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Effect of N-Acetylcysteine on Positive and Negative Syndrome Scale associated with Schizophrenia: A Meta-analysis

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ABSTRACT

Introduction: N-acetylcysteine (NAC), a precursor of L-cysteine with antioxidant, anti-inflammatory and neurotropic effects, is a promising agent in alleviating symptoms associated with schizophrenia. However, the role of NAC on parameters of Positive and Negative Syndrome Scale (PANSS) remain uncertain. This systematic review and meta-analysis explored the effect of NAC on parameters of PANSS in patients with chronic schizophrenia.

Methods: We searched Pubmed/MEDLINE™, PsycNET™, PsycLIT™, Scopus™ and Google Scholar™ for studies on the effect of NAC on PANSS in patients with schizophrenia from inception to March 2019. We adopted medical and non-medical subjects headings (MeSH, non-MeSH) and several keywords, including "NAC", "N-acetylcysteine", "N-acetyl cysteine", "Acetylcysteine", "N-Acetyl-L-cysteine", "schizophrenia", "psychotic disorder", "psychosis", "schizoaffective" and "dementia praecox".

Result: We identified seven trials with 274 patients meeting the inclusion criteria, with follow up between 8-52 weeks, and NAC supplementation between 1200-3600 mg/day. Significant improvements in PANSS were identified following NAC for total (SMD=-0.61, 95% CI = -0.91, -0.31 ; P<0.001), general (SMD = -0.58; 95% CI = -0.90, -0.26; P=0.0004); and negative (SMD = -0.56; 95% CI = -0.92, -0.21; P = 0.001) scores, respectively. No significant heterogeneity was found among studies. Significant reductions were observed following sub-group analysis in trials ≤ 24 weeks duration, with appreciable effect size for total (SMD= -0.83), general (SMD= -0.67) and negative (SMD=-1.09) scores.

Conclusion: Supplementation of NAC was effective in alleviating PANSS symptoms associated with schizophrenia in trials ≤ 24 weeks duration. The use of NAC as an adjunct seems promising and further investigation is warranted to determine its precise role.

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Introduction

Schizophrenia (SZ) is defined as a chronic mental disturbance characterized in part by depression, delusions, hallucinations, and conceptual disorganization: disorganized speech and disorganized behavior (1, 2).

The underlying pathophysiology of SZ remains uncertain, nonetheless the illness manifests as cognitive disturbance, functional decline, and emotional loss (3-5).

SZ involves positive (reality distortion: hallucinations and delusions, and disorganization effects), and negative (anhedonia, lack of emotion, interest, expression and inattention to social or cognitive input and cognitive impairment) symptoms, with a tendency for negative symptoms to resist antipsychotic treatment (6, 7).

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SZ remains a highly disabling condition manifested by poor quality of life which is exacerbated by anxiety, depression, emotional blunting and apathy, despite current antipsychotic medication [8]. Symptoms of schizophrenia may be episodic or continuous (9).

Defective antioxidant pathways may be important in the pathophysiology of SZ, with higher levels of oxidative stress, membrane defects, immune system dysfunction, abnormal lipids, and pathologies affecting Gamma-aminobutyric acid (GABA), dopamine, serotonin, noradrenaline, acetyl choline and glutamate systems (10, 11).

Previous studies have demonstrated lower concentrations of glutathione in plasma, cerebrospinal fluid (CSF), and the prefrontal cortex, of drug-naive first-episodic patients with SZ suggesting a potential role of antioxidants (12).

The mechanism(s) underlying negative symptoms including emotional apathy, and blunting, and cognitive impairment remain unknown (12).

This aspect is important as these symptoms are especially prone to resistance with antipsychotics; some of which are ineffective and associated with adverse health effects with their use (13).

The role of novel therapeutics including antioxidant agents have been indicated as an adjuvant to antipsychotics (13, 14).

N-acetylcysteine (NAC) is a precursor of L-cysteine, with antioxidant, anti-inflammatory and neurotropic effects, and ability to modulate glutamatergic and dopaminergic pathways (15-18).

It also regulates NMDA (N-methyl-D-aspartate) receptor activity and cysteine synthesis in patients with SZ (19, 200, and lowers oxidative stress associated with disorders of the mitochondria (21-24).

NAC is emerging as a promising agent in psychiatric and neurological pathologies alongside existing treatment possibly due to its antioxidant and immunomodulatory effects (25).

Clinically, N-acetylcysteine is adopted for acetaminophen poisoning treatment and in the prevention of hepatotoxicity and has been shown to stabilize psychomotor function and mood, violation and social interaction (26, 27).

