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Recycling N-acetylcysteine: A review of evidence for adjunctive therapy in schizophrenia

Robert J. Willborn, PharmD, MPH, BCPS, BCPP[1]
Colleen P. Hall, PharmD, BCPP[2]
Matthew A. Fuller, PharmD, BCPP, FASHP[3]

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Abstract

Introduction: All symptoms in schizophrenia may impact functioning. Although Food and Drug Administration-approved medications typically benefit positive symptoms, negative symptoms are generally refractory to medication interventions. N-acetylcysteine's (NAC) influence on glutamatergic neurotransmission has been established. An emerging body of research has attempted to correlate this action with reduction in symptom severity, evaluating response in positive, negative, and cognitive symptom domains.

Methods: A literature review was performed to analyze available data on NAC intervention and improvement in the positive, negative, and cognitive symptom domains in patients with schizophrenia. Quality of evidence was systematically assessed to determine level of certainty in results.

Results: Three randomized controlled trials were identified. Across studies, negative symptoms decreased more with NAC compared to placebo; ranging between 11.9% and 24.1%. The assessment determined a low level of certainty regarding benefit of NAC on negative and cognitive symptoms and moderate certainty for NAC regarding findings of side effects and lack of benefit on positive symptoms.

Discussion: Consistent reporting of benefit in negative symptoms is found across studies of NAC intervention. These improvements are notable for symptoms that have generally remained refractory to medication intervention. Inconsistent benefit was reported in positive and cognitive symptoms. GRADE (grading of recommendations assessment, development and evaluation) assessment of current evidence indicates a low certainty of benefit for negative symptoms with standard use of NAC in patients with schizophrenia. However, a trial of this low-risk intervention may be warranted in patients with resistant negative symptoms and subsequent impaired functioning despite appropriate antipsychotic therapy as they may experience additional benefit in this symptom domain.

Keywords: schizophrenia, NAC, negative symptoms, adjunctive therapy

[1] (Corresponding author) Clinical Pharmacy Specialist, VA Northeast Ohio Healthcare System, Cleveland, Ohio, robert.willborn@va.gov, ORCID: https://orcid.org/0000-0002-4634-8235; [2] Clinical Pharmacy Specialist, VA Northeast Ohio Healthcare System, Cleveland, Ohio; Associate Clinical Professor of Psychiatry, Case Western Reserve University, School of Medicine, Cleveland, Ohio, ORCID: https://orcid.org/0000-0003-1212-6754; [3] Clinical Pharmacy Specialist, VA Northeast Ohio Healthcare System, Cleveland, Ohio; Associate Clinical Professor of Psychiatry, Case Western Reserve University, School of Medicine, Cleveland, Ohio, ORCID: https://orcid.org/0000-0002-9404-1713

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Introduction

Schizophrenia is a thought disorder characterized by the variable presentation of positive and negative symptoms with subsequent mood and cognitive impairments contributing to functional decline. The negative symptom domain includes social withdrawal, impaired affective response, lack of interest, poverty of speech, and diminished goal-directed activity, whereas positive symptoms include hallucinations, delusions, and paranoia.[1] All patients with schizophrenia present with some positive symptoms, and many experience negative symptoms.[2] Positive symptoms have been shown to respond to medication interventions with response characterized to be a 20% improvement in symptom severity.[3] Negative symptoms often persist throughout the life span and are generally refractory to standard medication interventions.[4] Given the chronicity of illness and symptom persistence, patients with schizophrenia often attain lower levels of education, have a reduced quality of life, and develop impaired social and occupational functioning.[5,6] Additionally, negative symptoms contribute to enhanced mortality risk through influence on comorbidities, including metabolic syndrome and cardiovascular disease.[7,8] All symptoms in schizophrenia may impact functional capacity, and the severity of negative symptoms may serve as a clinically important prognostic factor of global health outcomes.

