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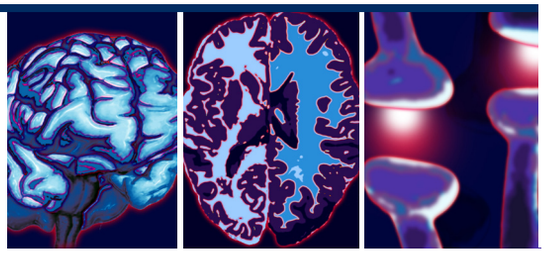

Diagnosis and treatment of trichotillomania

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Practice points

- Clinical characteristics
  - Repetetive hair pulling that causes significant hair loss, distress and impairment is a main feature of trichotillomania.
  - Trichotillomania is more common in females and typically begins around ages 11–13 years.
  - Comorbid psychiatric illness is common among individuals with trichotillomania.
- Etiology
  - Etiological factors include stress, emotional dysregulation, positive reinforcement and genetics.
  - Animal models suggestive of trichotillomania have been developed in birds and mice.
- Neurobiology
  - PET, SPECT, functional MRI and diffusion tensor imaging techniques have been used to investigate the role of various brain regions in individuals suffering from trichotillomania.
- Neurocognition
  - Cogntive investigations provide unclear results regarding neurocognitive functioning of individuals with trichotillomania and if neurocognitive functioning is indicitive of a vulnerability marker or a result of symptomatology.
- Assessment measures
  - The Trichotillomania Diagnostic Interview is the only diagnostic measure created for trichotillomania.
  - The Massachusetts General Hospital Hairpulling Scale, NIHM Trichotillomania Scale, the Psychiatric Institute Trichotillomania Scale, the Yale–Brown Obsessive–Compulsive Scale – Trichotillomania, and the Trichotillomania Scale for Children assess trichotillomania severity.
- Treatment
  - Limited psychotherapeutic research suggests that behavioral therapies may be helpful treatments for those with trichotillomania.
  - Limited pharmacological research has shown that *N*-acetyl cysteine, olanzapine and clomipramine may be beneficial in the treatment of individuals with trichotillomania.
- Treatment summary & recommendations
  - Treatment research is incomplete and, thus, no well-supported conclusion can be made regarding effective trichotillomania treatments.
- Future perspective
  - Future research is needed in all areas of trichotillomania to better understand the nature of the disease and what treatments are effective.

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SUMMARY Trichotillomania is characterized by repetitive hair pulling resulting in significant hair loss, distress, and social and/or occupational impairment. Co-occurring disorders are common among those with trichotillomania. Stress, emotional dysregulation, positive and negative reinforcement, and genetics have been explored as factors in the etiology of the disorder. Furthermore, animal models have been developed for investigating the possible development of trichotillomania, while brain imaging studies have provided evidence that several brain regions may be involved in trichotillomania. Psychological and pharmacological treatment data are incomplete, but behavioral therapy, *N*-acetyl cysteine and olanzapine may be helpful for individuals with trichotillomania.

Clinical characteristics

Trichotillomania is characterized by repetitive hair pulling leading to noticeable hair loss (criterion A), increasing tension prior to and when resisting pulling (criterion B), a sense of gratification, relief or pleasure when pulling (criterion C), is not better accounted for by another mental disorder or caused by a mental condition (criterion D) and results in distress or impairment in leisure, social and/or occupational functioning (criterion E) [1]. Large epidemiological studies are lacking. However, small studies examining the prevalence of trichotillomania among college students in the USA have found current estimates ranging from 0.5 to 3.9% [2–4]. One study in Israel found a lifetime prevalence of hair pulling to be 1% in a sample of 794 nonclinically referred 17-year olds, however, none met the full *Diagnostic and Statistical Manual* (DSM)-III-R criteria for trichotillomania [5]. It is likely this wide variance is caused by the extent to which criteria B and C are applied in each study. Christenson and colleagues found that only 0.6% of 2579 college students reported meeting strict DSM-III-R criteria; however, when broadening the criteria to also include individuals who do not necessarily experience urges before pulling or the post-pulling sense of relief, the percentage of college students increased to 2.5% [2]. Interestingly, one study found that 17% of 60 individuals with chronic hair pulling did not meet either tension or relief criteria [6]. Furthermore, not all hair pullers experience significant alopecia. A sample of 1697 hair pullers found that only 68% indicated losing between 30 and 100% of hair from their target pulling site [7]. Therefore, low estimates may represent the prevalence of individuals who meet official DSM criteria for trichotillomania, middle estimates may represent those with significant hair loss, while the high estimates may most accurately estimate anyone who pulls hair. Furthermore, since the majority of these studies sampled college populations, these prevalence rates of trichotillomania may not accurately reflect the rate within the general population.

