Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: http://www.tandfonline.com/loi/ieop20

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To cite this article: Rachel Rothbart & Dan J Stein (2014) Pharmacotherapy of trichotillomania (hair pulling disorder): an updated systematic review, Expert Opinion on Pharmacotherapy, 15:18, 2709-2719, DOI: 10.1517/14656566.2014.972936

To link to this article: https://doi.org/10.1517/14656566.2014.972936

Published online: 15 Nov 2014.

EXPERT OPINION

Pharmacotherapy of trichotillomania (hair pulling disorder): an updated systematic review

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Introduction: Individuals affected by trichotillomania (TTM) (hair-pulling disorder) consciously or non-consciously pull out their own body hair. The disorder has recently been incorporated into a chapter entitled, 'Obsessive-Compulsive and Related Disorders' in the diagnostic and statistical manual of mental disorders, fifth edition.
Areas covered: The review describes the literature currently available on the pharmacotherapy for TTM, including both randomized controlled trials and open-label trials of pharmacotherapy for TTM in adults or children.
Expert opinion: Early work focused on the serotonin reuptake inhibitors; however, the majority of the trials have been negative. There is a small body of evidence focused on pharmacotherapy for TTM. In future, larger trials are required to expand on the preliminary evidence available for N-acetylcysteine, olanzapine and dronabinol in recent trials.

Keywords: hair-pulling disorder, pharmacotherapy, treatment, trichotillomania

Expert Opin. Pharmacother. (2014) ***15****(18):2709-2719*

1. Introduction

Trichotillomania (TTM), also known as hair-pulling disorder, is a prevalent and disabling disorder mostly affecting women. It involves the conscious or non-conscious pulling out of one's own hair from different sites on the body. This most commonly occurs from the scalp; however it can also be from eyebrows, eyelashes, pubic, or peri-anal hair. An American college survey involving 2579 students reported a lifetime prevalence rate for TTM of 0.6% [1]. In another large college survey, 0.9% of students reported baldness and significant distress from hair pulling [2]. TTM often leads to low self-esteem, social isolation and low psycho-social functioning and is commonly co-morbid with depression and anxiety disorders [3].

TTM was incorporated into the DSM-5 in a chapter entitled, 'Obsessive-Compulsive and Related Disorders'. This reflects accumulating knowledge over the past several decades that the disorders in this category are phenomenologically and psychobiologically distinct from anxiety disorders and from impulse control disorders. There is also clinical utility in this grouping as there is a high degree of co-morbidity amongst the disorders in this category, and they require a somewhat similar assessment and management approach [4]. There is a particularly close relationship between TTM and excoriation disorder (skin-picking disorder).

Neuroimaging studies have shed some light on the brain regions involved in TTM. In a structural MRI study, it was found that TTM participants showed an increase in gray matter density in several brain regions involved in affect regulation, motor habits and top-down behavioral inhibition, namely the left striatum, left amygdalo-hippocampal formation, and multiple cortical regions (including the cingulate, supplementary motor, and frontal) bilaterally [5]. In a functional

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10.1517/14656566.2015.972936 © 2014 Informa UK, Ltd. ISSN 1465-6566, e-ISSN 1744-7666

Article highlights.

- Summarizes the literature available on the pharmacotherapy for trichotillomania, divided into different medication classes.
- Provides some explanation as to the rationale behind why the different medication classes have been trialed for management of this disorder based on phenomenology and neurobiology phenomena.
- Seeks to provide some direction for further research in the field based on the existing trials and current evidence available.

This box summarizes key points contained in the article.

neuroimaging study White *et al.* [6] recently showed relatively decreased nucleus acumbens activation for reward anticipation and exaggerated response to reward outcome in TTM subjects. The authors also showed reduced left putamen activation in the loss anticipation condition of the study.

In another functional imaging study, using SPECT, it was found that citalopram treatment was accompanied by a reduction in activity during treatment in both left and right inferior–posterior and superior–anterior frontal areas, and in a few regions outside the frontal lobe such as the right anterior-temporal region and left putamen [7]. The nucleus accumbens and putamen are areas involved in habit formation and motor learning and are mediated by dopaminergic circuits, which may explain the relative success of anti-psychotic agents in treating TTM symptoms in pharmacological studies. However, there is still much to be discovered about the neurobiology involved in TTM.

