N-Acetylcysteine Add-On Treatment in Refractory Obsessive-Compulsive Disorder

A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: This study aimed to evaluate the efficacy and safety of *N*-acetylcysteine, a glutamate-modulating agent, in patients with treatment-refractory obsessive-compulsive disorder as an adjunct to serotonin reuptake inhibitor treatment.

Methods: Forty-eight patients (36 women; mean ± SD age, 30.93 ± 4.99) with obsessive-compulsive disorder who failed to respond to a course of serotonin reuptake inhibitor treatment were randomized to a 12-week intervention period of *N*-acetylcysteine (up to 2400 mg/d) or placebo. Primary outcome measures were the change in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score from baseline to end point and the rate of full response in each group at the end of trial. Full response was defined as 35% or greater reduction in Y-BOCS score from baseline.

Results: Changes of Y-BOCS score were different over time ($P < 0.001$) and between groups ($P < 0.001$). *N*-acetylcysteine–assigned patients showed significantly improved mean Y-BOCS score ($P = 0.003$) and Clinical Global Impression–Severity of Illness scale score ($P = 0.01$) but not Clinical Global Impression—Improvement scale score at study end point. Of the patients in the *N*-acetylcysteine group, 52.6% were full responders at the end of the study, which was significantly higher than 15% of the patients in the placebo group ($P = 0.013$).

Conclusion: This trial suggests that *N*-acetylcysteine may be a safe and effective option to augment standard treatment in patients with refractory obsessive-compulsive disorder.

Key Words: acetylcysteine, obsessive-compulsive disorder, Yale-Brown obsessive compulsive scale, Clinical Global Impression scale, randomized controlled trials

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Nonresponsive obsessive-compulsive disorder (OCD) to standard treatment is a debilitating condition for patients to cope with. It is also a clinical challenge for clinicians and a theoretical enigma for researchers. Obsessive-compulsive disorder has a comparable clinical course to psychotic disorders in the rate of refractoriness and relapse after discontinuation of treatment.[1] It was estimated that OCD imposed a direct cost of $8.4 billion in addition to $6.2 billion of indirect costs to the community in the United States in 1990, which was approximately 18% of the costs of all anxiety disorders.[2]

Despite the fact that the efficacy of serotonin reuptake inhibitors (SRIs) has been demonstrated by many trials during the past 2 decades,[3,4] up to 40% to 60% of patients do not show a satisfactory response or maintain remission after an appropriate course of SRI treatment, which is defined as at least 10 to 12 weeks of highest tolerated dose of an SRI.[5–7] These patients are assumed to have nonresponsive or refractory OCD and are at high risk of disability and morbidity.[8] In an effort to define treatment response in patients with OCD, Pallanti and Quercioli[5] have proposed an operational categorization of treatment response based on the percentage of the Yale-Brown obsessive-compulsive scale (Y-BOCS) score reduction after treatment. They settled a threshold of 35% Y-BOCS reduction for "full response", 25% to 35% for "partial response", and less than 25% for "no response".[5]

To date, a variety of methods have been tried to augment the treatment response in nonresponsive patients, ranging from enhancing serotonergic action by increasing dosage or combining SRIs or using the intravenous route of administration[9,10] to adding cognitive behavioral therapy[11] or other agents such as neuroleptics, anticonvulsants, opioids, etc., or even the use of neurosurgical procedures.[12]

The success of serotonergic antidepressant drugs in alleviating OCD symptoms has led to the serotonergic dysfunction hypothesis of OCD.[13] Nevertheless, the substantial rate of refractoriness led to the theory of the involvement of other neurotransmitter systems in the pathophysiology of OCD.[14]

Publication of the results of some recent studies has drawn attention to the role of glutamate. Multiple imaging studies have shown an increased metabolism and activation in the cortico-striato-thalamo-cortical circuitry in patients with OCD. This circuit entails a complex network of neurotransmitters including serotonin, dopamine, glutamate, and gamma-aminobutyric acid, where glutamate is the primary excitatory neurotransmitter.[15] In line with this, Chakrabarty et al demonstrated that CSF glutamate in psychotropic patients with drug-naive OCD is significantly higher than psychiatrically normal controls.[16] Additional support was provided by animal models of OCD. In one study, transgenic mice with increased glutamate output to the striatum exhibited a phenotype similar to comorbid OCD and Tourette syndrome.[17]