Compulsive hair pulling has been noted in the literature for centuries. Although the first well-described cases of trichotillomania, in the 18th and 19th centuries, focused on adolescent and young adult males [8,9], some data suggest that trichotillomania may be more prevalent in females. An internet-based study of 1697 individuals with trichotillomania found that 93.2% were female [7]. It may be that males with trichotillomania are more reluctant to come forward for treatment or are more able to conceal hair loss resulting from pulling (e.g., by shaving). A study of 12 males and 65 females with grooming disorders revealed few clinical differences, although males tended to have a slightly later age of onset and scored higher on psychosocial impairment [10].

Hair pulling usually follows a chronic course and begins at a young age (between 11 and 13 years) [6,11]. Trichotillomania, however, has also been diagnosed in toddlers [12] and approximately 5% of individuals with trichotillomania symptoms had an age of onset of 6 years or younger [13]. Any site may be the focus of pulling, but the scalp is the most common (72.8%), followed by eyebrows (56.4%) [7,11]. Individuals who had an early age of pulling onset (i.e., between the age of 6 and 18 years) are more likely to pull their pubic hair compared with those who start pulling before or after this age range [13]. Most commonly, individuals pull from one or two sites [7], although pulling from more than two sites on the body is common. Individuals typically pull hairs with their fingers; however pulling may also be done with tweezers [6]. Triggers to pull include sensory cues (i.e., hair thickness, length and location, and physical sensations on scalp), emotional cues (i.e., feeling anxious, bored, tense or angry),

and cognitive cues (i.e., thoughts about hair and appearance, rigid thinking, catastrophizing and overgeneralizing) [14].

Pulling styles may be categorized as either automatic (no awareness of pulling) or focused (pulling is in response to a negative emotional state, thought/urge or to obtain symmetry). In addition, individuals may begin pulling automatically and then develop full awareness [6]. It is estimated that between 15 and 34% engage in focused pulling, 5–47% in automatic pulling, and 19–80% in both types of pulling [7]. When comparing focused, automatic, and both focused and automatic pullers, the only significant differences between these groups was that the focused group was significantly more likely to pull hair from the pubic area and experience more shame compared with the other two groups [15]. The Milwaukee Inventory for Subtypes of Trichtotillomania – Adults Version (MIST-A) has been used to assess focused (ten items) and automatic (five items) pulling and has demonstrated acceptable internal consistency, construct and discriminant validity [16]. There are some data to suggest that automatic pullers may receive more benefit from behavioral treatment (i.e., habit reversal therapy [HRT]), while focused pullers who more often experience negative emotions before and after pulling may respond better to interventions such as cognitive behavioral therapy and acceptance and comment therapy. Pullers with both focused and automatic pulling may benefit most from a combination therapy, such as acceptance-enhanced habit reversal [17].

Psychosocial dysfunction is common in trichotillomania sufferers. The impact of heightened levels of stress on psychosocial functioning has been examined in one study comparing individuals with trichotillomania to a control group [18]. The study found that trichotillomania subjects reported lower life satisfaction, higher levels of distress and lower levels of self-esteem [18]. In a sample of 1697 individuals with trichotillomania, 40% avoided social activities, 36% avoided group activities, 20% avoided going on vacation owing to pulling and 23% reported pulling interfered daily with their job duties [7]. Low self-esteem and social anxiety are also linked with trichotillomania, largely because of the resulting alopecia [7,18]. Distress results from both the need to avoid certain activities, owing to hair loss, and from the individual's inability to control the pulling. The negative self-evaluation and negative affect may serve to perpetuate the problem by prompting additional pulling episodes. Because individuals with trichotillomania go to great lengths to conceal their pulling (e.g., having special hair styles, wearing make-up or wigs), family, friends and treatment providers may not be aware of the pulling [18]. Even though trichotillomania has a significant impact on overall quality of life [19], the majority (approximately 65%) of individuals never seek treatment [7].

