N-Acetylcysteine in the Treatment of Pediatric Trichotillomania: A Randomized, Double-Blind, Placebo-Controlled Add-On Trial

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Objective: To examine the efficacy of *N*-acetylcysteine (NAC) for the treatment of pediatric trichotillomania (TTM) in a double-blind, placebo-controlled, add-on study. **Method:** A total of 39 children and adolescents aged 8 to 17 years with pediatric trichotillomania were randomly assigned to receive NAC or matching placebo for 12 weeks. Our primary outcome was change in severity of hairpulling as measured by the Massachusetts General Hospital–Hairpulling Scale (MGH-HPS). Secondary measures assessed hairpulling severity, automatic versus focused pulling, clinician-rated improvement, and comorbid anxiety and depression. Outcomes were examined using linear mixed models to test the treatment × time interaction in an intention-to-treat population. **Results:** No significant difference between *N*-acetylcysteine and placebo was found on any of the primary or secondary outcome measures. On several measures of hairpulling, subjects significantly improved with time regardless of treatment assignment. In the NAC group, 25% of subjects were judged as treatment responders, compared to 21% in the placebo group. **Conclusions:** We observed no benefit of NAC for the treatment of children with trichotillomania. Our findings stand in contrast to a previous, similarly designed trial in adults with TTM, which demonstrated a very large, statistically significant benefit of NAC. Based on the differing results of NAC in pediatric and adult TTM populations, the assumption that pharmacological interventions demonstrated to be effective in adults with TTM will be as effective in children, may be inaccurate. This trial highlights the importance of referring children with TTM to appropriate behavioral therapy before initiating pharmacological interventions, as behavioral therapy has demonstrated efficacy in both children and adults with trichotillomania. J. Am. Acad. Child Adolesc. Psychiatry; 2013;52(3):231-240. Clinical trial registration information—*N*-Acetylcysteine for Pediatric Trichotillomania; http://clinicaltrials.gov/; NCT00993265.
Key Words: trichotillomania, *N*-acetylcysteine, randomized controlled trial

Trichotillomania (TTM) has an estimated lifetime prevalence of 1% to 3%.[1,2] Children with TTM can experience significant impairment caused by peer teasing, avoidance of activities (such as swimming and socializing), difficulty concentrating on school-work, and medical complications resulting from pulling behaviors.[3] Although TTM has been rather sparsely studied in childhood, it typically has a childhood onset of 11 to 13 years of age.[4] Trichotillomania is usually characterized by a chronic course with a waxing-and-waning of symptom severity throughout the lifetime.[5]

This article is discussed in an editorial by Dr. Douglas W. Woods on page 223.

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A recent meta-analytic study of randomized treatment trials in adults demonstrated that behavioral treatments, mainly habit reversal therapy, have the greatest efficacy in treatment of trichotillomania.[6] Selective serotonin reuptake inhibitors (SSRIs) are the most widely used treatment for both children and adults with trichotillomania, despite evidence that their efficacy is no greater than placebo.[6] Clomipramine, a tricyclic antidepressant demonstrated some increased efficacy compared to control conditions in adults.[6] A more recent study has also suggested that olanzapine, an atypical antipsychotic, was more effective than placebo in a randomized, controlled trial in adults with trichotillomania.[7]

Although there are evidence-based treatments that appear to help hair pullers, a Trichotillomania

Impact Project survey showed that only 15% of adults with TTM reported experiencing significant improvement with treatment of their symptoms in the community.[8] This may be because of the ongoing difficulty of finding a therapist experienced in TTM treatments. More than 55% of persons in this survey believed that their clinician did not have sufficient knowledge of the disorder, and less than one-third were receiving evidence-based treatments for trichotillomania.[8]

