ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

ORIGINAL RESEARCH ARTICLE

Brain glutamate level after treatment with N-acetylcysteine in obsessive-compulsive disorder patients: A randomized trial

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Citation: Sonia SBA, Rahman MS, Shirin M, *et al.* Brain glutamate level after treatment with N-acetylcysteine in obsessive-compulsive disorder patients: A randomized trial. *INNOSC Theranostics and Pharmacological Sciences.* 2025;8(1):80-90. doi: 10.36922/itps.4887

Received: September 19, 2024

Revised: December 5, 2024

Accepted: December 18, 2024

Published online: January 17, 2025

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Abstract

Selective serotonin reuptake inhibitors (SSRIs) are routinely used to treat patients with obsessive–compulsive disorder (OCD); however, 40 – 60% of patients with OCD do not respond to SSRIs. Glutamate dysfunction may play a key role in OCD pathogenesis. N-acetylcysteine (NAC), a glutamate-modulating drug, targets the glutamatergic system. This study aimed to assess whether the addition of NAC reduces the severity of OCD symptoms in patients with SSRI-treated moderate-to-severe OCD. A total of 60 patients with OCD were diagnosed according to the DSM-5 criteria, and severity of the symptoms was assessed using the Yale–Brown obsessive–compulsive scale (Y-BOCS). Patients were administered 2,400 mg/day of SSRIs plus placebo (placebo arm) or 2,400 mg/day (NAC arm) of SSRIs plus NAC for 10 weeks. Serum alanine aminotransferase, aspartate aminotransferase, creatinine, and electrocardiogram were monitored to evaluate the safety of NAC. The Y-BOCS score was not significantly different between the two arms at baseline; however, it was significantly different between the two arms after 4 ($P = 0.03$) and 10 ($P = 0.00$) weeks. The NAC arm had a reduction of 8.4 (25.51 – 17.15) points compared with 1.42 (25.07 – 23.65) points for the placebo arm from baseline to 10 weeks. NAC was well-tolerated and caused mild gastrointestinal adverse events. Thus, NAC is an effective glutamate-modulating drug as and can be used as an augmentation therapy with standard treatment in patients with moderate-to-severe OCD.

Keywords: Glutamate; N-acetylcysteine; Obsessive–compulsive disorder; Yale–Brown obsessive–compulsive scale

1. Introduction

According to the American Psychiatric Association (2013), obsessive–compulsive disorder (OCD) is a chronic and debilitating mental illness, characterized by repetitive behaviors or mental activities (compulsions) and frequent and intrusive thoughts, images, or urges (obsessions).[1] The lifetime prevalence of OCD in the United States is 1 – 3%.[2,3] According to Algin *et al.* (2016), 70% of adult patients in Bangladesh have moderate-to-severe OCD.[4] OCD and other anxiety disorders are the sixth most common causes of non-fatal health loss worldwide.[5] OCD is predominantly related to disability and an increased risk of early death.[6,7] The American Psychiatric Association included OCD as a separate category in the Diagnostic and Statistical Manual of Mental Disorders (DSM)version 5,[8] replacing its previous classification as an anxiety disorder. Notably, patients with OCD also experience impairments in cognitive skills, such as attention, memory, decision-making, and inhibitory control.[9]

Although several mechanisms, including oxidative stress, infection, inflammation, autoimmune processes, and disorganized neurotransmission, have been proposed as underlying causes, the specific etiology of OCD remains unknown.[10,11] An abnormality in the serotonin pathway is considerably the primary cause of its development, due to its selective sensitivity to serotonergic medications. The involvement of glutamate, dopamine, and other neurochemicals has been reported.[12] Serotonergic antidepressants (selective serotonin reuptake inhibitors [SSRIs]) are recommended as first-line therapy by most clinical practice guidelines.[13,14] However, first-line treatments and other augmentation measures do not sufficiently treat 40 – 60%of patients with OCD.[15-18] In addition, psychological treatments take time and are not affordable for some patients. Moreover, full functional recovery is relatively rarely achieved, and high doses of SSRIs prescribed for patients with OCD involve side effects, such as sleepiness, insomnia, and sexual dysfunction.[19-21] These factors often demand the use of additional adjunctive treatments.[22-25] Numerous strategies have been attempted to improve treatment response, from adding cognitive behavioral therapy[26] to elevating serotonergic action by increasing the dosage, combining SSRIs, or using the intravenous route.[27,28] In addition, other medications have been attempted, including neuroleptics, anticonvulsants, opioids, and neurosurgical techniques.[29]

