Randomized, Double-Blind, Placebo-Controlled Trial of *N*-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder

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ABSTRACT

Objective: To evaluate the efficacy of serotonin reuptake inhibitor (SRI) augmentation with *N*-acetylcysteine (NAC), a glutamate modulator and antioxidant medication, for treatment-resistant obsessive-compulsive disorder (OCD).

Methods: We conducted a randomized, double-blind, placebo-controlled, 16-week trial of NAC (3,000 mg daily) in adults (aged 18–65 years) with treatment-resistant OCD, established according to *DSM-IV* criteria. Forty subjects were recruited at an OCD-specialized outpatient clinic at a tertiary hospital (May 2012–October 2014). The primary outcome measure was the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores. To evaluate the variables group, time, and interaction effects for Y-BOCS scores at all time points, we used nonparametric analysis of variance with repeated measures. Secondary outcomes were the severity scores for anxiety, depression, specific OCD symptom dimensions, and insight.

Results: Both groups showed a significant reduction of baseline Y-BOCS scores at week 16: the NAC group had a reduction of 4.3 points (25.6 to 21.3), compared with 3.0 points (24.8 to 21.8) for the placebo group. However, there were no significant differences between groups ($P = .92$). Adding NAC was superior to placebo in reducing anxiety symptoms ($P = .02$), but not depression severity or specific OCD symptom dimensions. In general, NAC was well tolerated, despite abdominal pain being more frequently reported in the NAC group (n [%]: NAC = 9 [60.0], placebo = 2 [13.3]; $P < .01$).

Conclusions: Our trial did not demonstrate a significant benefit of NAC in reducing OCD severity in treatment-resistant OCD adults. Secondary analysis suggested that NAC might have some benefit in reducing anxiety symptoms in treatment-resistant OCD patients.

Trial Registration: ClinicalTrials.gov identifier: NCT01555970

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Obsessive-compulsive disorder (OCD) is a chronic psychiatric disorder[1] characterized by recurrent, intrusive, and anxiety-provoking thoughts or images (obsessions) associated with repetitive physical or mental rituals (compulsions) aimed at relieving the discomfort associated with the obsessions.[2] It is accompanied by poor quality of life and impaired psychosocial functioning in both patients and caregivers.[3–6]

Treatment guidelines recommend serotonin reuptake inhibitors (SRIs) as first-line pharmacologic treatment for OCD.[7,8] Approximately half of OCD patients treated with 1 adequate trial of SRIs fail to fully respond to treatment.[9,10] Cognitive-behavior therapy (CBT) is another first-line treatment for OCD, but quality CBT for OCD is unavailable in many areas. CBT is often an additional effective treatment for SRI-refractory OCD.[11] The augmentation of selective SRIs (SSRIs) with an antipsychotic or clomipramine can be indicated for treatment-resistant OCD patients, but only one-third of those patients will show additional meaningful improvement with these strategies.[11–13] Moreover, the atypical antipsychotics have been associated with common adverse effects, such as weight gain and metabolic dysregulation.[14,15] Alternative pharmacologic strategies for SSRI-refractory disease are needed.

OCD is associated with hyperactivity in cortical-striatum-thalamus-cortical (CSTC) circuits.[16,17] Corticostriatal and thalamostriatal afferents use the excitatory neurotransmitter glutamate, and evidence suggests abnormal glutamate levels and/or homeostasis in OCD patients.[18,19] Thus, researchers have been testing glutamate-modulating medications, such as memantine, topiramate, ketamine, and lamotrigine, as augmentation agents in treatment-resistant OCD, with some evidence for efficacy.[20–22]

N-acetylcysteine (NAC), a cysteine prodrug, increases extracellular levels of glutamate by enhancing the activity of the cysteine-glutamate antiporter.[23] Studies in rats[24] suggest that the increase of free glutamate in the extracellular space stimulates inhibitory metabotropic glutamate receptors in hyperactive glutamatergic nerve terminals and can thereby reduce the synaptic release of glutamate in the nucleus accumbens. NAC also functions as an antioxidant: cysteine provided by NAC increases the cellular production of glutathione, the primary endogenous antioxidant, which may produce neuroprotective effects on the brain.[25]

To date, NAC has been tested for OCD in 3 small, controlled clinical trials,[26–28] with 2 of them demonstrating its superiority to placebo in reducing OCD severity.[26,28] Methodological differences between these trials are summarized in Table 1. We designed a 16-week, double-blind, randomized and placebo-controlled trial to test the efficacy of NAC as an augmentation agent in

Clinical Points

- The efficacy of *N*-acetylcysteine (NAC), a glutamate-modulating agent, for the treatment of obsessive-compulsive disorder (OCD) has been tested in 3 controlled trials, with divergent results.
- NAC was not superior to placebo in reducing OCD severity in this highly treatment-resistant sample of OCD patients. However, we found a potential benefit in reducing the severity of anxiety symptoms.

treatment-resistant OCD patients. We hypothesized that NAC would be more effective than placebo in reducing OCD symptom severity. Our study is unique in regards to a broad and detailed phenomenological assessment performed at baseline and at the end of the study, which included the evaluation of OCD severity and also the severity of depression and anxiety symptoms, the presence and severity of different dimensions of OCD symptoms, and the level of insight regarding OCD symptoms.