Nowadays, there is convincing evidence to support the role of glutamatergic hyperactivity in the genesis of OCD symptoms.[18–20] Therefore, a number of studies have been designed

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and conducted to evaluate the effects of glutamate-modulating agents (GMAs) such as riluzole and memantine on the severity of OCD symptoms as an add-on treatment; and promising results have been achieved.[21–23]

N-Acetylcysteine (NAC) is the *N*-acetyl derivative of L-cysteine, which is deacetylated in the body to form cysteine, a rate-limiting precursor of glutathione.[24] *N*-Acetylcysteine has been used in the treatment of acetaminophen overdose for more than 30 years.[25] Recently, some preclinical and clinical studies have revealed the glutamate-modulating properties of NAC in the central nervous system,[26] which makes it desirable to use in patients with OCD. Although evidence in this field is scarce, NAC has shown its beneficial effects in obsessive-compulsive spectrum disorders in animal and preliminary human studies.[27–30] Only one case report of OCD has been published to date by Lafleur et al[31] in which significant improvement of symptoms was reported after adding NAC to SRI regimen.

According to this indefinite but affirmative evidence, we hypothesized that NAC is beneficial in augmenting current first-line OCD therapeutics. Furthermore, NAC is favorable among GMAs according to its benign side effect profile. Therefore, we performed a double blind placebo-controlled trial to evaluate the efficacy and safety of NAC in patients with refractory OCD as an adjunct to SRI treatment.

MATERIALS AND METHODS

Study Design

This study was a 12-week randomized, double-blind, placebo-controlled, 2-center, parallel-assignment clinical trial. Patients' recruitment was done in Noor Hospital in Isfahan and Farshchian Hospital in Hamedan between May 2009 and May 2010.

A total of 82 patients were screened. Finally, a total of 48 eligible patients were enrolled and randomly allocated in a 1:1 ratio to either the NAC or placebo group. We used a randomized number list generated by a random-list generator software provided by a collaborating team of statisticians at Hamedan University of Medical Sciences, faculty of pharmacy. The same software was also used to assign random codes to each pill bottle. This procedure ensured that the investigators were blinded to the drugs, which were dispensed to each patient. Furthermore, researchers who took part in the patients' allocation process had no role in the treatment or collection of data. For more confidentiality, patients' codes were used in forthcoming follow-ups.

The study protocol and eventual study related risks were clarified for all the participants and a written informed consent was obtained. This trial was scientifically and ethically approved by the research council of the Behavioral Sciences Research Center affiliated to Isfahan University of Medical Sciences and registered in the Iranian Registry of Clinical Trials (www.irct.ir, identifier: IRCT138806101743N2). All phases of this trial were designed and performed with regard to the declaration of Helsinki.

Participants

Men and women aged 18 to 45 years with a primary diagnosis of OCD who had failed to clinically respond to at least 12 weeks of high-dose treatment with a selective serotonin reuptake inhibitor or clomipramine without any history of bipolar disorder, psychotic disorder, or eating disorder were eligible for the study.

Diagnosis of OCD and comorbid conditions was made by an experienced psychiatrist based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria. Treatment failure was defined as a Y-BOCS score of 16 or greater after at least 12 weeks of SRI treatment.

Patients with any of the following criteria were excluded from the study: uncontrolled or debilitating medical conditions, alcohol or drug abuse or dependence, current pregnancy or lactation or an intention to get pregnant within the period of intervention, convulsive disorders, suicidal thoughts, any contraindications of NAC usage or being under psychotherapy or behavioral therapy. The flow diagram of the study is presented in Figure 1.

Intervention

The participants in the intervention group received an initial dosage of 600 mg/d of NAC, which doubled weekly to a maximum dose of 2400 mg/d depending on the Clinical Global Impression—Improvement (CGI-I) scale scores and the patients' tolerance. Matching placebos were given to the patients of the other group. Serotonin reuptake inhibitor treatment continued throughout the study with the same dose as the preintervention phase. Commercially available NAC, 600-mg effervescent tablets manufactured by Hexal AG, Germany, were used; and matching placebos were made in the faculty of pharmacy, Hamedan University of Medical Sciences.