Previous studies have also shown that NAC may be effective in reducing some of the adverse effects experienced with second generation antipsychotics such as metabolic and neurological disturbances (26, 28), and it may also be a useful adjunct for working memory ([29).

Furthermore, NAC may also moderate other conditions including obsessive-compulsive disorders, bipolar, and depression (30, 31).

Previous studies showed the potential role of NAC in cognitive disturbance, general, positive and negative syndrome scale (PANSS) in those with psychosis or chronic SZ (32-34).

Nevertheless, there is limited information about NAC dosage, efficacy, pharmacological strategies, and chronic effects (35, 36). The present meta-analysis and systematicreview were conducted to investigate the effects of NAC on parameters of PANSS in patients with chronic SZ.

Methods

The research was implemented in accordance to (PRISMA) statement guidelines for performing and reporting items for systematic reviews and meta-analyses (37).

Search strategy and selection

Pubmed/MEDLINE™, PsycNET™, PsycLIT™, Scopus™ and Google Scholar™ were searched for studies published before 1st March 2019. Reference lists of articles included were manually searched to obtain additional data.

We adopted medical and non-medical subjects headings (MeSH, non-MeSH) and several keywords, including "NAC", "N-acetylcysteine", "N-acetyl cysteine", "Acetylcysteine", "N-Acetyl-L-cysteine", "schizophrenia", "psychotic disorder", "psychosis", "schizoaffective" and "dementia praecox". Inclusion criteria included: RCT design (either cross-over or parallel), English and/or Persian language; trials in which schizophrenic patients were enrolled, and patients with schizoaffective disorder (consistent with DSM-5 guidelines)(38).

Studies had to report mean changes with their associated standard deviations of the total, general, positive and negative syndrome scale (PANSS), and/or inclusion of data for their calculation (39).

Studies which did not satisfy the inclusion criteria were excluded if the effect of NAC on different disorders and/or interventions were reported, those with insufficient reports and/or data, non-original studies such as letters, editorials or reviews, and duplicate papers.

Data extraction

Two reviewers independently conducted the search process and articles included in the final review were reached by consensus among the team of researchers.

Data extraction included the trial design, sample size, place of study, clinical status of patients, inclusion and exclusion criteria, dose and formulation of NAC, co-supplementation and/or pharmacologic treatments used, PANSS scores, possible side effects of NAC supplementation, quality scores, study duration, and main outcomes of the study (Table 1).

Table 1: General characteristics of included trials and outcomes extracted. Abbreviation; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders. NAC, N-Acetyl Cysteine. PANSS, Positive and Negative Syndrome Scale

Author Year Country	Design	No of Subjects in case group	No of controls	Gender	Age(mean)-case group	Age(mean)-control	Inclusion criteria	Clinical Condition of Subjects (In/outpatients)	Follow-up Duration	Dosage	Significant Outcome
Breier 2018 United States	R, DB, PC	14	18	F/M	22.2±4.2	25±5.2	DSM-IV diagnosis of schizophrenia, 16-35 years and within three years of the first onset of a non-affective	In patients	52 weeks	NAC; 3600 mg/day	NAC significantly improved PANSS total, negative. The study failed to improve PANSS positive symptom
Farokhnia 2013 Iran	R, DB, PC	21	21	F/M	32.23±6.12	33.38±6.97	DSM-IV diagnosis of schizophrenia, 18-50 years, a minimum score of 60 on the PANSS, a score of 20 or greater on the PANSS negative subscale	Out patients	8 weeks	NAC; 1000 mg/day first week, 2000 mg/day weeks for subsequent 7 weeks	NAC improvement in the PANSS total and negative subscale scores than that in the placebo group, but this difference was not significant for positive and general psychopathology subscales.
Rapado Castro (a) 2015 Australia	R, DB, PC	27	30	F/M	36.5±9.7	36.2±11.1	DSM-IV diagnosis of schizophrenia, PANSS of ≥55	Out patients	24 weeks	NAC; 2000 mg/day	**A significant interaction between duration of the illness and response to treatment with NAC was consistently found for positive symptoms and functional variables, but not for negative or general symptoms or for side effect related outcomes.**
Rapado Castro (b) 2015 Australia	R, DB, PC	21	18	F/M	36.5±9.7	36.2±11.1	DSM-IV diagnosis of schizophrenia, PANSS of ≥55	Out patients	24 weeks	NAC; 2000 mg/day	A significant interaction between duration of the illness and response to treatment with NAC was consistently found for positive symptoms and functional variables, but not for negative or general symptoms or for side effect related outcomes.
Rapado Castro (c) 2015 Australia	R, DB, PC	11	14	F/M	36.5±9.7	36.2±11.1	DSM-IV diagnosis of schizophrenia, PANSS of ≥55	Out patients	24 weeks	NAC; 2000 mg/day	A significant interaction between duration of the illness and response to treatment with NAC was consistently found for positive symptoms and functional variables, but not for negative or general symptoms or for side effect related outcomes.
Sepehrmanesh 2018 Iran	R, DB, PC	40	39	F/M	38.7±1.9	39.4±2.2	DSM-IV diagnosis of schizophrenia, minimum PANSS score of 55, 18-65 years, treat with chlorpromazine equivalent to 300–1000 mg, had disease duration of at least 2 years.	Outpatients	12 weeks	NAC; 1200 mg/day	NAC-treated patients showed significantly improvement in the positive and negative PANSS subscale. Also the general and total PANSS score of NAC group declined over times. Regarding cognitive functions, improvement was observed in some explored areas, such as attention, short-term and working memory, executive functioning and speed of processing. There was no significant difference between the 2 groups in the frequency of adverse effects.