Based on the diagnostic criteria presented in DSM-5 [8], a diagnosis of TTM requires the following: that recurrent hair-pulling results in hair loss (criterion A); there must be evidence of an attempt to decrease or stop hair-pulling (criterion B); the diagnosis of TTM can be made only if hair-pulling is not better accounted for by another disorder (e.g., in response to a delusion, or as part of a body dysmorphic disorder) or is not a result of a general medical condition (criterion C); and recurrent hair-pulling must cause significant distress or impairment of functioning (criterion D).

A wide variety of pharmacologic agents have been evaluated for TTM, both in randomized controlled trials (RCTs) and open-label studies. This review summarizes the literature on pharmacotherapy for TTM to date.

2. Methods

We recently undertook an extensive search for RCTs in TTM as part of a Cochrane review [9]. For the purposes of the current review, we updated this search using PubMed, and also included open-label trials. Furthermore the references cited in published review articles were searched for additional studies. Both RCTs and open-label trials of pharmacotherapy for TTM in adults or children are described in this review.

3. Results

The search yielded a total of 19 trials published between 1989 and 2014; twelve of these are randomized controlled trials (RCTs) and another seven are open-label trials. Eighteen of these trials involved adults and there has been only one trial in children. The trials involved numerous medication classes including: serotonin reuptake inhibitors (SRIs), tricyclic antidepressants (TCAs), opioid antagonists, glutamate modulators, cannabinoid agonists, and antipsychotics. The characteristics of the trials are summarized below and in **Table 1**.

3.1 Serotonin reuptake inhibitors

Christenson *et al.* [10] published the first randomized, double-blind controlled trial involving SRIs. This was a cross-over trial involving 16 participants with TTM. Participants were randomized to either fluoxetine or placebo for 6 weeks and then after a 5-week wash-out period switched to the other condition. Participants took 20 mg/day of their assigned condition for 2 weeks, 40 mg/day for another 2 weeks and then 80 mg/day for the final 2 weeks. The primary outcome measures in the study were: the number of hair-pulling episodes per week, the estimated number of hairs pulled per week, the rating of the severity of the urge to pull hair, and the rating of the severity of hair pulling. Christenson *et al.* found that there was no statistically significant treatment effect of fluoxetine over placebo on any of the outcomes measured.

Another similar randomized controlled cross-over trial by Strechenwein *et al.* [11] involved 23 participants with TTM. In this study participants were randomized to either fluoxetine or placebo for 12 weeks with a 5-week wash-out period and then switched to the other condition. The primary outcome measures in the study were the same as in the study by Christenson and colleagues. Strechenwein *et al.* found that there was no statistically significant treatment effect of fluoxetine over placebo on any of the outcomes measured.

Dougherty *et al.* [12] reported a randomized controlled parallel-arm trial involving 37 participants in which 19 were randomized to sertraline and 18 to placebo for 12 weeks. The primary outcome measures were: the Massachusetts General Hospital Hair Pulling Scale (MGH-HPS), the Psychiatric Institute TTM Scale (PITS), and the TTM Impact Scale (TTMIS). This was the initial phase of a trial that subsequently involved a habit-reversal therapy arm as well. The results of the pharmacotherapy study are not available in the paper as the medication versus placebo phase of the trial was not the focus of the study. For our Cochrane review the data from the sertraline versus placebo phase of the trial were analyzed, and it was found that sertraline did not result in a statistically significant treatment effect compared to placebo in this study [9].

Another parallel randomized controlled trial involved three arms: a behavioral therapy group, a fluoxetine group and a waiting list control group [13]. This was a 12-week trial

Table 1. Characteristics of included studies.

