N-Acetylcysteine in Trichotillomania

Subjects: Dermatology

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N-acetylcysteine (NAC) ($C_5H_9NO_3S$) is the acetylated precursor of the amino acid L-cysteine and functions as a glutamate modulator and antioxidant. It is widely known as a mucolytic, an antidote for acetaminophen overdose, and a nephroprotective agent for contrast administration. Trichotillomania (TTM), excoriation disorder, onychophagia, and onychotillomania are categorized as body focused repetitive behavior (BFRB) disorders, causing damage to the skin, hair, and/or nails with clinically significant psychosocial consequences.

Keywords: N-acetylcysteine ; NAC ; body focused repetitive behavior ; BFRB

1. Introduction

Body-focused repetitive behavior (BFRB) disorders are self-inflicted, compulsive behaviors that cause physical damage to the skin, hair, and nails, often with psychosocial consequences. There is increased research interest in BFRBs, encompassing both psychiatry and dermatology disciplines. Approximately 30% to 40% of patients treated for dermatological conditions suffer from an underlying psychiatric disorder that worsens or causes the skin disease [1]. Common BFRBs include trichotillomania (TTM) (hair pulling), excoriation disorder (skin picking), onychophagia (nail biting), and onychotillomania (nail picking). Mild forms of these behaviors are relatively common in the general population; however, severe cases can cause significant distress or impede social functioning.

All BFRBs are now classified under obsessive compulsive and related disorders (OCRD) in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5) [2]. The DSM-5 makes a distinction between BFRBs and OCRDs, stating that BFRBs are not triggered by obsessions or preoccupations, but may be preceded or accompanied by feelings of anxiety or boredom [2]. In addition, OCRD behaviors do not arise from a fixation on the body, but are provoked by other factors [2][3]. It is estimated that 1 in 20 people suffer from a BFRB [4]. The prevalence ranges from 0.5–2% for TTM [1][2][5], 1.4–5.4% for excoriation disorder [2][6], 20–30% for onychophagia [7], and 0.9% for onychotillomania [7].

Although the pathophysiology of BFRBs is incompletely understood, neuroimaging studies in patients with OCD and OCRDs have consistently shown hyperactivity in the orbitofrontal cortex and striatum [8][9]. It is hypothesized that this hyperactivity is due to an increased excitation to inhibition ratio from increased glutaminergic excitation or reduced GABAergic inhibition, resulting in the compulsive behaviors seen in BFRBs [10][11].

Effective pharmacologic treatments for BFRBs are lacking. Currently, there are no Food and Drug Administration-approved drugs for BFRBs, and psychotropic drugs with numerous side effects are often used as first-line therapy with mixed results. However, there is a growing body of evidence for the use of glutaminergic agents for treating BFRBs and OCRDs, namely *N*-acetylcysteine (NAC).

NAC ($C_5H_9NO_3S$) is the acetylated precursor of the amino acid L-cysteine and functions as a glutamate modulator and antioxidant [12][13][14][15][16]. It is widely known as a mucolytic, an antidote for acetaminophen overdose, and a nephroprotective agent for contrast administration [15][17]. NAC attenuates glutaminergic hyperactivity by releasing glutamate, the main excitatory neurotransmitter in the central nervous system, into the extracellular space. This stimulates inhibitory glutamate receptors and reduces glutaminergic neurotransmission [1][16]. Excessive amounts of glutamate discharge results in neuronal damage and is associated with many repetitive and compulsive disorders. Significantly higher levels of glutamate have been found in the cerebral spinal fluid, orbitofrontal cortex, and caudate nucleus of OCD patients [18][19][20]. Through this mechanism of action, NAC has been successfully used as adjunctive treatment in many psychiatric mood disorders (i.e., depression, anxiety, and post-traumatic stress disorder (PTSD)) [12][21].