Quality assessment

The Jadad score was used in accordance with previous methods to determine the quality of included studies based on the presence of three parameters: randomization, blinding, and follow-up, with one point added for every "yes" answer to each of the first five items, and one point subtracted if inappropriate methods were used to describe randomization and blinding, for an overall score from 0–5(40).

Statistical analysis

We have used Review Manager Software (RevMan 5.3; Cochrane Collaboration, Oxford, England) for statistical analysis. Effect of NAC on PANSS indices were evaluated using the SMD (standardised mean difference) and 95% CI (confidence interval).

$\chi 2$ and I2 statistical methods and a random effects model were utilized to determine statistical heterogeneity, where $p< 0.05$ for $\chi 2$ and ≥ 50% for I2 determined significant heterogeneity between studies. To evaluate possible sources of heterogeneity, stratified and sensitivity analyses were performed sub-grouped by NAC dose, duration of studies, quality of study and duration of illness in accordance with the Cochrane guidelines (41).

To investigate the existence of possible publication bias, a funnel plot test was used, with an asymmetric pattern indicative of possible publication bias, and $p< 0.05$ considered statistically significant.

Results

The selection process and search details are presented in Fig 1. After searching the databases, 103 relevant articles were identified, and 75 total abstracts were eliminated as they were published in non-English/Persian language, non-original/review papers, duplicates, or trial protocols.

From the 28 studies, a further 23 were eliminated as they failed to meet the inclusion criteria due to insufficient reporting of the required data, case studies, studies with inappropriate design and/or irrelevant patient characterizations, or studies without appropriate controls.

Castro and colleagues applied three different treatment arms in their study design (42), and as stated in the guidance in the Cochrane handbook for systematic reviews of interventions (43),each group was considered as a separate arm in the analysis. 4 studies with six trials have met the criteria for our meta-analysis (42,44,46).

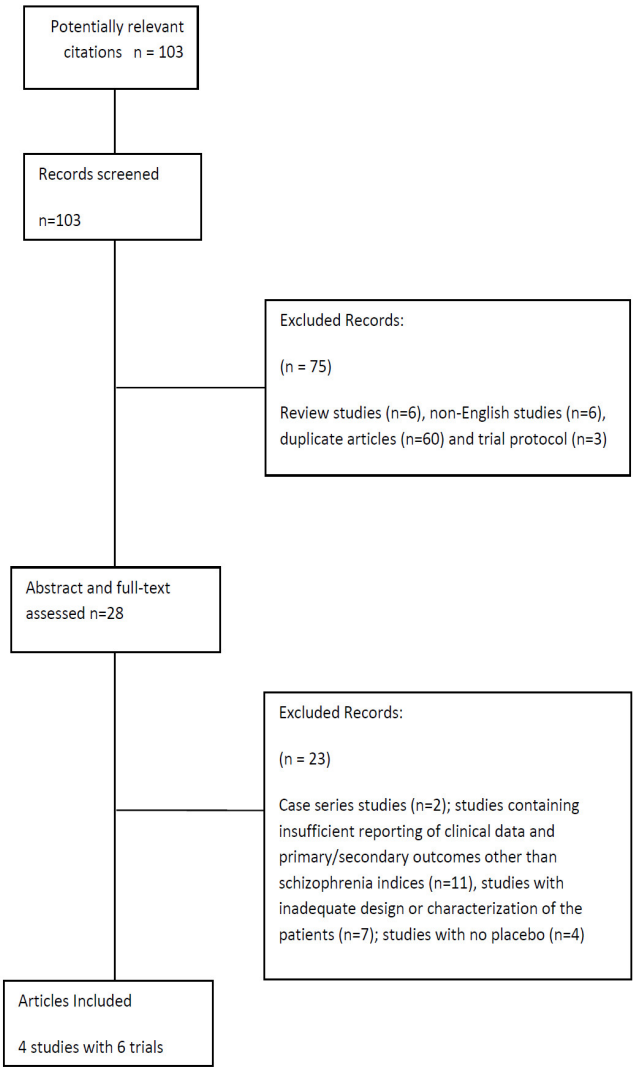


Figure 1: Meta-analysis Flow Diagram with details regarding the studies included in quantitative synthesis