■ Comorbidity

Co-occurring psychiatric disorders are common in individuals with trichotillomania. Studies consistently report that individuals with trichotillomania have elevated rates of formal depressive (29.2–52%), anxiety (8.3–27%) and alcohol use (33.3%) disorders [6,20], and even greater percentages of individuals with trichotillomania acknowledge problems with anxiety or depressed mood (66–68%) [21].

Etiology

Research has suggested that stress may play a role in the development of trichotillomania and that hair pulling soothes increasing tension. One study found that 40% of individuals with trichotillomania reported anxiety or an uncomfortable urge prior to pulling and through the act of pulling, hoped to reduce these unpleasant feelings [7]. Depressed or anxious individuals may engage in hair pulling to distract themselves from life stressors and unpleasant cognitions (i.e., negative reinforcement). People may therefore initially view the pulling as a mechanism of stress reduction and the risk of developing bald spots as a relatively minor setback. Ironically, the development of bald spots can in turn lead to exacerbations of depression and anxiety, leading to even more pulling in an attempt to manage symptoms. These emotional aspects may serve as a stimulus cue with the pulling reinforcing the behavior, which is often associated with decreases in tension, boredom, sadness and anger. Hair pulling may become a habitual means of coping with stress, eventually resulting in intra- and inter-personal distress.

Another perspective proposes that trichotillomania arises from positive reinforcement. One possible reinforcer for individuals with trichotillomania might be physiological arousal. A total of 39% of individuals with trichotillomania report pleasure or a sense of

accomplishment from the act of pulling [22]. Another positive reinforcer might be tactile stimulation either before pulling (e.g., twirling of hair) or after pulling (e.g., oral behaviors such as rubbing hair around their mouth, and biting, licking or eating the hair or hair root) [6,15]. These hedonically positive feelings associated with pulling may be why some have referred to trichotillomania, in certain individuals, as a type of behavioral addiction [18]. The positive reinforcement theory may also relate to the idea of trichotillomania as a habit disorder resulting from a problem with top-down inhibitory control. This perspective suggests abnormal functioning of the basal ganglia, which plays a role in habit formation and frontal lobe dysfunction relating to habit inhibition [23].

Genetics appear to contribute to the development of trichotillomania. A significantly different concordance rate for trichotillomania was found in monozygotic (38.1%) compared with dizygotic (0%) twins in 34 twin pairs [24]. Several studies have looked at genetic mutations in individuals with trichotillomania. The mutations of the *SLITRK1* gene, which plays a role in cortex development and neuronal growth, have been identified in two trichotillomania subjects that were absent in more than 2000 comparison subjects [25]. In a case–control study, researchers found significant differences in the distribution of the serotonin receptor $(5\text{-HT})_{2A}$ T102C variant when comparing individuals with trichotillomania (n = 39) to control subjects (n = 152) [26]. Zuchner and colleagues also found that a heterozygous variant of the postsynaptic synapse-associated protein 90/postsynaptic density-95-associated protein (SAPAP)3, which is involved in the excitatory transmissions at corticostriatal synapses, was present in only 1.1% of the controls compared with 4.2% of those diagnosed with trichotillomania or obsessive–compulsive disorder [27]. This suggests that SAPAP3 may be involved in the development of obsessive–compulsive spectrum disorders.

■ Animal models

Animal models have been useful in investigating the origins of compulsive behaviors that often seem to mimic the clinical manifestations of trichotillomania. Bordnick and colleagues found that captive birds may excessively pluck their feathers during times of stress, boredom or loneliness to receive attention from their owners [28]. Barbering (abnormal whisker and fur trimming) has been observed in mice. Similar to trichotillomania, it can be both self-directed or partner-directed, is more common in female mice, the hair is plucked from the scalp and around the eyes, and the age of onset is generally in puberty [29]. Greer and Capecchi reported that mice with mutations of the *Hoxb8* gene (expressed in the orbital cortex, the anterior cingulate, the striatum and the limbic system) groomed excessively to the point of hair removal and skin lesions compared with their control counterparts [30]. In addition, the genetic deletion of *SAPAP3* in mice has been associated with increased anxiety and resultant facial hair loss and skin lesions [31].

