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REVIEW

Review of available studies of the neurobiology and pharmacotherapeutic management of trichotillomania

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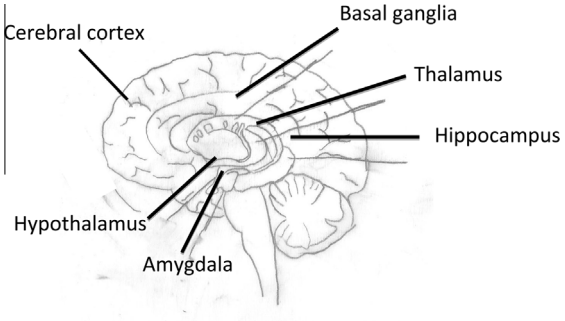
GRAPHICAL ABSTRACT



Brain regions implicated in the pathology of trichotillomania (TTM)

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ABSTRACT

Trichotillomania (TTM) is a psychiatric disorder characterized by an irresistible urge to pull out one's hair. Currently there are no FDA approved treatments for TTM, which makes it difficult for clinicians to select an appropriate therapeutic plan. The clinical studies that have been performed do not provide sufficient or consistent evidence regarding which drug classes should be administered. Unfortunately, most of the available data consist of case reports and clinical trials with limited sample size. This review provides an overview of currently available clinical

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literature that targets TTM. A summary of clinical trials as well as case reports is provided. The most common rating scales used for clinical assessment are also reviewed. The etiology of TTM remains unclear. Studies that examine various neuroanatomical, neurobiologic, as well as genetic factors associated with TTM are thoroughly discussed in this review. It is evident that clear understanding of TTM is crucial to provide better recognition, assessment, and treatment to patients of this disorder. Finally, despite research efforts for establishing pharmacological options for treatment, it is clear that new targets are warranted in order to ensure a clinically supported effective pharmacological approach to treat TTM.

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Introduction

Originally described by Hallopeau in 1889, trichotillomania (TTM) is a psychiatric disorder that is characterized by the incontrollable urge to pull out one's hair [1]. The preferred term for this condition is "hair pulling disorder", as the word "trichotillomania" may be perceived with a negative connotation [2]. It is currently classified under "Obsessive Compulsive and Related Disorders" in the *Diagnostic and Statistical Manual of Mental Disorders, DSM-V* [3]. Diagnostic criteria include the following: continuously pulling out one's own hair, which results in hair loss, multiple attempts to reduce or stop the hair pulling, clinically significant impairment in daily functioning (e.g. social gatherings, work), the hair pulling is not associated with another medical condition, and it cannot be explained by another mental disorder [3]. Previously in DSM-IV, TTM was classified under impulse control disorders (not classified elsewhere). Diagnostic criteria included an increasing sense of tension right before pulling out the hair or when resisting the urge, and pleasure, gratification, or relief when pulling out the hair [2]. As seen, this criterion was left out of DSM-V as not all TTM sufferers experience these occurrences. Christenson et al. [1] described TTM sufferers as either being aware or unaware of the hair pulling, or a combination of both. These observations led to the TTM subtypes/styles known as focused and automatic, respectively. Automatic hair pulling usually occurs during sedentary activities such as lying in bed, watching TV, or reading. Focused hair pulling, on the other hand, occurs when hair is intentionally pulled out possibly by searching for specific hairs to pull out. This more focused pulling may allow the individual to distract themselves from unwelcomed thoughts or feelings [4]. TTM has a lifetime prevalence of 0.6% (according to DSM-III-R) for both genders. However, Christenson et al. [1] concluded that for females the prevalence may be as high as 3.4% and 1.5% for males. Sufferers typically pull from the scalp, eyebrows, and eyelashes but may also pull from the face, axillary, and pubic regions [1,5]. Some individuals participate in hair-related rituals or behaviors once the hair is pulled out. These could include rolling the hair between finger, running the hair over the lips or through the teeth, biting the hair, and/or swallowing the hair (trichophagia). Others reported pulling out specific hairs based on characteristics such as texture, color, and length [5]. The average age of onset occurs around 13 years, which coincides with puberty [6].

TTM has also been thought to relate to, or overlap with other psychiatric disorders including obsessive compulsive disorder (OCD), Tourette's, and other impulsive disorders such as nail biting and skin picking [1,2,7]. This overlap is seen in TTM's symptomatology including similar ritualistic behavior and trigger cues as seen in body-focused repetitive behavioral disorders (BFRBD) [2]. The similarities observed between TTM and OCD include behaviors in response to urges, anxiety relief after performing the behavior, and the repetitive nature of the disorder [2]. Similarities with OCD also extend into the treatment modalities used. According to Christenson et al. [8] the lifetime prevalence of comorbid psychiatric disorders in TTM patients was found to be as high as 81%, with depression and anxiety subsequently reported as main contributing comorbid disorders to TTM. TTM is a poorly understood disorder. Behavioral therapy has proven effective in many TTM patients; however, the use of pharmacotherapy might be necessitated in some patients. Some individuals with TTM may respond to pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs), as do those with OCD [2].

Limited knowledge exists regarding the neurobiological basis of TTM. However, it is speculated that the disorder probably involves multiple pathways and a complex interaction between genetic, psychological, and social factors.

Studies suggest changes in reward processing and impulse control, with the neurotransmitters serotonin, dopamine, as well as GABA implicated in TTM [9]. Few brain imaging and genetic studies have reported gray matter density differences in various brain regions in TTM patients as compared to controls [10–12]. The contribution of genetic factors has gained research attention in the past decade, with reported mutations in SLITRK1 and HOXB8 genes in TTM patients and experimental animal models, respectively [13–15]. The current review provides an overview of available studies that examined the neurobiology and potential genetic determinants of the disorder as well as summarizes available literature regarding reported clinical studies/cases of various pharmacotherapeutic approaches. Future research directions that are needed for understanding and management of this disorder are identified.

Methods

A literature search was conducted using PubMed and Google Scholar. The search spanned the period between 1989 and February 2014. Key words, and their combinations, used for the search were trichotillomania, hair pulling, hair pulling disorder, clinical trial, case report, neurobiology, genetic, and animal model. A total of 875 potentially relevant articles were identified. The titles and abstracts of the articles were screened, and 712 were excluded. Excluded articles were clinical reviews as well as articles related to trichobezoar reports focused on surgical treatment. The abstracts of the remaining 163 articles were further examined, and 108 articles were excluded. Exclusion criteria were non-English language of the article, clinical trial of behavioral therapy approaches alone, and duplicates. The remaining fifty-five full text articles were retrieved and included in this review, and thirteen articles investigated the neurobiology, animal models, and genetic aspects of TTM, while the remaining forty-two articles focused on scoring scales and pharmacotherapeutic approaches of TTM. The latter included both clinical trials as well as case reports.