Description of included studies, treatments, patients and quality assessment

In total, 274 patients (n=134 NAC supplemented, and n=140 placebo group) were included from 6 trials (Table 1). All trials were conducted between 2013-2018, 2 studies were performed in Iran (45,46) and a further 2 studies were performed in the Australia and US (42,44).

NAC dosage supplemented in the trials ranged between 1200-3600 mg/day, and the average age of included participants was 33.8 and 34.4 years in the NAC supplemented and placebo groups, respectively. The duration of NAC supplementation ranged from a minimum of 8 weeks to a maximum of 52 weeks. The duration of illness ranged from 83 days to over 20 years. Two studies used Chlorpromazine equivalents (42,45) and remaining studies used

other antipsychotic medications including Risperidone [44, 46]. All studies utilized PANSS (including total, general, positive, and negative syndrome scale) as a measure of SZ symptoms. Table 2 presents the quality assessment of the included trials in accordance with the Jadad score, and three trials received a score of ≥3 (high-quality) [44-46] and a further three trials received a score of <3 (low-quality) [42].

Table 2: Quality of bias assessment of the included studies according to several scales consisting of randomization, blinding, withdrawals and dropouts description.

Study;Year	Blinding	Randomization	Withdrawals and dropouts descriptions	Score
Breier 2018	1	1	1	3
Farokhnia 2013	2	2	1	5
Rapado Castro (a) 2015	1	1	0	2
Rapado Castro (b) 2015	1	1	0	2
Rapado Castro (c) 2015	1	1	0	2
Sepehr-manesh 2018	2	2	1	5

Main outcomes

We have conducted a random effects model and pooled analysis of PANSS total scores demonstrated a significant increase following NAC compared with the placebo group (SMD=-0.61;95% CI=[-0.91,-0.31];P<0.001).Lower endpoint scores were observed following NAC compared to placebo in PANSS General score (SMD= -0.58; 95% CI = [-0.90, -0.26]; P<0.001);and PANSS Negative score (SMD=-0.56; 95% CI= [-0.92, -0.21]; P=0.001) (Figure 2).

There was no significance in heterogeneity of all PANSS scores (PANSS Total: I2=29%, p for heterogeneity=0.21; PANSS Positive: I2=5%, p for heterogeneity=0.38, PANSS General: I2=29%, p for heterogeneity=0.23, PANSS Negative: I2=50%, p for heterogeneity=0.07). Stratified analysis was conducted to detect any possible influence of the dose and duration of NAC supplementation, study quality, and duration of illness, on the overall findings.

Duration of NAC Supplementation

There were no statistical heterogeneities observed for PANSS scores in subgroup analysis <24 or ≥24 weeks of NAC supplementation. There was a significant effect size for PANSS Total, General and Negative scores in both <24 and ≥24 weeks of supplementation (<24 weeks: PANSS Total SMD=-0.79, P<0.001; PANSS General SMD=-0.62, P=0.001; PANSS Negative SMD=-1.09, P<0.001; ≥24 weeks: PANSS Total SMD=-0.5, P=0.01; PANSS General SMD=-0.51, P<0.001, P=0.1; PANSS Negative SMD=-0.3, P=0.05) in line with overall finding (Table 3).

Dose of NAC Supplement

A medium effect size was observed for PANSS Total (SMD=-0.58, P=0.001), General (SMD=-0.60, P<0.001) and Negative (SMD=-0.58, P=0.006) following NAC dosage of ≤ 2000 mg/day, and in the lower dose subgroup PANSS scores were similar to the overall synthesis (Table 3).

Illness Duration

Stratified analysis by illness duration showed a highly significant effect of NAC supplementation on illness duration ≤10 years for Total (SMD=-0.8, P<0.001), General (SMD=-0.84, P<0.001) and Negative (SMD=-0.56, P=0.02) symptoms.

The heterogeneity of all PANSS scores were not statistically significant in subgroup analysis by illness duration of ≤10 years or >10 years. Regarding analysis of the subgroup of illness duration of >10 years, the pooled estimate revealed a weak effect size of NAC supplementation for PANSS scores: Total (SMD=-0.39, P=0.10), General (SMD=-0.39, P<0.07), Positive (SMD=-0.1, P=0.70),and Negative (SMD=-0.52, P=0.08) scores, which is not in agreement with the overall results (Table 3).

