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Exploring the Role of N-Acetylcysteine in Pediatric Trichotillomania: A Review of Safety, Efficacy, and Therapeutic Potential amid Controversy

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Abstract

Pediatric trichotillomania, a complex psychodermatological disorder characterized by recurrent hair-pulling, remains poorly understood with an uncertain etiology. While a multifactorial origin is suspected, one key hypothesis involves hyperglutamatergic activity as a potential contributor. Additional potential contributing factors include genetic predispositions, environmental stressors, and underlying psychiatric conditions, which further complicate the pathophysiology of the disorder. N-acetylcysteine (NAC), a well-tolerated acetylated amino acid, has long been recognized for its ability to modulate glutamate levels and has demonstrated antioxidant and anti-inflammatory properties. Though NAC has demonstrated efficacy in adult trichotillomania, its effectiveness in the pediatric population is not yet well established. This review critically examines the existing literature on the safety, efficacy, and therapeutic potential of NAC in the management of pediatric trichotillomania, addressing the controversies surrounding its use. Furthermore, the review emphasizes the need for additional research to better understand optimal therapeutic strategies for this population and underscores the necessity of more rigorous studies to clarify the role of NAC in treating this complex condition in children.

1. INTRODUCTION

Trichotillomania (TTM), also known as hair-pulling disorder, is classified as an obsessive-compulsive or related disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [1]. It is a complex psychodermatological condition characterized by recurrent, self-induced hair-pulling, often resulting in noticeable hair loss. TTM typically begins during adolescence and follows a chronic course with waxing and waning symptom severity throughout life [2]. The etiology of TTM remains poorly understood, particularly in pediatric populations, despite the onset. It is suspected to have a multifactorial origin, likely arising from interactions among genetic predispositions, environmental stressors, neurobiological imbalances, and underlying psychiatric comorbidities [3-4]. This limited understanding of its pathophysiology further complicates both the identification of causative factors and the development of effective management approaches. Moreover, the variability in symptom presentation among individuals presents additional challenges in diagnosis and treatment selection.

Although TTM shares similarities with obsessive-compulsive disorder (OCD), its

treatment landscape differs significantly. While OCD has well-established first-line treatments with robust efficacy and safety data, no gold-standard medications are approved for TTM management [5-6]. TTM treatment often involves a multidisciplinary approach, including primary care providers, dermatologists, psychiatrists, and psychologists, utilizing multiple modalities. Cognitive behavioral therapy (CBT) and habit reversal training are the commonly studied therapeutic techniques [7]. These approaches aim to address the underlying behavioral patterns and provide patients with practical tools to reduce hair-pulling episodes. However, access to specialized behavioral interventions can be limited, necessitating the exploration of alternative treatment strategies.

Pharmacologically, selective serotonin reuptake inhibitors (SSRIs) and antipsychotics such as olanzapine, aripiprazole, and quetiapine are often employed, though their efficacy remains inconsistent [6]. Additionally, N-acetylcysteine (NAC), a glutamate modulator, has shown promise in adult TTM, but its effectiveness in pediatric populations remains uncertain. Preliminary findings suggest potential benefits, yet response variability and a lack of standardized dosing protocols hinder clinical implementation. Treatment recommendations for pediatric TTM often vary by age, further complicating management [6]. Given these gaps, this review aims to critically evaluate the safety, efficacy, and therapeutic potential of NAC in managing pediatric trichotillomania.

2. Pediatric Trichotillomania Overview

Despite often being described as a disorder that provokes significant distress and functional impairments in various life domains, trichotillomania (TTM) remains a condition that is inherently burdensome to manage [8]. TTM appears to stem from a variety of contributing factors that influence its development. Current hypotheses include glutamatergic hyperactivity, a genetic predisposition, and psychological components.