Authors and year	Pharmacological agent	Adults or children	Study design	Sample size	Maximum and average dose of medication	Trial length	Symptom rating scales	Results
Christenson *et al.* (1991) [10]	Fluoxetine versus placebo	Adults	RCT, crossover	16	Maximum dose 80 mg/day, average dose not reported	6 weeks	Number of hair-pulling episodes/week; estimated number of hairs pulled/week; counted number of hairs pulled/week; rating of severity of urge to pull hair/week; rating of severity of hair pulling/week	Fluoxetine did not demonstrate a statistically significant treatment effect compared to placebo
Strechenwein *et al.* (1995) [11]	Fluoxetine versus placebo	Adults	RCT, crossover	23	Maximum dose 80 mg/day, average dose not reported	12 weeks	Number of hair-pulling episodes/week; estimated number of hairs pulled/week; counted numbers of hairs pulled/week; rating of severity of urge to pull hair/week; rating of severity of hair pulling/week	Fluoxetine did not demonstrate a statistically significant treatment effect compared to placebo
Dougherty *et al.* (2006) [12]	Sertraline versus placebo	Adults	RCT	37	Dose range 50 mg-200 mg/day, average dose not reported	12 weeks	MGH-HPS, PITS, TTMIS	Sertraline did not demonstrate a statistically significant treatment effect compared to placebo
Van Minnen *et al.* (2003) [13]	Fluoxetine versus behavioral therapy versus waitlist control	Adults	RCT	43	All patients achieved dose of 60 mg/day	12 weeks	MGH-HPS	BT was superior to both fluoxetine and postponement of treatment. BT had a statistically significant treatment effect
Stanley *et al.* (1997) [14]	Fluvoxamine	Adults	Open label	21	Information not available	12 weeks	The YBOCS-T, the NIMH TSS and TIS, PITS	Treatment effect was not statistically significant
Stein *et al.* (1997) [15]	Citalopram	Adults	Open label	14	Information not available	12 weeks	YBOCS, the NIMH, NIMH-OCS modified for TTM, and the CGI scale	YBOCS ($t = 4.1$, $p = 0.002$) and NIMH-OCS ($t = 3.5$, $p = 0.004$)

BT: Behavioral therapy; CBT: Cognitive behavioral therapy; CGI: Clinical global impressions; MGH-HPS: Massachusetts general hospital hair pulling scale; NAC: *N*-acetylcysteine; NIMH: National institute of mental health; NIMH-OCS: National institute of mental health-obsessive-compulsive rating scale; PITS: Psychiatric institute trichotillomania scale; RCTs: Randomized controlled trials; SRI: Serotonin reuptake inhibitor; TIS: Trichotillomania impairment scale; TSC: Trichotillomania scale for children; TSS: Severity scale; TTM: Trichotillomania; TTMIS: Trichotillomania impact scale; YBOCS: Yale-brown obsessive-compulsive Scale; YBOCS-T: Yale-brown obsessive-compulsive scale for trichotillomania.

Table 1. Characteristics of included studies (continued).

Authors and year	Pharmacological agent	Adults or children	Study design	Sample size	Maximum and average dose of medication	Trial length	Symptom rating scales	Results
Ninan *et al.* (2000) [16]	CBT versus clomipramine versus placebo	Adults	RCT	23	Maximum dose 250 mg/day, average dose 116.7 mg/day	9 weeks	NIMH-TSS, NIMH-TIS, CGI	Statistically significant treatment effect for CBT compared to clomipramine and placebo
Swedo *et al.* (1989) [17]	Clomipramine versus desipramine	Adults	RCT, crossover	13	Maximum dose 250 mg/day, average dose clomipramine was 180.8 mg/day, desipramine 173.1 mg/day	5 weeks	NIMH-TSS, NIMH-TIS, physician-rated clinical progress (scored out of 20)	Clomipramine had a statistically significant treatment effect based on NIMH-TIS ($p = 0.03$) and physician-rated clinical progress ($p = 0.006$), compared to desipramine. However, this was not shown on the NIMH-TSS
Ninan *et al.* (2000) [16]	CBT versus clomipramine versus placebo	Adults	RCT	16	Information not available	9 weeks	NIMH-TSS, NIMH-TIS, CGI	CBT had a statistically significant effect compared to both clomipramine ($p = 0.016$) and placebo ($p = 0.026$)
Christenson *et al.* (1994) [18]	Naltrexone versus placebo	Adults	RCT	17	All participants -50 mg/day	6 weeks	NIMH-TSS, NIMH-TIS, number of hair pulling episodes, estimated number of hairs pulled	No statistically significant treatment effect, except for on the NIMH-TSS ($p = 0.02$)
Grant *et al.* (2014) [19]	Naltrexone versus placebo	Adults	RCT	51	50 mg/day	8 weeks	MGH-HPS	Did not demonstrate statistically significant treatment effect compared to placebo