METHODS

Setting

This trial was conducted at the outpatient clinic of the OCD Spectrum Disorders Program, Institute of Psychiatry, University of São Paulo Medical School, Brazil. Subjects were recruited by clinical referral and advertisement. Data were collected from May 2012–October 2014. The local research ethics committee approved the protocol, and all participants provided written informed consent (ClinicalTrials.gov identifier: NCT01555970).

Participants

Subjects were eligible if they (1) were aged 18–65 years; (2) had a *DSM-IV* primary diagnosis of OCD; (3) failed to respond to at least 1 previous adequate pharmacologic treatment for OCD (clomipramine or an SSRI at the maximum recommended or tolerated dose for at least 12 weeks); (4) had a baseline Yale-Brown Obsessive Compulsive Scale[29,30] (Y-BOCS) total score ≥ 16, or ≥ 10 for the presence of only compulsions; and (5) had OCD symptoms of at least moderate severity on the Clinical Global Impression–Severity (CGI-S) scale.[31]

All patients were taking at least an SRI under stable dosage, in accordance with international OCD treatment guidelines.[7,8] Mood stabilizers, stimulants, sedatives, and hypnotics were allowed as long as their dosages had been stable for at least 1 month. Antipsychotics and clomipramine (in this case, in association with an SSRI) were also allowed, as long as they had been prescribed at least 2 months prior to study initiation and their dosages were stable for at least 1 month. All medications in use at the time of randomization were maintained at the same dose across the 16 weeks of the study.

There is no consensus in the literature regarding the definition of resistance to treatment.[32] The main reason for recruiting OCD individuals resistant to at least 1 adequate SRI trial was that, if NAC proves to be effective, it might be an augmentation strategy recommended prior to the prescription of antipsychotics, which are associated with severe side effects.

Exclusion criteria included the presence of a psychotic disorder; liver disease, asthma, previous psychosurgery, current drug abuse or dependence, suicide risk, any comorbidity that precluded the use of the protocol medications, previous exposure to NAC, pregnancy, lactation, or women not using reliable birth control methods.

Sample Size Calculation

The sample size (approximately 20 per arm) was calculated with the following parameters: a difference between endpoint and baseline total Y-BOCS scores of 5 points (deemed the minimal difference with clinical significance), an estimated standard deviation of 6.0 based on previous OCD augmentation trials,[33] a power of 75%, and an α of 5%.