Abnormalities in the dopamine pathway are associated with psychiatric disorders including schizophrenia, addiction, depression, and attention deficit hyperactive disorder (ADHD). NAC indirectly regulates dopamine release through glutaminergic neurotransmission, acting on the presynaptic mGlu2/3 receptors [22]. Additionally, dopamine, glutamate, and

their oxidized metabolites can be cytotoxic and contribute to oxidative stress [23][24][25]. NAC protects cells against oxidative stress by replenishing glutathione, a major antioxidant made up of glutamate, glycine, and cysteine. NAC contributes cysteine, the rate-limiting substrate of glutathione synthesis [15]. Cysteine is also an effective free radical scavenger, further minimizing inflammatory and oxidative stressors. Reduction of cellular oxidative stress is thought to block the reinstitution of compulsive behaviors [3][17].

Compared to other glutaminergic agents, NAC has received much attention for its use in treating BFRBs given its low cost and benign side effect profile. More recently, there is increasing evidence on the efficacy of NAC in treating BFRBs.

2. NAC in Trichotillomania

TTM is repetitive hair pulling of one's own hair from the scalp, eyebrows, eyelashes, and pubic region, leading to nonscarring patchy hair loss with short hair. Patients have a negative hair pull test on physical examination. This condition is exacerbated by stress and can cause significant distress, shame, and low self-esteem. First-line pharmacologic treatments for TTM are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), specifically clomipramine [1]. Other drugs studied for treating TTM include olanzapine, inositol, and naltrexone with limited success [1][26][27][28]. NAC has been studied in several clinical trials for TTM treatment (**Table 1**) [29][30][31][32][33][34][35][36][37][38][39][40].

Table 1. Summarizes all NAC treatment studies for TTM, which includes one adult and one pediatric randomized double-blind controlled trials and nine case reports.

Summary of NAC Treatment Studies in Trichotillomania

Study	Design	Patients	Age (Year)	Comorbidities	NAC Dose	Other Concurrent Medications	Outcomes
Grant, Odlaug, and Kim (2009) [29]	RDBPCT	Adult (*n* = 50)	18–65	Depression, anxiety, OCD, PTSD, SPD, bulimia	1200–2400 mg/day	SSRIs, SNRIs, stimulants, psychotherapy	The NAC group showed higher efficacy ($F_{1,47}$ = 32.152, p < 0.001) compared to the placebo group based on MGH-HPS. The NAC group also showed improvement in hair pulling severity ($F_{1,47}$ = 18.245, p < 0.001) and resistance and control ($F_{1,47}$ = 37.067, p < 0.001) compared to placebo.
Bloch et al. (2013) [30]	RDBPCT	Pediatric (*n* = 39)	8–17	ADHD, depression, anxiety, OCD, tic disorder, SPD	600–2400 mg/day	SSRIs, antipsychotics, atomoxetine, psychotherapy	No significant difference between NAC and placebo group based on MGH-HPS (p = 0.55). Moderate decrease in hair pulling noted in both groups (p = 0.002).
Zhao et al. (2021) [32]	Case report	Adult (*n* = 1)	25, F	BED, anxiety, depression	600–1800 mg/day	Fluvoxamine 150 mg/day, bupropion 300 mg/day	After 2 weeks, stable mood and reduced hair pulling behavior reported. At 14 weeks, patient reported no hair pulling or binge eating episodes, and improved anxiety and depression.
Jones, Keuthen, and Greenberg (2018) [33]	Case report	Adult (*n* = 1)	18, F	OCD, depression, anxiety, SPD	2700 mg/day	Fluoxetine 40 mg/day, psychotherapy	After 16 weeks, patient had significant reduction in hair pulling, skin picking, depression, anxiety, and OCD symptoms. Full remission was not reached.