BT: Behavioral therapy; CBT: Cognitive behavioral therapy; CGI: Clinical global impressions; MGH-HPS: Massachusetts general hospital hair pulling scale; NAC: *N*-acetylcysteine; NIMH: National institute of mental health; NIMH-OCS: National institute of mental health-obsessive-compulsive rating scale; PITS: Psychiatric institute trichotillomania scale; RCTs: Randomized controlled trials; SRI: Serotonin reuptake inhibitor; TIS: Trichotillomania impairment scale; TSC: Trichotillomania scale for children; TSS: Severity scale; TTM: Trichotillomania; TTMIS: Trichotillomania impact scale; YBOCS: Yale-brown obsessive-compulsive Scale; YBOCS-T: Yale-brown obsessive-compulsive scale for trichotillomania.

Table 1. Characteristics of included studies (continued).

Authors and year	Pharmacological agent	Adults or children	Study design	Sample size	Maximum and average dose of medication	Trial length	Symptom rating scales	Results
Grant *et al.* (2009) [20]	NAC versus placebo	Adults	RCT	50	Dose range 1200 – 2400 mg/day	12 weeks	MGH-HPS, PITS, CGI	NAC had a statistically significant treatment effect as measured by MGH-HPS ($p < 0.001$), PITS ($p = 0.001$) and CGI ($p = 0.003$, 'much or very much improved')
Bloch *et al.* (2013) [21]	NAC versus placebo	Children (ages 8 – 17)	RCT	39	Maximum dose 2400 mg/day	12 weeks	MGH-HPS, NIMH-TSS, TSC child-report and parent-report	No statistically significant treatment effect as measured by any of the scales used
Grant *et al.* (2011) [22]	Dronabinol	Adults	Open label	14	Maximum dose 15 mg/day, average dose 11.6 mg/day	12 weeks	MGH-HPS, CGI, NIMH-TSS	Statistically significant treatment effects as measured by MGH-HPS ($p = 0.001$), NIMH-TSS ($p < 0.001$), CGI ($p < 0.001$)
Stein and Hollander (1992) [23]	Pimozide augmentation of an SRI	Adults	Open label	7	Information not available	Information not available	Information not available	Authors report that augmenting SRI with pimozide lead to an improvement in TTM symptoms in six out of seven patients
Van Ameringen *et al.* (1999) [24]	Haloperidol augmentation of an SRI or haloperidol alone after sub-optimal response to SRI	Adults	Open label	9	Maximum dose 2.0 mg/day, average dose 1.1 mg/day	Varied	Response to treatment was based on descriptions of hair pulling, quantity of hair pulled, and severity of depilation at hair pulling sites (unstandardized ratings)	Authors report eight of nine women responded to haloperidol treatment, with seven experiencing complete or near complete cessation of hair pulling
Stewart and Nejtek (2003) [25]	Olanzapine	Adults	Open label	18	Maximum dose 10 mg/day	12 weeks	MGH-HPS, CGI	Statistically significant treatment effect based on MGH-HPS ($p < 0.001$) and CGI ($p < 0.001$)

BT: Behavioral therapy; CBT: Cognitive behavioral therapy; CGI: Clinical global impressions; MGH-HPS: Massachusetts general hospital hair pulling scale; NAC: *N*-acetylcysteine; NIMH: National institute of mental health; NIMH-OCS: National institute of mental health-obsessive-compulsive rating scale; PITS: Psychiatric institute trichotillomania scale; RCTs: Randomized controlled trials; SRI: Serotonin reuptake inhibitor; TIS: Trichotillomania impairment scale; TSC: Trichotillomania scale for children; TSS: Severity scale; TTM: Trichotillomania; TTMIS: Trichotillomania impact scale; YBOCS: Yale-brown obsessive-compulsive Scale; YBOCS-T: Yale-brown obsessive-compulsive scale for trichotillomania.

Table 1. Characteristics of included studies (continued).