For instance, Peris et al. conducted a study using magnetic resonance spectroscopy and found that TTM patients with higher glutamate (Glu) levels in the pregenual anterior cingulate cortex (pACC) and thalamus were associated with more severe TTM symptoms. Additionally, symptom improvement seemed to be linked with treatments focused on reducing the brain's direct pathway, particularly by increasing GABA levels in the putamen [9]. These findings suggest that treatment options tailored to modulating neurotransmitters such as glutamate and GABA may provide a promising alternative for individuals managing TTM. Neurochemical imbalances could translate into viable treatment options; thus, future research should focus on deeply exploring the effect of these imbalances on disease progression and developing potential mechanisms to correct them via pharmacological therapy.

Beyond the potential role of neurotransmitter imbalances in individuals with TTM, there is increasing evidence that TTM also contains a genetic factor. A previous concordance study, commonly used to assess genetic influence and heritable traits, found significantly higher rates of TTM in monozygotic (MZ) twins compared to dizygotic (DZ) twins, strongly suggesting a genetic component. However, since concordance was not 100%, additional factors likely contribute to the condition's pathogenesis [4]. While a genetic component is highlighted given the increased prevalence among MZ twins, additional non-genetic contributors, such as epigenetic and behavioral factors, must be taken into account when developing more personalized approaches to treatment and prevention.

An individual's current mental state may also influence the progression of TTM. Elevated levels of various personality traits, including anxiety, depression, perceived stress, and particularly neuroticism, were found to be significantly associated with increased TTM symptoms [10]. The significant association between psychological traits and increased TTM symptoms underscores the demand for more treatment options that integrate approaches addressing behavior, genetics, and neuronal imbalances. Effective treatments for TTM are likely to involve strategies combining psychotherapy and pharmacological alternatives.

Further research focused on elucidating the exact etiology and progression of TTM is necessary, which is a fact that is highlighted particularly when discussing present and future treatments. Moreover, current interventions, such as acceptance and commitment therapy (ACT), cognitive-behavioral therapy (CBT), and habit reversal training, have been shown to improve the detrimental symptoms associated with TTM [11]. Indeed, the improvements seen with various branches of psychotherapy may provide patients with an alternative way to manage their

condition, particularly given the increasing prevalence of other psychiatric disorders, such as anxiety and depression, in this population. Nevertheless, this approach remains insufficient given TTM's proposed multifactorial etiology. Additionally, the cost and significant time commitment required for psychotherapy present further barriers. Considering the probable physiological basis of this disorder, exploring potential pharmacologic interventions is essential.

Currently, there is still no pharmacological therapy that is FDA-approved for TTM, and existing evidence on the efficacy of pharmacological approaches remains limited [12]. Commonly used therapies, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), have not shown significant improvement in symptoms. Moreover, TCAs were found to be significantly less effective than cognitive behavioral therapy in reducing symptoms, with adverse effects such as dry mouth, constipation, and sedation frequently reported. As a result, alternative treatments for TTM continue to be explored, with NACemerging as a promising candidate. The potential of NAC, particularly in combination with other therapies, warrants further investigation.

3. N-Acetylcysteine Overview

N-acetylcysteine (NAC) serves as a precursor to L-cysteine, a key substrate in the biosynthesis of glutathione (GSH), a potent antioxidant. This biochemical pathway plays a critical role in alleviating oxidative stress and promoting detoxification processes within the body [13-14]. One of NAC's most widely recognized clinical applications is in the management of acetaminophen overdose, where it facilitates the restoration of depleted GSH levels. Additionally, NAC demonstrates mucolytic activity by cleaving disulfide bonds in mucus, enhancing its clearance [15]. Furthermore, NAC exerts anti-inflammatory effects by inhibiting the nuclear factor kappa B (NF-κB) pathway, leading to the reduction of pro-inflammatory cytokines, including TNF-alpha, IL-6, and IL-1β [14, 16]. These properties make NAC a valuable therapeutic agent not only in managing oxidative stress but also in conditions where inflammation plays a central role in disease pathogenesis. Beyond these applications, NAC's ability to modulate glutamate and mitigate oxidative stress has led to its investigation as a potential treatment for neuropsychiatric disorders, including TTM. Together, these diverse mechanisms underline NAC's broad therapeutic potential across a range of medical conditions, from liver toxicity to inflammatory diseases and neuropsychiatric disorders.

