

Original Article

Role of Novel Dietary Supplement N-acetyl Cysteine in Treating Negative Symptoms in Schizophrenia: A 6-Month Follow-up Study

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ABSTRACT

Background: Abnormal metabolism of dopamine and glutamate in schizophrenia induces oxidative stress that is exacerbated by brain glutathione (GSH) deficiency. N-acetyl cysteine (NAC) increases brain GSH levels and is being used as an adjunctive agent in patients with schizophrenia. This open-label exploratory study in a naturalistic setting was conceived to examine the efficacy of NAC augmentation in treating negative syndrome in schizophrenia. **Aims:** To examine the efficacy of add-on NAC (1200 mg) in treating negative symptoms measured using Scale for the Assessment of Negative Symptoms (SANS) and clinical global impression (CGI) at baseline and 24 weeks. **Subjects and Methods:** In a 24-week feasibility study with open-label design, thirty patients with the International Classification of Diseases-Tenth Edition diagnosis of schizophrenia were recruited. Eligible patients were required to have been treated with stable dose of clozapine or amisulpride for negative symptoms for a minimum period of 8 weeks were selected for the study. The subjects were assigned to receive NAC (1.2 g/day) as an add-on treatment. Severity of negative symptoms was measured using SANS and CGI-severity at baseline and improvement with NAC measured using CGI-improvement at 24 weeks. Serum interleukin-6 was assessed before NAC initiation at baseline. **Results:** NAC augmentation showed a significantly greater improvement in negative symptoms on total SANS and CGI scores at 24 weeks. **Conclusions:** NAC may be effective as an adjunct for the treatment of negative symptoms in schizophrenia.

Key words: *N-acetyl cysteine, negative symptoms, schizophrenia*

INTRODUCTION

Glutathione (GSH) is the most fundamental antioxidant substrate. Abnormalities of brain GSH metabolism and related enzymes imply that the brain is vulnerable to oxidative stress in schizophrenia and offers a new

target for pharmacological intervention.^[1] Brain GSH levels are decreased in schizophrenia contributing to its pathogenesis. N-acetyl cysteine (NAC) may be beneficial in the treatment of schizophrenia by targeting both oxidative and inflammatory systems. Alterations

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in pro-and anti-inflammatory cytokines, including interleukin (IL)-6, IL-1 β , and tumor necrosis factor- α , have been reported in populations with schizophrenia. The reduction in inflammatory cytokines by NAC treatment may be a potential mechanism, by which NAC modulates the symptoms of psychiatric disorders. In pre-clinical studies, NAC increases brain GSH in rodents.^[2] In literature search, three clinical trials were identified pertinent to the use of NAC as an adjuvant agent in schizophrenia.^[1,3] In a large-scale placebo-controlled, randomized trial, 140 participants were recruited and received NAC at a dose of 2 g twice daily in addition to existing medication over 6 months. Improvements were seen in the negative symptoms as assessed by Positive and Negative Symptoms Scale. Further improvements in global function and improved abnormal movements, particularly akathisia, were also reported. One study has shown a significant improvement in mismatch negativity in NAC group in addition to increased GSH level.^[4] In all studies, NAC was well tolerated, with no severe adverse reactions reported. Studies from India have been sparse in this area. Keeping this in mind, this study was designed as an open-label pilot study in a naturalistic setting to examine the efficacy of NAC as an adjuvant agent in treating negative symptoms in schizophrenia and also to assess the outcome at baseline and 24 weeks using Scale for the Assessment of Negative Symptoms (SANS) and clinical global impression (CGI).

SUBJECTS AND METHODS

Study design

In a 24-week open-label pilot study (January to June 2016), patients with schizophrenia fulfilling the inclusion criteria were recruited from inpatient and outpatient departments of Schizophrenia Research Foundation, Chennai, India. Serial sampling technique was used. A total of 36 eligible patients were approached, and thirty consented to participate in the study. Written informed consent was obtained. Institutional Ethics Committee clearance was obtained before the commencement of the study.

Inclusion and exclusion criteria

To be included, participants were required to meet International Classification of Disorder-Tenth Edition criteria for schizophrenia with predominant negative symptoms as measured by SANS total scores ≥ 75 at baseline or have a CGI-severity (CGI-S) ≥ 3 . The age of participants should be above 18 years and in good physical health (with no reported infections or autoimmune diseases). In a naturalistic study, patients who were on stable dose of clozapine or amisulpride for a minimum period of 8 weeks for negative symptoms were recruited. Both inpatients and outpatients were

eligible. Exclusion criteria included uncooperative patient due to severity of illness. Patient with history of neurological disorder, mental retardation, drug/alcohol dependence, pregnant females were excluded from the study. Individuals with a prior adverse reaction to NAC or any component of the preparation or who were unable to comply with the treatment protocol were also excluded.