Authors and year	Pharmacological agent	Adults or children	Study design	Sample size	Maximum and average dose of medication	Trial length	Symptom rating scales	Results
White *et al.* (2011) [26]	Aripiprazole	Adults	Open label	12	Maximum dose 15 mg/day, average dose 7.5 mg/day	8 weeks	MGH-HPS, CGI	Statistically significant treatment effect based on MGH-HPS ($p < or = 0.01$) and CGI ($p < or = 0.01$)
Van Ameringen *et al.* (2010) [27]	Olanzapine versus placebo	Adults	RCT	25	Maximum dose 20 mg/day, average dose 10.8+/-5.7 mg/day	12 weeks	MGH-HPS, YBOCS, CGI	Statistically significant treatment of effect based on YBOCS ($p = 0.01$) and CGI ($p = 0.001$), but not the MGH-HPS (0.30)

BT: Behavioral therapy; CBT: Cognitive behavioral therapy; CGI: Clinical global impressions; MGH-HPS: Massachusetts general hospital hair pulling scale; NAC: *N*-acetylcysteine; NIMH: National institute of mental health; NIMH-OCS: National institute of mental health-obsessive-compulsive rating scale; PITS: Psychiatric institute trichotillomania scale; RCTs: Randomized controlled trials; SRI: Serotonin reuptake inhibitor; TIS: Trichotillomania impairment scale; TSC: Trichotillomania scale for children; TSS: Severity scale; TTM: Trichotillomania; TTMIS: Trichotillomania impact scale; YBOCS: Yale-brown obsessive-compulsive Scale; YBOCS-T: Yale-brown obsessive-compulsive scale for trichotillomania.

involving 43 participants with TTM. The treatment effects were evaluated using the MGH-HPS and it was found that behavioral therapy was superior to both fluoxetine treatment (at 60 mg/day) and postponement of treatment. On the MGHHS total scale, effect sizes were found to be high for the behavioral therapy group (3.80) and moderate to low for the fluoxetine (0.42) and waiting list control groups (1.09).

Stanley and colleagues published an open-label treatment trial of fluvoxamine involving 13 participants with TTM [14]. Twenty-one participants with TTM were enrolled but only 13 completed a 12-week open-label trial of fluvoxamine. Four clinician-rated instruments were used to assess the severity of TTM symptoms: The Yale-Brown Obsessive-Compulsive Scale for TTM (YBOCS-T), the National Institute of Mental Health (NIMH) TTM Severity Scale (TSS) and TTM Impairment Scale (TIS), and the PITS. The study found no statistically significant difference in TTM symptoms at the end of the trial compared to the beginning.

Another open-label treatment trial of citalopram showed statistically significant treatment effects of this medication [15]. This was a 12-week trial that enrolled 14 participants with TTM. The rating instruments used in this study were the YBOCS, the NIMH-Obsessive-Compulsive Rating Scale (NIMH-OCS) modified for TTM, and the Clinical Global Impressions (CGI) scale. Of the 13 completers of the study, a significant difference between week 0 and week 2 in scores on the YBOCS ($t = 2.5$, $p = 0.03$) and the NIMH-OCS ($t = 2.4$, $p = 0.03$) were detected. Significant differences from week 0 continued for the remainder of the study; at week 12 there were significant differences on the YBOCS ($t = 4.1$, $p = 0.002$) and NIMH-OCS ($t = 3.5$, $p = 0.004$). Of the completers, 38.5% were responders (CGI score of 2 or less) at week 12.

3.2 Tricyclic antidepressants

Two RCTs involving TCAs for TTM have been published. The first is a three armed parallel trial, Ninan *et al.* [16], that compared cognitive behavioral therapy (CBT) to placebo, and CBT to clomipramine in a trial lasting 9 weeks. In this trial there were 10 participants randomized to clomipramine and 6 to placebo. The primary outcome measures in this study were the NIMH TSS, the NIMH TTM Impairment Scale, and the CGI scale. The study found no statistically significant treatment effects of clomipramine compared to placebo.

In another study, Swedo *et al.* compared clomipramine to desipramine in a randomized cross-over head to head trial [17]. The study involved 13 participants with TTM half of whom took clomipramine and half desipramine for 5 weeks before crossing over to the other condition (with no washout period). The primary outcomes in the study were the NIMH TSS, the NIMH TIS, and physician-rated clinical progress (maximum score 20). This study found that clomipramine had a statistically significant treatment effect based on NIMH-TIS scores ($p = 0.03$) and physician-rated clinical progress (0.006),

compared to desipramine. However, this statistically significant treatment effect was not shown on the NIMH TSS .