Efficacy Measures

Basic information was collected by a precise interview and standard methods of measurement. The participants were visited at baseline and every 4 weeks thereafter. They were evaluated by the semi-structural clinical interview of *DSM-IV* in addition to Y-BOCS questionnaire in every visit. Severity of symptoms was assessed using the CGI Severity of Illness (CGI-S) scale at the beginning and on weeks 4 and 12. Clinical improvement on weeks 4 and 12 was assessed using CGI-I scale.

Our primary outcome measures were the changes in the Y-BOCS score from baseline to end point and the rate of response in each group at the end of the trial. The Y-BOCS and CGI questionnaires were filled by or under the supervision of the same psychiatrist on every visit in each center. To categorize the treatment response, we used previously suggested criteria[5] based on the percentage of the Y-BOCS score reduction after treatment. The criteria are as follows: 35% or greater Y-BOCS reduction is considered as "full response", 25% to 35% as "partial response", and less than 25% as "no response".

The Y-BOCS was used to quantify the severity of OCD symptoms and to evaluate the level of response to treatment. The Y-BOCS is a reliable clinician-rated instrument consisting of 10 items. Each item is rated from 0 (no symptoms) to 4 (extreme symptoms). Total score ranges from 0 to 40, with separate subscales for obsessions and compulsions.[32]

Clinical Global Impression is a clinician-rated scale consisting of 3 independent items: severity of symptoms (CGI-S), global improvement (CGI-I), and efficacy index (CGI-E). The CGI-S has a 7-point scale, but CGI-I and CGI-E each has a 4-point scale.[33]

Safety Assessments

Safety and tolerability of NAC in patients with OCD were mentioned as secondary outcomes. The patients were screened by taking a thorough medical history and physical examination (including evaluation of sitting blood pressure) at baseline and every 4 weeks throughout the study with emphasis on detecting any possible adverse event. A blood specimen to assess liver aminotransferases was also obtained at baseline and on weeks 8 and 12.

