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.

CG Clinical guidance is available at the end of this article.

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

informed assent, and parents provided informed consent under an IRB approved protocol before enrollment in the trial. Families were made aware of other options for evidence-based treatment of trichotillomania before study enrollment. Families received $200 compensation for participation in the trial.

Intervention

Subjects were randomized in a ratio of 1:1 to receive treatment with NAC (Swanson Nutraceuticals) or placebo. NAC is an acetylated form of the amino acid cysteine, which is commonly found in food and synthesized by the body. NAC is generally well tolerated and has been extensively used in the treatment of acetaminophen overdose/toxicity at high doses for many years. NAC has been well tolerated in several previous trials of psychiatric conditions in both adults and children.[15–18]

NAC (or placebo) was titrated up to a maximum dose of 2400 mg over the course of 4 weeks. Subjects were assigned a 600-mg tablet at dinner for 1 week, then 600 mg twice a day for 1 week, then 600 mg in the morning and at dinner for 1 week, and then remained on a dose of 1200 mg twice a day for the remainder of the 12-week study. After completion of the study, all subjects receiving placebo were offered NAC treatment.

Subjects, their parents, investigators, and persons performing the assessments remained blind to treatment assignment from the time of randomization until the completion of the study. Randomization data were kept by the investigational pharmacist and were kept strictly confidential until the time of unblinding, after all study assessments were complete. The identity of the treatment was concealed by the use of study drugs that are identical in packaging, labeling, schedule of administration, appearance, and smell. Blinding of treatment is particularly challenging in studies of NAC because of its strong, distinctive sulfur odor. Peppermint-scented oil was added to the outside of both NAC and placebo capsules to make them nearly identical in appearance and smell. In addition, placebo capsules were stored in bottles with active NAC for several weeks before dispensation, to mimic the smell of NAC in the placebo capsules. At the time of dispensation, placebo capsules contained no appreciable trace of active NAC. Adequacy of blinding was assessed by asking both subjects and the treating clinician, at the end of the trial, whether they thought they were assigned to NAC or placebo. Neither subjects ($\chi^2 = 0.01$, $p = 0.92$) or treating clinicians ($\chi^2 = 1.4$, $p = 0.24$) were significantly better than chance when determining treatment allocation. Both subjects (70%) and the treating clinician (54%) tended to guess assignment to the placebo group. Medication compliance was assessed during each visit by asking the child and the family whether they were still taking the study medication and estimating the medication doses that they missed since the last visit. Three subjects (two NAC and one placebo) reported missing a significant number of doses of study medications (more than two doses per week). One of those three subjects (on active NAC) was withdrawn from the study because she reported not having taken any study medication in the previous week. We did not perform any pill counts during the course of the trial.

Assessments

Baseline assessment consisted of a clinical evaluation involving a psychiatric history, mental status examination, and clinical assessment of past medication and behavioral treatment. A medical assessment including vital signs, physical examination and urine drug screen and pregnancy test (if appropriate) by the lead study investigator. Clinical rating scales were conducted to assess severity of TTM, depression and anxiety symptoms as well as medication side effects. Subject assessments were conducted at baseline, and at 1, 2, 3, 4, 6, 8, 10, and 12 weeks after the start of study medication. Rating scales included the following: Massachusetts General Hospital–Hairpulling Scale (MGH-HPS)[20]; Trichotillomania Scale for Children–Child and Parent versions (TSC-C,P)[21]; National Institute of Mental Health–Trichotillomania Severity Scale (NIMH-TSS)[22]; Milwaukee Inventory for Styles of Trichotillomania–Child (MIST-C)[23]; Multidimensional Anxiety Scale for Children (MASC)[24]; Children's Depression Inventory (CDI)[25]; the Clinical Global Impression (CGI) scale[26]; and the Pediatric Adverse Events Rating Scale (PAERS).[27] The MGH-HPS, TSC-C,P, CGI, and PAERS were assessed at every subject visit, whereas the NIMH-TSS, MIST-C, MASC, and CDI were performed only at baseline and weeks 4, 8, and 12. The principal investigator conducted all clinical ratings at baseline weeks 0, 4, 8, and 12. A research assistant who has extensive experience with trichotillomania and observed all study visits conducted the ratings at weeks 1, 2, 3, and 6. The same rater conducted ratings of both efficacy and side effects in this trial. Subjects also received basic psychoeducation about trichotillomania at baseline and throughout the trial. Psychoeducation generally consisted of discussion about the basic aspects of trichotillomania (prevalence, common causes of impairment and distress, and discussion of alternative treatments [mainly habit reversal therapy]) and available support groups (Trichotillomania Learning Center).