A further study by Ninan *et al.* compared the effect of CBT and clomipramine with placebo in the treatment of TTM [16]. Sixteen participants with TTM completed a 9-week parallel arm randomized placebo-controlled study of CBT versus clomipramine. Efficacy was evaluated by the TSS, the TTM Impairment Scale, and the CGI-Improvement scale, conducted by an independent assessor blinded to the treatment condition. CBT had a dramatic effect in reducing symptoms of TTM and was significantly more effective than clomipramine (p = 0. 016) or placebo (p = 0. 026). Clomipramine resulted in symptom reduction greater than that with placebo; however, this was not statistically significant.

3.3 Opioid antagonists

An unpublished study [18] compared naltrexone to placebo in a 6-week parallel arm trial. Seventeen participants with TTM were randomized to either naltrexone or placebo. The primary outcome measures of the study were the NIMH TSS, the NIMH TIS, number of hair-pulling episodes, and estimated number of hairs pulled. The authors report a statistically significant treatment effect for naltrexone versus placebo on only one out of the four primary outcome measures, the NIMH TSS (p value = 0.02).

A recently published study [19] comparing naltrexone to placebo enrolled 51 adults with TTM in an 8-week randomized controlled trial. This study found no statistically significant difference in response of TTM symptoms between the naltrexone and placebo groups, as measured by the MGH-HPS and other secondary measures.

3.4 Glutamate modulators

A more recent study [20] compared *N*-acetylcysteine (NAC) to placebo in 50 participants with TTM. This was an RCT involving randomization to either NAC or placebo for 12 weeks. The primary outcome measure in the study was the MGH-HPS, a validated scale for measuring TTM severity. In this study, those randomized to NAC demonstrated a statistically significant treatment effect. On the MGH-HPS, mean scores in the NAC group were 17.6 at baseline and 10.4 at study endpoint, and in the placebo group, mean scores were 16.7 at baseline and 16.0 at endpoint (p value < 0.001). The treatment effect was detected by 9 weeks into treatment (p value = 0.002).

In contrast to the Grant study, an RCT looking at the efficacy of NAC in a pediatric population observed no benefit of NAC for the treatment of children with TTM. The study involved 39 children and adolescents aged 8 – 17 years who were randomly assigned to receive NAC or matching placebo for 12 weeks [21].

3.5 Cannabinoid agonists

There has been a single study of dronabinol in the treatment of TTM. This was a 12-week open-label treatment study involving 14 female participants with TTM [22]. 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 subjects were considered 'much or very much improved' on the CGI scale. Additionally these results were obtained in the absence of cognitive side effects, as assessed by various measures.

3.6 Anti-psychotics

Stein and Hollander [23] treated seven TTM patients who had not responded to SRIs to an open trial augmentation with low dose pimozide. In this trial the authors reported that six out of seven patients had an improvement in symptoms after the addition of pimozide. A similar augmentation study by Van Ameringen *et al.* used open-label augmentation of SRI treatment in non-responders with haloperidol [24]. In this study eight out of nine patients experienced an improvement in TTM symptoms. Response was measured using descriptions of hair pulling, quantity of hair pulled, and severity of depilation at hair pulling sites. Neither of these trials used standardized rating scales to measure symptom severity.

The first open-label study of monotherapy involving an antipsychotic was a study of olanzapine in the treatment of TTM [25]. This study of 17 patients showed a statistically significant treatment effect based on the two outcome measures MGH-HPS and the CGI (p < or = 0.001 respectively).

An 8-week open-label flexible-dose trial of aripiprazole involving 11 completers showed a significant mean reduction on both primary outcomes, the MGH-HPS and the MGH-HPS Actual Pulling Scale (p < = 0.01 and < = 0.02 respectively) [26]. These two studies, like the augmentation trials, have the limitations of open-label design and lack of control group as well as small sample sizes.

The most recent published study of anti-psychotics in the treatment of TTM was a randomized controlled trial comparing olanzapine to placebo in 25 participants [27]. Participants were randomized to either olanzapine or placebo in a parallel arm study for 12 weeks' duration. This study yielded strong evidence that olanzapine is effective when compared to placebo in improving TTM severity on all primary outcome measures, with the exception of the MGH-HPS. On the CGI-I, mean scores in the olanzapine group were 3.38 and 1.69 in week 2 and at endpoint, respectively, and 3.41 and 3.41 in week 2 and at endpoint, respectively, in the placebo group (p = 0.001). On the CGI-S, mean scores in the olanzapine group were 5.08 and 3.15 at baseline and endpoint, respectively, and 5.00 and 4.83 in the placebo group (p value < 0.001). On the Yale-Brown Obsessive Compulsive Scale (TTM-YBOCS), mean scores in the olanzapine group were 20.70 and 10.54 at baseline and endpoint, respectively, and 20.67 and 18.17 in the placebo group (p < 0.01). Finally, on the MGH-HPS, mean scores in the olanzapine group were 15.46 and 8.38 at baseline and endpoint, respectively, and 16.58 and 13.25 at baseline and endpoint for placebo (p = 0.30).