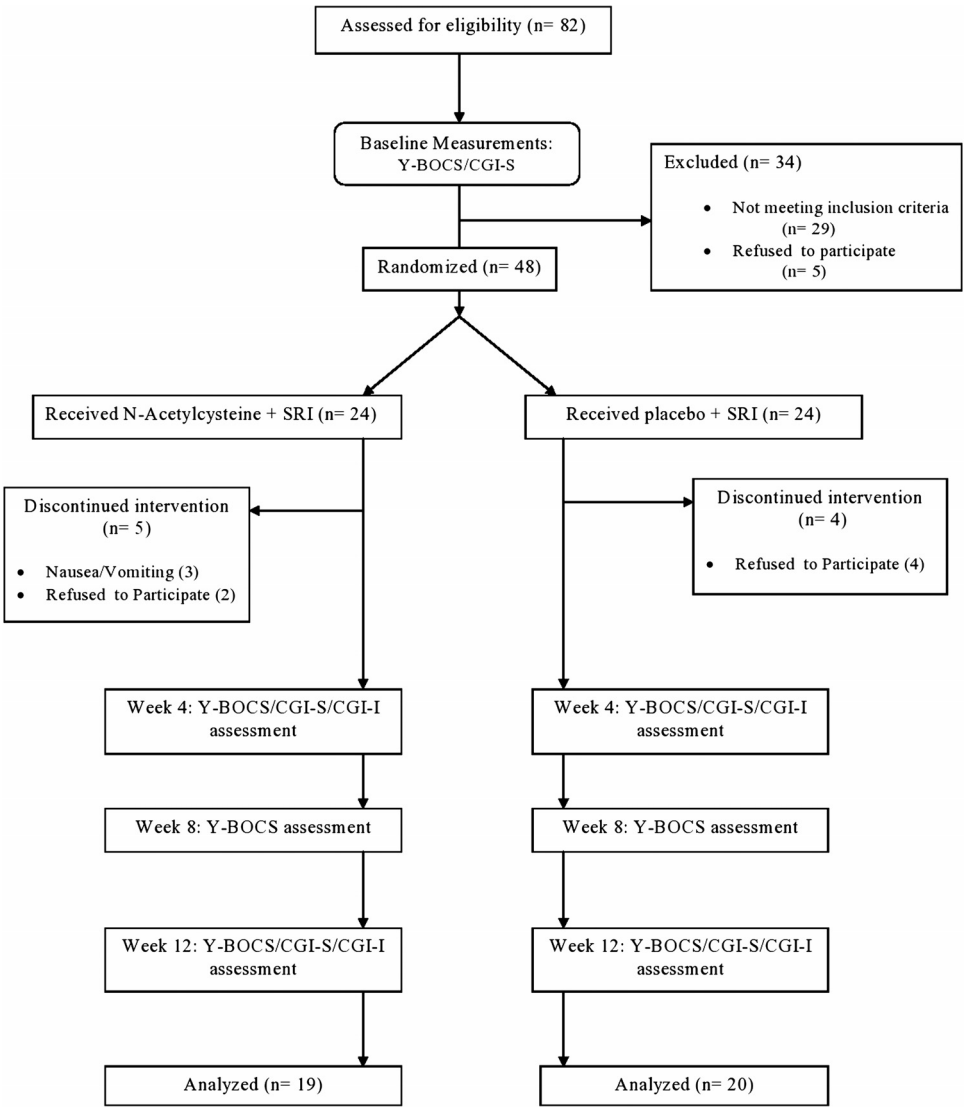

FIGURE 1. Study flow diagram.

Statistical Analyses

Baseline demographic data are presented as mean ± SD or number (percent) where appropriate. Independent *t* test was used to compare the quantitative variables and the χ^2 test to compare sex, marital status, and response rate between the 2 groups. The Fisher exact test was also used to evaluate the significance of difference in the rate of adverse effects between the NAC and placebo groups.

The primary analysis was by intention-to-treat (with missing values imputed according to the "last observation carried forward" and "random intercept model" methods) using repeated-measures multivariate analysis of variance (RM-ANOVA) in general linear model (GLM) to ascertain both between-group and within-group differences of repeated measurements of Y-BOCS score in our groups in weeks 0, 4, 8, and 12. For each assessment, the score reduction percentage was defined as a separate variable. Therefore, 4 levels of recording were accessible to compare between and within the groups. At the same time, repeated-measures multivariate analysis of covariance (RM-ANCOVA) of GLM was used to examine the interactive influence of age, sex, and duration of illness on differences between Y-BOCS score reductions between the groups.

The Statistical Package for Social Sciences software version 15.0 (SPSS Inc, Chicago, Ill) and Stata 7.0 for Windows (StataCorp LP, College Station, Tex) were used for analyses. $P \leq 0.05$ was considered statistically significant.

RESULTS

Patients' Characteristics

The mean ± SD age of the 48 patients was 30.93 ± 4.99 years (range, 23–44 years). Thirty-six patients (75%) were women, and the remaining patients were men. The patients were enrolled in the NAC (n = 24) or placebo (n = 24) group. Table 1 shows the demographic characteristics of the patients at baseline. There were no statistically significant difference regarding age, sex, marital status, age of OCD onset, and duration of illness between the 2 groups. Similarly, the Y-BOCS score and CGI-S scale score were comparable between the 2 groups at the beginning of the intervention.

TABLE 1. Baseline Characteristics of the Patients in NAC and Placebo Groups

	NAC + SRI	Placebo + SRI	P*
Age, mean ± SD, y	30.62 ± 5.35	31.25 ± 4.70	0.66
Age at onset of OCD, mean ± SD, y	16.21 ± 9.32	17.39 ± 9.86	0.71
Duration of OCD, mean ± SD, y	15.49 ± 8.56	16.42 ± 9.38	0.72
Preintervention treatment regimen (dose equivalent to fluvoxamine), mg	167.70 ± 30.82	157.29 ± 34.95	0.62
			P†
Sex, n (%)			
Male	6 (25)	6 (25)	1.00
Female	18 (75)	18 (75)	
Marital status, n (%)			
Married	16 (66.6)	14 (58.3)	0.38
Unmarried	8 (33.3)	10 (41.6)	

*t test;
†χ^2 test.