3.1. Safety and Adverse Effects

NAC is generally well-tolerated in clinical practice, with most side effects being mild and transient. The most commonly reported adverse events are gastrointestinal symptoms, including nausea, vomiting, and diarrhea. These effects are typically dose-dependent and resolve once the dosage is adjusted or treatment is discontinued. While NAC is considered safe for oral use in most patients, rare but severe adverse events have been associated with its intravenous administration, including anaphylactic reactions and fatalities, particularly when administered inappropriately or in high doses [13]. This highlights the importance of cautious administration and monitoring, particularly when considering NAC for vulnerable populations, such as children.

In pediatric populations, NAC is typically safe, though certain risks need to be considered. While gastrointestinal issues are common, some reports have highlighted the emergence of more concerning side effects, such as aggressive behaviors following NAC therapy [17]. This underscores the importance of careful monitoring in children. Assessing the risk-benefit profile is crucial when considering NAC for pediatric patients, as their physiological responses may differ from those of adults.

3.2. Role for NAC in Pediatric Body-Focused Repetitive Behaviors

In addition to its role in treating acetaminophen toxicity, N-acetylcysteine (NAC) has shown promise in addressing various psychiatric and behavioral disorders, including obsessive-compulsive disorder, skin-picking disorder, and other body-focused repetitive behaviors. It offers patients a potential therapeutic option to reduce the frequency and severity of these conditions. An open-label pilot study by Miller et al. suggested that NAC may help alleviate skin-picking behaviors in individuals with Prader-Willi syndrome, with all 35 participants showing improvements in skin-picking symptoms [18]. This finding indicates NAC's potential to target specific behavioral symptoms associated with genetic conditions, highlighting its broader

applicability in treating skin-picking disorders beyond traditional treatments.

A case report by Percinel & Yazici also demonstrated the successful use of NAC in treating skin picking disorder in a pediatric patient, following the failure of other treatments. Significant improvements were observed in reducing compulsive skin-picking, healing physical lesions, and enhancing the patient's mental and social well-being, further supporting NAC as an effective treatment for this disorder [19]. This case reinforces the idea that NAC can be a viable option for patients who have not responded to other treatments, especially in pediatric populations, where options may be limited.

A double-blind, randomized, placebo-controlled trial by Ghanizadeh et al. indicated that NAC might reduce nail-biting behaviors in children and adolescents in the short term, with notable improvements observed after one month. However, the effects were not sustained after two months. Despite some mild side effects leading to a high dropout rate, NAC was generally well tolerated, suggesting that further investigation with longer trials is warranted [20]. The short-term efficacy seen in this study is promising, but the lack of sustained effects over a longer period and the high dropout rate highlight the need for further research into the long-term benefits and potential side effects of NAC for these behaviors.

Additionally, a case study by Ghanizadeh & Derakhshan found that NAC (800 mg/day) significantly improved social interactions and reduced aggressive behaviors in a child with autism over a two-month period [21]. This case suggests that NAC may have a broader neuropsychiatric effect, improving not only specific behavioral symptoms but also broader social and emotional functioning in children with autism. These findings contribute to the growing interest in NAC as a treatment for various psychiatric and behavioral conditions, though larger studies are needed to confirm its efficacy in broader populations.