4. Discussion

Over the past 25 years, investigation into the pharmacological treatment of TTM has led to trials spanning several medication classes. The use of multiple medication classes in part reflects that the neurobiology of TTM remains poorly understood, as well as the fact that early trials often failed to demonstrate efficacy.

The earliest trials involved the SRIs due to the recognition of the overlapping characteristics of TTM and OCD and the hypothesis that they perhaps have a similar neurobiological basis [28]. Many patients report that hair pulling is preceded by urges and that hair pulling involves ritualistic behaviors redolent of OCD. However, these urges do not always exists in hair-pullers, and in fact, the behavior can occur without any conscious awareness.

Co-morbidity is observed between TTM and OCD, with some authors reporting the rate of OCD as 10.7% in a TTM population sample [29]. In another study, 23.6% of children with TTM had at least one diagnosis of an anxiety disorder, attention-deficit/hyperactivity disorder, OCD, a mood disorder, and a tic disorder [30]. However, TTM trials have not focused on patients with comorbid disorders.

The literature regarding SRIs in the treatment of TTM is small, involving four RCTs and two open-label trials of various different SRIs. None of the RCTs had statistically significant treatment results. The open-label trial of citalopram did show a statistically significant treatment effect for this medication on a small sample of 13 completers [15]; however a controlled trial has never been conducted in order to corroborate these findings.

There have been three trials involving TCAs, one of which provides limited evidence for a treatment effect of the SRI clomipramine when compared to desipramine on two out of the three outcome measures [17]. This was a small proof of principle trial involving 13 participants, and there is no other RCT of clomipramine that corroborates these findings.

The opioid antagonist naltrexone has been used with some success to treat self-injurious behavior, pathological gambling, hypersexual disorder, and internet addiction. Hypothesizing that repetitive hair pulling could represent a form of addictive behavior, two trials have investigated naltrexone for the treatment of TTM. Neither of these two trials to date yielded statistically significant treatment results [18,19].

Another set of medications that has been investigated for treatment in TTM is comprised of glutamate modulating agents. The glutamatergic system is involved in mediating a range of behaviors, perhaps including obsessive-compulsive symptoms [30,31]. Two RCTs exist of NAC versus placebo have been undertaken, one in adults and one in children, [20,21]. The trial by Grant and colleagues provides persuasive evidence that NAC is effective, and given that this agent is relatively well-tolerated, many clinicians would consider this a potential first line agent. However, the negative findings in children by Bloch *et al.* emphasize the need for further research.

A further medication class that has been trialed in the treatment of TTM is comprised of the cannabinoid agents, with an open-label trial of dronabinol having been undertaken [22]. This medication has been used with some success in treating disorders with a compulsive motoric component such as Tourette's syndrome and other tic disorders [32,33]. The open-label trial of dronabinol for the treatment of TTM symptoms showed statistically significant treatment effects and the study of this medication deserves extension in a follow-up RCT.

The limited efficacy of serotonergic agents in TTM, and the role of the dopaminergic system in other obsessive-compulsive-related disorders has given impetus to some study of dopamine blockers in TTM. There is strong evidence of involvement of the dopamine system in animal models of grooming, and it is also possible that TTM is mediated in part by reward centers such as the nucleus accumbens. One study involving mutant mice with a knock-down mutation of the dopamine-transporter gene leading to elevated dopamine levels in the neostriatum, showed that the hyperdopaminergic mutant mice have stronger and more rigid syntactic grooming chain patterns than wild-type control mice [34]. A study of deer mice in which the mice were given various medications and their level of stereotypic behaviors observed demonstrated that states of spontaneous stereotypy are attenuated by 5-HT(2A/C) and dopamine D2 receptor agonists, providing further evidence for dopaminergic circuit involvement in stereotypic behaviors [35].