TABLE 2. Analysis of Changes in the Severity of Symptoms of OCD, Improvement Indices, in NAC and Placebo Groups

	NAC + SRI		Placebo + SRI			
	Mean	SD	Mean	SD	t	P
Y-BOCS score						
Baseline	27.70	5.52	27.62	3.95	0.06	0.95
Change after 4 wks	0.19	5.92	−1.69	4.98	2.32	0.02
Change after 8 wks	−5.39	4.83	−2.71	5.61	−2.39	0.03
Change after 12 wks	−10.87	2.94	−5.73	3.16	−3.23	0.003
CGI-S score						
Baseline	4.41	0.88	4.33	1.00	0.30	0.76
Change after 4 wks	−0.30	0.87	−0.06	0.94	−0.69	0.49
Change after 12 wks	−1.10	1.04	−0.45	0.61	−2.72	0.01
CGI-I scale score						
Week 4	2.82	0.80	3.00	0.70	−0.67	0.50
Change after 12 wks	−0.32	1.07	−0.19	0.91	−1.49	0.14

Nine patients (18%) withdrew early from the study before week 4: 5 patients (20%) from the NAC group and 4 patients (16.6%) from the placebo. Of those randomized to the NAC group, 19 were available for at least one of the follow-up assessments, and 20 of those randomized to the placebo group were available for at least one follow-up (Fig. 1).

Efficacy Results

General linear model multivariate test indicated significant values for repeated assessments (within-subject factor; $Z = 2.94$, $P = 0.016$), and between-group analyses (between-group factor; $Z = 7.50$, $P < 0.001$), which means both contributed to the model.

Within-group analyses using RM-ANOVA showed significant differences of the Y-BOCS score ($Z = 7.88$; $P < 0.001$) and the CGI-S scale score ($Z = 4.03$; $P < 0.001$), but no significant difference was seen in the CGI-I scale scores ($Z = 0.18$; $P = 0.418$) during the trial. Between-group analyses showed that the Y-BOCS score was significantly different in the NAC group compared with the placebo group ($Z = 4.12$; $P < 0.001$). The same significance was seen in between-group analysis of CGI-S scale score ($Z = 2.65$; $P = 0.027$). Conversely, difference of changes of CGI-I scale score was not statistically significant in the model ($Z = 0.86$, $P = 0.39$). Consequently, RM-ANOVA showed significant values for interaction of assessments (baseline vs week 8 vs week 12) and groups for all measures except for CGI-I scale score. Therefore, it can be inferred that the effects of NAC on our primary outcome measure were significant over time and in comparison with the placebo group. No interactive effect of patients' age, sex, marital status, and duration of illness as covariates were found by repeated-measures multivariate analysis of covariance of GLM.

Pairwise analyses of changes of efficacy measures for each time point are reported in Table 2. As shown, the Y-BOCS score reduction in the NAC group was significantly different from that of the placebo group by the study end point ($P = 0.003$). Improving effect of NAC on the Y-BOCS score was first detected at the end of week 8 ($P = 0.03$, Fig. 2).

Of the 19 patients in the NAC group, 10 patients (52.6%) had full clinical response. Such ratio in the placebo group was 15% (3/20), which was significantly lower than that in the NAC group ($P = 0.013$). Rates of response of each group in each time interval are presented in Figure 3.

The difference of improvement in the CGI-S scale score between the groups was statistically significant only in week 12 ($P = 0.01$). However, the difference of reduction of the CGI-I scale score was not significant comparing the NAC group with the placebo group.

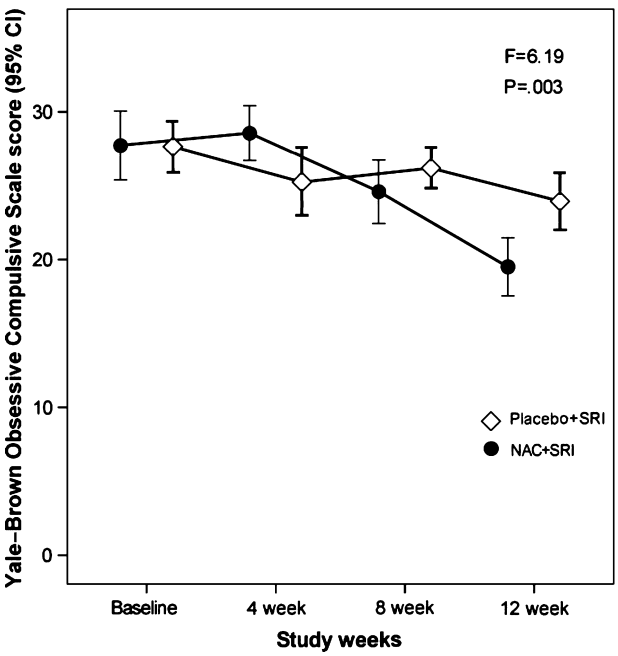

FIGURE 2. Trend of changes of Y-BOCS score over time in NAC group versus placebo group.