Numerous glutamate-modulating medications, such as lamotrigine, riluzole, and memantine, have been evaluated as monotherapy or augmentation therapies for OCD treatment.[30] Reportedly, the pathophysiology of OCD may be influenced by an impaired glutamatergic system. This system has recently gained interest as a possible treatment target for OCD.[10,30,31] Glutamatergic drugs can function as ion-channel modulators, coagonists, reuptake inhibitors, and receptor antagonists. Changes in glutamate levels could influence the onset and persistence of OCD symptoms.[32] Glutamate is the primary excitatory neurotransmitter of the cortico-striatal-thalamo-cortical (CSTC) circuit and is essential for the proper development of the CSTC circuitry, neuronal transmission, plasticity, and general brain function.[33] Increasing evidence correlates the pathophysiology of OCD to disruptions in glutamate neurotransmission, in addition to the serotonin transporter system.[34-38] Reportedly, the cerebrospinal fluid of patients with OCD has a substantially higher glutamate level than that of healthy controls.[37,39] High glutamate levels are associated with oxidative stress and excitotoxicity and can be related to the intensity of OCD symptoms.[40,41]

Due to the importance of glutamate, new treatment approaches have been developed. The glutamatergic system is targeted and modulated by N-acetylcysteine (NAC), a derivative of the amino acid cysteine. NAC contributes to cysteine, which is essential for glutathione (GSH) production. Although cysteine is not used in this process, it is transported across the blood–brain barrier by sodium-dependent mechanisms. After entering the central nervous system, it undergoes oxidation to produce cysteine.[42] Through a cystine–glutamate antiporter, astrocytes exchange cysteine for glutamate, which is released into the extracellular space. This activation of inhibitory metabotropic glutamate receptors mGLuR2/3 on glutamatergic nerve terminals reduces the amount of synaptically released glutamate.[43,44]

Furthermore, GSH enhances the NMDA receptor response to glutamate in the brain. Consequently, altered neuronal GSH levels may directly affect glutamatergic function, in addition to changing the amount of accessible glutamate.[45] NAC may also have biological effects on the brain, which are potentially related to OCD, such as reducing the production of inflammatory cytokines and modifying dopamine release. These characteristics would increase growth factors, such as brain-derived neurotrophic factor, and regulation of neuronal cell death through the expression of B-cell lymphoma 2, in addition to oxidative stress reduction and glutamatergic balance restoration.[42,44]

To the best of our knowledge, only seven randomized controlled trials have examined the potential effectiveness of NAC as an augmentation treatment for OCD, four of which revealed that taking 2,000 – 3,000 mg/day significantly decreased the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) scores.[46-52] In a 12-week

study, Afshar *et al.* (n = 48) found that the total Y-BOCS score of the NAC group decreased by 10.9 points, whereas that of the placebo group decreased by 5.7 points (P = 0.003).[52] Paydary *et al.* conducted a 10-week study in which 44 patients with OCD who had stopped taking psychiatric medicines 6 weeks earlier were randomized to receive 200 mg/daily fluvoxamine + placebo or 200 mg/daily fluvoxamine plus 2 g/daily of NAC. According to Paydary *et al.* (2016), the NAC augmentation group experienced a higher slope of treatment response than the placebo augmentation group (P = 0.012).[50] In contrast, Sarris *et al.* (n = 44) and Costa *et al.* (n = 40) reported that NAC is not beneficial on the overall Y-BOCS scores by the study endpoint, despite having longer trial lengths and greater NAC dosages (16-week trials with a 3 g/day dosage).[49,51] Sarris *et al.* found no table improvements favoring NAC on the "compulsions" subscale of Y-BOCS at week12. Compared with placebo, another study did not find evidence that the use of NAC as an augmentation therapy mitigated the OCD symptoms.[46] In a case series and case report of patients with OCD treated with SSRIs and NAC, the Y-BOCS score decreased, and symptoms improved considerably.[53,54] Further studies with larger sample sizes are needed considering the conflicting findings from previous RCTs of NAC for OCD. In addition, long trial periods might be necessary to identify the possible advantages of NAC.[55] These results suggest that NAC can effectively supplement the existing first-line treatments for OCD. NAC has been proposed as a practical augmentation due to its low cost and excellent tolerability, particularly in the refractory subset of patients with OCD, in which insufficient responses are noted and few alternatives are available.[56] Even at very high dosages, NAC was reportedly safe.[42] Thus, this randomized, double-blind, placebo-controlled study aimed to assess the safety and effectiveness of NAC as a glutamate-modulating drug in patients with moderate-to-severe OCD who were using SSRIs.