Neurobiology of trichotillomania

Although TTM is classified according to DSM-V under obsessive compulsive and related disorders, the classification of TTM still remains controversial. As mentioned earlier, behavioral therapeutic approaches have proven to be more effective than pharmacotherapy in most patient cases. However, some patient might require pharmacologic intervention. As will be evident in later sections, pharmacotherapeutic approaches to treating TTM include a wide variety of drug classes, primarily antidepressants. So far, the FDA has not approved any pharmacological treatment for TTM. Such lack of solid pharmacotherapeutic approaches might be partly attributed to our deficient understanding of the etiology and neurobiology of the disorder. Current research has focused on neuroanatomical studies that attempt to unravel any brain abnormalities that might correlate with the symptoms of TTM. Grachev [10] used MRI-based morphometric topographic parcellation to study the differences in the human neocortex of 10 females with trichotillomania compared to 10 females without (TTM). In this study, researchers were interested in investigating volumetric changes of the sensorimotor cortex, supplementary motor cortex (juxtaparacentral lobule cortex) and operculum between TTM and TTM-free participant. The study included 10 right-handed females with TTM that met DSM-IV criteria for TTM, and did not have OCD, Tourettes, psychosis, major depression, substance abuse or significant medical or neurological illnesses. The 10 female controls were also right-handed and were similar in age and educational background. All subjects had to have normal CBC, coagulation, and thyroid tests. Control subjects though did not have a psychiatric, neurologic, and physical examination. All 20 patients were free of psychoactive medications for at least 4 weeks. The average age of TTM patients was 31.1 years and 28.5 years in control patients. Researchers used MRI scans for brain images and a standard 3-D brain coordinate system was used for positional normalization. Statistically significant volumetric differences were found between the TTM patients and control groups in the left inferior frontal gyrus, triangularis division, and the right cuneal cortex. The volume of the triangularis division was reduced by 27% while the right cuneal cortex was increased by 40%. There were no statistically significant differences in the total cerebral cortex volume. The increase in the right cuneal cortex in TTM patients may stem from failure of interactions between the visual and sensorimotor cortices that cause increased neuronal stimuli to reach targets leading to the repetitive or compulsive behavior seen in TTM [10]. Chamberlain et al. [11] investigated gray and white matter abnormalities in terms of the whole brain in 18 individuals with TTM as compared to 19 healthy individuals. Participants were medication-free for >6 months and had no previous diagnosis of depression or OCD. However, patients with TTM showed significantly higher Montgomery-Åsbery Depression Rating Scale (MADRS) scores and dysphoric mood compared to healthy volunteers but neither demonstrated clinically significant depression in regard to the MADRS score. Significant differences were found in terms of increased gray matter density in 3 clusters. These consisted of the striatum (left putamen) and left amygdalo-hippocampal complex, bilateral frontal regions (cingulate, supplemental motor and superior cortices) and the left occipital and parietal regions. No significant differences were reported in white matter density. The findings of Chamberlain et al. [11] add more evidence that link TTM and OCD together. Increased gray matter has been reported in studies of OCD. The increased gray matter may be due to neuroplastic changes that occur when using brain regions involved in grooming, habit-learning and motor skill training. Dysfunction or abnormalities of the striatum, which is involved in habit learning and automated action sequences, may disrupt the ability to perform choreographed grooming sequences. This finding implicates the role of the basal ganglia in the development of pathological habits. The abnormalities seen in the cingulate and prefrontal lobes could be responsible for cognitive issues seen in TTM patients. The abnormalities found in the amygdalo-hippocampal region may cause the arousal and emotional learning differences seen in hair pulling episodes. This study provides baseline differences seen in different brain regions of TTM patients. Some of the findings are inconsistent with other available literature which leads to the need of future studies that include more patients (including left-handed individuals to see whether there are differences in implicated brain regions), screening not only for depression but also for anxiety,

and the inclusion of using cognitive tasks simultaneously with the neuroimaging. Other researchers have shown that neurons found in the anterior dorsolateral regions of the caudate–putamen are activated during grooming movements [16]. The graphical abstract summarizes the brain regions implicated in the pathology of TTM.

A recent study by Odlaug et al. [12] examined impaired response inhibition and cortical thickness in TTM patients, their unaffected first degree family members, and control subjects. The study reported a significant impairment of response inhibition performance in TTM patients as compared to controls. In addition, a significant increase in cortical thickness was observed in TTM patients and their relatives compared to controls. The areas affected by the change were primarily localized in regions controlling response inhibition including the right inferior/middle frontal gyri, left precuneus, left superior temporal cortex, and right lingual gyrus.

Although TTM is currently classified under obsessive compulsive and related disorders, previous research has focused on its relevance to impulse control disorders (ICDs). Extensive research has been conducted that focused on neurobiological role of various neurotransmitters in the pathology of ICD and their relevance to TTM. Serotonin (5-HT) has been implicated in OCD as well as ICD because of its role in impulse control as well as repetitive motor behaviors. Animal studies have previously shown that serotonin depletion leads to impulse choices and motor behavior [17,18]. The activation of serotonergic systems using SSRIs has been explored as a treatment option for TTM patients. However, as seen in later sections of the review, data from various clinical studies and case reports show mixed results and the efficacy of SSRIs for TTM treatment remains unclear. Dopaminergic systems are implicated in both OCD and ICD. The use of antipsychotic agents that block dopaminergic D2 receptors has been effective in the management of a subset of TTM patients, as discussed in later section [19–21]. The inhibitory neurotransmitter GABA has been functionally and anatomically connected to dopaminergic systems. A retrospective study by Nikolaus et al. [9] demonstrated regulation of dopamine by both GABA and 5-HT neurotransmitters in pooled patients with OCD and anxiety disorders. Both GABA and 5-HT exert inhibitory effect on dopamine, and their reduction leads to enhanced dopaminergic activity in the mesolimbic system, playing a role in the development of anxiety and obsessive compulsive disorders [9]. The recent studies that demonstrated efficacy of the glutamate modulator N-acetylcysteine (NAC) in TTM patients have drawn research attention to the role that glutamate might play in the pathophysiology of TTM [22,23].

It is evident that data available so far suggest that a complex interaction between various neurobiological systems might play a role in the pathophysiology of TTM, and further studies are certainly warranted.

Genetics studies

In addition to neuroanatomical studies, research efforts have also emphasized the role of genetics in TTM. Abelson et al. [13] reported a 1 bp deletion in SLITRK1 gene in a boy with Tourette's syndrome and attention deficit hyperactivity disorder (ADHD). The boy's mother carried the same mutation and suffered from severe TTM. In a 2006 letter to the editor Zuchner et al. [14] proposed that a sequence variation on SLITRKI may play a role in the development of TTM. The research group sequenced the whole SLITRKI gene of 44 TTM families where at least one member met DSM-IV criteria for TTM. Researchers discovered two distinct non-synonymous changes in two independent TTM subjects. Both occurred between the second LRRCT domain and the transmembrane domain of SLITRKI. Zuchner et al. [14] suggest that mutations in this position may be associated with TTM without Tourettes since mutations that were previously observed by Abelson et al. [13] were located in a different area of the protein. In the study 2192 non-TTM Caucasian controls were screened for this variation and none were found. Researchers concluded that these sequence variations are significantly associated with the TTM phenotype.