Power Calculation and Data Analysis

We planned to enroll 40 participants in this trial. A sample size of 40 subjects would give us 80% power to detect a treatment effect size of 0.9, setting alpha at 0.05 and assuming a dropout rate of 10%. Our primary outcome measure was MGH-HPS. By comparison, the double-blind, placebo-controlled add-on trial of NAC in the treatment of adults with TTM demonstrated an effect size of 1.2 on the MGH-HPS.[19] The primary

investigator decided to stop enrollment at 39 subjects so that we could present the results of the trial at the annual Trichotillomania Learning Conference meeting, where many of the subjects were in attendance.

We used the PROC MIXED statement in SAS version 9.2 (SAS Institute, Cary, NC) to analyze all outcomes related to NAC efficacy. We used mixed models with restricted maximum likelihood (REML) solution and an unstructured covariance matrix. We examined treatment, time and treatment by time interaction in the mixed model. Time was treated as a repeated measure within subject. The treatment × time interaction on the MGH-HPS was the main outcome of interest in the trial. As secondary outcomes we examined the TSC-C,P, NIMH-TSS, MASC, CDI, and CGI. Mixed-models analysis uses intention-to-treat principles and accounts for missing data. A χ^2 test was used to compare dichotomous outcomes such as proportion of treatment responders and frequency of side effects between the NAC and placebo groups. A positive treatment response was defined as a CGI of 1 or 2 on the final study visit. For all dichotomous outcomes, the last observation carried forward was used in the analyses.

RESULTS

Subjects

Figure 1 is a CONSORT diagram that describes the flow of subjects through the trial. Table 1 compares the demographic characteristics of the children randomly assigned to NAC and placebo. Subjects averaged 13 years of age, with a duration of illness of slightly less than 4 years. At baseline, the hairpulling severity of our sample (MGH-HPS) was fairly comparable to those in recently published studies of children and adults with TTM. Children in the placebo group had greater hairpulling severity compared to the NAC group as judged by the MGH-HPS at baseline ($t = 1.7$, $p = 0.1$). Most children (59%) in our trial had previously taken SSRI pharmacotherapy, with 41% concurrently taking SSRIs while enrolled in our trial. Depressive and anxiety disorders were the most common comorbid conditions in our sample. We had four dropouts during the course of the trial who all were in the active NAC group. One child experienced a full body rash at week 4 that dissipated after discontinuation of NAC. Two children were discontinued from the protocol at week 4 after necessitating a change in concomitant medications. One subject was discontinued at week 6 after she stopped taking the study medication because of lack of efficacy.

Efficacy of NAC

Our trial failed to show any benefit of NAC over placebo in improving hairpulling severity as measured on our primary outcome. All subjects, regardless of group assignment, had a clinically modest but statistically significant improvement in hairpulling symptoms over time. Figure 2 depicts the change in MGH-HPS for both

FIGURE 1 CONSORT diagram of participant flow through randomized, double-blind placebo-controlled trial of *N*-acetylcysteine (NAC) in pediatric trichotillomania.