Study Design

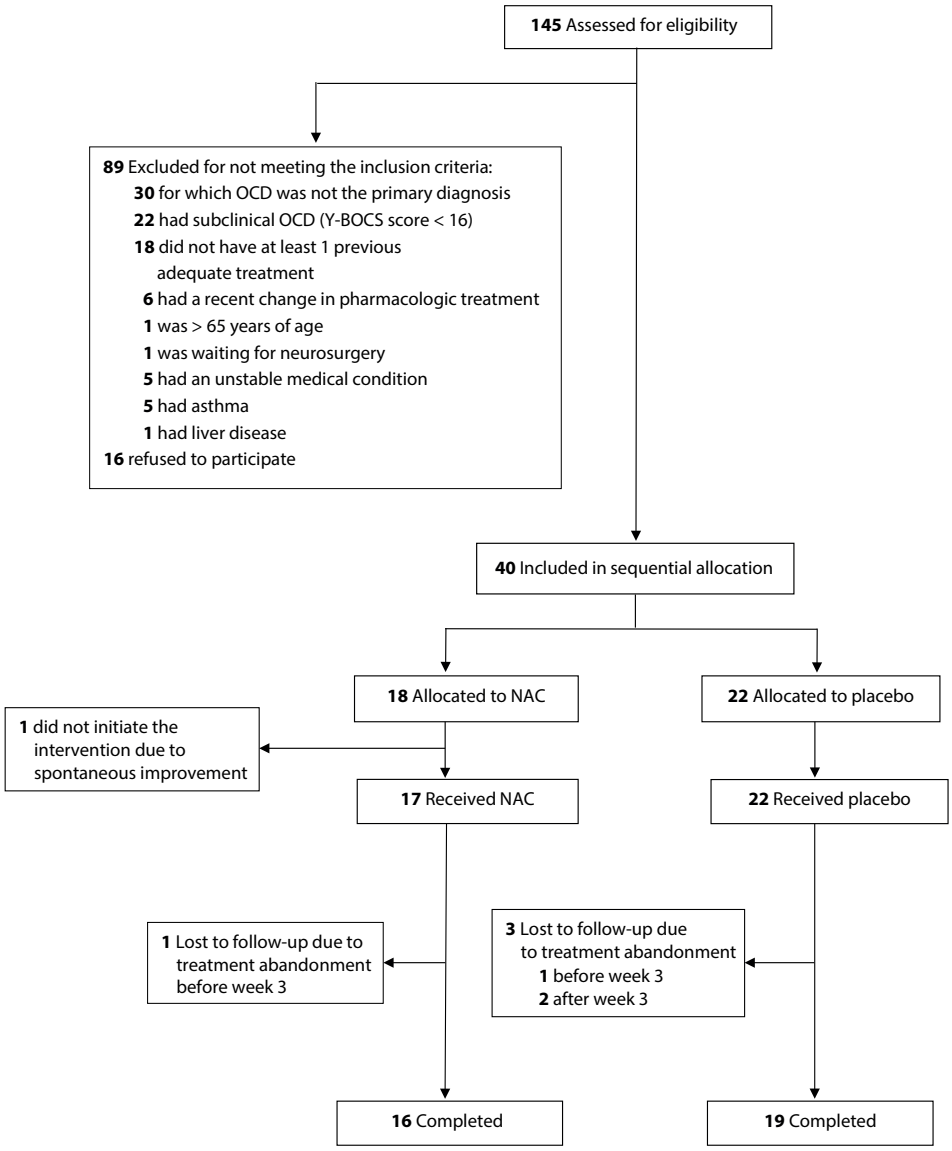
This was a 16-week, randomized, double-blind trial of SRI augmentation with NAC or placebo. Patients were sequentially allocated to treatment arms according to a minimization procedure developed specifically for this

Table 1. Characteristics of the Controlled Studies Testing the Efficacy of NAC in OCD

Study	Initial Y-BOCS Score, Mean (SD)	Final Y-BOCS Score, Mean (SD)	Target Dose (mg/d)	Trial Duration (wk)	Previous Treatment Profile	Treatment During Study
Afshar et al[26] (n = 48)[a]			2,400	12	Patients who failed to respond to at least 12 weeks of high-dose treatment with an SRI	SRI only
NAC	27.7 (5.5)	16.8[b]				
Placebo	27.6 (4.0)	21.9[b]				
Sarris et al[27] (n = 44)			3,000	16	Patients were required to be on either no treatment or a stable treatment regimen for at least 4 weeks of current treatment and a minimum of 12 weeks if it was their first OCD treatment	Selective SRI, selective SNRI, antipsychotic, TCA, GABA agents, glutamate antagonist, monotherapy
NAC	26.6 (5.7)	21.8 (8.0)				
Placebo	25.6 (4.9)	21.1 (9.3)				
Paydary et al[28] (n = 44)[a]			2,000	10	Patients received no psychotropic medications 6 weeks prior to the study	SRI only (SRI and NAC or placebo were initiated at the same time)
NAC	27.0 (4.4)	Not available				
Placebo	25.8 (3.8)	Not available				

[a]Trials that demonstrated a significant superiority of NAC over placebo in reducing OCD severity, as measured by the Y-BOCS scores.
[b]Standard deviations of final Y-BOCS scores were not available.
Abbreviations: GABA = γ-aminobutyric acid, NAC = *N*-acetylcysteine, OCD = obsessive-compulsive disorder, SNRI = serotonin-norepinephrine reuptake inhibitor, SRI = serotonin reuptake inhibitor, TCA = tricyclic antidepressant, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 1. CONSORT Diagram



Abbreviations: NAC = *N*-acetylcysteine, OCD = obsessive-compulsive disorder, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

trial. In brief, we used a computer-based intentional allocation that, in addition to preserving the random aspect of treatment arm allocation, had the advantage of being flexible, effective, and feasible for maintaining group balance regarding covariates that may be prognostic factors (sex, age, initial severity of OCD symptoms, and number of previous adequate treatments). This method is more fully described elsewhere[34] and has been used in another clinical trial conducted by our group.[13]

Treatments

During the first week, patients started the trial with either NAC 1,200 mg (one 600-mg capsule twice a day) or an equivalent number of placebo capsules. In the second week, the dosage was increased to 4 capsules per day (NAC 2,400 mg [2 capsules twice a day] or an equivalent number of placebo capsules). Finally, on the third week, the target dose of 5 capsules per day was reached (NAC 3,000 mg [2 capsules in the morning and 3 in the evening] or an equivalent number of placebo capsules) and sustained for the remainder of the study.