The other gene implicated in TTM is the HOXB8 gene. Animal studies conducted by Greer and Capecchi reported that variations in the HOXB8 gene of mice result in excessive grooming that leads to bald sports and skin lesions. They suggest a link between this behavior and the behavior seen in TTM [15]. Many brain areas are involved in initiating a cascade of signals that lead to movements seen in grooming sessions. These brain regions include the brainstem and striatum. Excessive grooming has been observed in OCD and TTM but influential genes in these two disorders have not been elucidated. Greer et al. point out that mice that are homozygous for a loss-of-function mutation in HOXB8 show excessive grooming behavior. The hox genes are responsible for embryonic development, hair formation in adult mice, and maturation of breast tissue in pregnant females. The HOXB8 homozygous mutant mice not only demonstrate excessive self-grooming behavior but also excessively groom control cage mates [15]. Researchers videotaped individual mice from 7 littermate pairs of one wild and one mutant for a 24-h period in order to see under what conditions the HOXB8 mutants removed their hair. Each mouse was scored for eating, drinking, sleeping and grooming. All aspects were similar in wild type and mutants except for grooming behaviors which showed that grooming time was doubled in the mutants compared to the wild type. The mutants also initiated grooming more frequently than controls. The researchers point out that the mutant mice groomed all parts of their body which is different from TTM where sufferers focus their pulling on specific areas of the body such as the scalp, eyebrows/lashes, and pubic area. Mutant mice also spent about one hour less time sleeping than controls as this hour was devoted to grooming [15]. When mutants and wild type mice were housed together, "the wild type showed large bald areas on their back and tops of their heads". Following video analysis, it was obvious that the wild type mice were being groomed by the mutants.

Greer and Capecchi [15] conducted a transgenerational study in which they backcrossed F1 generation HOXB8 mutants for 5 generations. The grooming behavior was seen in all homomutants using the home cage and misting-induced grooming assay. The mutants showed a 2-fold increase in grooming behavior during the induced-grooming assay compared to controls. Hair removal and skin lesions were visually observed in the mutants as well. Using an RT-PCR assay, researchers showed the presence of the HOXB8 gene in the adult mouse CNS. Expression was found in the olfactory bulb, basal ganglia, hippocampus, cortex, cerebellum and the brainstem of the wild type adult.

It is interesting to note that HOXB8 gene is expressed in the ''OCD circuit'' which includes the orbitofrontal cortex, the anterior cingulate cortex and the caudate nucleus. Abnormal metabolic activity is seen in OCD patients within the cells of this circuit [24]. Overall, Greer et al. state that the excessive grooming behavior observed in mice without HOXB8 function is very similar to that seen in TTM. They argue that due to the expression pattern of HOXB8 in the CNS and the behavior analysis, TTM should be classified as an OC-spectrum disorder. Based on the information presented, they believe TTM may be caused by ''misregulation of an innate autogrooming behavior that results in excessive repetition of this behavior''. Further studies are needed to determine whether human TTM patients show the mutations reported in the HOXB8 gene [15].

Our current understanding of the neurobiology of TTM is rather incomplete. Despite the fact that most available studies have focused on neuroimaging, the exact neural circuitry involved in the disorder is not entirely delineated. The overlap between TTM and other impulsive–compulsive disorders should be further investigated through examining the neurocircuits associated with impulsive and compulsive behavior. Such studies might help identify various subtypes of TTM as they relate to impulse or compulsive disorders. Additional imaging studies are needed that include unaffected family members of TTM patients. Coupled to imaging studies, future research should include investigation of receptor distribution and binding in TTM patients as compared to controls. Serotonin, noradrenergic, dopaminergic, glutamatergic, and other receptors involved in effective processing, impulsivity, and compulsion could be examined for abnormal binding using radioligand PET. Additional studies are needed to examine the role of glutamatergic dysfunction in animal models of TTM as well as in TTM patients, especially that recent data show that abnormalities in glutamatergic function might play a role in OCD pathogenesis. Furthermore, the role of biological and environmental risk factors in the pathogenesis of TTM needs to be studied.

Animal models of trichotillomania

Animal models are important for studying the pathology of various human diseases and disorders [25]. They are valuable tools to systematically study innumerable disorders as well to investigate potential treatments in a preclinical setting. However, there are a few limitations associated with developing an animal model, including the fact that most disorders do not develop spontaneously in the animal being studied and must be induced [25]. However, there are certain behaviors that do develop spontaneously in confined animals that can be used to mimic human disorders. The following represent examples of each type of animal model that can be used in studying TTM in experimental animals.

Garner et al. [26] proposed the barbering mouse model as an experimental model to investigate treatment efficacy for TTM. Barbering is a spontaneous abnormal behavior that commonly develops in caged animals. Researchers believe that because barbering is an abnormal behavior seen in laboratory mice, and because it occurs spontaneously, such model would be sufficient to mimic TTM. Results showed that the demography is similar to TTM (age and gender). It also showed similar phenomenology (pulling from scalp, around the eyes, and genitals) and etiology [26].

Greer and Capecchi [15] demonstrated that HOXB8 homozygous mutant mice show an increase in grooming behaviors. These mice display excessive hair removal and increased amount of time spent grooming compared with wild type mice. They also initiate grooming behaviors more often than controls, and groom their wild type cage mates. Greer and Capecchi [15] suggest that TTM may occur due to a misregulation of a natural autogrooming behavior that results in the excessive repetition of this behavior that is characteristic of the disorder.

Both animal models show similar characteristics to that of TTM. Either one can be a useful model when trying to determine the efficacy of treatments for TTM. However, further studies of these models with regard to neurobiology, imaging changes in brain structure and function, and correlation to changes in TTM patients are warranted in order to validate these models. Establishing a reliable experimental model of TTM will certainly provide a valuable tool for evaluating preclinical pharmacotherapeutic options for TTM patients.

Commonly used rating scales

Assessment of TTM is a challenging task, as it requires integrating information from multiple sources, as well as the fact that it might heavily rely on patient self-assessment, which can be challenging, particularly in children. Initial diagnosis of the disorder certainly depends heavily on accurate assessment. Several assessment scales have been developed over the past decade. These assessments include symptoms' presentation, severity, functional impairment, as well as comorbidity. The following section summarizes a few of the commonly used clinical scales for the assessment of TTM.