Several open-label trials have shown statistically significant treatment effects of antipsychotics in TTM [23-26]. Additionally, a single RCT by Van Ameringen *et al.* provides some preliminary evidence for the use of anti-psychotics to treat TTM [27]. However, given the adverse event burden of antipsychotics, benefits and risks must be carefully weighed up.

Although this review focused on pharmacotherapy for TTM, it is important to mention the role of non-pharmacological treatments for TTM. Behavioral treatments for TTM generally involve two elements: stimulus control and habit reversal training [36]. Stimulus control involves identifying situational factors that trigger pulling and then modifying these factors in a way that reduces pulling. For example, some patients with TTM get tactile reinforcement from rolling the pulled hair between their fingers. A way to reduce this reinforcing stimulus would be to get the patient to wear bandages on her fingers. Habit reversal training involves helping the patient develop awareness of the pulling behavior and then training a competing response, for example making a fist every time the urge to pull comes [36]. There is strong evidence that a combination of stimulus control and habit reversal training are effective interventions in TTM [37].

5. Conclusion

Overall there is a small body of evidence of pharmacotherapy for TTM spanning several diverse medication classes. Based on the available evidence it is not possible to say that any one class of medication demonstrates efficacy in the treatment of TTM; however there are some promising preliminary studies that deserve replication.

6. Expert opinion

The pharmacotherapy trials to date have had small study populations, the largest RCT involving only 50 participants [20]. Long-term data is also lacking; therefore the efficacy and tolerability of medications for long-term management of TTM is not yet known. There is a need for more multi-arm studies that combine pharmacotherapy and psychotherapeutic interventions and compare the combination with use of a single intervention. In addition, data on the treatment of TTM in children and adolescents is relatively lacking [12,13]. Finally, in the trials to date participants have little co-morbidity, which as we know does not reflect the reality for patient's living with TTM. There is a need for more pragmatic trial designs in order to better understand this population.

Given the gaps in the current research base there is a lack of data generally on which to base decisions on pharmacological treatment for TTM. As there is a paucity of RCTs in this field we chose to expand the current review to include open-label trials. It is hoped that promising open-label trials will lead to future RCTs in the field.

The largest body of evidence is comprised of work on the SRIs, and although clomipramine showed promise in an early trial, subsequent SSRI trials were negative. Several open-label and one RCT support the value of low-dose antipsychotics in the management of TTM; this needs to be weighed against the adverse event profile of these agents. NAC may be a useful agent with which to start treatment, given the positive trial by Grant *et al.*, and given that it is a safe and relatively well-tolerated agent. In addition, medication selection should be based on the comorbidities that often occur in TTM.

In a recent Cochrane Review on pharmacotherapy for TTM, we also emphasized that the available RCTs are methodologically dissimilar and therefore could not be combined in meta-analysis [9]. This is in part due to the prior lack of consensus in the field on rating scales in TTM research, with studies using several different rating instruments. In addition, many of the scales used have not been well validated, which diminishes the quality of the evidence [9]. Use of a validated symptom severity measure, such as the MGH-HPS, will allow for data from trials to be compared and/or combined in analysis in the future.

The underlying neurobiology of TTM deserves additional exploration, and future trials are needed to expand on the preliminary evidence available for NAC, olanzapine, and dronabinol in recent trials [20,27,22]. Larger RCTs investigating these medications are needed to extend the available evidence.

As our knowledge of the neurobiology of TTM expands, it is hoped that endophenotype measures will be included in the trials, consistent with the Research Domain Criteria project of the NIMH. The ultimate goal is to have enough data to be able to do predictor analysis and to develop a personalized medicine approach to this prevalent and disabling condition. The challenge is a relative lack of funding in this area; however, fortunately consumer advocacy has increased lobbying for such funding. Hopefully the inclusion of TTM in a chapter on Obsessive-Compulsive and Related Disorders in the DSM-5 will give further impetus to research in this area.

Acknowledgments

DJ Stein is supported by the Medical Research Council of South Africa.

Declaration of interest

DJ Stein has received research grants and/or consultancy honoraria from Abbott, ABMRF, Astrazeneca, Biocodex, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, National Responsible Gambling Foundation, Novartis, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Sun, Takeda, Tikvah, and Wyeth. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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