Neurobiology

Few brain studies have been performed in trichotillomania, and the results are often difficult to interpret. Structural imaging research has found no abnormalities in caudate volumes between trichotillomania subjects and controls [32], reduced left inferior frontal gyrus and increased right cuneal cortex volumes in trichotillomania patients compared with controls [33], and smaller left putamen volumes [34]. A study using morphometric MRI and parcellation techniques, reported that compared with controls (n = 12), individuals with trichotillomania (n = 14) had reduced cerebellar volumes [35]. In a study using voxel-based morphometry in a sample free of comorbidity, trichotillomania was also associated with increased gray matter density in the striatum, left amygdalohippocampal formation, and multiple cortical regions, including the cingulated, supplementary motor cortex and frontal cortex (i.e., areas involving affect regulation, motor habits and top-down cognition) [36].

In a PET study, normalized resting cerebral glucose metabolic rates were found to be increased in the bilateral cerebellum and right parietal cortex in patients with trichotillomania (n = 10) compared with controls (n = 20) [37]. However, in a qualitative study of a pair of genetically identical twins with trichotillomania, both showed decreased perfusion of the temporal lobes during SPECT, and the more severely affected twin showed more widespread temporal involvement [38]. In the only functional MRI study, researchers found no significant differences between patients and controls in terms of brain activation during an implicit sequence learning task [39]. Using diffusion tensor imaging techniques, Chamberlain and colleagues found

that trichotillomania was associated with reduced integrity of white matter tracts connecting the bilateral orbitalfrontal cortex and anterior cingulated cortices, left presupplementary motor area and the left temporal lobe in a sample of 18 individuals with trichotillomania compared with 19 healthy controls [40]. This suggests that there may be a disconnect between neural regions associated with motor activity and emotional processing in individuals with trichotillomania. However, no relationship was found between the reduced white matter tracts and severity of illness or depression [40].

Neurocognition

Although several studies have examined neurocognitve function associated with trichotillomania, the day-to-day impact of any deficits reported has yet to be characterized. It is also unclear whether any reported deficits occur in people at increased genetic risk of the condition, perhaps reflecting a vulnerability marker, or rather occur as a consequence of symptoms themselves.

The first cognitive investigation in trichotillomania used the Stylus Maze test, in which volunteers attempt to learn the correct path for navigating across a peg board using a stylus. Subjects with trichotillomania (n = 21) showed problems with spatial processing compared with controls (n = 16) [41]. In a subsequent study using a similar test (the Austin Maze task), there was no evidence for deficits in trichotillomania patients (n = 11) who were free from current major depression and psychosis versus controls (n = 11) [42].

Two studies using the Wisconsin Card Sorting Test (measuring cognitive flexibility and rule learning) found individuals with trichotillomania did not perform significantly differently from controls [43,44]. Stanley and colleagues also found that trichotillomania subjects had significantly more problems with allocating attention between two separate tasks compared to controls [43]. Chamberlain and colleagues found no significant differences between untreated subjects with trichotillomania and controls on a computerized analog of the Wisconsin Card Sorting Test (the intradimensional/extradimensional set-shift task) assessing cognitive flexibility and rule learning [45].

Studies assessing motor impulsivity have reported mixed results. In a study comparing controls (n = 26) to individuals with trichotillomania (n = 25), no significant differences were found in the overall performance of the go/no-go task [46]. Another study, which used a stop-signal task to measure the ability of subjects to actively inhibit an already triggered motor command, found that patients with trichotillomania (n = 17) exhibited impaired inhibitory control (i.e., increased stop signal reaction times) versus controls (n = 20) [47].

Assessment measures

Different assessment instruments capture different dimensions of trichotillomania including diagnostic criteria, symptom severity and associated psychosocial impairment. For diagnostic purposes, the Trichotillomania Diagnostic Interview [48] is a semi-structured interview consisting of three-point item ratings assessing the DSM-III-R diagnostic criteria for trichotillomania.

For purposes of assessing trichotillomania symptom severity, there are several instruments available. The most widely used scale is the Massachusetts General Hospital Hairpulling Scale (MGH-HPS) [49], a self-report seven-item instrument for the assessment of hair pulling severity (frequency and intensity of urges, ability to control urges, frequency of hair pulling, resistance to and control over hair pulling and associated distress). Other scales include the NIMH Trichotillomania Severity Scale (NIMH-TSS) [50], a five-item, clinician-rated scale assessing pulling frequency, urge intensity, urge resistance, subjective distress and interference with daily activities. The Psychiatric Institute Trichotillomania Scale [51] is a semi-structured instrument with a guided interview format consisting of six items assessing pulling sites, duration, resistance, interference, distress and severity. The Yale–Brown Obsessive–Compulsive Scale – Trichotillomania [52] is a ten-item scale for rating the severity of obsessions and compulsions in trichotillomania. The Trichotillomania Scale for Children (TSC) [53] is a 12-item scale assessing hairpulling severity, distress and impairment with parallel child (TSC-C) and parent (TSC-P) versions.