NIMH trichotillomania questionnaire

This questionnaire consists of 2 scales, the NIMH Trichotillomania Severity Scale (NIMH-TSS) and the NIMH Trichotillomania Impairment Scale (NIMH-TIS). These scales stemmed from the Yale-Brown Obsessive Compulsive scale (Y-BOC scale). NIMH-TSS contains five questions regarding the average time the patient spent pulling, time spent pulling on previous day, ability to resist the urge to pull, resulting distress, and daily interference. The scoring range is from 0 to 25 and higher scores indicate greater severity. The NIMH-TIS classifies the level of impairment from no impairment to severe impairment using a 10-point scale. This scale takes into account level of embarrassment as well as interference of daily activities caused by noticeable hair loss. Again, a higher score indicates greater impairment [27].

Clinical Global Impression (CGI) scale

The CGI is a tool used in psychiatry that has the clinician rate, their current patient's illness severity, improvement, and therapeutic response based on past experiences with patients who also had the disease/disorder. The severity portion is rated on a 7-point scale with higher points corresponding to the most severely ill (CGI-S). The improvement portion (CGI-I) is also rated on a 7-point scale with higher numbers indicating that the patient is very much improved. The therapeutic

response is rated based on only drug effect. This takes into account both the level of symptom resolution and impairment due to side effects [28].

Massachusetts General Hospital-Hair Pulling Scale (MGH-HPS)

This is a self-report scale that measures the urge to pull, actual hair-pulling, and the consequences of hair-pulling. It is rated on a scale from 0 to 4 with higher numbers corresponding to negative outcomes. The section regarding the urge to pull takes into account the frequency and intensity of the urges, and the ability to control the urges. The second section, which rates the actual pulling on a 0–4 scale, takes into consideration how often the patient pulled their hair, the frequency of resisting the urge, and how often the patient was able to control the hair-pulling. For the final section regarding the consequences of hair-pulling, the patient is asked how uncomfortable or distressed the hair-pulling made them feel [29].

Milwaukee Inventory for Styles of Trichotillomania-Adult Version (MIST-A)

This scale focuses on separating subtypes into 2 distinct classes, automatic and focused. "Automatic" pulling refers to a patient who is not aware that they are pulling out their hair while "focused" pulling refers to a patient who is intentionally pulling out their hair. The scale is comprised of 15 statements divided into 10 regarding focused pulling and 5 regarding automatic pulling. Responses to these statements will help classify patients into 1 of the 2 subtypes [30].

Psychiatric Inventory Trichotillomania Scale (PITS)

The PITS is a tool that is administered by a physician that rates the symptoms of hair pulling during the previous week. It is a 6-item scale and each item is rated from 0 to 7 with higher numbers corresponding to greater severity. Items being assessed in this scale include the number of hair pulling sites, time spent pulling and thinking about pulling, resistance to urges, distress, and interference with daily activities [31].

Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a clinician-rated scale that measures the degree of anxiety. It consists of 14 items, each being scored from 0 to 4 with 4 denoting severe. Each item is a phrase about the patient's feelings followed by a list of symptoms. Total score ranges from 0 to 56 with higher numbers indicating very severe anxiety [32].

The availability of multiple TTM-specific rating scales has been crucial in order to properly assess individuals with the disorder. These scales have been instrumental to clinical trials as they provide an objective assessment of the efficacy of the proposed therapy and patients' response to treatment. However, currently available assessment tools do suffer from some shortcomings. Physician-rated scales are liable to inter-rater variability. While self-reported instruments are crucial, particularly in the initial baseline assessment of symptoms, many TTM patients lack awareness of hair pulling. In addition, self-monitoring may induce reactivity responses in the patients. Advancement in digital photography might help researchers and contribute to future accurate quantification of hair density in TTM patients.

Clinical studies/cases for pharmacotherapeutic treatment of TTM

So far the FDA has not approved any pharmacological treatment for TTM. Cognitive behavioral therapy (CBT) and habit reversal therapy (HRT) proved to be effective therapeutic interventions in many cases of TTM. While behavioral therapeutic approaches of TTM are not the focus of this review, it is important to note that several randomized controlled trials have reported behavioral therapy to be effective for the management of TTM patients. On the other hand, available literature regarding pharmacotherapy of TTM reports equivocal outcomes. Overall, most research studies are comprised of small case reports, small size trials, and with heavy emphasis on behavioral therapy. Studies that explored pharmacological treatment of TTM have spanned a variety of drug classes, ranging from antidepressants, antipsychotics, to CNS stimulants, and others. The next few paragraphs summarize the current literature for TTM pharmacotherapy.

CNS stimulants

Very few clinical studies have focused on CNS stimulants as possible treatment options for TTM. Two studies have suggested that the symptom often seen in TTM patients, the irresistible urge to pull out one's hair is indicative of dysfunction of the inhibitory neuronal circuits [33,34]. One study reported that TTM patients (n = 17) showed statistically significant impaired inhibitory control when compared to non-TTM patients (n = 20) [32]. Aron et al. [35] correlated the disruption in stop signal, which is observed in cases of TTM, to a dysfunction in the right inferior frontal gyrus, which causes an increase in stop signal response. Chamberlain et al. [36] tested the response inhibition of atomoxetine (selective norepinephrine reuptake inhibitor) and citalopram (SSRI) on the norepinephrine and serotonin systems, respectively. The goal of this experiment was to define the contribution of the serotonin and norepinephrine systems to response inhibition and probabilistic learning. Researchers reported that inhibition of serotonin reuptake, by way of citalopram, had no effect on response inhibition while norepinephrine reuptake inhibition improved response inhibition in healthy volunteers. Due to these observations, researchers have implicated norepinephrine and inhibitory system dysfunction in the pathophysiology of TTM with the prospect of utilizing CNS stimulants that up-regulate NE system to manage symptoms of TTM [37]. One such study examined the effects of modafinil on motor inhibitory control in TTM [37]. Researchers believed that due to modafinil's possible effects on norepinephrine transmission, this medication might improve impaired inhibitory control seen in TTM patients. In this 2-week crossover double-blind, placebo-controlled study, modafinil did not show any significant improvement effects on inhibitory control or cognition enhancement [37]. Similarly, Golubchik et al. [38] performed a study to assess the efficacy and tolerability of methylphenidate in the treatment of TTM

(with comorbid ADHD) in children and adolescents. No significant improvement in the severity of TTM was observed. A case report involving a 30 year-old white female with an 11-year history of TTM that received fenfluramine 20 mg showed a drastic decrease in the urge to pull her hair [39]. It is obvious that there is limited literature regarding the use of CNS stimulants in the treatment of trichotillomania making it difficult to conclude whether they offer any benefit in the management of the disorder. More controlled trial studies are certainly needed.