Summary of NAC Treatment Studies in Trichotillomania

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Kilic and Keles (2018) [34]	Case report	Adult (*n* = 1)	18, F	Depression, anxiety	1200 mg/day	Fluoxetine 40 mg/day	After 3 weeks, patient showed decreased hair pulling urges and behavior. All depression and anxiety symptoms ceased. At 6-month follow-up, no hair pulling was noted.
Pino et al. (2017) [35]	Case report	Pediatric (*n* = 1)	12, F	Not specified	2400 mg/day	Doxepin 10 mg/day, fluoxetine 20 mg/day, pimozide 2 mg/day	After 6 months, patient had improved hair density and dermoscopy findings.
Barroso et al. (2017) [36]	Case report	Pediatric (*n* = 1)	11, M	Asthma, atopic dermatitis	1200–1800 mg/day	None	After 3 months, patient showed improvement at 1200 mg/day. Remission with complete hair regrowth was achieved at 1800 mg/day for 3 months.
Ozcan and Seckin (2016) [37]	Case report	Adult and pediatric (*n* = 2)	30, F; 14, F	Not specified; ADHD	1200 mg/day	None; methylphenidate	Case 1: After 2 months, hair pulling decreased with complete remission within 4 months. No recurrence of hair pulling was noted at 7-month follow-up. Case 2: After 2 weeks, significant improvement of hair pulling noted with complete hair regrowth after 6 months. No recurrence of hair pulling noted at 8-month follow-up.
Taylor and Bhagwandas (2014) [38]	Case report	Adult (*n* = 1)	58, F	Unexplained weight loss	1200 mg/day	None	After 4 weeks, patient showed noticeable regrowth of hair, which further improved at 10 weeks. Progress continued and maintained at 32 weeks.
Rodrigues-Barata et al. (2012) [39]	Case report	Adult (*n* = 2)	23, F; 19, F	Alopecia; Not specified	1200 mg/day	None	Case 1: Within 2 months, hair regrowth was observed; Case 2: Complete regrowth was observed after 3 months of treatment.
Odlaug and Grant (2007) [40]	Case report	Adult (*n* = 2)	28, M; 40, F	ADHD, nail biting; Not specified	600–1800 mg/day; 600–2400 mg/day	None	Case 1: Dose was increased from 600 to 1800 mg/day over several weeks. Complete cessation of hair pulling after 1 week on 1800 mg/day. Case 2: Dose was increased from 600 to 2400 mg/day. Complete cessation of urges and hair pulling after 2 weeks on 2400 mg/day.

NAC, N-acetylcysteine; RDBPCT, randomized double blind placebo controlled trial; ADHD, attention deficit hyperactive disorder; OCD, obsessive-compulsive disorder; SPD, skin picking disorder; TTM, trichotillomania; PTSD, post-traumatic stress disorder; BED, binge eating disorder; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-

norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MGH-HPS, Massachusetts General Hospital-Hair Pulling Scale; NE-YBOCS, Yale-Brown Obsessive Compulsive Scale; CGI, Clinical Global Impression.

In a 12-week randomized, double-blind, placebo-controlled trial of 50 adult patients with TTM ages 18–65 years, half of the patients received NAC (1200 mg/day), while the other half received placebo pills for six weeks. The dose was increased to 2400 mg/day in the treatment group for another six weeks, unless clinical improvement (i.e., cessation of all hair pulling) was achieved at the lower dose. Using the Massachusetts General Hospital-Hair Pulling Scale (MGH-HPS), there was a significant treatment effect after nine weeks of active medication use ($p = 0.002$) and higher efficacy in the NAC group ($F_{1,47} = 32.152$, $p < 0.001$) compared to the placebo group. Patients in the NAC group showed improvement in hair pulling severity ($F_{1,47} = 18.245$, $p < 0.001$) and resistance and control ($F_{1,47} = 37.067$, $p < 0.001$) compared to the placebo group [29].