Treatment

■ Psychotherapeutic interventions

A small number of controlled psychological treatment studies have been completed for trichotillomania. One study compared HRT (subjects develop an increased awareness of pulling and learn specific techniques to decrease pulling)

with negative practice (subjects complete the motions of pulling out hair without actually pulling out hair while standing in front of a mirror) in 34 subjects with trichotillomania, who were followed for 22 months. Statistical analysis found a reduction in hair pulling by more than 90% for 4 months in the HRT group, compared to a 52–68% reduction in the negative practice group [54].

A more recent study of acceptance commitment therapy with habit reversal found that in 25 subject randomized to receive either acceptance commitment therapy or wait-list control for 12 weeks (ten sessions), those in the acceptance commitment therapy group significantly reduced their hair pulling compared to wait-list control. Furthermore, this difference was sustained at the 3-month follow-up visit [55]. Diefenbach and colleagues evaluated the effectiveness of different types of group therapy. Compared to supportive group therapy, behavior group therapy resulted in a significant reduction in trichotillomania symptoms in 24 subjects randomized to either supportive group therapy or behavior group therapy for eight sessions [56]. At the 1-, 3- and 6-month follow-up visits, however, the behavior group therapy had a significant worsening of treatment advancements compared to supportive group therapy.

The only controlled treatment study in children (between ages 7 and 17 years) assessed the efficacy of behavioral therapy in 24 children with trichotillomania. Subjects were randomly assigned to receive behavioral therapy or minimal attention control for 8 weeks. Severity scores improved from baseline to study completion. The findings also indicated that the three youngest subjects receiving behavioral therapy responded just as well, if not slightly better than the nine older subjects [57].

■ Pharmacological treatment

Currently, seven controlled pharmacological studies have been completed for trichotillomania, with four investigating serotonergic antidepressant medications. The first pharmacological study for trichotillomania compared clomipramine to desipramine in 13 females randomized to a 10-week, cross-over trial (5 weeks on each agent) with a 2-week single-blind placebo lead-in. The study found that clomipramine produced significant reductions in the severity, frequency and intensity of hair-pulling episodes. Both groups reported constipation, dry mouth, and tremors during the study, none of which were significantly different between the two groups [50].

With the exception of clomipramine, other serotonergic medications have not demonstrated benefit for trichotillomania. In fact, a recent meta-analysis found that although clomipramine was superior to placebo, selective serotonin reuptake inhibitors were not more efficacious compared to placebo [58]. An 18-week, double-blind, cross-over trial (6 weeks on each agent, with a 5-week washout period between treatment periods) compared fluoxetine with placebo in 21 subjects. Statistical analysis found both the treatment and placebo groups performed similarly on measures of hair pulling urges, frequency and severity. Side effects associated with fluoxetine included nausea, tremors, insomnia, dry mouth and anorgasmia [59]. Similar disappointing results were found by Streichenwein and Thornby in a 31-week, placebo-controlled, randomized, cross-over trial with 16 subjects [60]. The fluoxetine treatment and placebo groups reported similar reductions in hair pulling [60]. Pigott and colleagues (as cited in [61]) completed another randomized, cross-over 20-week trial with a 2-week placebo lead-in comparing fluoxetine with clomipramine in 12 subjects. Findings indicated that both fluoxetine and clomipramine performed well but did not significantly differ from each other on measures of hair-pulling severity [61].

The remaining three pharmacological studies have looked at naltrexone (an opioid antagonist), olanzapine (an atypical neuroleptic) and *N*-acetyl cysteine (NAC; a glutamateric agent) for the treatment of trichotillomania. Christenson and colleagues (as cited in [61]) randomized a sample of 17 individuals with trichotillomania to receive either naltrexone or placebo for 6-weeks. Compared to zero subjects on placebo, approximately half (three of seven) of the naltrexone group had significant reductions of at least 50% in hair-pulling symptoms [61].