Antiepileptic drugs

Due to TTM being classified by DSM-IV as an impulse control disorder, it is thought that mood stabilizers may be efficacious in its treatment [40]. The effectiveness of topiramate, an antiepileptic drug that Blocks neuronal voltage-dependent sodium channels, enhances GABA(A) activity, antagonizes AMPA/kainate glutamate receptors, and weakly inhibits carbonic anhydrase enzyme, and oxcarbazepine (that primarily acts by blocking voltage-sensitive sodium channels) might be attributed to the inhibition of the glutamatergic pathway, that is implicated in compulsive and repetitive behaviors. One of the mechanisms of actions of valproic acid is the modulation of the GABA system, which is responsible for "calming" the nerves down. Topiramate has been used in the treatment of other impulse control disorders including binge-eating, skin-picking, pathological gambling, and kleptomania. However, other recent studies have shown that anticonvulsants are ineffective in treating impulse control disorders [41,42]. A case report of an obese patient with binge eating disorder and comorbid TTM was treated with oxcarbazepine 1200 mg/day. Complete cessation of TTM symptoms was seen after 6 months of treatment. A follow-up visit after 9 months showed no relapse in hair-pulling and more stable mood [43]. Another case report of a 9 year-old African American girl, with several comorbid psychiatric disorders, experienced a dramatic reduction of TTM symptoms after an increase in her valproic acid medication. Valproic acid acts primarily by blockade of voltage-gated Na^+ channels and by increasing availability of gamma-aminobutyric acid (GABA) [44]. The patient was already treated with valproic acid for seizures. When the dose of valproic acid was increased to control the seizure attacks, it was noted that the urge to pull hair significantly decreased. Lochner et al. [40] conducted an open-label, flexible dose study that assessed the efficacy of topiramate in 14 adults with TTM. Although topiramate led to a reduction in hair-pulling as the primary outcome measure, there was no statistical significance.

Due to the lack of evidence-based support, it is hard to decide whether antiepileptics are useful in the treatment of TTM. It is also apparent that the randomized control trials that are available all suffer from a small sample size.

Opioid antagonists

Opioid antagonists are used clinically in the treatment of ethanol dependence, pathological gambling, and adult kleptomania [45]. These disorders were classified in DSM-IV as impulse control disorders, along with trichotillomania. Currently, trichotillomania (hair-pulling disorder) is classified under obsessive–compulsive and related disorders along with hoarding, excoriation (skin-picking) disorder, substance-/medication-induced obsessive–compulsive and related disorder, and obsessive–compulsive and related disorder due to another medical condition. Gambling is listed under substance related and addictive disorders and kleptomania is classified under disruptive, impulse-control, and conduct disorders. The main characteristic observed in TTM patients is hair-pulling; despite the association of hair-pulling with detrimental effects, including pain, the patient typically disregards these consequences [45]. These observations led researchers to speculate that opioid system dysfunction may be implicated in TTM.

A 10-month long pilot study of 14 children with TTM evaluated the efficacy of the opioid receptor antagonist, naltrexone on TTM. Patients showed a statistically significant reduction in CGI-S, hair-pulling, frequency and urge intensity of hair-pulling [46]. On the other hand, Grant et al. investigated the efficacy of naltrexone in a double-blind placebo controlled trial with 51 TTM patients randomized to naltrexone or placebo. The study showed no difference between naltrexone and placebo in hair pulling frequency, but significant improvement of cognitive flexibility was observed [46].

Since there are only 2 studies that have tested the efficacy of the opioid antagonist, naltrexone, with obvious variable outcomes, there is a need for more studies to provide a more consistent result. Since both studies showed different results it is difficult to draw a conclusion about whether naltrexone should be used for the treatment of TTM.

Glutamate modulators

Glutamate is the main excitatory neurotransmitter in the CNS, and excessive amounts of glutamate are known to cause neuronal damage. Since glutamatergic dysfunction has been seen in patients with OCD, a disorder that may be linked to TTM, researchers believe that using glutamate modulators, such as N-acetylcysteine (NAC), may help restore glutamate concentrations in the brain to a lower level [22]. NAC is an antioxidant most commonly known for its hepato-protective effects. NAC is metabolized into cysteine, a substrate for the cysteine-glutamate anti-porter that allows for the uptake of cysteine. The uptake of cysteine causes the reversal transport of glutamate into the extracellular space. This in turn stimulates inhibitory metabotropic glutamate receptors reducing the synaptic release of glutamate [22].

Following a case report of using NAC in a TTM patient, researchers conducted a 12-week, double-blind, placebo-controlled trial in order to determine the efficacy and tolerability of NAC in adult patients with TTM [22]. Patients in the NAC group showed statistically significant improvement for hair pulling [22]. However, more studies are needed to determine the efficacy of N-acetylcysteine in the treatment of TTM. Future studies should include a large sample size and a long-term study interval.

Bloch et al. [23] conducted a double-blind placebo controlled study that investigated the efficacy of NAC as an add-on treatment for TTM in a pediatric population. A change in severity of TTM was the primary outcome of the study, and the results revealed no significant difference between NAC and placebo-treated patients.

Table 1 Summary of clinical studies/case reports of potential pharmacotherapy of trichotillomania.

Study	Agent/drug	Subjects	Dosage and treatment duration	Assessment measure	Main outcome	Side effects
Effects of acute modafinil on cognition in trichotillomania [37]	Modafinil (CNS stimulant)	18 patients (14 female and 4 male), with a mean age of 33.4	200 mg for the 1st week and placebo the second week	Inhibitory control and cognitive enhancement	No significant improvement	Not stated
Methylphenidate treatment in pediatric patients with attention-deficit/ hyperactivity disorder and comorbid trichotillomania: a preliminary report [38]	Methylphenidate (CNS stimulant)	Nine children (6 female and 3 male), aged 6–18 years, were treated with methylphenidate	0.5–0.7 mg/kg for 12 weeks	Severity of TTM and tolerability of treatment	No significant improvement in severity of TTM	Decrease in appetite Headache Excessive preoccupation with one's hair Abdominal pain Motor tic exacerbation
Fenfluramine and trichotillomania [39]	Fenfluramine (CNS stimulant)	Case report of a 30 year old female received fenfluramine after an 11 year history of TTM. The patient was partially responsive on fluoxetine and sertraline	Fenfluramine, 20 mg, was added to the daily regimen of sertraline (100 mg) and alprazolam (1 mg). Patient continued on fenfluramine alone for remission	Urge to pull hair	Significant decrease in urge to pull hair	Not stated
Oxcarbazepine for the treatment of trichotillomania [43]	Oxcarbazepine (anticonvulsant, mood stabilizer)	Case report of a 43-year-old woman with binge eating disorder and comorbid TTM	Flexible dosing of oxcarbazepine up to 1200 mg/day	Hair pulling and eating behavior	The patient reported improvement in hair pulling and eating behavior after 6 months of treatment, and with no relapse after 9 months	Sleepiness Confusion Asthenia
Trichotillomania: a case response to valproic acid [44]	Valproic acid (anticonvulsant, mood stabilizer)	Case report of a 9 year-old African American girl, with several comorbid psychiatric disorders	Patient was already on valproic acid for seizures. Dosing regimen was increased with trough levels range between 115 and 125 mg/100 mL	TTM symptoms and urge to pull hair	Patient reported a significant decrease in urge to pull hair and an increase in hair growth	Not stated
Topiramate in the treatment of trichotillomania; an open-label pilot study [40]		14 adults (13 female and 1 male), aged 19–43 years, for the treatment of TTM	A 16-week open-label, flexible dose study; the initial dose was 25 mg every evening for 7 days. On day 8, the dose was increased to 50 mg and increased again to 75 mg on day 15. Dose increases of 25 mg were allowed at the beginning of weeks 4–7 and a final increase in weeks 8–12 to a maximum of 250 mg	TTM severity by the MGH-HPS	A non-significant reduction in TTM severity	Paraesthesia Speech/language difficulty Increased anxiety Weight loss Nausea Headache/migraine Insomnia Myalgia Depressed mood Double/blurry vision Dry mouth