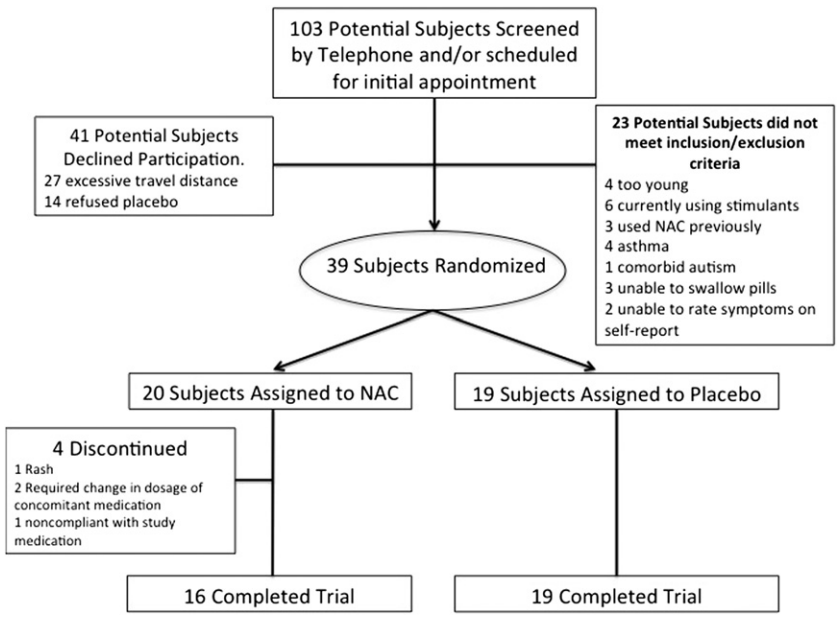


TABLE 1 Baseline Comparison of Children With Trichotillomania Randomly Assigned to *N*-Acetylcysteine (NAC) or Placebo

Characteristic	NAC (n = 20)	Placebo (n = 19)
Age, mean ± SD	14.0 ± 2.4	13.1 ± 3.1
Gender, female, n (%)	17 (85)	17 (89)
Age of onset, y, mean ± SD	9.7 ± 2.2	9.8 ± 2.3
Duration of illness, y, mean ± SD	4.4 ± 2.6	3.3 ± 2.4
Symptom severity, mean ± SD		
MGH-HPS Total*	13.2 ± 5.3	16.6 ± 4.8
TSC-Child Report	2.35 ± 0.74	2.52 ± 0.85
TSC-Parent Report	2.20 ± 0.71	2.32 ± 0.71
MIST-automatic pulling subscale	12.1 ± 9.3	16.3 ± 9.8
MIST-focused pulling subscale	94.0 ± 35.2	90.8 ± 30.5
MASC	48.7 ± 19.0	52.9 ± 18.6
CDI	12.4 ± 6.8	10.8 ± 8.5
Medication Use (current/ever), n (%)		
Serotonin reuptake inhibitors	8 (40)/12 (60)	8 (42)/13 (68)
Antipsychotics	2 (10)/4 (20)	1 (5)/4 (21)
Psychostimulants	0/2 (10)	0/2 (11)
Atomoxetine	2 (10)/2 (10)	0
Habit reversal therapy	6 (30)/12 (60)	4 (21)/11 (58)
Comorbid Psychiatric Disorders (current/ever), n (%)		
Depression	4 (20)/6 (30)	4 (21)/7 (37)
Anxiety disorder	5 (25) /5 (25)	3 (16)/4 (21)
Obsessive–compulsive disorder	1 (5)/1 (5)	1 (5)/1 (5)
Tic disorder	1 (5)/1 (5)	1 (5)/2 (11)
ADHD	2 (10)/2 (10)	2 (11)/2 (11)
Skin picking	0	1 (5)/1 (5)