The identity of treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, and appearance. Of note, both NAC and placebo capsules included a flavoring substance in order to disguise the NAC's sulfur-like odor.

Assessments

The initial evaluation comprised several clinical measures, some OCD-specific and others comorbidity-related.

Table 2. Demographic and Clinical Characteristics of the Sample at Baseline

Characteristic	NAC (n = 18)	Placebo (n = 22)	All (n = 40)
Age, y, mean (SD)	37.8 (10.5)	38.2 (11.3)	38.0 (10.8)
Age at OCD onset, mean (SD), y	11.8 (6.0)	11.7 (5.2)	11.8 (5.5)
Male, n (%)	8 (44.4)	13 (59.1)	21 (52.5)
Married/partnered, n (%)	8 (44.4)	9 (40.9)	17 (42.5)
White, n (%)	10 (55.6)	18 (81.8)	28 (70.0)
Education, mean (SD), y[a]	13.2 (3.6)	12.8 (1.9)	13.0 (2.8)
Employed, n (%)	9 (50.0)	8 (36.4)	17 (42.5)
Y-BOCS score, mean (SD)			
Obsessions	12.4 (2.2)	12.7 (2.4)	12.6 (2.3)
Compulsions	13.2 (2.5)	12.1 (2.5)	12.6 (2.5)
Total	25.6 (4.4)	24.8 (3.8)	25.2 (3.9)
Symptom dimensions presence (DY-BOCS), n (%)			
Aggression/violence	15 (83.3)	20 (90.9)	35 (87.5)
Sexual/religious	13 (72.2)	18 (81.8)	31 (77.5)
Ordering/symmetry/counting	14 (77.8)	19 (86.4)	33 (82.5)
Contamination/cleaning	14 (77.8)	16 (72.7)	30 (75.0)
Hoarding	6 (33.3)	11 (50.0)	17 (42.5)
Miscellaneous	15 (83.3)	18 (81.8)	33 (82.5)
BDI scores, mean (SD)	18.2 (9.9)	19.0 (8.3)	18.6 (9.0)
BAI scores, mean (SD)	17.2 (10.7)	16.5 (7.2)	16.9 (8.8)
Insight level (BABS score), mean (SD)	9.2 (5.1)	7.6 (5.9)	8.3 (5.6)
Number of previous adequate treatments, mean (SD)	3.3 (2.1)	3.5 (2.0)	3.4 (2.0)
Sensory phenomena, n (%)			
Any	6 (33.3)	11 (50.0)	17 (42.5)
Physical sensations	3 (16.7)	6 (27.3)	9 (22.5)
Just-right sensations	5 (27.8)	9 (40.9)	14 (35.0)
Feelings of incompleteness	2 (11.1)	0	2 (5.0)
Energy release	3 (16.7)	1 (4.5)	4 (10.0)
Urge only	0	1 (4.5)	1 (2.5)
Current Axis I diagnoses, n (%)			
OCD only	5 (27.8)	4 (18.2)	9 (22.5)
Depressive disorder[b]	3 (16.7)	3 (13.6)	6 (15.0)
Anxiety disorder[c]	10 (55.6)	14 (63.6)	24 (60.0)
OCD spectrum disorder[d,e]	8 (44.4)	4 (21.1)	12 (32.4)
Current adjunctive psychiatric medication, n (%)			
SRI only	4 (22.2)	6 (27.3)	10 (25.0)
SRI + antipsychotic	9 (50.0)	6 (27.3)	15 (37.5)
Selective SRI + clomipramine	3 (16.7)	2 (9.1)	5 (12.5)
SRI + other[f]	2 (11.1)	8 (36.4)	10 (25.0)
Current SRI dose, mg/d, mean (SD)			
Clomipramine (n = 3)	237.5 (17.7)	75.0 (…)	183.3 (94.6)
Imipramine equivalent	280.8	88.6	216.6
Citalopram (n = 1)	60.0 (…)		60.0 (…)
Imipramine equivalent	228.7		228.7
Escitalopram (n = 4)	20.0 (…)	15 (7.1)	17.5 (5.0)
Imipramine equivalent	152.4	114.3	133.4
Fluoxetine (n = 9)	70.0 (20.0)	72 (17.9)	71.1 (17.6)
Imipramine equivalent	240.1	247.0	243.9
Fluvoxamine (n = 2)	300 (…)	200 (…)	250.0 (70.7)
Imipramine equivalent	287.2	191.5	239.4
Sertraline (n = 21)	194.4 (30.0)	203.8 (33.4)	200.0 (31.6)
Imipramine equivalent	270.8	283.9	278.6