2. Materials and methods

2.1. Study design and participants

Patients with moderate-to-severe OCD were recruited from the outpatient departments of Bangabandhu Sheikh Mujib Medical University (BSMMU) and Combined Military Hospital (CMH), Dhaka, and participated in this randomized, double-blind, placebo-controlled, 10-week multi-center trial from March 2020 to January 2022. A total of 60 patients were recruited, with 30 patients in the intervention and 30 in the control arms. Patients in the two arms randomly received SSRIs plus placebo (2,400 mg/day) and SSRIs plus NAC (2,400 mg/day). The dose of NAC at week 1 was 600 mg/day, which was increased to 1,200 mg/day in two divided doses at week 2. The daily dose for NAC from weeks 3 to 10 was 2,400 mg/day (1,200 mg bd). Two sets of random numbers were assigned as patient code numbers. One set was designated as the intervention arm, whereas the other set was the control arm.

Eligible patients were newly diagnosed patients aged ≥18 years. Only patients with SSRIs (fluoxetine, sertraline, or fluvoxamine)-treated OCD who met the DSM-5 criteria and had a Y-BOCS score of ≥16 (moderate-to-severe) were enrolled. The Y-BOCS scale is considered the gold-standard clinician-rated scale with subtotals for the degree of obsessions and compulsions. Each item is evaluated from 0 (no symptoms) to 4 (severe symptoms). The total score of 0 – 40, with separate subscales for obsessions and compulsions.[57] Patients who had a history of any other psychiatric disorders and/or medical conditions before exposure to NAC within the last 2 months and those who did not provide consent were excluded from the study.

2.2. Outcomes

The primary outcome measure was the reduction of OCD severity from baseline to after 10 weeks measured by Y-BOCS-10. Secondary outcome measures were the safety and tolerability evaluations of NAC by serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and electrocardiography (ECG) for evaluating the liver, kidney, and heart functions at baseline and after 10 weeks that NAC was given at a high dose.

2.3. Study procedure

The enrollment and recruitment of patients were performed according to the principle of Consolidated Standards of Reporting Trials. NAC, 600 mg effervescent tablets, and placebo tablets were purchased from the Unimed and Unihealth Manufacturers (Dhaka, Bangladesh) at the original market price.

2.4. Randomization and masking

Randomization was performed by online graph pad software using a computer. After providing the necessary inputs (sample size and number sets), the software generates two distinct sets of random numbers. The calculated number of samples was randomly allocated in two arms. Subsequently, the set of code numbers that belong to the intervention arm was written as patient code numbers on the packages containing NAC tablets. Conversely, the set belonging to the control arm was designated as patient code numbers on the packages containing placebo tablets. The entire randomization process was performed by people unrelated to this research. Thus, the participants, outcome assessor, and analyst were unaware of the received treatment.

2.5. Intervention and assessments

A competent clinical psychologist diagnosed patients with OCD were diagnosed based on the DSM-5 criteria. After obtaining informed written consent, 60 patients were enrolled. Next, address, phone number, and demographics were collected using a prepared data sheet. However, three patients from the placebo arm and three from the NAC arm dropped out of the trial. Therefore, 27 and 27 patients from the placebo and NAC arms completed the trial. Therefore, the intention-to-treat protocol included 60, and the per-protocol treatment included 54 patients, who were available to complete the study. At baseline, the patients were assessed by Y-BOCS. Subsequently, patients were given NAC and placebo boxes. The study included three visits: one baseline visit and two follow-up visits after 4 and 10 weeks with a visit window of ±4 days. Patients were visited to assess their response to treatment using the Y-BOCS after 4 and 10 weeks.

2.6. Statistical analysis

All data were presented as a mean ± standard deviation, and analysis was performed using Microsoft Excel. For quantitative and qualitative variables, an unpaired t-test and Chi-squared (χ^2) test were used, respectively. $P < 0.05$ was considered significant.