Note: Randomly assigned groups differed in baseline severity of hairpulling as measured by the Massachusetts General Hospital–Hairpulling Scale (MGH-HPS). ADHD = attention-deficit/hyperactivity disorder; CDI = Children's Depression Inventory; MASC = Multidimensional Anxiety Scale for Children; MIST-C = Milwaukee Inventory for Styles of Trichotillomania–Child; TSC-Child/Parent = Trichotillomania Scale for Children–Child and Parent versions.
**Significant baseline difference between groups (p < .05).*

treatment groups. Similar results were observed for all secondary measures of hairpulling severity, including the TSC-child and parent versions and the NIMH-TSS. Table 2 presents the results from primary and secondary measures in our trial. Of the subjects in the NAC group, 25% were judged as treatment responders (CGI = 1 or 2) compared to 21% in the placebo group.

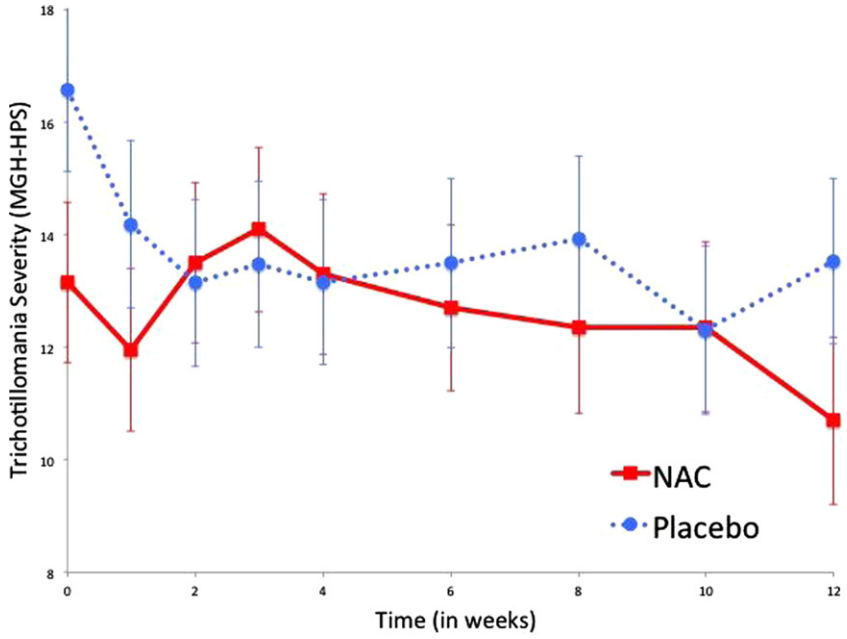
Safety

Table 3 lists the side effects reported in the NAC and placebo group. There were no significant differences in side effect rates between the NAC and the placebo group. As previously mentioned one girl in the NAC group experienced a full body rash at week 4 that was considered to likely be related to NAC treatment and that dissipated after the NAC was discontinued. Nausea was reported significantly more frequently in the placebo group than the active NAC group.

DISCUSSION

We observed no benefit of NAC as an add-on treatment for children with trichotillomania. Children receiving NAC significantly improved over time, but children in the placebo group improved similarly. All rating scales of hairpulling, whether child, parent or clinician rated, failed to demonstrate any significant benefit of NAC, or even to demonstrate a modest non-statistically significant effect. Our findings stand in stark contrast to a previous, similarly designed trial in adults with TTM, which demonstrated a very large, statistically significant benefit of NAC that was evident within 6 weeks of starting treatment.[19] In light of our differing results, it is important to examine differences between these trials. Several

FIGURE 2. Effects of *N*-acetylcysteine (NAC) and placebo on hairpulling severity (Massachusetts General Hospital–Hairpulling Scale [MGH-HPS]) in NAC and placebo. Note: Linear mixed model analysis demonstrated a significant effect of time but no treatment–time interaction, indicating that subjects improved significantly with time but that this improvement was not related to treatment assignment.



differences including differences in study populations (e.g., children and adults) or study design (e.g., blinding procedures or, less plausibly, frequency of trial assessments or titration schedule of NAC) could have affected the study results. In addition, the NAC and placebo groups differed in baseline severity of trichotillomania (as measured by the MGH-HPS) due to random chance. Although baseline differences between the groups are controlled for in our method of analysis, the increased severity of the placebo group at baseline may have decreased our ability to detect treatment effects on the MGH-HPS. That being said, we saw no benefit of NAC across multiple different ratings of trichotillomania severity.