3.3. NAC for Adult Trichotillomania

In adults, NAC has emerged as an effective therapeutic option for managing trichotillomania. Clinical studies suggest that NAC can help reduce hair-pulling behaviors, making it a promising adjunct to traditional therapies. By modulating glutamate levels and reducing oxidative stress, NAC targets neurobiological factors underlying trichotillomania, positioning it as a valuable tool in managing this challenging condition. In a double-blind, placebo-controlled study by Grant et al., NAC significantly reduced hair-pulling symptoms in adults with trichotillomania. Over 12 weeks, 56% of participants in the NAC group experienced a 50% or greater reduction in symptoms, compared to just 16% in the placebo group. NAC was well-tolerated, with no significant differences in adverse effects between the two groups, suggesting that it is both an effective and safe treatment option for this condition [22]. When incorporated into a comprehensive treatment plan, NAC can enhance outcomes for individuals with trichotillomania, providing them with a valuable tool for managing their symptoms.

Several case studies have reported successful treatment outcomes for TTM using NAC in adults. Zhao et al. described a 25-year-old woman with TTM and comorbid binge eating disorder, who, despite previous unsuccessful treatments, showed significant and sustained improvement in both her hair-pulling and binge eating behaviors after NAC was added to her medication regimen [23]. This case suggests that NAC could be an effective adjunctive treatment, particularly for TTM complicated by other obsessive-compulsive and related disorders. Similarly, Jones et al. reported a case of an 18-year-old with severe hair-pulling behaviors, OCD, depression, and anxiety, who showed notable improvement after 16 weeks of NAC (2700 mg/day), alongside Habit Reversal Training (HRT), Dialectical Behavior Therapy (DBT), and fluoxetine, though full remission was not achieved [12]. This highlights NAC's potential in managing both TTM and its comorbid symptoms, suggesting it may be more effective when combined with other therapeutic approaches.

A case reported by Kiliç & Keleş involved a 31-year-old woman with a 20-year history of TTM who responded well to NAC treatment, demonstrating NAC's efficacy and good tolerability for managing obsessive-compulsive behaviors [24]. This reinforces NAC as a promising alternative for long-standing TTM, especially in cases resistant to other treatments. In a case presented by Taylor & Bhagwandas, a 58-year-old woman with unexplained weight loss and dysphagia who developed significant hair loss during hospitalization showed noticeable hair regrowth after four weeks of NAC treatment (1200 mg daily) [25]. This suggests NAC’s

potential to stimulate hair regrowth in cases of non-psychological hair loss.

Rodrigues-Barata et al. reported two patients with TTM who achieved hair regrowth after two to three months of NAC treatment (1200 mg/day), with no adverse effects noted in either case [26]. These cases suggest that NAC can effectively promote hair regrowth in individuals with TTM, providing an additional treatment avenue. Odlaug et al. presented the case of a 28-year-old male with co-occurring nail biting (NB) and TTM who experienced significant improvement after increasing his NAC dosage to 1200 mg/day [27]. This case highlights NAC's potential to treat both TTM and NB, emphasizing the importance of dosage adjustments for optimal results. Another case by Odlaug et al. involved a 40-year-old woman with a long history of TTM, who achieved complete cessation of hair-pulling after gradually increasing her NAC dosage to 1800 mg/day [27]. This suggests that NAC may be particularly beneficial for individuals with chronic, treatment-resistant TTM. Together, these cases support NAC as a promising adjunctive treatment for TTM, especially in the presence of comorbid conditions, and emphasize the importance of tailored dosing.

While current evidence on N-acetylcysteine (NAC) for adult trichotillomania (TTM) is promising, it is limited by small sample sizes, variability in study design, and inconsistent dosages. Larger, well-designed randomized controlled trials (RCTs) with diverse participants and standardized protocols are needed to confirm NAC's effectiveness and optimal dosage. Treatment durations and doses in current studies range from 1200 mg to 2400 mg, over one to eight months [17]. However, further research is necessary to determine the best approach. These promising results observed in adults suggest that NAC could also offer potential benefits for pediatric populations with trichotillomania.