An open-label pilot study of naltrexone in childhood-onset trichotillomania [45]	Naltrexone (opioid antagonist)	Nine (9) girls and 5 boys (mean age of 9) with TTM as primary diagnosis were included in a 10 month pilot study. Only those receiving naltrexone as monotherapy were included. Exclusion criteria were those receiving concomitant CBT or psychotherapy and those with other diagnoses	Naltrexone started at 25 mg/day and was increased to a maximum of 100 mg (based on symptoms) after 1 week	CGI-S, hair pulling, frequency, and intensity of hair pulling	A statistically significant reduction in all TTM measured parameters was observed	None experienced
The opiate antagonist, naltrexone, in the treatment of trichotillomania: results of a double-blind, placebo-controlled study [46]	Naltrexone (Opioid antagonist)	Fifty-one (51) TTM patients, males and females, mean age of 32.7	Patients were given naltrexone over an 8 week period. Dose started at 50 mg/d, and increased to 10 mg/d after 2 weeks, then to 150 mg/d after 4 weeks	TTM severity using MGH-HPS and cognitive function using the intradimensional /extradimensional differences between c	No significant effect on hair pulling Naltrexone group showed significant improvement of cognitive flexibility	Mild sedation No significant effect on liver function
N-Acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study [22]	N-Acetylcysteine (NAC) glutamate modulator antioxidant	Fifty (50) adults (45 women and 5 men), aged 18–65 years old	Patients were given NAC 1200 mg/d, or placebo, for 6 weeks. At week 6, the dose was increased to 2400 mg/d for the next 6 weeks	TTM severity by MGH-HPS, CGI, PITS psychosocial functioning, depression, and anxiety	Significant decrease in hair pulling (MGH-HPS and PITS)	Nausea Diarrhea Cough
N-Acetylcysteine as an add-on treatment for TTM in children and adolescents [23]	N-Acetylcysteine (NAC) Glutamate modulator Antioxidant	Thirty-nine (39) children/adolescents between the ages of 8 and 17 years old who had a primary diagnosis of TTM, but no other psychiatric, mental, developmental disorder, asthma, or substance use disorder All participants were receiving pharmaco- and psychotherapy that started >3 months prior to the trail and continued the therapy during the trial	NAC was titrated over the course of 4 weeks to a maximum dose of 2400 mg. The study continued for 12 weeks	TTM severity MGH-HPS, TSC-C, P), NIMH-TSS, MIST-C, CGI (Clinical Global Impression) depression, anxiety, and adverse effects	No significant improvement in hair pulling in response to NAC treatment	Nausea, diarrhea, fatigue, insomnia, rash, depression, and difficulty in swallowing the pills were reported by both NAC and placebo groups. Nausea was more significantly reported in the placebo compared to the NAC group

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Table 1 (*continued*)

Study	Agent/drug	Subjects	Dosage and treatment duration	Assessment measure	Main outcome	Side effects
Dronabinol, a cannabinoid agonist, reduces hair pulling in TTM [47]	Dronabinol Synthetic Δ^9-Tetrahydrocannabinol	14 patients (all female), aged 18–65, were started on dronabinol	Dronabinol administered at 2.5 mg/d for 3 weeks, and at week 3, the dose was increased to 5 mg/d for 3 weeks, and then increased to 10 mg/d at week 6 for 3 weeks, and to 15 mg/d at week 9 for 3 weeks	TTM severity by MGH-HPS and CGI scale neurocognitive tests	Statistical significant improvement in TTM score, with no significant effect on cognitive functions	No significant adverse effects on cognition reported
Escitalopram treatment of trichotillomania [48]	Escitalopram Antidepressant; SSRI	20 women, aged 18–60	Patients started on escitalopram 10 mg/day for 4 weeks, then the dose could be increased to 20 mg/day based on clinical responsiveness, and at 8 weeks the dose was increased to 30 mg/day	TTM severity by TSS and ITT	Significant decrease in TTM severity	Nausea Insomnia Fatigue Lethargy Sweating Dilated pupils Decreased libido Orgasmic Dysfunction Bruising Skin rash
Use of the selective serotonin reuptake inhibitor citalopram in the treatment of trichotillomania [49]	Citalopram Antidepressant; SSRI	14 patients, not currently receiving a SSRI, 13 female and 1 male, aged 20–45	Citalopram was given initially at 20 mg/day and was increased every 2 weeks, based on clinical response, to a maximum of 60 mg/day	TTM severity by Y-BOCS, NIMH-OCS, and CGI scale depression	Significant reduction in TTM severity and comorbid depression	Headache Diminished sexual desire Sleepiness/sedation Tension Orgasmic dysfunction Decreased salvation Nausea/vomiting Tremor Weight gain Constipation Weight loss Orthostatic dizziness Palpitations/tachycardia Increased yawning
A long-term, double-blind, placebo-controlled crossover trial of the efficacy of fluoxetine for trichotillomania [50]	Fluoxetine Antidepressant; SSRI	16 patients (14 women and 2 men), aged 20–68	Patients were initially given fluoxetine 20 mg/day that was increased to 80 mg/day over 12 weeks. The study started with a 2-week placebo washout period, followed by a 12-week treatment period, 5-week washout period, and a 12-week crossover treatment period	Severity of TTM, severity of hair pulling, urge to pull, days of hair pulling, and daily hair counts	No significant effect of fluoxetine on severity of TTM	Nightmares Insomnia Dizziness Irritability Anxiety Nausea Diarrhea Constipation Anorgasmia Decreased appetite Increased weight