[a]Years of education unknown for 5 subjects.
[b]Major depressive disorder and dysthymia.
[c]Generalized anxiety disorder, panic disorder with and without agoraphobia, agoraphobia, social and specific phobias, posttraumatic stress disorder, and anxiety disorder not otherwise specified.
[d]Body dysmorphic disorder, hypochondriasis, any eating disorder, and any grooming disorder.
[e]OCD spectrum disorder unknown for 3 subjects.
[f]Mood stabilizers, sedatives, hypnotics, other antidepressants, and stimulants.
Abbreviations: BABS = Brown Assessment of Beliefs Scale, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, DY-BOCS = Dimensional Yale-Brown Obsessive Compulsive Scale, NAC = *N*-acetylcysteine, OCD = obsessive-compulsive disorder, SRI = serotonin reuptake inhibitor, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.
Symbol: … = no SD is provided in those cells where n = 1.

Patients were interviewed by researchers trained in the application of the following instruments: Y-BOCS (OCD severity); CGI-S; Dimensional Y-BOCS[35] (DY-BOCS; assesses time, interference, and distress associated with specific OCD symptom dimensions: aggression/violence, contamination/cleaning, symmetry/order/counting, sexual/religious, hoarding, and a miscellaneous dimension that includes symptoms of body dysmorphic disorder, skin-picking, trichotillomania, and somatoform disorders); Beck Depression Inventory[36] (BDI); Beck Anxiety Inventory[37] (BAI); Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Patient Edition[38]; Structured Clinical Interview for *DSM-IV-TR* Impulse Control Disorders[39]; the University of São Paulo Sensory Phenomena Scale[40]; Systematic Assessment for Treatment Emergent Events (SAFTEE),[41] which assesses the presence and severity of 7 domains of adverse events; and the Brown Assessment of Beliefs Scale[42] (BABS). Y-BOCS scores were also obtained at weeks 1, 2, 3, 5, 7, 9, 11, 13, and 15. The SAFTEE was applied at weeks 1, 2, 3, and 11. At the end of study (week 16), the Y-BOCS, DY-BOCS, Clinical Global Impression–Improvement scale[31] (CGI-I), BDI, BAI, and BABS were reapplied. Patients, investigators, staff, and raters remained blind to treatment identity from randomization to data analysis. Blinded raters who were not involved in patient care obtained the Y-BOCS scores at weeks 0 and 16. The study clinician (also blind to treatment allocation) obtained the intermediate measures (at weeks 1, 2, 3, 5, 7, 9, 11, 13, and 15) during routine consultations (weekly during the first 3 weeks and biweekly from the third week to end of study).

Statistical Analysis

All statistical analyses were conducted using the software R: A Language and Environment for Statistical Computing, Version 3.2.3 (The R Foundation for Statistical Computing).

Categorical variables were described as absolute and relative values and continuous variables were described as means and standard deviations (SD). Comparisons between characteristics of the individuals allocated to receive NAC or placebo at baseline were performed using the Pearson χ^2 and the Fisher 2-sided tests for categorical variables, and the Student *t* and the Mann-Whitney tests for continuous and discrete variables.

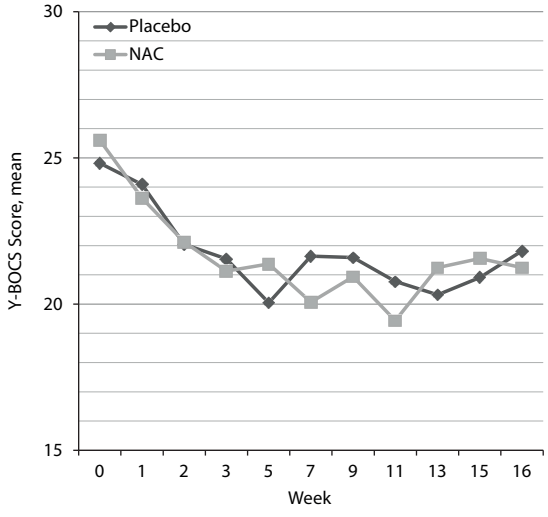
We utilized a modified intent-to-treat analysis. Individuals who dropped out before week 3 were excluded from the analysis. Missing data of those who dropped out after week 3 were imputed using the last observation carried forward. Sensitivity

Table 3. Observed Outcomes[a]