2.7. Patient assessment tools

DSM-5 and Y-BOCS were used as patient assessment tools.

3. Results

As shown in Figure 1, 60 patients were enrolled based on the eligibility criteria. Patients were randomized into two arms to receive SSRIs plus placebo and SSRIs plus NAC.

Table 1 shows the demographic characteristics of the patients (n = 54) at baseline. No significant difference was found in age and sex between the two arms (P = 0.10 and 0.61).

Table 2 shows the Y-BOCS score of the patients at baseline and after 4 and 10 weeks. At baseline, the Y-BOCS scores in the placebo (25.07 ± 2.21) and NAC (25.51 ± 3.05) arms were not significantly different (P = 0.55). Toward the end of this trial, the Y-BOCS score reduction in the NAC arm was significantly different from that in the placebo arm ($P < 0.05$). The Y-BOCS score decreased from 25.51 ± 3.05 to 17.15 ± 5.20 in the NAC arm (Figure 2). The score in the placebo arm changed from 25.07 ± 2.21 to 23.65 ± 2.20. By the end of week 4, the first sign of an improving effect of NAC on the Y-BOCS score was noted (P = 0.03, Figure 2). Of 27 patients in the NAC arm, 20 (74.06%) reported a complete clinical response. In the placebo arm, this ratio was 7.40% (1/27).

Table 3 shows the safety parameters between the placebo and NAC arms at baseline and after 10 weeks of

Table 1. Demographic characteristics of patients (n=54) during enrollment

Variables	Placebo+SSRI (n=27) (Mean±SD)	NAC+SSRI (n=27) (Mean±SD)	P
Age in years	29.00±9.18 Range (18 – 48)	26.83±5.53 Range (18 – 42)	0.10[x]
Sex			
Male	12/27 (44.44%)	11/27 (40.74%)	
Female	15/27 (55.55%)	16/27 (59.25%)	0.61[y]

Note: [x]Unpaired t-test; [y]Chi-squared (χ^2) test
Abbreviations: NAC, N-acetylcysteine; SD, standard deviation; SSRI: Selective serotonin reuptake inhibitor.

Table 2. Comparison of the Y-BOCS scores between the control and intervention arms (at baseline and after 4 and 10 weeks of treatment)

Variable	Placebo+SSRI (n=27) Mean±SD	NAC+SSRI (n=27) Mean±SD	P[x]
At baseline	25.07±2.21	25.51±3.05	0.55
After 4 weeks	24.15±3.66	21.96±3.53	0.03
After 10 weeks	23.65±2.20	17.15±5.20	0.00

Note: [x]Unpaired t-test.
Abbreviations: NAC: N-acetyl cysteine; SSRI: Selective serotonin reuptake inhibitor; Y-BOCS: Yale–Brown obsessive scale.

Table 3. Safety parameters between the placebo and NAC arms (at baseline and after 10 weeks of treatment)

Variables	Placebo+SSRI (n=27) Mean±SD	NAC+SSRI (n=27) Mean±SD	P[x]
Serum ALT (U/L)			
At baseline	27.50±18.17	26.96±14.38	0.90
After 10 weeks	28.81±18.99	26.18±13.25	0.56
Serum AST (U/L)			
Atbaseline	26.84±13.74	24.41±8.32	0.44
After 10 weeks	28.23±1.98	23.81±6.47	0.15
Serum creatinine (mg/dL)			
At baseline	0.79±0.19	0.79±0.16	0.85
After 10 weeks	0.80±0.17	0.78±0.13	0.48
ECG			
Normal	5	12	0.07[z]
Abnormal	0	1	

Note: [x]Unpaired t-test; [z]Chi-squared (χ^2) test.
Abbreviations: ALT: Alanine transaminase; AST: Aspartate aminotransferase; ECG: electrocardiogram; NAC: N-acetylcysteine; SD: Standard deviation; SSRI: Selective serotonin reuptake inhibitor.

