The Use of N-acetylcysteine Supplementation to Decrease Irritability in Four Youths With Autism Spectrum Disorders

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Children and adolescents with autism spectrum disorder (ASD) often experience high levels of irritability, which adversely affects their functioning and behaviors. N-acetylcysteine (NAC), an antioxidant precursor to glutathione, has recently been studied for a variety of neuropsychiatric disorders. There is growing evidence to support its use to decrease irritability and self-injurious behaviors in youth with ASD. However, previous studies were limited to outpatient youth with mild symptoms of irritability, maintained on stable medication regimens, who do not meet criteria for higher levels of care. We describe the use of NAC among 4 youths (14–17 years) with ASD who had Aberrant Behavior Checklist-Irritability (ABC-I) scores of ≥ 20 and other psychotropic medication trials prior to treatment with NAC. In all of the cases, NAC appeared to be well tolerated. There was a reduction of symptoms of irritability and/or antipsychotic medication dosages in these cases; despite this, the authors cannot know whether use of NAC or other medication or behavioral strategies were responsible for such changes because this study was not a controlled trial.

ABBREVIATIONS ABC-I, Aberrant Behavior Checklist-Irritability; ASD, autism spectrum disorder; NAC, N-acetylcysteine

KEYWORDS autism spectrum disorder; case series; irritability; N-acetylcysteine; youth

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Introduction

N-acetylcysteine (NAC) is an over-the-counter, complementary medication used in a variety of medical settings. Recent studies have suggested that NAC may improve irritability, self-injurious behaviors, stereotypic and repetitive behavior, and hyperactivity in youth with autism spectrum disorder (ASD) (Table).^{1–7} Currently, commonly prescribed psychopharmacologic agents for youth with ASD and severe behavioral symptoms include atypical antipsychotics (e.g., risperidone and aripiprazole), off-label use of α -2 agonists, and off-label use of mood stabilizing medications.⁸ These medications carry the possibility of undesirable side effects including weight gain, metabolic syndrome, and extrapyramidal symptoms.⁹ NAC may reduce the need for other pharmacologic agents and associated adverse effects.

To date, studies of NAC for youth diagnosed with ASD have been limited to those seen in the outpatient setting with mild behavioral symptoms and prescribed few medications. It is important to extend the literature to a severely ill population affected by: 1) unsafe behavioral symptoms requiring inpatient admission; 2) severe ASD-associated symptoms (i.e., marked cognitive and language impairment); 3) serious psychiatric comorbidity; 4) medical comorbidity; and 5) polypharmacy. This

case series reviews the use of NAC in 4 such patients who met most or all of the above criteria. Although this is not a controlled trial and conclusions cannot be drawn about the efficacy of NAC in this population, the authors nevertheless seek to describe its use in a clinically relevant patient sample.

Case Descriptions

Four cases of patients started on oral capsules of NAC (TwinLab, Boca Raton, FL) were selected by a team of clinicians at a university-affiliated children's hospital that hosts a comprehensive inpatient, day treatment, and outpatient service for youth with autism and other neurodevelopmental disorders. Inclusion criteria were not defined prospectively for the patients selected for review, but rather cases were identified retrospectively based on clinician recollection of patients started on NAC treatment during repeated team meetings on this subject. The clinicians attempted to titrate NAC on a schedule modified from that used in current literature: 600 mg twice daily for 1 week, 600 mg in the morning and 1200 mg at night for 1 week, and then 1200 mg twice daily. As a routine part of clinical care, Aberrant Behavior Checklist-Irritability (ABC-I) scale scores were collected before initiation of NAC and again after at least 4 weeks of being on a stable, final dosage. The

Table. Review of Literature Evaluating N-Acetylcysteine Supplementation in Youth With Autism Spectrum Disorder