Effect of study quality

Following stratified analysis by quality assessment, a significant effect size was observed following NAC supplementation in high quality studies for PANSS Total (SMD=-0.77, P<0.001), General (SMD=-0.62, P=0.001) and Negative (SMD=-0.83, P<0.001) scores. This result is in accordance with the main results. The heterogeneity of all PANSS scores was insignificant after subgroup analysis by low and high quality studies (Table 3).

Sensitivity analysis

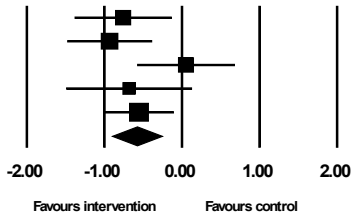
Sensitivity analysis was performed to detect the effect of individual trials on the general findings of the present meta-analysis.

Data was meta-analysed repeatedly after excluding single trials singularly. The effect size was re-calculated and the effect of single trials on the general effect size was examined (47).

There were no effects observed from individual trials on the general effect size of PANSS Total which varied from −0.52 unit (95% CI: −0.82, -0.23) after omitting the trial by Farokhnia et al. [45], to −0.74 unit (95% CI −1.00, -0.47) after elimination of Rapado Castro (b) et al 42] (Figure 3).

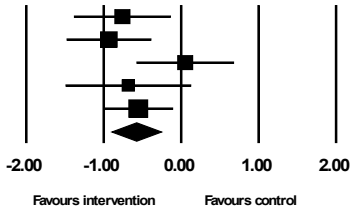
A)Total PANSS score

Study name	Std diff in means	Variance	Lower limit	Upper limit	Z-Value	p-Value
Farokhnia 2013	-0.759	0.102	-1.385	-0.132	-2.374	0.017582
Rapado Castro(a) 2015	-0.933	0.078	-1.480	-0.385	-3.340	0.000839
Rapado Castro(b) 2015	0.052	0.103	-0.577	0.682	0.163	0.870906
Rapado Castro(c) 2015	-0.682	0.172	-1.494	0.130	-1.647	0.099554
Sepehrmanesh 2018	-0.554	0.053	-1.004	-0.105	-2.418	0.015606
	-0.581	0.027	-0.901	-0.260	-3.552	0.000382



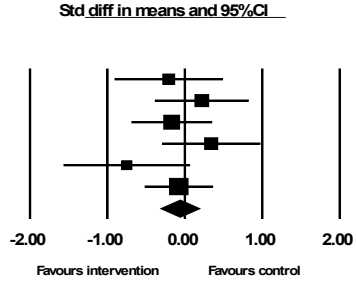
B) General PANSS score

Study name	Std diff in means	Variance	Lower limit	Upper limit	Z-Value	p-Value
Farokhnia 2013	-0.759	0.102	-1.385	-0.132	-2.374	0.017582
Rapado Castro(a) 2015	-0.933	0.078	-1.480	-0.385	-3.340	0.000839
Rapado Castro(b) 2015	0.052	0.103	-0.577	0.682	0.163	0.870906
Rapado Castro(c) 2015	-0.682	0.172	-1.494	0.130	-1.647	0.099554
Sepehrmanesh 2018	-0.554	0.053	-1.004	-0.105	-2.418	0.015606
	-0.581	0.027	-0.901	-0.260	-3.552	0.000382



C)Positive PANSS score

Study name	Std diff in means	Variance	Lower limit	Upper limit	Z-Value	p-Value
Breier 2018	-0.208	0.128	-0.908	0.492	-0.583	0.560226
Farokhnia 2013	0.219	0.096	-0.387	0.826	0.709	0.478265
Rapado Castro(a) 2015	-0.169	0.071	-0.690	0.352	-0.637	0.524280
Rapado Castro(b) 2015	0.341	0.105	-0.293	0.975	1.054	0.292104
Rapado Castro(c) 2015	-0.750	0.174	-1.567	0.067	-1.800	0.071810
Sepehrmanesh 2018	-0.077	0.051	-0.519	0.364	-0.343	0.731395
	-0.065	0.016	-0.316	0.185	-0.511	0.609564



D) Negative PANSS score

Study name	Std diff in means	Variance	Lower limit	Upper limit	Z-Value	p-Value
Breier 2018	-0.411	0.130	-1.116	0.295	-1.141	0.253966
Farokhnia 2013	-1.152	0.111	-1.805	-0.499	-3.456	0.000548
Rapado Castro(a) 2015	-0.270	0.071	-0.793	0.252	-1.014	0.310475
Rapado Castro(b) 2015	-0.227	0.104	-0.858	0.405	-0.704	0.481425
Rapado Castro(c) 2015	-0.172	0.163	-0.963	0.619	-0.425	0.670473
Sepehrmanesh 2018	-1.020	0.057	-1.489	-0.551	-4.264	0.000020
	-0.569	0.033	-0.925	-0.213	-3.134	0.001722