Tools

1. A semi-structured pro forma specifically designed to collect information regarding the socio demographic data, illness, and treatment-related variables
2. SANS^[5] is a rating scale to measure negative symptoms in schizophrenia. It was first published in 1984 by Nancy Andreasen. SANS is split into five domains, and within each domain, separate symptoms are rated from 0 (absent) to 5 (severe)
3. CGI^[6] is a three-item observer-rated scale that measures illness severity (CGI-S), global improvement (CGI-I), or change (CGI-C) and therapeutic response. The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) to 7 (among the most severely ill patients). CGI-C scores range from 1 (very much improved) to 7 (very much worse).

Procedure

The subjects were assigned to receive (1.2 g/day) of NAC in addition to taurine weeks. Patients were telephonically monitored weekly for any adverse events and for adherence. Medical records were accessed to collect the socio demographic data and illness related variables using the semi-structured pro forma. Negative symptoms of the patients were assessed using SANS at baseline and 24 weeks. The SANS scores and CGI scores were used as the outcome measures. Serum IL-6 was assessed from the same laboratory using electrochemiluminescent immunoassay before starting NAC. The reference value ranges from 0.00 to 7.00 pg/ml. Patients were regularly monitored on a weekly basis for any adverse events and adherence to NAC.

Follow up

Of the 30 recruited, five dropped out within a week because of metallic taste of NAC.

The remaining 25 patients were assessed using SANS and CGI-I at 24 weeks.

Data analysis

Analysis of data was done using the Statistical Package for Social Sciences version 16. (SPSS Inc., Chicago, Illinois U.S.A.). The data were analyzed using the descriptive statistics such as mean and standard deviation for continuous variables and frequency and

percentage for categorical variables. Mean scores of SANS and CGI were compared using Student's *t*-test.

RESULTS

Table 1 depicts the illness related variables of the 30 patients recruited in the study. Nearly 83.3% of patients completed the duration of the study. Five patients withdrew consent due to metallic taste of the medicine. Majority were paranoid subtype of schizophrenia. Statistically significant difference ($P < 0.001$) was found on comparing mean CGI scores at baseline and 24 weeks. Mean IL-6 measured at baseline was 7.62. Figure 1 depicts comparison of mean SANS scores at baseline and 24 weeks which was found to be statistically significant on all subscale domains ($P < 0.001$).

DISCUSSION

Role of NAC and inflammatory hypothesis of schizophrenia has gained recognition in recent times.^[7]

Table 1: Clinical profile of patients (n=30)

Variables	Mean (SD)/n (%)
Gender	
Male	24 (80.0)
Female	6 (20.0)
Mean age±SD (years)	32.8±7.2
Duration of illness (years)	
<5	2 (6.6)
5-10	10 (33.3)
>10	18 (60.0)
Diagnosis	
Paranoid schizophrenia	20 (66.6)
Nonparanoid type	10 (33.2)
Dose of medications in mg/day	
Amisulpride (n=17)	635±176
Clozapine (n=12)	245±62
Mean SANS score**	
Baseline	83.75
24 weeks (n=25)	52.43
Mean CGI score**	
CGI-severity	6.32
CGI-improvement (n=25)	2.88

** $p < 0.001$. SD – Standard deviation; SANS – Scale for the Assessment of Negative Symptoms; CGI – Clinical global impression

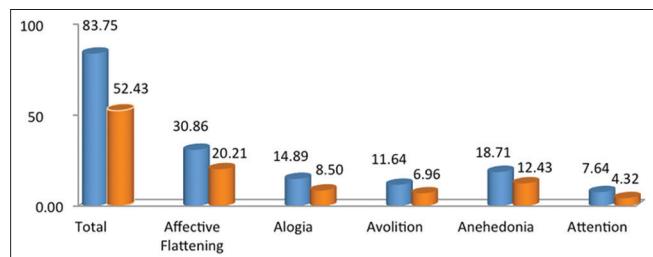


Figure 1: Mean Scale for the Assessment of Negative Symptoms and sub-domain scores from baseline to 24 weeks (n=25)

GSH an endogenous antioxidant responsible for the detoxification of reactive oxygen and other radical species found to be decreased in schizophrenics. Oral NAC rapidly increases plasma cysteine levels, replenishing depleted GSH pools systemically. Patients had been on clozapine (245 ± 62 mg) or amisulpride (635 ± 176 mg) for a relatively long time with no sufficient improvement in negative symptoms. In the present study, adding NAC to patients who were on stable doses of clozapine or amisulpride had shown significant improvement in negative symptoms on total SANS and CGI ratings at 24 weeks. These findings are consistent with recent studies using NAC in schizophrenia. High IL levels at baseline could be explained on the basis of the antioxidant–GSH hypothesis of schizophrenia. Majority of patients tolerated NAC and caused no major side effects. This present study gives a new insight in augmenting clozapine or amisulpride with NAC for additional benefits in improving negative symptoms in schizophrenia.

Limitation

The pilot study, smaller sample size, and IL levels posttreatment could have given more robust findings to correlate with clinical improvement.

CONCLUSIONS

NAC may be a potential adjuvant to antipsychotics for the treatment of negative symptoms in schizophrenia. However, a larger sample frame using ILs as a putative marker pre- and post-treatment with NAC in a double-blind design for 12 months duration will possibly generate more salient findings.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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