Few randomized, controlled clinical trials had been published for pediatric TTM. Habit reversal therapy was recently demonstrated to be superior to minimum attention control in a randomized trial of children with TTM[9] in the first randomized, controlled study conducted on any treatment for pediatric TTM. This is a promising finding, although locating a clinician who is knowledgeable about TTM and is also developmentally trained is enormously challenging. No randomized, placebo-controlled trial of any pharmacotherapy has been completed in pediatric TTM. Not surprisingly, only 17% of children reported significant improvement of their TTM symptoms with community treatment.[10]

N-acetylcysteine (NAC) is a naturally occurring amino acid and over-the-counter supplement that acts as a glutamate modulating agent and antioxidant. NAC has been demonstrated to be a glutamate modulating agent. NAC is converted to cystine, a substrate for the glutamate/cystine antiporter located on glial cells. The uptake of cystine by glia causes glial release of glutamate into the extra synaptic space, where it appears to stimulate inhibitory metabotropic glutamate receptors on glutamatergic nerve terminals and thereby reduces the synaptic release of glutamate.[11] NAC has also been demonstrated to have antioxidant properties.[12,13] Specifically, NAC provides cysteine, which is the rate-limiting substrate in the production of glutiathione.[13] Glutiathone is the major antioxidant in the brain.[14] NAC has been demonstrated in randomized, double-blind, placebo-controlled studies to be effective for the treatment for bipolar depression, schizophrenia, substance abuse, and possibly repetitive behaviors in autism spectrum disorders.[15–18] In addition, a randomized, controlled trial of 50 adults demonstrated the efficacy of NAC compared to placebo, after 12 weeks, for the symptoms of TTM.[19] Adults given NAC showed significant improvements in their trichotillomania symptoms compared to placebo on the Massachusetts General Hospital–Hairpulling Scale ($p < .001$). The improvement in trichotillomania symptoms was statistically significant by 6 weeks of treatment. Of adults with TTM treated with NAC, 56% were treatment responders, compared to just 16% on placebo. We conducted a similar double-blind, placebo-controlled add-on trial to examine the efficacy of NAC in treating children with TTM.

METHOD

Participants

Children were recruited through a tertiary Tourette syndrome (TS) / obsessive–compulsive disorder (OCD) specialty clinic. Local pediatricians, child psychiatrists,. and pediatric behavioral therapists were made aware of the trial through a mass mailing. Children were also referred through the Trichotillomania Learning Center, a national patient advocacy organization that helped fund this trial. Many subjects also became aware of the trial through our listing on clinicaltrials.gov (NCT00993265).

Children and adolescents were required to be 8 to 17 years of age, to have a primary diagnosis of TTM, and to have been pulling their hair for at least 6 months. Children who did not meet criteria B or C of *DSM-IV* criteria for TTM (i.e. do not experience either an increasing sense of tension before pulling or pleasure, gratification, or relief after pulling) were allowed to participate as a substantial fraction of children with impairing hair-pulling do not experience these symptoms (15–20%).[10] Children were required to be on a stable medication and psychotherapy regimen during the course of the trial. A stable medication regimen was defined as no recent addition, discontinuation, or dosing change in medications that have potential effects on TTM severity (such as SSRIs, clomipramine, naltrexone, lithium, psychostimulants, anxiolytics, or antipsychotics) in the previous 4 weeks. Children were also not allowed to enroll in the trial if they had started in behavioral therapy treatment for TTM in the prior 3 months. Children who were already engaging in behavioral treatments for TTM (for a period of >3 months) were encouraged to continue the behavioral therapy throughout the trial. Children were excluded if they met any of the following exclusion criteria: had bipolar disorder, psychotic disorder, substance use disorder, developmental disorder, or mental retardation according to *DSM-IV* criteria as diagnosed by the lead study investigator; were currently taking a psychostimulant medication (case reports have linked use to TTM); or had asthma requiring use of an inhaler in the previous 6 months (because of case reports associated with asthma exacerbation when given intravenous NAC administration). Adolescents over the age of 13 years were administered a urine drug screen, and postpubertal female participants were administered a pregnancy test. Subjects would have been excluded if they tested positive on either screen. Children provided