Using a 12-week, placebo-controlled design with 35 subjects, Van Ameringen *et al.* found that olanzapine, an atypical neuroleptic, significantly improved the severity of trichotillomania compared to placebo, and significantly more individuals on active medication were rated as full responders (85 and 17% in olanzapine and placebo, respectively) [62]. Although the olanzapine and placebo group did not significantly

differ from baseline to end point on the MGH-HPS, the olanzapine group (46.8%) had a significantly higher mean change on the MGH-HPS compared to placebo (17.9%). Weight gain was a common adverse event (reported in 38% of olanzapine-treated individuals compared to 8% of placebo). Given the potential adverse side effect profile associated with olanzapine (e.g., sedation and increased glucose and cholesterol) [63], the risks must be weighed against possible benefits of this medication when considering its use in therapy.

The largest pharmacological study to date in trichotillomania used NAC in 50 subjects in a 12-week, placebo-controlled study. Recipients of NAC had significantly larger reductions in trichotillomania symptomatology and a higher percentage were rated as 'much' or 'very much' improved compared to placebo (56 and 17% on NAC and placebo, respectively). No adverse events were experienced by subjects receiving NAC [64].

■ Comparison studies

Only three comparison studies have been completed to date. In one such study, 23 subjects (16 completers) were randomized to receive either 9 weeks of cognitive behavioral therapy (CBT) or clomipramine. The CBT modality utilized was derived from the HRT used in Azrin and colleagues' study [54]. Clomipramine failed to demonstrate superiority to CBT or placebo in a 9-week, randomized, parallel-treatment study in 16 subjects. CBT resulted in significantly reduced hair pulling compared to clomipramine and placebo [65].

Another controlled comparison trial randomized 43 subjects (40 completers) to either behavioral therapy, fluoxetine or wait-list for 12 weeks. While 64 and 20% of those in behavioral therapy and the wait-list control group, respectively, reported a clinically significant change in hair pulling, only 9% on fluoxetine reported a significant change. Additionally, compared to the fluoxetine group, the wait-list control group experienced a significantly larger decrease in time spent pulling [66]. At the 2-year follow-up, the behavioral therapy group improvement was not maintained [67].

Dougherty *et al.* assessed the effectiveness of combining CBT with pharmacotherapy in sertraline nonresponders [68]. After completing a 12-week double-blind trial of sertraline versus placebo, subjects without significant improvement (defined as less than a 40% decrease in trichotillomania symptoms) received two, 1 h sessions of HRT in addition to their treatment regimen. Attrition was high, with only 26 of the original 43 subjects (60.5%) completing the trial. A total of 13 subjects received only sertraline or HRT, while 11 subjects received both treatment modalities and two were placebo responders, receiving no additional treatment. Both single and dual modality groups experienced reductions in hair pulling. The dual modality group, however, experienced a significantly greater decrease in symptoms compared with the single modality group. This study experienced high attrition rates and sertraline responders were compared with nonresponders and, therefore, these results must be interpreted with caution.

Using meta-analysis to compare psychotherapy and pharmacotherapy, Bloch and colleagues found that HRT was more efficacious than either clomipramine or selective serotonin reuptake inhibitor treatment [58]. NAC was not evaluated by the meta-analysis as the study was not yet performed at that time.

Treatment summary & recommendations

Overall, data regarding psychological and pharmacological treatments of trichotillomania are incomplete. No studies have been successfully replicated to make a well-supported judgment about treatment efficacy. Inadequate sample sizes limit the statistical power of these studies, and short (8–12 weeks) follow-up periods make it difficult to assess long-term efficacy of these treatments. Furthermore, no studies have specifically investigated how comorbid conditions impact treatment, which is important owing to the high proportion of trichotillomania subjects with co-occurring psychiatric conditions. Despite these limitations, behavioral therapy and several medications have shown promise in treating trichotillomania and should be explored further. NAC, olanzapine (although with notable side effects), and possibly clomipramine may be beneficial for individuals suffering from trichotillomania, but data regarding selective serotonin reuptake inhibitors do not support their use.

Future perspective

Given the overall lack of research regarding trichotillomania, continued research regarding prevalence rates, clinical characteristics,

etiology, neurobiology and treatment is needed. It has been suggested for the DSM-V that trichotillomania be reclassified as an 'Anxiety and Obsessive–Compulsive Spectrum Disorder', rather than as an 'Impulse Control Disorder – Not Otherwise Specified' [101], and therefore future research needs to continue developing models for understanding and treating trichotillomania. Additionally, further treatment research is needed before clear recommendations can be made regarding efficacious interventions.

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