Bupropion XL for the sustained treatment of trichotillomania [51]	Bupropion Antidepressant; Dopamine, norepinephrine-reuptake inhibitor	Case report, 35 year old with 8-year history of TTM had been treated with psychotherapy, pharmacotherapy, and hypnosis, in addition to	Bupropion given at 150 mg/day, was increased after 1 week to 300 mg/day, and again after 2 weeks to 450 mg/day	Frequency of hair pulling	Patient reported complete cessation of hair pulling after 2 weeks of bupropion treatment	Decreased appetite Weight loss
A case of trichotillomania successfully treated with clomipramine [52]	Clomipramine Antidepressant; Tricyclic antidepressant	Case report, 17-year-old girl with TTM initially underwent psychotherapy for treatment with no avail	Patient prescribed clomipramine, 30 mg/day for 2 weeks	Urge to pull hair	Patient reported the ability to resist the urge to pull out hair after 2 weeks of treatment	Not stated
Lithium treatment of chronic hair pulling [39]	Lithium Antimanic	Ten patients	Lithium 900–1500 mg administered for 2–14 months	Hair pulling and hair regrowth	Eight patients reported decreased hair pulling and mild-moderate hair growth	Increased thirst Weight gain Tremor
Lithium treatment of trichotillomania with comorbid bipolar II disorder [54]	Lithium Antimanic	A case report of a 26-year old woman with TTM, exacerbated postpartum, bipolar II disorder, panic disorder, and cannabis dependence. She had been previously prescribed various medications for treatment including sertraline, paroxetine, risperidone, and quetiapine	Lithium treatment was initiated, then the dose was slowly increased to 900 mg	TTM severity	TTM symptoms improved within 4 days. Complete cessation of that hair pulling urge was reported following 7 months treatment with a higher lithium dose	Not stated
Lithium treatment of trichotillomania with comorbid bipolar II disorder [54]	Lithium Antimanic	A case report of a 27-year old pregnant woman, with TTM and co-morbid bipolar II disorder	Patient treated with lithium	TTM severity and urgency to pull hair	A significant reduction in TTM score and urgency to pull her hair was observed after 6 weeks of treatment	Not stated
A randomized, double-blind, placebo-controlled trial of olanzapine in the treatment of trichotillomania [20]	Olanzapine Antipsychotic	Twenty-five (25) patients (17 women and 8 men), aged 18–65 years, randomly assigned The primary efficacy measure was the CGI-I scale	Flexible dose olanzapine (2.5–20 mg/d) or placebo. Patients were given 2.5 mg/d for weeks 0–3, up to 5 mg/d for weeks 4 and 5, up to 10 mg d for weeks 6 and 7, and up to 20 mg/d for weeks 8–12	TTM severity	Olanzapine significantly reduced TTM severity as compared to placebo group	Dry mouth Fatigue Increased appetite Headache Weight gain

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Table 1 (*continued*)

Study	Agent/drug	Subjects	Dosage and treatment duration	Assessment measure	Main outcome	Side effects
The potential role of haloperidol in the treatment of trichotillomania [19]	Haloperidol First generation antipsychotic	Nine (9) patients (all women, with an average age of 32.8 years)	Six patients who had a partial response or no response to SSRIs were treated with haloperidol and an SSRI. The three other patients only received haloperidol. Doses ranged from 0.25 mg/d to 2 mg/d. Four patients received fluoxetine as their SSRI, 1 received paroxetine, and another received fluvoxamine	Researchers used the Structured Clinical Interview for DSM-III-R and a modified Minnesota Trichotillomania Assessment Inventory to evaluate patients. Response to treatment was based on descriptions of hair pulling, quantity of hair pulled, and severity of depilation at hair pulling sites	Eight of the nine patients responded to haloperidol with near complete cessation of hair pulling. Two patients discontinued haloperidol but experienced a relapse in hair pulling	Sedation Increased heart rate Restlessness Constipation
Reversal of trichotillomania with aripiprazole [21]	Aripiprazole Second generation antipsychotic	Case report of a 32-year old woman with a 19-year history of TTM, co-morbidity of major depression and mild/moderate OCD	Aripiprazole started at 15 mg/day, continued till hair pulling cessation	Severity of TTM, cessation of hair pulling, monitor for relapse	The patient reported a reduction of hair pulling by day 10 and complete cessation by day 21. Complete cessation continued for 24 months with no recurrence	Not stated
Resistant trichotillomania and risperidone [54]	Risperidone Second generation antipsychotic	Case report of a 22-year-old woman with antisocial personality disorder and comorbid TTM	Risperidone treatment started and dosage was increased to 4 mg/day	TTM symptoms' cessation	Patient reported complete cessation of TTM symptoms for 8 months	Not stated

Synthetic Δ^9-Tetrahydrocannabinol (Δ^9-THC)

As previously stated, there has been interest in targeting glutamatergic dysfunction in the treatment of TTM. Δ^9-THC, a phytocannabinoid constituting the major active ingredient of cannabis, interacts with the endocannabinoid system (through the cannabinoid CB1 and CB2 receptors) that serves as a neuromodulator for a myriad of neurotransmitters, including glutamate. Grant et al. [47] have shown that dronabinol, a synthetic THC, targets the overproduction of glutamate that is implicated in the symptoms seen in TTM. THC binds to cannabinoid receptors (CB1Rs) inhibiting the release of glutamate onto CA1 neurons. The activation of CB1 receptor has been shown to inhibit glutamate-induced excitotoxicity, and it is believed that in trichotillomania there is a loss of function in these receptors. Hence, Grant et al. examined the effect of dronabinol in the management of TTM [47]. In a 12-week open-label study, researchers hypothesized that dronabinol would reduce hair pulling behavior in TTM patients. Statistically significant improvements were observed for TTM scores. Grant and colleagues also included neurocognitive testing to determine any adverse effects of THC on memory, attention, executive function, and psychomotor speed. The results showed that there were no significant effects on any of these cognitive factors. Targeting CB1 receptors represents a newer area of research that should be further explored. Based on the results from Grant et al. [47] more research is needed to elucidate the possible efficacy of the cannabinoid agonist, dronabinol or other analogs, in the treatment of TTM. Longer duration of the studies is also needed to assess long term effects of these compounds.

Antidepressant agents

The use of antidepressants in the treatment of TTM stems from the belief that TTM is linked to OCD due to the presentation of repetitive symptoms [7]. Some authors believe that TTM should be classified with OCD along with other disorders that have similar behavioral symptoms [7]. In a 12-week, open-label, flexible-dose study, Gadde et al. reported a significant decrease in the trichotillomania severity in patients treated with the SSRI, escitalopram [48]. A similar study was previously conducted by Stein et al. [49], whereby a 12-week, open-label trial was performed using the SSRI, citalopram, in TTM patients. The study reported a significant reduction in TTM severity as well as in comorbid depression. On the other hand, a 31-week, double blind, placebo-controlled crossover trial showed no statistically significant effect of fluoxetine on TTM severity [50].

Despite the conflicting results with the SSRI antidepressant trials, a few scattered case studies report positive response of individual TTM patients to antidepressant therapy. A case report involving a 35-year-old with an 8-year history of TTM had been treated with psychotherapy, pharmacotherapy, and hypnosis. Previous medication included clomipramine, sertraline, paroxetine, citalopram, escitalopram, klonopin, aripiprazole, and 4 trials of fluoxetine. Bupropion XL, a dopamine and norepinephrine reuptake inhibitor, was started and within 2 weeks of starting treatment, the patient reported complete cessation of hair pulling [51]. Similarly, a 17-year-old girl with TTM initially underwent psychotherapy for the treatment with no avail. She was prescribed clomipramine, a tricyclic antidepressant, and after 2 weeks reported the ability to resist the urge to pull out her hair [52].