Outcome	NAC Week 0	NAC Week 16	Placebo Week 0	Placebo Week 16	*P* Value		
Secondary[b]							
BAI	17.2 (10.7)	10.9 (8.1)[c]	16.6 (7.2)	16.2 (9.5)[d]	.02		
BDI	18.2 (9.9)	14.3 (9.3)[c]	19.0 (8.3)	16.6 (7.8)[d]	.39		
BABS	6.9 (5.3)	6.2 (4.5)[c]	9.5 (5.6)	10.2 (5.9)[d]	.60		
DY-BOCS							
Aggression/violence	6.5 (4.3)	5.2 (3.7)[c]	7.1 (4.0)	5.1 (4.0)[d]	.15		
Sexual/religious	5.2 (4.9)	4.5 (4.2)[c]	6.4 (3.9)	5.7 (3.2)[d]	.97		
Ordering/symmetry/counting	7.1 (4.7)	6.3 (4.1)[c]	6.1 (3.7)	5.5 (3.8)[d]	.60		
Contamination/cleaning	6.6 (4.2)	5.2 (3.8)[c]	6.5 (4.9)	6.4 (4.9)[d]	.97		
Hoarding	1.8 (3.2)	1.8 (3.3)[c]	2.0 (2.7)	2.1 (2.4)[d]	.79		
Miscellaneous	6.9 (4.2)	5.4 (3.5)[c]	5.5 (4.1)	5.1 (4.1)[d]	.19		
Total	20.1 (4.6)	16.8 (4.7)[c]	20.2 (4.4)	18.3 (4.8)[d]	.35		
Primary[e]					Time Effect	Group Effect	Time × Group Interaction
Y-BOCS							
Obsessions	12.4 (2.2)	9.9 (4.1)	12.7 (2.4)	10.5 (2.9)	< .001	.95	.93
Compulsions	13.2 (2.5)	11.4 (4.3)	12.1 (2.5)	11.4 (4.3)	< .001	.84	.41
Total	25.6 (4.4)	21.3 (8.1)	24.8 (3.8)	21.8 (6.0)	< .001	.92	.92

[a]At week 0, there were no significant differences in any of these measures. All values are mean (SD) unless otherwise noted.
[b]Reduction of baseline scores of the different instruments were analyzed with Mann-Whitney-Wilcoxon test.
[c]n = 16.
[d]n = 20.
[e]Analyzed with nonparametric analysis of variance.
Abbreviations: BABS = Brown Assessment of Beliefs Scale, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, DY-BOCS = Dimensional Yale-Brown Obsessive Compulsive Scale, NAC = *N*-acetylcysteine, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 2. Change in Symptom Severity During Augmentation[a]



[a]Nonparametric analysis of variance was used to model change in severity of obsessive-compulsive disorder (OCD) as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) in 40 adults who were receiving at least a stable dose of a serotonin reuptake inhibitor and who were sequentially allocated to the addition of 16 weeks of *N*-acetylcysteine (n = 18) or pill placebo (n = 22). There were no differences regarding change of OCD severity at week 16 between individuals allocated to NAC or placebo. The x-axis is weeks of augmentation. The y-axis is OCD severity as measured by the Y-BOCS.

analyses were performed with worst-case (no effect of NAC compared to placebo in those who did not complete the trial) and best-case scenarios (best effect of NAC compared to placebo) for the primary outcome measure. The primary outcome measure was the Y-BOCS score. To evaluate the variables' group, time, and interaction effects for Y-BOCS scores at all time points, we used nonparametric analysis of variance (ANOVA) with repeated measures.[43]

The secondary outcomes were the mean reduction of baseline BDI, BAI, BABS, and DY-BOCS scores, whose medians were compared using the Mann-Whitney-Wilcoxon test. Proportions of patients responding (Y-BOCS score decrease ≥ 25%[44]) and proportions of individuals whose OCD improved, according to CGI-I ratings, were compared across groups using the Pearson χ^2 test of association.

The level of statistical significance was set at $P \leq .05$ (2-tailed).

RESULTS

Sample

As shown in Figure 1, 145 patients were assessed for eligibility, 56 fulfilled the inclusion criteria, 40 were randomized (NAC: n = 18; placebo: n = 22), 39 initiated the intervention, and 35 completed the trial. Dropout did not significantly differ by treatment group (NAC: 1 of 17 [5.9%]; placebo: 3 of 22 [13.6%]; $\chi^2 = 0.63$; $P = .43$).

Demographics and clinical characteristics at baseline did not differ significantly between treatment groups and are presented in Table 2.

Primary Outcome Measure

As compared to placebo, NAC did not offer a significant benefit as an SRI-augmentation strategy in treatment-resistant OCD (Table 3). Figure 2 demonstrates that all subjects had a reduction of OCD severity, as measured by the Y-BOCS. However, the modified intent-to-treat analysis revealed a nonsignificant interaction between treatment

and time (F = 0.33; *P* = .92), with the NAC group having a Y-BOCS reduction of 4.3 points (25.6 [SD = 4.4] to 21.3 [SD = 8.1]) from baseline to week 16, compared with 3.0 points (24.8 [SD = 3.8] to 21.8 [SD = 6.0]) for the placebo group. Sensitivity analyses indicated that the absence of group differences was not related to the missing-data imputation method (worst-case scenario: *P* = .68; best-case scenario: *P* = .85). Likewise, no significant interaction between treatment and time was found on the obsessions (*P* = .93) or compulsions (*P* = .41) subscales.