3.4. N-Acetylcysteine in Pediatric Trichotillomania

3.4.1. Controversy

While N-Acetylcysteine (NAC) has shown benefits for adults with trichotillomania (TTM), there is still controversy surrounding the use of NAC in pediatric populations. As a body-focused repetitive behavior disorder, TTM is widely thought to be worsened by dysregulation in glutamate pathways [22]. NAC's effectiveness lies in its modulation of glutamatergic activity by increasing extracellular levels of glutathione, which reduces glutamate release and excitotoxicity. The current controversy regarding the efficacy of NAC in pediatric patients with TTM stems from conflicting study results. A key study published in the Journal of the American Academy of Child and Adolescent Psychiatry in 2013 found no significant difference between NAC and placebo in reducing hair-pulling severity in children and adolescents with TTM. This study involved 39 participants aged 8 to 17 years and used the Massachusetts General Hospital-Hairpulling Scale (MGH-HPS) as the primary outcome measure. Both the NAC and placebo groups showed improvement over time, but no significant difference was observed between the two groups [28]. Furthermore, pediatric psychiatric trials often report a stronger placebo effect compared to adult trials, which can obscure the efficacy of active treatments. For example, a meta-analysis by Bridge et al. found that the placebo response rate in pediatric trials of antidepressants was nearly double that observed in adults [29]. This heightened placebo response may similarly impact studies on interventions for pediatric trichotillomania, making it challenging to discern the specific effects of NAC.

The differing responses to NAC in pediatric versus adult populations highlight the complexity of its potential role in treating TTM. A 12-week trial involving 50 TTM patients found that NAC improved symptoms in adults without causing side effects, but pediatric patients in the same study showed unsatisfactory results [30]. This discrepancy underscores the need for further research into age-related differences in response to NAC. Factors such as small sample sizes, medication interactions, and patient behavior may have influenced these findings. As discussed earlier, previous trials in adults with trichotillomania showed significant improvements with NAC. This discrepancy suggests that pharmacological interventions effective for TTM in adults may not necessarily be effective in children. The failure to replicate these findings in pediatric populations indicates potential developmental or neurochemical differences between children and adults, limiting the applicability of adult-based research to younger patients. The findings highlight the importance of prioritizing behavioral therapy, which has demonstrated efficacy in both children and adults with TTM, before considering pharmacological treatments [28]. Additionally, a

review published in The Annals of Pharmacotherapy in 2023 also noted that while NAC showed some promise in treating obsessive-compulsive and related disorders in children and adolescents, the evidence for its efficacy in pediatric TTM remains limited and inconclusive. This review emphasized the need for further research to establish the clinical effectiveness of NAC in this population [31]. Overall, the controversy is rooted in the differing outcomes of NAC treatment in pediatric versus adult populations, underscoring the necessity for more robust, large-scale studies to clarify its role in managing pediatric TTM.

3.4.2. Case Reports Supporting the Use of NAC in Pediatric Trichotillomania

Despite the lack of conclusive evidence in pediatric populations, case reports have shown NAC's potential as an alternative treatment for TTM in younger patients, particularly when traditional therapies such as cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) have failed. One case involved a 14-year-old girl who achieved complete cessation of hair-pulling within two weeks of NAC therapy at 1200 mg/day, followed by full hair regrowth within six months, with no side effects [32]. Another case involved a 17-year-old male with chronic hair-pulling and patchy alopecia, who experienced dramatic improvement after six months of NAC therapy at 1200 mg twice daily, despite previous unsuccessful treatments, including CBT [33]. Both patients reported significant reductions in hair-pulling urges and near-complete hair regrowth, further supporting NAC's potential as a well-tolerated and effective treatment option. NAC's mechanism of action, which involves modulating glutamate levels in the nucleus accumbens, likely contributes to its ability to reduce compulsive behaviors, making it a promising option for those resistant to standard therapies.