Although research on the developmental course of trichotillomania is sparse, there is some evidence to suggest that children and adults experiencing hairpulling are fundamentally different. Specifically, adults with hairpulling are reported to pull from a greater number of sites and have increased impairment and distress associated with their pulling.[8,28] In addition, in a cross-sectional study, we demonstrated that among children with hairpulling, frequency of reported urges, severity of focused pulling and overall severity of hairpulling increases with age.[29] It has been hypothesized that NAC may work in hairpullers by reducing the frequency and intensity of the urge to pull.[19] This hypothesis derives from the substance abuse literature, in which NAC has been demonstrated to modulate glutamate in the nucleus accumbens and reduce drug-associated cravings.[30–33] If it is true that NAC acts by reducing pulling associated urges, it may be that NAC has decreased efficacy in children, as children tend to engage in more automatic pulling and report less awareness of pulling-associated urges. Within the context of this trial, however, we did not find any significant effect of NAC compared to placebo on any questions that specifically probed the frequency, intensity, or control over urges (MGH-HPS items 1–3).

Overall, our trial was designed to be as similar as possible to the adult NAC trial, but it remains possible that slight differences could have affected measured treatment effects. We used the same brand of over-the-counter NAC as in the adult study (Swanson Nutraceuticals, J.E.G., personnel communication); however, as the quality control of over-the-counter supplements is largely unregulated, it remains possible that our active NAC capsules differed. Also, we took great care to attempt to make the placebo capsules not only appear but also smell similar to the NAC capsules, which have a strong sulfur-like odor. We attempted to mask these differences by adding

TABLE 2 Treatment Response of Children With Trichotillomania Randomly Assigned to *N*-Acetylcysteine (NAC) or Placebo

	NAC (n = 20) Mean ± SD (Range)		Placebo (n = 19) Mean ± SD (Range)		Time		Treatment		Treatment × Time	
Outcome	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**F**	***p***	**F**	***p***	**F**	***p***
MGH-HPS Total	13.15 ± 1.43 (7–23)	10.70 ± 1.49 (0–18)	16.58 ± 1.47 (10–27)	13.53 ± 1.47 (3–26)	**9.31**	**.002**	0.36	.55	0	1
TSC-Child Report	2.35 ± 0.21 (0.86–3.51)	2.00 ± 0.22 (0.57–3.46)	2.52 ± 0.21 (1.00–4.00)	2.08 ± 0.22 (0.20–3.51)	**7.65**	**.006**	0.41	.52	0.09	.76
TSC-Parent Report	2.20 ± 0.17 (1.09–3.43)	1.83 ± 0.18 (0.00–3.00)	2.32 ± 0.18 (1.14–3.71)	1.88 ± 0.18 (0.00–3.29)	**6.40**	**.01**	0.19	.66	−0.29	.59
NIMH-TSS	11.00 ± 0.91 (3–20)	9.56 ± 0.71 (4–16)	12.32 ± 1.28 (3–24)	10.89 ± 1.24 (1–21)	0.99	.33	0.77	.34	0.53	.47
MIST-automatic subscale	12.10 ± 1.91 (0–31)	13.24 ± 1.98 (4–30)	16.26 ± 1.96 (0–32)	13.16 ± 1.96 (2–26)	1.17	.28	1.20	.28	**−4.17**	**.04**
MIST-focused subscale	94.0 ± 7.9 (28–154)	90.8 ± 8.1 (44–131)	90.8 ± 8.1 (41–140)	79.6 ± 8.1 (19–138)	2.49	.11	0.56	.46	−0.39	.53
MASC	48.7 ± 4.2 (19–96)	48.4 ± 4.3 (22–75)	52.9 ± 4.3 (22–94)	49.8 ± 4.3 (18–71)	0.67	.41	0.54	.47	−0.46	.50
CDI	12.4 ± 1.9 (3–26)	10.9 ± 1.9 (2–32)	10.8 ± 1.9 (3–24)	7.8 ± 1.9 (0–23)	**11.3**	**.001**	0.60	.44	−0.69	.41