Secondary Outcome Measures

Data for all secondary outcomes are presented in Table 3. BAI scores showed a greater reduction among individuals receiving NAC than placebo (mean [SD]: NAC = 7.8 [11.7]; placebo: –0.55 [7.9]; *U* = 89; *P* = .02).

There were no significant group differences in the following measures from baseline to endpoint: BDI (mean [SD]: NAC = 4.6 [11.7]; placebo = 2.3 [5.7]), BABS (mean [SD]: NAC = 1.4 [4.5]; placebo = –0.05 [7.2]), severity of specific OCD symptom dimensions: aggression (mean [SD]: NAC = 1.0 [4.9]; placebo = 1.8 [2.1]), sexual/religious (mean [SD]: NAC = 0.88 [4.4]; placebo = 1.1 [2.6]), symmetry (mean [SD]: NAC = 1.0 [4.7]; placebo = 0.20 [3.0]), contamination (mean [SD]: NAC = 1.44 [2.0]; placebo = –0.40 [2.4]), hoarding (mean [SD]: NAC = 0.25 [3.5]; placebo = 0.10 [2.5]), miscellaneous (mean [SD]: NAC = 2.1 [5.0]; placebo = 0.50 [3.3]), and total DY-BOCS score (mean [SD]: NAC = 3.4 [5.9]; placebo = 1.6 [4.6]).

Moreover, there were no significant differences regarding the proportion of responders (Y-BOCS decrease ≥ 25%) between individuals allocated to NAC (n = 6 [40.0%]) or placebo (n = 5 [26.3%]) ($\chi^2 = 0.72$; *P* = .40). Similarly, there were no significant group differences in the proportion of individuals whose OCD improved (minimally, much, and very much improved) according to the 16-week CGI-I ratings (NAC = 11 [73.3%]; placebo = 10 [52.6%]; $\chi^2 = 1.52$; *P* = .22).

Adverse Events

The most frequently reported adverse events are described in Supplementary eTable 1. There were no significant differences in the frequency of side effects between groups, except for stomach/abdominal pain (n [%]: NAC = 9 [60.0]; placebo = 2 [13.3]; $\chi^2 = 7.03$; *P* < .01). There were only 2 reports of severe adverse events (somnolence and nervousness), which were obtained at week 2 by an individual allocated to placebo. None of the dropouts were related to side effects.

DISCUSSION

This controlled trial testing the efficacy of NAC in treatment-resistant OCD patients demonstrated no benefit of NAC as an SRI-augmentation agent for primary OCD symptoms, as indexed by the Y-BOCS. Individuals receiving NAC significantly improved over time, but those in the placebo group improved similarly. In secondary analyses, adding NAC to stable SRI treatment was superior to placebo in reducing the severity of anxiety symptoms. We investigated in detail other clinical features that could have been sensitive to the effects of NAC, such as the specific OCD symptom dimensions and insight level, but their outcomes did not differ among the 2 groups.

Our findings corroborate a previous and similarly designed trial,[27] but stand in contrast with 2 other studies, which demonstrated a significant benefit of NAC on OCD severity.[26,28] Methodological differences between these trials are presented in Table 1. Trials that demonstrated benefit of NAC had a shorter duration, employed lower doses of NAC (up to 2,400 mg per day), and included subjects taking only an SRI. Afshar et al[26] included patients who failed to respond to SRI treatment, while Paydary et al[28] included patients who did not receive any psychotropic medications 6 weeks prior to the study, ie, SRI and NAC or placebo were initiated at the same time.

NAC efficacy compared to placebo has been reported for several conditions including autism,[45] schizophrenia,[46] and depression.[47,48] Efficacy in the treatment of adults with trichotillomania (TTM) and excoriation disorder (ED) has been recently reported.[49,50] In both studies, NAC was used in monotherapy in otherwise treatment-free patients. In the *DSM-5*, ED and TTM are classified as OCD Related Disorders, due to the phenotypic similarities and common putative neurobiological underpinnings with OCD.[51] It has been hypothesized that NAC may work in TTM and ED by reducing the frequency and intensity of the urge to pull or pick.[49,50] This hypothesis derived from studies of NAC in cocaine-exposed rats and subsequent magnetic resonance spectroscopy studies in humans demonstrating the ability of NAC to modulate glutamate in the nucleus accumbens and reduce drug-associated cravings.[52–55]