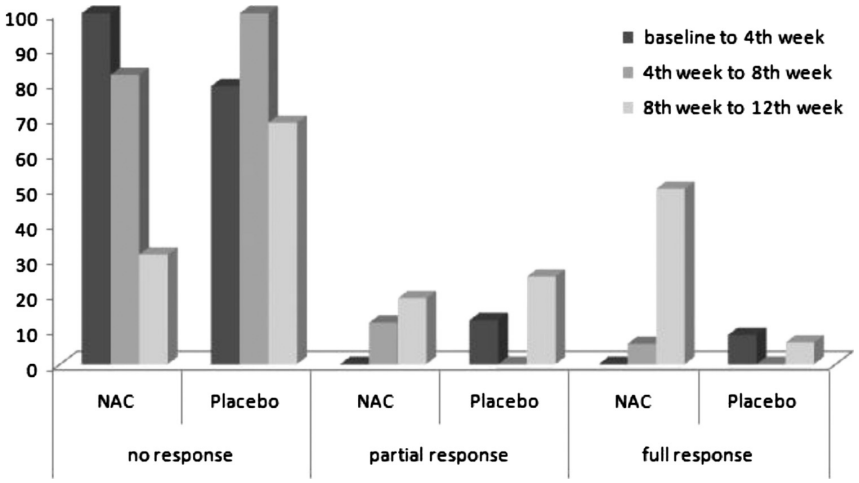

FIGURE 3. Response rates of time intervals in the NAC and placebo groups.

Safety and Tolerability

N-Acetylcysteine was well tolerated by most patients, and no unusual or serious adverse event was observed. The adverse events reported during trial were only gastrointestinal. Eight patients in the NAC group reported nausea/vomiting of mild to moderate intensity compared with 2 patients in the placebo group ($\chi^2 = 5.267$; $P = 0.03$, Fisher exact test). Mild diarrhea was reported by 4 patients in the NAC group but none of the patients in the placebo group ($\chi^2 = 4.692$; $P = 0.047$). Three patients in the NAC group discontinued the study because of the adverse effects of medication. Liver aminotransferases did not increase significantly at the end of the intervention period in any of the 2 groups, and no significant difference between the groups was recorded ($P = 0.15$ and $P = 0.38$ for alanine aminotransferase and aspartate aminotransferase change, respectively). Furthermore, no clinically important elevation was reported. No hypersensitivity reaction, alteration in blood pressure, respiratory adverse effect, or dizziness was observed.

DISCUSSION

In this study, NAC added to SRI regimen showed superior efficacy over placebo in reducing the severity of OCD in treatment-resistant patients. The Y-BOCS score was significantly reduced in the NAC group, and more importantly, more than half of the NAC-treated patients showed full clinical response after 12 weeks of follow-up, which was significantly higher than that of the placebo group.

The results of this study confirm the previous reports about the efficacy of modulation of glutamate neurotransmission network in the cortico-striato-thalamo-cortical circuitry in the treatment of OCD. Some observational studies and uncontrolled trials have been published in this regard so far. Stewart et al[23] reported the efficacy of memantine through a case-control study. Convergent outcomes have been achieved with memantine in an open label trial.[22] Likewise, Coric et al[21] reported the efficacy of a course of 6 to 12 weeks of riluzole in improving Y-BOCS score.

It is important to consider that contradictory results have also been reported on GMAs by studies on lamotrigine[34] and topiramate.[35] These findings may represent the role of unique characteristics of each agent, other than glutamate modulation, in alleviating OCD symptoms. They can also result from the small sample size of the limited available studies, making such findings inconclusive.