Note: Table presents mean and standard error at baseline and endpoint for the NAC and placebo group. Also presented are results of the linear mixed model examining treatment effects. Treatment × Time interaction is the measure examining differences in efficacy between NAC and placebo. Positive F values for the treatment × time interaction term favors greater improvement in the NAC group. Boldface numbers are statistically significant findings at the p < .05 level. The main effect of time examines whether subjects improved significantly over time regardless of treatment assignment. The main effect of treatment examines if subjects differed based on which treatment they were randomly assigned at baseline. CDI = Children's Depression Inventory; MASC = Multidimensional Anxiety Scale for Children; MGH-HPS = Massachusetts General Hospital–Hairpulling Scale; MIST-C = Milwaukee Inventory for Styles of Trichotillomania–Child; NIMH-TSS = National Institute of Mental Health–Trichotillomania Severity Scale; TSC-Child/Parent = Trichotillomania Scale for Children–Child and Parent versions.

TABLE 3 Adverse Events in Children Randomly Assigned to *N*-Acetylcysteine (NAC) or Placebo

Side Effect	NAC (n = 20), n (%)	Placebo (n = 19), n (%)
Nausea [a]	6 (30)	12 (63)
Diarrhea	1 (5)	1 (5)
Fatigue	0	2 (11)
Insomnia	0	1 (5)
Rash	1 (5)	0
Depression	1 (5)	0
Difficulty swallowing pills	2 (10)	1 (5)

Note: [a] *Nausea was reported significantly more frequently in the placebo than the active NAC group* ($\chi^2 = 4.31$, $p = 0.04$).

peppermint-oil to both capsules and storing the placebo tablets for several weeks in bottles with NAC. However, if the capsules were left open to air for several weeks, the smell of the placebo capsules would dissipate, leaving the two capsules potentially distinguishable. The adequacy of blinding in previous trials with NAC is difficult to establish and could potentially influence study results.[34] In small pilot trials, NAC has demonstrated initial efficacy compared to placebo for several conditions including autism, schizophrenia, and bipolar depression using newer preparations of NAC, which have greatly improved blinding.[15–17] Therefore, problems with blinding cannot explain the demonstrated efficacy of NAC across all conditions.[15–17]