A growing literature indicates that some OCD patients do not report obsessions preceding compulsions, but report subjective experiences such as urges, sensations, or a need to repeat a behavior until they feel complete or just right.[2,56] These sensory phenomena have phenomenological similarities to drug cravings and to the urges accompanying hair-pulling in TTM and skin-picking in ED. It may be that NAC can be beneficial in OCD through moderation of these sensory phenomena and thus be especially efficacious in that subset of patients with prominent sensory phenomena. If so, the lack of superiority of NAC over placebo in the present study might be related to the very low frequency of sensory phenomena associated with OCD symptoms reported in this sample (only 1 individual in the placebo group; see Table 2).

Another characteristic that might have influenced the primary outcome of our study concerns the participants' degree of resistance to treatment. We aimed to recruit treatment-resistant individuals, defined in the literature as the absence of satisfactory response to any first-line therapy for OCD.[57,58] However, in our sample, subjects reported on average 3.4 previous adequate treatments, comprising a

highly resistant sample. This is probably a consequence of the fact that this trial was conducted at a tertiary facility, which enhances the chance of recruiting more severe and treatment-resistant individuals. It has already been described that the proportion of responders decreases with sequential treatments for OCD.[12]

Despite the absence of significant differences in treatment efficacy between groups, all patients significantly improved from OCD over the 16-week follow-up. This phenomenon deserves a few comments. Ernst and Resch[59] define a range of factors that contribute to change in trials and distinguish specific treatment effects, placebo effects, and nonspecific effects. Nonspecific effects include the natural course and variation in the disease, regression toward the mean, other time effects, and unidentified parallel interventions. Moreover, continuous improvement with SSRI treatment has been shown for periods longer than 12 weeks,[13,60,61] suggesting that treatment response in OCD is slow and progressive rather than abrupt and stable. All these factors might have contributed to the observed reduction of the Y-BOCS scores.

Adding NAC to an SRI was superior to placebo in reducing anxiety symptoms. This result might be related to NAC's glutamate-modulating property. Results from animal studies have demonstrated a relationship between early-life stress and increased glutamate activity in brain regions implicated in anxiety or fear responses.[62] It has also been shown that glutamate modulators suppress stress hormonal responses and facilitate conditioned fear extinction.[63,64] Moreover, in open-label trials, riluzole, a glutamate modulator, was effective for patients with generalized anxiety disorder[65] and improved anxiety in patients with OCD.[66] Further studies with glutamate-modulating agents in anxiety disorders are needed to clarify these findings.

Study Limitations

Several limitations must be considered. First, we recruited patients already receiving an SRI. Consequently, we could not quantify the degree of previous SRI response. Second, the sample size was determined to detect significant differences between groups. Subtle differences with neurobiological significance but no clinical relevance might have been missed with this design. However, considering the difference of the final Y-BOCS scores and SD observed in the intervention groups, the sample size required to detect a statistical significance defined as $P < .05$ and power of 80% would be approximately 3,000 individuals in each arm. Third, participants were resistant to multiple previous treatments, which may have reduced the probability of further improvement.

CONCLUSION

As compared to placebo, NAC did not offer a significant benefit in reducing OCD symptoms as an SRI augmentation agent in treatment-resistant OCD. Future trials including subjects with a lower degree of resistance to SRI treatment and having sensory phenomena among the target symptoms are warranted in order to establish the profile of OCD individuals that might benefit from NAC augmentation of SRIs. In a secondary analysis, NAC significantly reduced anxiety in OCD patients as compared to placebo. This finding deserves replication in randomized, placebo-controlled trials in primary anxiety disorders.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Randomized, Double-Blind, Placebo-Controlled Trial of *N*-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder

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List of Supplementary Material for the article

1. **eTable 1** Frequency of Side Effects

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Supplementary eTable 1. Frequency of side effects

Side effect	NAC	Placebo	*P* value
Somnolence, n (%)[a]	8 (57.1)	7 (41.2)	.38
Stomach/abdominal pain, n (%)[b]	9 (60.0)	2 (13.3)	< .01
Constipation, n (%)[c]	3 (23.1)	6 (37.5)	.40
Dizziness, n (%)[d]	4 (30.8)	4 (26.7)	.81
Headache, n (%)[d]	4 (30.8)	4 (26.7)	.81
Nausea, n (%)[d]	2 (15.4)	5 (33.3)	.27
Fatigue, n (%)[c]	3 (23.1)	4 (25.0)	.90
Dysphoric mood, n (%)[e]	1 (8.3)	4 (26.7)	.22

[a] n= 31
[b] n= 30
[c] n= 29
[d] n= 28
[e] n= 27