A randomized double-blind, placebo-controlled trial of 39 pediatric TTM patients ages 8–17 years demonstrated conflicting results. Participants in the NAC group were titrated up from 600 to 2400 mg/day over four weeks, and remained on the maximum dose for the remainder of the 12-week study. The research failed to show any benefit of NAC over placebo in improving severity of TTM using the MGH-HPS ($p = 0.55$). However, all subjects, regardless of assigned group, had clinically moderate, but significant improvement in hair pulling symptoms over time ($p = 0.002$) [30]. In a follow-up longitudinal study assessing for long-term outcomes in 30 of the 39 pediatric TTM patients who stopped taking NAC, hair pulling severity on average did not differ significantly over the 3-year follow-up period ($p = 0.77$). Based on the Clinical Global Impression (CGI)-Improvement scale, 20% of patients reported very much or much improved hair pulling behavior, 40% reported no changes in their symptoms, 22% had worsened hair pulling, and 17% had significantly worsened hair pulling during the follow-up period. Subjects also reported significantly increased anxiety ($p = 0.009$) and depressive ($p = 0.0001$) symptoms at follow-up that were correlated with increased hair pulling behavior [31].

NAC has shown benefit in treating TTM in several case reports. A 40-year-old female patient with a 36-year history of TTM was successfully treated with NAC for 10 weeks. Previous treatments for her TTM included citalopram 60 mg/day, venlafaxine extended release 300 mg/day, escitalopram 30 mg/day, fluoxetine 80 mg/day, paroxetine 60 mg/day, bupropion sustained release 300 mg/day, clomipramine 150 mg/day, lithium 900 mg/day, and olanzapine 10 mg/day, with each medication trial lasting at least 16 weeks. Additionally, the patient received cognitive behavioral therapy (CBT) and habit reversal therapy (HRT) for 12 weeks without any decrease in her hair pulling symptoms. The patient was started on NAC 600 mg/day and gradually increased to 1800 mg/day. After 4 weeks, her hair pulling urges decreased. After another dose increase to 2400 mg/day for 2 weeks, the patient noted compete cessation of hair pulling behavior with maintenance of results after 5 months [40].

In another case, a 58-year-old female with TTM was successfully treated with NAC 1200 mg/day for 32 weeks with complete and sustained recovery. After 4 weeks on NAC, the patient noticed modest regrowth of her scalp, which further improved at 10 weeks. The patient remained on the dose for a total of 32 weeks. This is the longest reported treatment duration for any BFRB with NAC. The patient also did not report any adverse side effects during the entire treatment duration [38].

Of note, some cases reported combined treatments of NAC with other psychotropic medications, making it unclear whether NAC alone would produce similar results. For example, a 25-year-old female with TTM comorbid with binge eating disorder, depression, and anxiety was treated with NAC starting at 600 mg/day and titrated up to 1800 mg/day, fluvoxamine 150 mg/day, and bupropion 300 mg/day with significantly reduced hair pulling behavior and binge eating urges. After two weeks of treatment, the patient had almost no hair pulling and noted hair thickening. At 14 weeks, the patient reported no hair pulling behavior or binge eating episodes with improved anxiety and depression symptoms [32].

A 14-year-old girl with TTM comorbid with ADHD saw significant improvement of hair pulling behavior after 2 weeks of treatment with NAC 1200 mg/day. Before starting NAC, the patient was taking haloperidol and methylphenidate for her ADHD for 6 months and 3 years, respectively. Upon starting NAC, haloperidol was discontinued. There was significant improvement in hair pulling after 2 weeks and complete hair growth was noted after 6 months [37].

In another case, an 18-year-old female was treated with NAC 2700 mg/day, fluoxetine 40 mg/day, and psychotherapy for TTM comorbid with excoriation disorder, OCD, depression, and anxiety. After 16 weeks of treatment, the patient reported significant reduction of her hair pulling and skin picking behavior and decreased severity of her comorbid psychiatric symptoms. Although the patient did not achieve complete remission, she was satisfied with the improvement in symptoms. This is the highest reported dosage for NAC in hair pulling, as 2400 mg/day is usually the maximum dose prescribed. The patient did not report any adverse effects despite the high dosage [33].

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