Study	Design	Study Population	Intervention	Results
Dean ¹	6-mo, randomized, placebo-controlled study (N = 98). Pts were 3–9 yr of age Primary outcome: Social Responsiveness Scale, Children's Communication Checklist-Second Edition, and Repetitive Behavior Scale-Revised	Outpatient youth with ASD. Stable medical conditions; stable medication regimen for at least 2 wk prior NAC. Not receiving other medications that contain glutathione or its precursors	NAC 500 mg daily or placebo (500 mg capsules—manufacturer not reported)	No significant differences in any primary outcomes between NAC and placebo. Common adverse effects (GI, colds/cold-like symptoms) reported equally among both tx groups.
Ghanizadeh ²	8-wk, double-blind, randomized, placebo-controlled, parallel group study (N = 40). Pts were 3.5–16 yr of age. Primary outcome: ABC-I	Outpatient youth with ASD. Stable medical conditions; stable medication regimen for at least 2 wk prior NAC. Not receiving other medications that contain glutathione or its precursors	Group 1: NAC 600 mg twice daily plus risperidone 0.5 mg/day (PharmaNAC, BioAdvantex Pharma Inc) Group 2: Placebo plus risperidone 0.5 mg/day Risperidone titrated up to 2–3 mg daily over 3 wk	Irritability significantly decreased at wk 8 in Group 1 (ABC-I: 13.2–9.7) compared with Group 2 (p < 0.035). No significant improvements in stereotypic behavior, hyperactivity, social withdrawal, or lethargy. Common adverse effects (e.g., constipation, increased appetite, fatigue, nervousness, daytime drowsiness) reported equally among both tx groups.
Hardan ³	12-wk, double-blind, randomized, placebo-controlled study (N = 33). Pts were 3–12 yr of age. Primary outcome: ABC-I	Outpatient youth with ASD. No active medical or psychotic disorders; stable medication regimen that did not include other medications with antioxidant properties CGI-S ≥ 4 based on clinical evaluation of irritability	NAC 900 mg daily × 4 wk NAC 900 mg twice daily × 4 wk NAC 900 mg 3 times daily × 4 wk (PharmaNAC, BioAdvantex Pharma Inc)	Significantly reduced irritability (ABC-I: 16.9–7.2, p < 0.001) at wk 12. Trends in improved stereotypic and repetitive behavior, though not significant. Common adverse effects included constipation, diarrhea, changes in appetite
Marler ⁴	Case report of 4-yr-old child with ASD prescribed NAC for ongoing self-injurious behaviors	Pt with disfiguring face scratching since 6 mo of age, resulting in bleeding, erosions, excoriations, and scarring. Additionally, daily tantrums, hyperactivity, and irritability.	NAC 450 mg daily × 1 wk NAC 900 mg daily × 1 wk NAC 1350 mg daily × 1 wk NAC 1800 mg daily (PharmaNAC, BioAdvantex Pharma Inc)	Significant improvement in self-injurious behaviors as reported by provider and family. Allowed for excoriation healing. No adverse effects reported.

ABC-I, Aberrant Behavior Checklist-Irritability; ASD, autism spectrum disorder; CGI-I, Clinical Global Impressions – Improvement Scale; CGI-S, Clinical Global Impressions – Severity Scale; ID, intellectual disability; NAC, N-Acetylcysteine; pts, patients; tx, treatment

Table. Review of Literature Evaluating N-Acetylcysteine Supplementation in Youth With Autism Spectrum Disorder (*cont*)

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ABC-I is a validated tool for assessing behavioral and emotional difficulties in youth with ASD or intellectual disabilities. The irritability section contains 15 questions using a 0 to 3 Likert scale with score range of 0 to 45 and in 1 validation sample of children with autism a mean score of 11.8 and standard deviation of 9.2.¹⁰ Pertinent data were gleaned through a review of electronic medical records. Verbal consent was obtained from parents/legal guardians to allow the authors to describe the medical narrative of these patients.