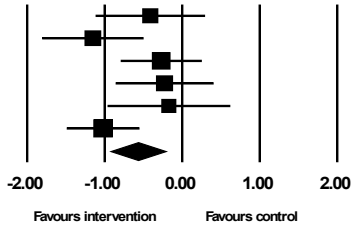


Figure 2: Forest plots showing the association between NAC supplementation and schizophrenia symptoms; Total PANSS score (A), General PANSS score (B), Positive PANSS score (C) and Negative PANSS score (D); d. Random effects model was used to pool the mean change of indicators. Abbreviation; PANSS, Positive and Negative Syndrome Scale

Table 3: Subgroup analysis of the effect of possible mediators including duration of studies, N-acetyl cysteine dosage, illness duration and quality of study variables on PANSS scales

Subgroup*		PANSS Total		PANSS General		PANSS Positive		PANSS Negative	
		SMD (95% CI)	Test for heterogeneity(I2, P)	SMD (95% CI)	Test for heterogeneity(I2, P)	SMD (95% CI)	Test for heterogeneity(I2, P)	SMD (95% CI)	Test for heterogeneity(I2, P)
Duration of studies	<24 weeks	-0.79 [-1.20, -0.38]	15%, p=0.28	-0.62 [-0.98, -0.25]	0%, P = 0.62	0.02 [-0.33, 0.38]	0%, P = 0.45	-1.09 [-1.47, -0.72]	0%, P = 0.69
	≥24 weeks	-0.50 [-0.88, -0.12]	36%, P = 0.2	-0.51 [-1.13, 0.10]	62%, P < 0.07	-0.15 [-0.50, 0.20]	28% , P = 0.24	-0.29 [-0.58, 0.00]	0%, P = 0.95
NAC dosage	≤2000 mg/d	-0.58 [-0.93, -0.23]	41%, P = 0.14	-0.60 [-0.91, -0.28]	30%, P = 0.22	-0.05 [-0.33, 0.24]	19%, P = 0.29	-0.58 [-1.00, -0.17]	58%, P =0.05
	>2000 mg/d	-0.74 [-1.26, -0.21]	Not applicable	Not applicable	Not applicable	-0.21 [-0.71, 0.30]	Not applicable	-0.41 [-0.92, 0.11]	Not applicable
Illness duration	≤10 years	-0.80 [-1.12, -0.47]	0%, P < 0.62	-0.84 [-1.26, -0.43]	0%, P < 0.68	-0.08 [-0.39, 0.23]	0%, P = 0.53	-0.56 [-1.04, -0.08]	55%, P <0.11
	>10 years	-0.39 [-0.87, 0.09]	45%, P = 0.16	-0.39 [-0.80, 0.03]	28%, P = 0.25	-0.10 [-0.60, 0.40]	50%, P = 0.13	-0.52 [-1.11, 0.07]	63%, P =0.07
Quality of study	High quality	-0.77 [-1.07, -0.46]	0%, P = 0.55	-0.62 [-0.98, -0.25]	0%, P = 0.62	-0.21 [-0.73, 0.32]	67%, P = 0.05	-0.83 [-1.27, -0.39]	50%, P = 0.14
	Low quality	-0.39 [-0.90, 0.11]	45%, P = 0.16	-0.51 [-1.13, 0.10]	62%, P = 0.07	-0.14 [-0.67, 0.39]	51%, P = 0.13	-0.23 [-0.59, 0.13]	0%, P = 0.98

Abbreviations: CI, confidence interval; NAC, N-Acetyl Cysteine; PANSS, Positive and Negative Syndrome Scale; SMD, standard mean difference

