for trichotillomania and skin-picking disorder, we find that studies of behavioral therapy using habit reversal techniques had effect sizes between 1.13 and 1.66 (Cohen's d) (compared with waiting list control conditions) (6, 40); a study of olanzapine had an effect size of 0.94 (Cohen's d) (6, 41); a study of clomipramine had an effect size of 0.69 (Cohen's d) (6, 29); and a study of NAC had an effect size of 1.05 (Cohen's d) (6, 17). These comparisons suggest that memantine might be considered a first-line treatment equal to behavioral therapy in the treatment algorithm for these conditions. Of course, some caution is needed when comparing effect sizes across different studies, including in the use of different effect size metrics. At the same time, Cohen's d and Hedges' g can be considered to be very similar metrics for interpretational purposes.

While this study has a number of positive features, such as the methodological design to minimize risk of bias and a focus on disorders that are highly neglected in clinical trials research, several limitations should also be considered. First, both trichotillomania and skin-picking disorder appear to be chronic diseases that likely require treatment beyond 8 weeks (full remission of all symptoms was uncommon in the present study). Longer-term effects of memantine treatment thus require evaluation.

Second, we used scales originally created for trichotillomania to assess skin-picking disorder symptoms. Although there are other skin-picking disorder symptom scales, we chose to modify the trichotillomania scales to be able to assess both groups (including those with both disorders) in a single clinical trial setting, which we believe to be a valuable, useful, pragmatic approach. Although the modified scales lack prior psychometric analyses, they provide good face validity, as trichotillomania and skin picking share numerous phenomenological features. The scales ask the same types of questions, which are clinically relevant to both disorders, such as amount of time picking/pulling, urges to pick/pull, and associated distress. Furthermore, there was no significant effect of diagnosis in the analysis using the scales, further supporting their suitability for use in this study.

Third, the average symptom severity for individuals in this study was mild to moderate, and therefore future clinical trials should examine medication effects in individuals with more severe symptoms. At the same time, we observed evidence of significant symptom benefit even in more severe cases in a secondary analysis. Fourth, all study visits were conducted virtually, and while we believe this approach reduced the overall placebo response rate, it may have made detailed physician assessments of skin damage and hair loss more difficult.

Participants were, however, examined virtually for hair loss and severity of excoriations, and this became part of the assessment for overall severity. Fifth, CBT has shown benefit for trichotillomania and skin-picking disorder and should be considered in conjunction with medication; it is nevertheless important to first establish efficacy for medication or therapy separately in clinical trials before then exploring sequencing and combined approaches. Finally, we did not examine the optimal memantine dosage; whether some individuals would have responded to a higher dosage merits further evaluation.

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Examination Questions for Double-Blind Placebo-Controlled Study of Memantine in Trichotillomania and Skin-Picking Disorder

1. **The following is considered the first-line treatment for trichotillomania and skin picking disorder:**
   A. Fluoxetine
   B. Psychodynamic psychotherapy
   C. Lamotrigine
   D. Behavioral therapy
2. **Memantine's effectiveness for trichotillomania and skin picking may be due to its modulation of which neurochemical system?**
   A. Cannabinoid
   B. Glutamatergic
   C. Noradrenergic
   D. Opioidergic
3. **This study used a maximum dose of 20 mg of memantine for trichotillomania and skin picking. At that dose, which of the following was the most common side effect reported?**
   A. Anorgasmia
   B. Cognitive blunting
   C. Dizziness
   D. Fatigue/drowsiness