Treatment with antipsychotic medications leads to a response in positive symptom reduction for more than two thirds of patients.[9] Their benefit for negative symptoms are less evident. Furthermore, negative symptoms secondary to antipsychotic activity on mesocortical dopaminergic pathways are difficult to differentiate from primary negative symptoms of schizophrenia.[10] The interaction of social deprivation, depressive symptoms, substance use disorders, and personality disorders also may lead to negative symptoms. The 2009 Patient Outcomes Research Team schizophrenia guidelines indicate that no pharmacologic treatment for negative symptoms has sufficient evidence to support a treatment recommendation.[4] Investment into treatment interventions targeting this area of need have yielded useful information. Particularly interesting is the focus on repurposing other currently available medications with the intention of improving all symptom domains, including recent and pending evaluations on the use of N-acetylcysteine (NAC).

Research has indicated that pharmacologic manipulation of glutamatergic neurotransmission via glycine (d-serine) reuptake, specifically at the N-methyl-D-aspartate (NMDA) receptor, may serve as a unique target for symptoms of schizophrenia.[11] The glutamate hypothesis of schizophrenia posits that dysfunction in the tight physiologic control of this major excitatory neurotransmitter may contribute to the development of schizophrenia.[12] However, no specific pharmacotherapy targeting glutamate has demonstrated consistent improvement in symptoms of schizophrenia. The complexity of the condition and glutamatergic neurotransmission activity, including NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (commonly referred to as AMPA), kainite, and metabotropic receptors (commonly mGluR), makes the identification of specific contributory mechanisms or drug targets difficult.

N-acetylcysteine serves as a glutathione precursor, which is the major antioxidant of the central nervous system. The NMDA receptor is sensitive to reduction-oxidation reactions (redox), where reduction of redox sites increases and oxidation decreases NMDA-mediated activity.[12] Glutathione helps to regulate this balance by mitigating oxidative stress from free radical compounds, thereby reducing oxidation-mediated NMDA receptor hypofunction. N-acetylcysteine also serves as an L-cysteine derivative, which is a substrate for the glial cysteine-glutamate antiporter.[13] Cysteine binding at this antiporter leads to increased extrasynaptic glutamate, helping to regulate glutamatergic neurotransmission through negative feedback.[14]

Initial clinical studies[15-17] involving NAC supplementation in schizophrenia focused on glutathione and redox dysregulation as an etiology for oxidative stress in schizophrenia and sought to quantify glutamatergic functioning in patients with schizophrenia and the impact of NAC supplementation. Researchers[15-17] used electroencephalogram measurements to characterize associations with NMDA-receptor functioning. Findings suggested that, compared to sex- and age-matched controls, NAC supplementation improved NMDA receptor function. Lavoie et al[15] postulated that modulating glutathione levels might serve as a promising approach although their studies were not powered to detect a difference in clinical symptom presentation.

Antipsychotic medications have been in use for more than 50 years, yet only about 70% of patients respond to antipsychotic monotherapy with a 20% symptom reduction.[18] Current therapies do not robustly or consistently improve negative symptoms of schizophrenia, which impair function and significantly influence morbidity and mortality.[19] Despite ongoing study of novel and repurposed compounds targeting specific symptom domains, there is a need to improve the disposition of this vulnerable population. The purpose of this review is to assess and apply grading of recommendations assessment, development and evaluation (GRADE) methodology to the evidence informing use of NAC as adjunctive therapy to standard treatments in patients with schizo-

phrenia targeting positive, negative, or cognitive symptom domains.

Methods

A literature search was performed through query of PubMed, Web of Science, and EBSCOHOST for randomized controlled trials assessing treatment of schizophrenia with NAC using the keywords *N-acetylcysteine* or *NAC* and *schizophrenia*. All randomized controlled trials published in peer-reviewed literature using human participants were included without date specification and limited to English language. The National Library of Medicine's (NLM) clinical trials database was reviewed to capture unpublished data sources and provide discussion on pending research on this topic. Query of NLM's database was performed similar to the aforementioned search criteria.