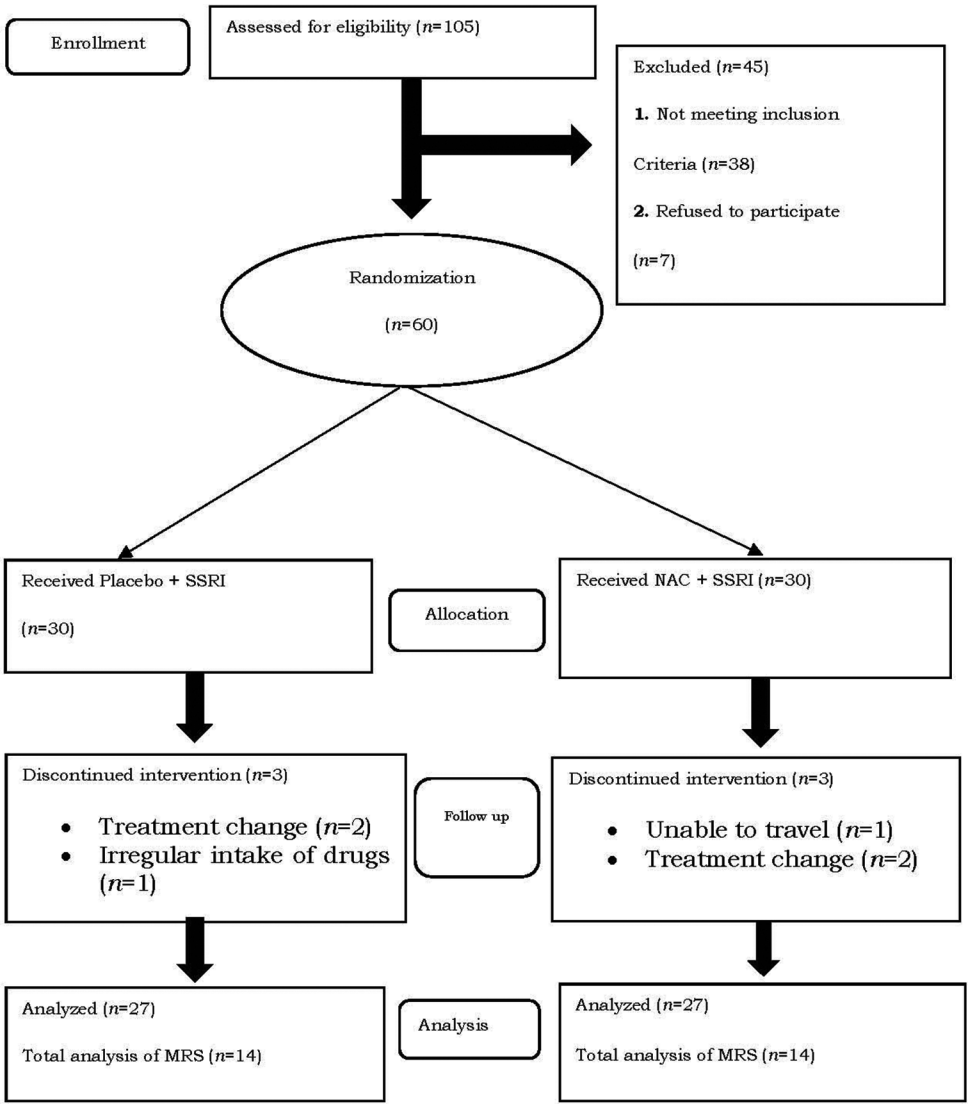


Figure 1. CONSORT Flowchart
Abbreviation: CONSORT: Consolidated Standards of Reporting Trials.

treatment. Liver aminotransferases and serum creatinine did not increase significantly at the end of the intervention period in any of the two arms, and no significant difference was recorded between the arms (P = 0.56, 0.15, and 0.48 for ALT, AST, and serum creatinine, respectively). Furthermore, no clinically significant elevations have been reported. No abnormalities were detected on the ECG.

Table 4 shows the number of adverse effects in the NAC and placebo arms during the treatment. The difference between the two arms was not significant after 10 weeks of treatment (P = 0.89). Adverse effects in the placebo arm were constipation (n = 2), headache (n = 2), insomnia (n = 2), dizziness (n = 1), diarrhea (n = 1), and nausea (n = 1), and those in the NAC arm were nausea (n = 2), diarrhea (n = 2), constipation (n = 1), headache (n = 1), dizziness (n = 1), and insomnia(n=1). All adverse effects were mild and did not require treatment discontinuation.