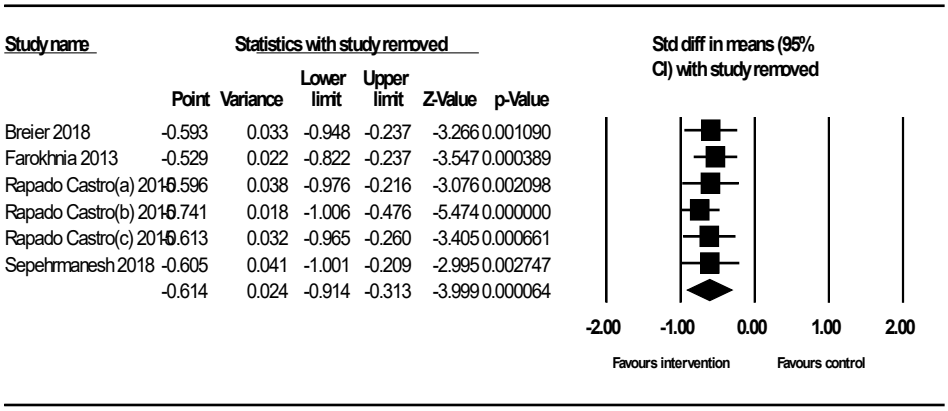


Figure 3: Overview of a Sensitivity Analysis of selected parameters (PANSS total). Abbreviation; PANSS, Positive and Negative Syndrome Scale

Publication Bias

There was no publication bias detected for PANSS scores, as shown by the symmetry observed in the funnel plots in Figure 4.

Discussion

The present meta-analysis included 274 patients with SZ from 6 RCTs. NAC supplementation improved general, total and negative PANSS in SZ patients and this was in agreement in three of the six RCTs evaluated in this meta-analysis (44-46).

It would therefore appear likely that any potential benefit of NAC may only be relevant to those with stable chronic illness, as the majority of the clinical trials were indicated in subjects with chronic schizophrenia (48).

However, due to the small number of trials with acute-phase SZ patients, this remains undeter-

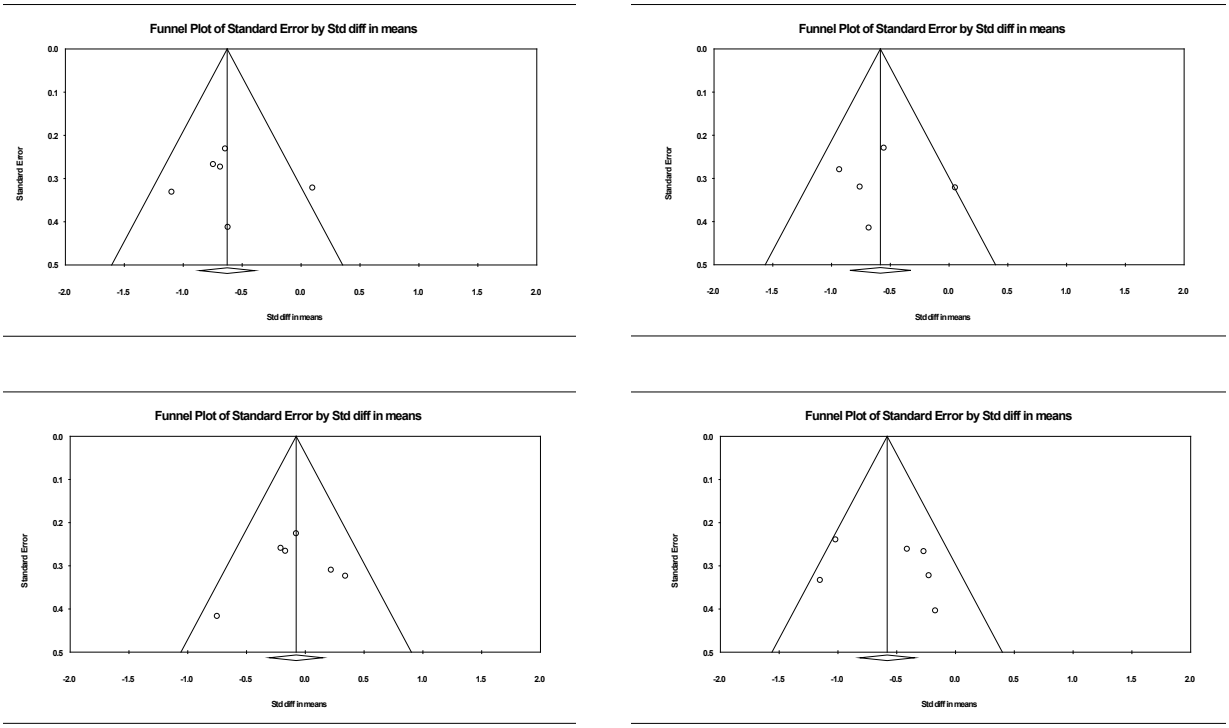


Figure 4: Funnel plot of trials included in the present meta-analysis for the outcome of Total PANSS score (A), General PANSS score (B), Positive PANSS score (C) and Negative PANSS score (D) . MD = Mean Difference, SE = standard error. Abbreviation; PANSS, Positive and Negative Syndrome Scale

mined. A recent study assessed the effect of antioxidants (including NAC) as an adjuvant with anti-psychotics in SZ patients (49).