Case 1. A 17-year-old minimally verbal white male with ASD, moderate intellectual disability, constipation, obesity, and seizures was admitted as an inpatient with severe behavioral decompensation and aggression. Oral medications upon admission included clonidine 0.05 mg 3 times daily, propranolol 20 mg 3 times daily, aripiprazole 1 mg twice daily, citalopram 5 mg in the morning, polyethylene glycol, and lansoprazole. Multiple medication changes occurred during the admission including discontinuation of aripiprazole, citalopram, and propranolol, and initiation of olanzapine and lamotrigine. After several months of hospitalization, NAC was started at 600 mg twice daily. ABC-I scale at the start of NAC treatment was 24. Initially, there were concerns from staff that the adolescent was experiencing headaches but they self-resolved quickly. The dose of NAC was increased after 9 days and reached a target dosage of 1200 mg twice daily after another 7 days. During the titration period, the youth continued to display aggressive behaviors. Other medication changes included a trial of haloperidol, discontinuation of lamotrigine and initiation of topiramate, and tapering off olanzapine. All antipsychotics were eventually discontinued approximately 2 months after achieving the target dosage of NAC. His ABC-I score decreased to 17 3 months after initiating NAC and achieving stable doses of his other medications. His regimen prior to transfer to a long-term care facility eventually consisted of NAC 1200 mg twice daily, clonidine 0.05 mg in the morning, 0.05 mg in the afternoon, and 0.2 mg at night, topiramate 100 mg twice daily, polyethylene glycol, lansoprazole, docusate, senna, cholecalciferol, and melatonin.

Case 2. A 15-year-old white male with bipolar I disorder, ASD, severe intellectual disability, and obsessive compulsive disorder was admitted to the inpatient unit for 5 days (and subsequently following-up in the outpatient clinic for several months) due to decompensated behaviors including poor sleep, aggression, disrobing, regression in toileting, yelling, and incongruent laughter. At the time, he was taking risperidone 2 mg in the morning and 1 mg at night; delayed-release divalproex 250 mg in the morning, 250 mg in the afternoon, and 500 mg at night; and gabapentin 100 mg in the morning. Over the next few months, he was cross-tapered from divalproex to chlorpromazine in an attempt to stabilize his mood and decrease his problematic behaviors. He

continued to experience irritability (ABC-I score of 20); hence, NAC was then initiated. Further medication changes included an increase in chlorpromazine to 25 mg at night, initiation of lithium at 150 mg twice daily, and discontinuation of gabapentin. After 6 weeks at target dosage of NAC and 2 weeks of no additional medication changes, his ABC-I score decreased to 10.

Case 3. A 13-year-old white male, who was regularly seen in our outpatient clinic and periodically admitted to the inpatient unit, was admitted for out-of-control behavior consisting of self-injury, pulling caregivers' hair, disrobing in public, urinating and defecating outside of bathroom spaces, elopement, and poor sleep onset and quality. His diagnoses included ASD, generalized anxiety disorder, disruptive mood dysregulation disorder, moderate intellectual disability with deficit of verbal language, constipation, and a history of eosinophilic esophagitis. At the time of admission, he was taking clonidine 0.1 mg in the morning and 0.3 mg in the evening, propranolol 20 mg 3 times daily, melatonin 5 mg in the evening, polyethylene glycol, and ferrous sulfate. One week into this hospitalization, he was started on NAC at 600 mg twice daily for irritability (ABC-I score of 32). During NAC therapy, he was observed chewing the NAC capsule, and the alternative oral solution was unpalatable because of the noxious smell and thus never trialed; however, he was able to swallow the capsule with honey, which significantly improved compliance. Given potential gastrointestinal side effects of NAC and this patient's history of constipation, the nursing staff tracked his bowel movements, and he did not experience any gastrointestinal symptoms during NAC supplementation. He remained on NAC despite an up-and-down psychiatric course over 6 months, during which time propranolol was discontinued, clonidine dose was slightly adjusted, delayed-release divalproex was trialed and discontinued, and an evening dose of 12.5 mg of quetiapine was administered. After 6 months of treatment, the ABC-I score had decreased from an initial score of 32 to a score of 14.