4. Discussion

This randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of NAC as augmentation therapy with SSRIs in patients with moderate-to-severe OCD. Both arms were followed up for 10 weeks, and their treatment response was evaluated using Y-BOCS. The addition of NAC to an SSRI medication was more effective than a placebo on lowering OCD severity. The results showed a significant reduction in the total Y-BOCS scores

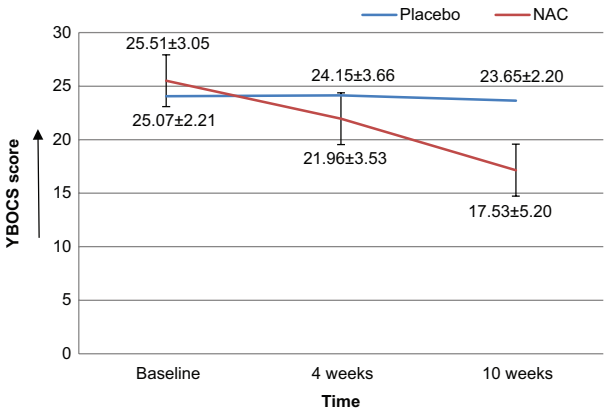


Figure 2. Changes in the Y-BOCS score over time in the placebo and NAC arms
Abbreviations: Y-BOCS: Yale–Brown obsessive–compulsive scale; NAC: N-acetylcysteine.

Table 4. Adverse effects in the placebo and NAC arms during treatment

Adverse effect	Placebo+SSRI (*n*=27) (%)	NAC+SSRI (*n*=27) (%)	*P*[x]
Constipation	2 (7.69)	1 (3.84)	0.89
Dizziness	1 (3.84)	1 (3.84)	
Headache	2 (7.69)	1 (3.84)	
Insomnia	2 (7.69)	1 (3.84)	
Diarrhea	1 (3.84)	2 (7.69)	
Nausea	1 (3.84)	2 (7.69)	

Note: [x]Chi-square (χ^2) test was done.
Abbreviations: NAC: N-acetylcysteine; SSRI: Selective serotonin reuptake inhibitor.

of patients in the NAC arm compared with those in the placebo arm during the trial.

Recently, the role of glutamate signaling pathways in the pathophysiology of OCD has been recognized.[37,58] Consequently, the use of medicines that modulate glutamate levels has been proposed as a new approach to treating OCD. Despite the lack of studies in this area, two studies explored the use of glutamate-modulating medications as a monotherapy or augmentation strategy in the OCDtreatment.[10] Considering the neurotransmission-regulating qualities of NAC[59] and the involvement of oxidative stress in psychological illnesses,[60] NAC was suggested as a psychoactive substance and was studied for various psychological disorders.[44] NAC targets the glutamatergic system and improves the general condition of patients with OCD. Despite the limited studies on its effect on OCD symptoms, NAC is reasonably available and safe.[61,62] To our understanding, NAC affects the severity of OCD symptoms in three mechanisms. First, it can modulate glutamate. NAC can cross the blood–brain barrier and enhance extraneuronal cysteine levels. An antiporter predominantly found on glial cells facilitates the reverse transfer of glutamate and cysteine. This will increase the presence of free glutamate in the extracellular extrasynaptic region. When inhibitory metabotropic glutamate receptors (group 2) on nerve terminals are stimulated, extrasynaptic glutamate can decrease the release of synaptic glutamate.[59] Second, NAC acts in general antioxidant activities via metabolic assistance to GSH formation by supplying an extra concentration of cysteine.[63] Increased GSH availability reduces oxidative and nitrosative stress, and consequently cell damage, by scavenging toxic by-products of glutamatergic and dopamine metabolism.[64] NAC improves the removal of synaptic glutamate in the central nervous system by sparing glial cells from glutamate toxicity.[65] The anti-inflammatory effects of NAC are possibly the other mechanism underlying its benefits for OCD. In addition to a few studies that demonstrated the ability of NAC to reduce some inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α,[66] this idea was derived from the underlying role of inflammatory cytokines in some psychiatric disorders, including OCD.[44]