Emphasis was given to the change in symptom severity assessed using the positive and negative symptom scores of the Positive and Negative Syndrome Scale (PANSS). Clinical outcomes were compared to treatment response criteria, which posits a change of 20% as the minimum that can be routinely detected.[3] Additionally, clinical assessments of cognition were reviewed. Tolerability of NAC intervention was characterized by prevalence of adverse events, and total discontinuations for any reason were included.

We assessed the quality of evidence informing the role of NAC in schizophrenia treatment by using the GRADE framework via GRADEpro GDT online software.[20] We utilized GRADE as a systematic approach to analyze available evidence and postulate recommendations based on the certainty of evidence gathered. Certainty is influenced by risk of bias, imprecision, inconsistency, indirectness, and publication bias. Through assessment of GRADE criteria in developing clinical recommendations, we aimed to provide a reproducible and transparent framework for our conclusions. The outcomes of GRADE are interpreted in the context of the certainty of evidence and the clinical outcomes in relation to symptom response.

Results

Three randomized controlled trials[21-23] with 2 post hoc subgroup analyses from 1 of the trials were identified. Summaries of the literature findings are collated in Table 1.

The first randomized controlled trial was conducted by Berk and colleagues[21] to evaluate the safety and effectiveness of oral NAC as an adjunct to maintenance medication for the treatment of chronic schizophrenia. This multicenter, double-blind study randomized 69 patients to NAC 1 g twice daily and 71 patients to matching placebo for 24 weeks concomitant with usual care. Patients were included if they were on antipsychotic therapy and presented with a PANSS total score of at least 55 or at least 2 of the positive and/or negative items being 3 or having a Clinical Global Impression of Severity score $\geq$3. Patients were excluded if they had other significant systemic medical disorders or were on a concurrent mood stabilizer (lithium or anticonvulsant) or another current antioxidant therapy.

Participation at week 24 was achieved by 42 of the NAC and 42 of the placebo-allocated participants. Predominate antipsychotic therapy was clozapine (45%) or olanzapine (20%), and there were no baseline differences between intervention cohorts. Mean (SD) age was 36.6 years ($\pm$10.9), duration of illness was 12.2 years ($\pm$8.9), and sex distribution was 70% men among all participants. Baseline PANSS positive and negative scores were 15.9 ($\pm$5.3) and 16.9 ($\pm$6.2) for placebo and 16.4 ($\pm$5.5) and 15.1 ($\pm$6.1) for the NAC-treated group. The least squares mean difference in PANSS negative symptoms at week 24 was 1.8 ($\pm$1.5) between NAC and placebo ($P < .05$). The effect size for this difference was 0.52 (95% confidence interval: 0.17-0.88). At week 28, after 4 weeks of washout, no difference persisted between groups in negative symptom scores. The mean score difference for positive symptoms was 0.5 ($\pm$1.6), which was not significant. The authors stated that "no effects on cognition were seen in the subset of subjects that received cognitive assessment."[21(p365)]

The second trial was conducted by Farokhnia and colleagues[22] to evaluate the safety and effectiveness of oral NAC as an adjunct to risperidone treatment in an inpatient population with active phase schizophrenia. This multicenter, double-blind study randomized 23 patients to NAC 1 g daily for 1 week then titrated to twice daily and 23 patients to matching placebo over an 8-week treatment period. Eligibility included a minimum score of 60 on the PANSS and 20 on the PANSS negative score with at least 2 years of illness duration. Patients were excluded if they presented with any other psychiatric or substance use disorder, serious medical comorbidity, additional psychiatric medication use, or any recent antipsychotic or electroconvulsive therapy use prior to enrollment.