3.4.3. Summarizing the Evidence

N-Acetylcysteine (NAC) has garnered attention as a potential treatment for trichotillomania, although its use in pediatric populations remains a subject of ongoing debate. Its demonstrated reduction of trichotillomania symptoms in adults, as evidenced by multiple studies, yields promise for its utility in pediatric patients as well. Case reports have also suggested potential benefits in children and adolescents, providing hope for families seeking alternatives to standard pharmacological treatments [34]. NAC's favorable safety profile further supports its appeal [17, 31]. It is generally well-tolerated and associated with relatively benign side effects compared to selective serotonin reuptake inhibitors (SSRIs) or other psychotropic medications, which often carry risks of significant adverse effects. However, the efficacy of NAC in pediatric trichotillomania is not well-established and studies on its efficacy in children are inconsistent. This lack of robust evidence raises questions about its utility as a primary treatment in younger populations. Additionally, while severe side effects are rare, there have been isolated reports of significant aggression in children using NAC, emphasizing the need for careful monitoring [17]. These factors highlight the complexity of NAC's role in pediatric trichotillomania treatment and the importance of balancing potential benefits against these uncertainties.

Given the mixed evidence, clinicians should consider NAC as a supplementary option rather than a standalone treatment, particularly for patients who are not candidates for conventional medications or whose families prefer to avoid psychotropic drugs. Regular monitoring for both efficacy and potential side effects is essential to ensure the best outcomes. Although NAC shows promise for managing pediatric TTM, further research is necessary to clarify its effectiveness and to establish evidence-based guidelines for its use in this vulnerable population.

4. FUTURE RESEARCH

While existing studies highlight the impact of N-acetylcysteine (NAC) in treating compulsive behaviors like trichotillomania, its efficacy and safety in pediatric populations remain underexplored. To date, current data are primarily from adult studies or limited case reports, underscoring the need for more targeted investigations of NAC usage in children. Well-designed, large-scale randomized controlled trials in pediatric populations would be beneficial to develop a deeper understanding of its role and efficacy in children. In addition to large-scale, randomized controlled trials, neuroimaging studies can help understand the mechanism of NAC, providing insight into the neurochemical and behavioral changes that can result in the pediatric population.

Furthermore, gaining deeper insight into the long-term safety profile of NAC usage in children is an imperative area for future

development. While its safety has been documented in adults, with the most common side effect being mild gastrointestinal symptoms, it is essential to investigate the full spectrum of potential side effects in children, particularly because this may vary based on the dosage and developmental age. This approach would enable the development of age-specific treatment recommendations for NAC in the future, optimizing its therapeutic benefits while minimizing the risk of adverse effects.

Another compelling direction for future research lies in comparative studies to learn more about the effectiveness of NAC for pediatric trichotillomania when used as a monotherapy versus in combination with traditional therapies, such as CBT and SSRIs. Long-term follow-up is also crucial to determine the sustainability of these treatment efforts. Exploring these aspects could profoundly influence the standard of care for pediatric trichotillomania and pave the way for more effective and precise management strategies.

5. Conclusion

N-acetylcysteine (NAC) has emerged as a promising yet underexplored therapeutic option in the management of pediatric trichotillomania, offering hope in addressing this challenging and often misunderstood condition. In contrast to the more extensive research on NAC's efficacy in adult trichotillomania, where it has demonstrated significant symptom reduction, the evidence for its use in pediatric populations remains limited and inconclusive. While NAC's safety profile and role in glutamate modulation offer therapeutic potential for children and adolescents, the lack of large-scale, pediatric-specific studies leaves important questions unanswered. This review draws attention to the promising efficacy of NAC in reducing hair-pulling behaviors among younger patients, particularly in cases resistant to conventional treatments, while highlighting its safety and tolerability in this vulnerable demographic. In addition, the variability in study outcomes reveals a critical gap in our understanding of its long-term benefits and optimal application. As NAC continues to gain attention amid controversy over its clinical utility, this paper advocates for rigorous, well-designed studies to confirm its efficacy and refine its role in pediatric trichotillomania treatment. By addressing these gaps, the medical community can better harness NAC's potential, providing a much-needed alternative for young patients and their families navigating the challenges of this condition.

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