Case 4. A 14-year-old white male with Down syndrome was being monitored in the outpatient psychiatric setting for management of disruptive mood dysregulation disorder, ASD, moderate intellectual disability, and attention-deficit/hyperactivity disorder. Additional medical diagnoses included obstructive sleep apnea and hypercholesterolemia. He exhibited aggression, defiance, elopement, skin picking, and irritability. At the onset of his NAC trial, he was taking atomoxetine 25 mg twice daily, clonidine 0.05 mg 3 times daily, quetiapine 25 mg 3 times daily, polyethylene glycol, and fluticasone nasal spray. After noting an ABC-I score of 37, the youth was started on NAC and titrated over 2 weeks to a dose of 2400 mg. Initially, the patient's mother reported seeing no improvements with the addition of NAC. Due to the severity of the patient's continued behaviors, divalproex was eventually started.

Upon re-evaluation, his mother reflected that although it had not seemed to mitigate irritability (follow-up ABC-I score was 36), the patient's skin picking had completely resolved since starting NAC. The patient tolerated the NAC without side effects, and it continues to be a part of his medication regimen.

Discussion

NAC is commercially available in a variety of formulations, including capsules, effervescent tablets, and as solution for delivery via oral, inhalation, or intravenous routes. The authors' clinical team consistently recommended oral capsules for practical reasons including lower cost, formulary availability, ease of administration, and improved palatability. The hospital formulary stocks 600 mg oral capsules of NAC (TwinLab); however, this dosage of NAC capsules are available at most retail pharmacies or online so patients can continue with supplementation following discharge. The exact mechanisms by which NAC may improve aberrant behaviors associated with ASD are theorized to include a reduction in excessive excitatory signaling via glutamate pathways¹¹ and/or decreased oxidative stress via glutathione pathways.¹²

Previous studies have demonstrated the benefits of using NAC in patients with ASD, particularly in improving irritability as measured by the ABC-I (Table). Additionally, these studies showed that adverse effects (most commonly related to gastrointestinal distress) were limited and did not occur at a significantly higher frequency as compared with placebo. Studies that did not demonstrate the effectiveness of NAC (as compared with placebo) may have used subtherapeutic dosages,¹ or had expected symptom change related to core social impairment rather than irritability as outcomes.^{1,7} In sum, the current literature pertaining to NAC supplementation is notable for demonstrating a decrease in irritability for patients in an outpatient setting; however, in this report the authors sought to describe the use of NAC supplementation in a complex patient population with more severe behavioral dysregulation than those previously studied.

The review of the 4 cases presented in this report suggests that NAC was overall well tolerated in our patients with the exception of possible gastrointestinal side effects. There is no evidence that NAC affects the metabolism of other medications as it is not cleared by nor does it affect the cytochrome system. Consistent with this, NAC did not appear to affect the efficacy of any concurrently administered medications. Likewise, it did not increase or enhance the side effects of other medications. Use of NAC was associated with maintenance or reduction of antipsychotic medications and ABC-I scores in this limited sample. There was no worsening of psychiatric or medical comorbidities in our patients. Although the potential benefits of NAC in

these cases could alternatively be explained by other factors (i.e., other medication changes, behavioral interventions, or passage of time), this case series does illustrate that NAC can feasibly be given in an inpatient setting for this population without causing harm and potentially benefitting symptoms. Typically, youth with these behaviors are prescribed multiple medications, potentially with negative side effects or interactions, which make the alternative use of NAC an intriguing and exciting option for clinicians. We are encouraged by the potential use of NAC in children with ASD who have more severe emotional or behavioral difficulties (e.g., irritability, self-injurious behaviors, obsessive-compulsive behaviors). Our titration recommendation in this population mirrors that used elsewhere in the literature: oral capsules 600 mg twice daily for 1 week, 600 mg in the morning and 1200 mg at night for 1 week, and then 1200 mg twice daily. A trial of 8 to 12 weeks (at a minimum) should be considered to determine the effectiveness of this agent. Further large prospective research studies of these more complex patients are needed to support this approach.

ARTICLE INFORMATION

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Ethical Approval and Informed Consent Given the nature of this study, the institution review board/ethics committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission under exempted criterion.

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