As this trial represents the first randomized, placebo-controlled trial of a pharmacological intervention in pediatric TTM, we believe that it is important to convey some practical lessons we learned from conducting this trial. Although any of these changes in trial design would have made it more likely to detect a treatment effect, we do not believe that they would have significantly affected the results of this trial. Many of these suggestions cannot be supported by hard data, but are based solely on the investigators' experience in conducting this trial. First, some children in this trial exhibited a dramatic improvement in symptoms within the first couple weeks of treatment that was likely unrelated to the effects of the study medication and was more likely a response to the psychoeducation about trichotillomania and structured support of assessments within the trial. A placebo lead-in period in future pediatric TTM trials may help address this issue. In addition, less frequent monitoring, early on, in pharmacological in pediatric TTM is probably advisable. The high frequency of assessments could have potentially increased the response with time in the placebo (and NAC groups) as these assessments provided a greater opportunity to receive psychoeducation or support. On the other hand, this observation may also suggest that psychoeducation, support, and structured assessment of symptom severity may modestly improve hairpulling symptoms over time. Second, a clinician-rated measure (such as NIMH-TSS) rather than self-reports (TSC-C or MGH-HPS) would be recommended as the primary outcome in future studies for children. Validating the MGH-HPS in pediatric populations will be an important contribution to the literature. Relying on self-reports in children at the younger age range of our trial (<10 years) may be problematic. For our trial specifically, it is unlikely this problem influenced our trial findings, because no measures (clinician, child, or parent rated) demonstrated a treatment effect. In addition, larger clinical trials that are powered to detect smaller treatment effects are advisable for trichotillomania. Similarly, a larger trial would have increased power to detect possible side effects associated with study medication. All four subjects who dropped out early from the trial were in the active NAC group. These dropouts include two subjects who were switched concomitant medications at week 4, including one subject with a worsening of depression and anxiety symptoms. It remains possible that rare significant side effects of NAC are present, which small pilot trials are underpowered to detect. Furthermore, the trial could have been improved if the following were true: if pill counts were used to assess subject compliance; if we measured interrater reliability between the assessments performed by the trained research assistant and trial physician; and if severity ratings were performed by a rater blind to medication side effects.

Future research in pediatric trichotillomania should focus on understanding the developmental and clinical course of this condition in children. Specifically, longitudinal studies examining the likelihood of children remitting over time are critical to properly understand, treat, and research this condition. For instance, understanding the proportion of children who spontaneously remit after pulling for 1 month, 6 months, or 1 year is critical to determining the ideal pediatric

population to recruit into clinical trials (to minimize response in the control group). Examining prognostic factors that inform clinical course in pediatric trichotillomania will also be important for clinicians and researchers alike. There is also significant heterogeneity in the clinical presentation of adults and especially children with trichotillomania. Currently, trichotillomania research focuses on a behavior (hairpulling) with little understanding of the potential multiple pathophysiologies that may lead to pulling as a symptom in children. Children (and adults) with trichotillomania may pull their hair for a variety of reasons (e.g., in response to a sensory urge, for mood or anxiety regulation, and/or to trigger a parental or social response). Further efforts to better understand the causes of hairpulling (through better clinical characterization, neuroimaging, and genetic studies) will be critical to better understand this disorder. In addition, NAC trials in both adult and pediatric trichotillomania populations should be replicated, given the discordant results. It is possible that the true efficacy of NAC in both populations remains somewhere in between the estimates of effect from the two trials. However, it is also possible that these divergent results regarding the efficacy of NAC for the treatment of TTM in pediatric and adult populations are both accurate and reliable. An improved understanding of the developmental course of TTM may help to explain this apparent discrepancy.

For clinicians treating children with TTM, this trial highlights the importance of referring children with TTM to appropriate behavioral therapy before initiating pharmacological interventions. 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 (i.e., clomipramine and olanzapine) will be as effective in children may be inaccurate. By contrast, habit reversal therapy has demonstrated efficacy in controlled trials of both adults and children, although larger trials are needed to confirm this effect. Unfortunately, given the scarcity of skilled behavioral therapists familiar with trichotillomania (not to mention comfortable working with children), the fact that a substantial portion of children do not respond to even properly administered habit reversal training, and the significant impairment in social and family functioning experienced by many children with trichotillomania, other effective treatments are urgently needed. Only through more properly controlled trials will we learn more about this disorder and find more effective treatments for this neglected population. &

CG Clinical Guidance

- *N*-acetylcysteine did not show any benefit compared to placebo in the treatment of pediatric trichotillomania.
- Habit reversal therapy has a demonstrated benefit compared to control conditions in the treatment of pediatric trichotillomania.
- We recommend that children with trichotillomania be initially treated with behavioral therapy before any pharmacological intervention in indicated.
- Selective serotonin reuptake inhibitors are the most commonly used intervention to treat trichotillomania across the lifespan, despite substantial evidence that they are no more effective than placebo.

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