Herein, after unblinding, no significant differences were observed in age or sex between the placebo and NAC arms. After 4 weeks, daily administration of NAC resulted in a significant reduction of the Y-BOCS score in the NAC arm; however, no reduction was noted in the placebo arm, and a significant difference was noted between the placebo and NAC arms. Considerably, the improvement attributed to the addition of NAC is significant after 4 weeks. After 10 weeks, this reduction was even greater, with an average reduction of 8.4 points from baseline, and the difference between the placebo and NAC arms was significant. Herein, NAC was more effective than placebo in lowering the severity of OCD symptoms. Furthermore, after 10 weeks of follow-up, over half of the patients in the NAC arm demonstrated full clinical response, which was more than that of the placebo arm. This finding was consistent with the results of prior clinical trials and case reports on the efficacy of NAC.[48,50,52,54] This may be due to the same NAC doses and study duration. This finding was inconsistent with those of other studies,[46,49,51] potentially due to the longer OCD duration, comorbidities, and treatment-resistant OCD. Previous studies involving patients with substance use disorders, addiction, and depression have produced conflicting results regarding the effectiveness of NAC as augmentation therapy.[67] Herein, the findings did not align with those of another case series,[68] which may be due to the presence of refractory OCD in the case series.

Furthermore, this study analyzed the adverse effects of NAC on OCD symptoms. NAC was well-tolerated. No

significant adverse effects were recorded, and the rates of various adverse effects were not different between the NAC and placebo arms. Compared with previous studies examining the effectiveness of NAC in OCD, this study had a larger sample size, double-blind, randomized, placebo-controlled design, and clearly specified inclusion/exclusion criteria.

5. Limitations

NAC was administered at the highest dosage starting in week 3. Thus, to effectively treat OCD symptoms, long durations or high dosages are needed. A small sample was analyzed; thus, results with a larger sample size might be trustworthy and accurate. Furthermore, whether the effects of NAC are durable or if the symptoms would recur if NAC was stopped is unclear. Finally, the use of magnetic resonance spectroscopy, a neuroimaging approach, to evaluate glutamate activity and other important biomarkers or pharmacodynamic pathways in the brain would have been adequate.

Considerably, this study does not support the suggestion that NAC should be used regularly as an adjuvant drug to treat adult OCD symptoms. Therefore, the effect of NAC on OCD must be examined. Future studies should examine how NAC works in conjunction with other drugs to treat OCD.

6. Conclusion

NAC is safe and effective to be used as augmentation therapy with standard treatment (SSRIs) in adult patients with moderate-to-severe OCD, results in earlier and greater reduction of OCD symptoms, and reduces the burden of this distressing illness.

Acknowledgments

The authors gratefully appreciate the contribution of Prof. M. M. A. Shalahuddin Qusar, Department of Psychiatry, BSMMU, Brig. Gen. M Kumrul Hasan, Adviser Specialist in the Department of Psychiatry, CMH, Dhaka. The authors would like to express my gratitude to Prof. Ahmed Abu Saleh, Department of Microbiology, BSMMU, for his kind-hearted support regarding randomization and blinding procedures of this research. The authors also grateful to Dr. Monirul Islam, Research Assistant of the Department of Psychiatry, BSMMU, for his valuable advice and help during the study period and permitting me to use the validated Bangla version of Y-BOCS in this research. I would like to give thanks to all the officers of CMH, Dhaka, for their valuable advice and cooperation throughout my study period.

Funding

None.

Conflict of interest

The authors declared that they have no competing interests.

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Ethics approval and consent to participate

The Helsinki Declaration and subsequent changes were followed in conducting the study. The research protocol was approved by the institutional review board (IRB) of Bangabandhu Sheikh Mujib Medical University, Dhaka, BD, on March 15, 2021 (approval number BSMMU/2021/2300). This clinical trial was registered on ClinicalTrials.gov with the trial ID number NCT04904952. Every patient provided written, informed consent, and every patient was informed about the intervention and the study objectives. They were also informed that there was the least possible chance of any harm to the patient by inclusion in this study, and if any complication arose due to the intervention, they were offered free treatment for that complication. Patients were informed that they could participate in this study of their own free will and that they were free to refuse to participate or to withdraw at any time without compromising their medical care. Patients who took part in the study willingly with written consent were interviewed. Patient's confidentiality was strictly maintained. Patient's personal data regarding name, age, sex, and other information were not disclosed anywhere and were used for research purposes only.

Consent for publication

Not applicable.

Availability of data

The data that support the findings of this study are not publicly available due to the presence of information that could compromise the privacy of research participants but are available from the corresponding author.

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