Although antidepressants were once thought to be the first line of choice in treating the TTM, research has shown that antidepressants do not offer consistent positive results. However, SSRIs might be useful in the management of comorbid depression or anxiety symptoms associated with TTM. A recent random effect meta-analysis study conducted by McGuire et al. [53] examined the efficacy of SSRI therapy in 11 randomized controlled trials. The study reported a moderate treatment pooled effect size of SSRIs. Current research is focused on examining the potential effectiveness of other drug classes with different mechanisms of action.

Antimanic mood-stabilizing drugs

Since TTM was previously classified as an impulse control disorder and does not currently have any FDA-approved treatment option, a wide variety of medications are used to attempt to treat it [54]. Among these medications lithium is the most commonly used antimanic. An early study reported that, in an uncontrolled trial of lithium, 8 out of 10 patients showed decrease in hair pulling and a tendency for hair regrowth [55]. Sharma and Corpse [54] reported two case reports of effective use of lithium in TTM patients. A case report of a 26-year-old pregnant woman with TTM had experienced symptom exacerbations postpartum. Lithium was initiated and within 4 days the patient reported a decrease in the urge to pull out her hair. Another case report of a 27-year-old woman (at 24 week gestation), with bipolar II disorder and a history of TTM was given lithium and reported a reduction in the urge to pull hair.

The limited reported studies described above do not provide concrete evidence of the effectiveness of antimanic drugs in TTM. Additionally, the existence of comorbid bipolar disorder in these cases suggests that positive findings might be attributed to the mood stabilizing effects of these agents.

Antipsychotic agents

Although many researchers believe TTM is similar to OCD, others believe the behavior observed in TTM resembles tics seen in Tourette's syndrome [19]. Both hair pulling and tics occur unconsciously and do not respond well to SSRIs. Due to the fact that Tourette's syndrome responds well to antipsychotic medications, researchers believe TTM might too. So far, trials have been concluded with the antipsychotics olanzapine, haloperidol, and aripiprazole. In a 12-week, double-blind, placebo-controlled trial researchers tested the efficacy of olanzapine, a potent antagonist of serotonin, dopamine, histamine, and alpha$_1$-adrenergic receptors, in the treatment of TTM. Olanzapine was shown to be significantly superior to the placebo in reducing TTM severity score [20]. The same research group conducted an open trial of haloperidol in the treatment of TTM. Haloperidol is a high potency first generation antipsychotic that blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors [19]. Van Ameringen et al. conducted a study on nine TTM patients. Six patients who had a partial response or no response to SSRIs were treated with haloperidol and an SSRI. The three other patients only received

haloperidol. Eight of the nine patients responded to haloperidol with near complete cessation of hair pulling. Two patients eventually discontinued haloperidol and experienced a relapse in hair pulling [19]. Only one case study reported complete cessation of hair-pulling, with no relapse up to 24 months. The case was of a 32-year old woman with a 19-year history of TTM with co-morbidity of major depression and mild/moderate OCD. The patient was administered aripiprazole (a second generation antipsychotic that serves as a partial agonist at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors) for the treatment of TTM. The patient reported a reduction of hair pulling by day 10 and complete cessation by day 21. Complete cessation continued for 24 months with no recurrence [21]. Another case reported a 22-year-old woman with antisocial personality disorder and comorbid TTM treated with risperidone. Risperidone is another second generation antipsychotic agent that acts as a selective monoaminergic antagonist with a strong affinity for serotonin Type 2 (5-HT2) receptors and a slightly weaker affinity for dopamine Type 2 (D2) receptors. A decrease in hair pulling was seen after 4 weeks of treatment. Complete cessation of TTM symptoms was reported and continued for 8 months following increasing the risperidone dose [54]. As evident, the currently available literature evaluating the use of antipsychotics in TTM is scattered, with a few isolated case reports and a couple of trials that suffer from small sample size as a major shortcoming. As such it is hard to reach any conclusions regarding the effectiveness of this class of drugs and its potential contribution to the therapeutic management of TTM.

Table 1 summarizes the details and results of the available clinical trials and case reports reviewed. Based on these studies it is apparent that there is still no consistent treatment option available for TTM. Researchers have explored a variety of drug classes, with different mechanisms of action in an attempt to provide an effective treatment strategy. From stimulants to anti-depressants to an opioid antagonist, future studies are warranted, especially that there are several problems associated with many of the currently available trial studies. A few of these problems are, of course, the scarcity of trials, the small sample sizes, inconsistencies in inclusion criteria (concurrent psychotherapy and pharmacotherapy), short trial duration, and lack of follow-up data. Furthermore, as seen in Table 1, many of these pharmacotherapies employed so far are associated with adverse effects that impede patient's compliance, especially for long term usage. Based on the limited data at hand, it seems that NAC, dronabinol, and naltrexone might provide potential treatment options for TTM. However, more clinical trials with large sample sizes are needed in order to conclusively study their effectiveness. Although previous studies showed statistically significant results, it remains to be seen whether that would hold true in a larger population.

Conclusions

Trichotillomania (TTM) is a disabling disorder in which individuals have the urge to pull their hairs out. Unfortunately, TTM is under recognized and there is a lack of research and funding devoted to the disorder. Most of the research of TTM has been focused on whether it should be considered an OCD subset instead of aiming to explain and treat the disorder. Our current lack of understanding of the etiology and pathophysiology of the disorder certainly hinders the efforts for proper treatment, let alone the proper classification of the disorder. The never ending debate of TTM classification as an impulse versus OCD necessitates further insights into the neurobiology of the disorder. Future research should focus on utilizing advanced imaging technology, coupled to experimental animal models, for mechanistic investigation of neural circuits involved in the disorder. Additional studies that explore the role of various neurotransmitter pathways in the etiology and pathophysiology of the disorder are certainly warranted. The serotonergic, dopaminergic, and glutamatergic pathways are among the top candidates to be investigated, and the role of genes of these pathways in the pathogenesis of TTM needs to be examined.

So far, behavioral approaches seem to be the first line of therapy for most patients. The use of NAC as a first line pharmacological treatment, particularly in adult TTM patients is increasing. However, the use of pharmacotherapy, either alone, or as add-on treatments, needs to be further investigated. Currently, the various pharmacological approaches adopted for TTM lack solid clinical evidence because of unavailability of controlled studies with suitable sample size. In addition, effectiveness seems to be highly individualized, and might be hindered by the side effect profile associated with these medications. Accordingly, controlled trials are needed to assess the effectiveness of this approach as well as to compare it with behavioral alternatives.

Finally, it is imperative to bring awareness to TTM and for it to be recognized as a debilitating disorder. Not only do individuals struggle emotionally but also physically, as they have to endure the embarrassment and shame of hair loss. Those with TTM often resort to social isolation due to embarrassment, and better understanding and awareness of the disorder is certainly the first step toward helping these patients.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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