After discovering the neurotransmission-regulating properties of NAC[26] and finding the role of oxidative stress in psychiatric disorders,[36] NAC was proposed as a psychoactive agent; and it was tried in a wide range of psychiatric disorders.[37] Regarding its unique characteristics, NAC may have some advantages compared with other GMAs. *N*-Acetylcysteine showed promising efficacy in some OC-spectrum disorders including trichotillomania, pathological gambling,[30] and skin picking.[29] In the only case report to investigate the efficacy of the agent in refractory OCD, Lafleur et al[31] reported the case of a 58-year-old woman who was not responsive to multiple courses of treatment with SRIs and alprazolam. *N*-Acetylcysteine (titrated upward to 3 g/d) was added to fluvoxamine and continued for 13 weeks. A dramatic decrease of Y-BOCS score and significant improvement in symptoms was achieved after the trial.[31]

To the best of our knowledge, the effects of NAC on severity of OCD symptoms are attributable to 3 mechanisms. First is its glutamatergic-modulating property. *N*-Acetylcysteine can penetrate the blood-brain barrier and increase the concentration of the extraneuronal cystine. Glutamate and cystine are reversely transported through an antiporter located preferentially on glial cells. Therefore, the level of free glutamate in extracellular-extrasynaptic space will rise. Extrasynaptic glutamate can reduce synaptic release of glutamate by stimulating inhibitory metabotropic glutamate receptors (group 2) on nerve terminals.[26]

The second mechanism is NAC's antioxidant function. Besides restoring glutathione content of cells, NAC can reduce free radicals directly.[38] Considering the change in overall oxidative status in OCD,[39,40] this property could be of benefit to patients with OCD. In the central nervous system, NAC protects glial cells against glutamate toxicity and consequently enhances the clearance of synaptic glutamate.[40,41]

The other mechanism assumed to be responsible for the benefits of NAC in OCD is its anti-inflammatory properties. This idea has been derived from the evidence of underlying role of inflammatory cytokines in some psychiatric disorders including OCD,[37,42] in addition to a few studies that showed the ability of NAC in reducing some inflammatory cytokines such as IL-6 and tumor necrosis factor α.[43,44]

N-Acetylcysteine was well tolerated by our patients. However, participants of the intervention group experienced

significantly higher rates of gastrointestinal adverse events. Slight elevations of liver aminotransferases did not reach the statistically significant level both within and between the groups. These findings are consistent with the reports of previous trials of NAC with the same dose and route of administration, which showed the agent to be safe and well tolerated.[30,45]

Although this study has the advantage of being randomized and placebo controlled, we would like to note that generalizability of the conclusions might be influenced by some limitations. First is our notable dropout rate. The second limitation is that comorbidities were not included in our evaluations and analyses. These conditions are considered important because they necessitate a more strict treatment and negatively impress the treatment adequacy and outcome.[5] The next limitation is the dose of NAC used in this trial, which is not the highest conceivable dose. It is possible that higher doses could result in better outcomes. However, the optimal dose is still awaiting determination. Another important issue is the sulfur smell of NAC effervescent tablets. We tried to minimize its effect by using fruit-flavored medication and placebo tablets. However, that is still a limitation. The last one is that we did not use any clinical instruments to evaluate the patients before starting SRI treatment.

In conclusion, NAC may be a safe and effective option to augment standard treatment in patients with refractory OCD. Our results are yet to be proved by forthcoming large-scale controlled trials.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Erratum: Metabolic Effects of Paliperidone Extended Release Versus Oral Olanzapine in Patients With Schizophrenia: A Prospective, Randomized, Controlled Trial

The authors notified us of two errors they missed in proofs in their article "Metabolic Effects of Paliperidone Extended Release Versus Oral Olanzapine in Patients With Schizophrenia: A Prospective, Randomized, Controlled Trial" in the August 2012 issue of the *Journal of Clinical Psychopharmacology (J Clin Psychopharmacology*. 2012;32:449–457).

Abstract (page 449, line 16) and Results (page 452, 3rd paragraph, line 6): The numbers "0.097 ± 2.72" should be "0.97 ± 2.72".

On page 450, first paragraph, line 8: The words "paliperidone ER" should be "paliperidone palmitate" to say: "A 13-week, double-blind, head-to-head, comparative trial of paliperidone palmitate versus risperidone long-acting injectable in adults with schizophrenia showed similar efficacy and tolerability with both treatments,…".

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Schreiner A, Niehaus D, Shuriquie NA, et al. Metabolic effects of paliperidone extended release versus oral olanzapine in patients with schizophrenia: a prospective, randomized, controlled trial. *J Clin Psychopharmacology*. 2012; 32:449–457.