The study demonstrated some beneficial effects with improvements in psychotic signs in those taking antioxidants alongside treatment compared with anti-psychotics alone (49).

However, there were no significant effects in their subgroup analysis between each group, which is contradictory to our findings in the our meta-analysis (49).

It is possible that their findings were limited by the small sample size, included studies, and a limited follow-up. The study reported on rating scales only and excluded factors considered to be of clinical significance in SZ, such as quality of life and acceptability. These are key elements in the interpretation of the effect of an adjuvant to antipsychotic treatment.

The oral intake of NAC, a safe well-tolerated agent with no adverse effects, has been demonstrated to be beneficial in settings where glutathione deficiency occurs (e.g., diabetes, cystic Fibrosis and HIV infection) (50).

NAC could be useful alongside antipsychotics in alleviating the symptoms of SZ, and may improve certain elements of cognitive dysfunction in psychosis signs, such as Working Memory (32).

A high number of patients with SZ do not respond to clozapine treatment, and in the region of 40–60 % of patients display residual cognitive and negative signs, often leading to increased dosage, intolerable adverse effects, and compromised quality of life [8, 51].

In the present study, significant improvements in general, negative, and total PANSS scores were observed with NAC duration > 24 weeks or ≤ 24 weeks, and with lower doses ≤ 2000 mg/day with acceptable homogeneity. Moreover, patients with a duration of illness ≤10 years as well as those experiencing considerable clinical improvements, suggest that NAC may be more effective in those with a medium-term duration of illness. PANSS was not significantly lower following subgroup analysis by duration of illness >10 years, and it is possible that the efficacy of NAC could decrease with time. The reasons are unclear at this juncture and further research is needed to understand the pharmacodynamics and pharmacokinetics of NAC.

Although the precise mechanism(s) of action of NAC are undetermined, evidence indicates its potential role in several processes including neurogenesis, oxidative stress, neuroinflammation, mitochondrial disturbance, cell-death and dysregulation of neurotransmitter systems; processes important in the pathophysiology of SZ and other psychiatric and neurological conditions (52).

As a GSH precursor, NAC may be important in the regulation of glutamatergic and dopaminergic pathways (53).

It may ameliorate negative symptoms associated with SZ through indirect modulation of these systems, and studies have demonstrated its capacity to penetrate the blood-brain-barrier, where it may act via neurotropic, glutamatergic, and inflammatory pathways (18,54).

In the present study, significant improvements on PANSS were more apparent in those trials supplemented with lower doses of NAC (≤ 2000 mg/day), durations of (≤ 24 weeks) and a duration of illness (≤ 10 years). Moreover, some studies demonstrated that it may be an important co-adjuvant in the treatment of SZ. Administration of NAC orally was generally well accepted and considered to be safe with no indication of adverse effects or withdrawals in the included RCTs (29, 55, 56).

The optimal dosage was not clear from the trials included in this study, nonetheless lower doses of NAC were associated with greater improvements in general, negative, and total PANSS compared with higher doses. Higher doses of NAC in the region of 3000-4800 mg/day have been used in clinical studies including attention deficit hyperactivity disorder (ADHD) with no clear indication of greater efficacy (57).

Indeed, one study reported possible neutropenia with doses in the region of 6000 mg/day [58]. Based on the existing evidence to date, NAC dosage in the region of 2000-4000 mg/day appears to be safe, and well tolerated. However, further research from clinical studies for various psychiatric and neurological conditions is necessary.

This study presents some limitations. The number and size of included RCTs was limited and the sample size was relatively small. It has been demonstrated that a smaller sample size may be more susceptible to producing larger and considerable effect sizes (59).

The quality of RCTs is considered as a potential limitation, as three trials in our study were assessed as low quality. We did not control for confounding factors, including extrapyramidal symptoms, positive, and depressive signs (60), which may have influenced our results. Dietary administration of animal proteins could also be considered as a potential confounder because they provide a rich source of cysteine, a precursor of NAC. However, to our knowledge no dietary guidance or indeed analysis of dietary intake was included in any of the RCTs investigated.

Nonetheless, we evaluated subgroup analyses and sensitivity which reduced the effects of influential factors, including varying doses of NAC supplementation, duration of trials and duration of illness, on the final findings.

Conclusions

The meta-analysis demonstrated beneficial effects on PANSS following NAC supplementation in patients with chronic SZ. NAC may be effective in alleviating SZ symptoms with lower doses (≤ 2000 mg/day), duration of (≤ 24 weeks) and a duration of illness (≤ 10 years). These findings may be used to improve and design of future RCTs investigating NAC as an adjunct treatment for SZ.

Conflicts of interest

The authors declare no conflicts of interest.

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