Two patients from each group dropped out before study end due to either withdrawal of consent or previously undisclosed substance use. There was no significant difference in baseline characteristics reported between groups. Mean (SD) age was 32.2 ($\pm$6.1) versus 33.4 ($\pm$7.0) years in NAC and placebo groups, respectively, with even

TABLE 1: Summary of randomized trial literature

Study	Intervention	N	Findings
Berk et al[21] (2008)	NAC 1 g twice daily vs placebo for 28 wk	140	In predominately clozapine- or olanzapine-treated patients with chronic schizophrenia: • PANSS negative scores improved, which was no longer evident at 4 wk post-NAC discontinuation • PANSS positive scores were not different between intervention groups • No effects on cognition were seen in the subset of subjects that received cognitive assessment
Farokhnia et al[22] (2013)	NAC 1 g daily for 1 wk then twice daily vs placebo for 8 wk	42	Among inpatients concomitantly initiated on risperidone for treatment of active phase schizophrenia: • A significant improvement was seen in PANSS negative scores • No change found in PANSS positive scores • No assessment of cognition was performed
Sepehrmanesh et al[23] (2018)	NAC 600 mg twice daily vs placebo for 12 wk	84	In patients with chronic schizophrenia but not managed on clozapine: • PANSS positive and negative scores were significantly improved • Improved cognitive assessment scores were noted

NAC = N-acetylcysteine; PANSS = Positive and Negative Syndrome Scale.

sex distribution. Similarly, duration of illness was 6.9 (±3.4) versus 7.4 (±3.7) years. Baseline PANSS positive and negative scores were 32.3 (±5.5) and 27.3 (±6.1) for placebo and 30.2 (±3.7) and 27.4 (±4.4) for the NAC-treated group. Greater decrease in negative symptoms was characterized in the NAC group with a mean difference at week 8 of 6.6 (95% confidence interval: 4.1-9.1; $P < .01$). This was not found for positive symptoms with a mean difference of –0.9 (±3.4). Multivariate linear regression revealed that NAC treatment assignment was the strongest predictor of negative symptom score reduction compared to patient variables or changes in other scaled assessment scores.

Most recently, a trial conducted by Sepehrmanesh and colleagues[23] sought to evaluate the clinical effects of lower dose oral NAC as an add-on to maintenance medication in the outpatient management of chronic schizophrenia. Investigators performed a single-center, double-blind trial that randomized 42 patients to NAC 600 mg twice daily and 42 patients to matching placebo over a 12-week treatment period. Inclusion criteria included a minimum score of 55 on the PANSS with at least 2 years of illness duration. Reasons for exclusion included any additional psychiatric diagnosis, other neurologic or organic illnesses, intelligent quotient of <70 based on clinical judgment, additional antioxidant supplementation, additional psychiatric medication use, and clozapine-managed patients.

Two patients from the NAC and 3 from the placebo cohorts dropped out of study due to withdrawal of consent. Mean (SD) age was 38.7 (±1.9) versus 39.4 (±2.2) years in NAC and placebo groups, respectively, with similar sex distribution. Duration of illness was 13.5 (±9.9) years in the treatment group versus 17 (±11.5) in placebo. Notable baseline differences between groups included residence, where the NAC cohort was more likely to be urban-dwelling (65%) versus those on placebo (43.6%). Significant differences in baseline PANSS total and scores were characterized. NAC-treated patients had a mean PANSS positive score of 22.9 (±10.8) and a negative score of 30.4 (±7.3), whereas placebo had a positive score of 17.7 (±5.8) and a negative score of 26.5 (±6.2). At 12 weeks, inversion of mean negative symptoms scores was reported between NAC (23.8) and placebo (27.1) groups. Positive symptom scores were 21.9 and 17.6 for NAC- and placebo-treated patients at 12 weeks, respectively. Neither data distribution nor mean differences were reported. This limited our GRADE analysis to a focus on the certainty of the data as it was not possible to aggregate the effect size from NAC intervention on clinical outcomes due to these data omissions. The authors reported results from their ANOVA test for between-group differences of negative symptoms ($F = 0.2$, $df = 1$, $P = .65$) and positive symptoms ($F = 5.47$, $df = 1$, $P = .02$). Also reported were improvements in mean cognitive function score using the mini-mental status exam, digit span test (forward and backward), digit symbol substitution test, and Stroop test (letter and color); all significant ($P < .01$).

The 3 clinical trials[21-23] reviewed did not show between-group differences in reported adverse drug events. Data

TABLE 2: Summary of grading of recommendations assessment, development and evaluation (GRADE) analysis in randomized trials

	Certainty Assessment				
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Certainty
Negative symptom domain (follow up: range 8 to 24 wk; assessed with PANSS negative score)					
3	Serious[a]	Serious[b]	Not serious	Not serious	++○○ Low
Cognition symptom domain (follow up: range 12 to 24 wk; assessed with various scales)					
2[c]	Not serious	Serious[d]	Not serious	Serious[e]	++○○ Low
Positive symptom domain (follow up: range 8 to 24 wk; assessed with PANSS positive score)					
3	Serious[f]	Not serious	Not serious	Not serious	+++○ Moderate
Treatment attrition for any reason (follow up: range 8 to 24 wk; assessed with all-cause discontinuation)					
3	Not serious	Serious[g]	Not serious	Not serious	+++○ Moderate

PANSS = Positive and Negative Syndrome Scale.

[a]Selective reporting and incomplete outcomes data in study by Sepehrmanesh et al[23]; did not include prespecified between-group differences in mean PANSS score changes at trial end point. Instead, included findings with *F* statistic from ANOVA. No SD reported with mean PANSS score, yielding inability to complete *t* test analysis through independent investigator using summarized data.

[b]Although consistency of findings were reported among all 3 trials,[21-23] the statistics provided by Sepehrmanesh et al[23] did not show a between-group difference as stated in the text. So evidence is lacking to state that all 3 studies were consistent in finding.

[c]Publications by Berk et al[21] and Sepehrmanesh et al[23] evaluated for cognitive symptom improvement.

[d]Berk et al[21] found no differences in subgroup of patients analyzed, whereas Sepehrmanesh et al[23] found benefits with N-acetylcysteine across all cognitive function assessments.

[e]Cannot assess magnitude of effect given published data from Sepehrmanesh et al[23] and unable to assess sample size in each group within Berk et al[21] study, which was likely not powered to detect a difference.

[f]Selective reporting and incomplete outcomes data in study by Sepehrmanesh et al[23]; did not include prespecified between-group differences in mean PANSS score changes at trial end point. Instead, included findings with *F* statistic from ANOVA. No SD reported with mean PANSS score, yielding inability to complete *t* test analysis through independent investigator using summarized data.

[g]Large variability in reported drug reactions and discontinuations between studies.

available from these trials on adverse events secondary to NAC intervention were pooled for concise review. Adverse events from the placebo group were similarly reported. Abdominal discomfort or indigestion occurred most often in both NAC (25.7%) and placebo (20%) treated groups although the study by Farokhnia and colleagues[22] did not assess for this specifically. Nausea (16.9% vs 16.8%) and diarrhea (17.7% vs 11.5%) were also often reported for NAC versus placebo, respectively. Overall, discontinuation of treatment for any reason was similar between groups with study retention across trials at 76.9% for NAC and 75% for placebo groups. The most common reasons for attrition were withdrawal of consent, nonadherence to intervention or placebo, or change to maintenance psychiatric medication.

The GRADE analysis resulted in a low level of certainty in findings concerning the impact of NAC on negative and cognitive symptoms in patients with schizophrenia. There was a moderate level of certainty in the findings related to treatment attrition and the lack of benefit of NAC for positive symptoms. Data aggregation and effect size assessment were excluded from the GRADE analysis due to issues in the reporting of data. Collated results from GRADE are provided in Table 2.

Discussion

Overall, the literature evaluating adjunctive NAC in schizophrenia is limited to a few clinical trials with significant heterogeneity, making inferences from this data difficult. Notably, negative symptoms were the only domain reported across studies to improve with NAC supplementation. When evaluating any improvement seen in PANSS scores, extrapolation of response criteria may be appropriate to characterize the significance of any reported improvements seen in the literature. Response to therapy is characterized by a 20% decrease in severity of symptoms in patients with schizophrenia. Comparing mean score changes on the PANSS negative score in the Berk et al,[21] Farokhnia et al,[22] and Sepehrmanesh et al[23] publications, NAC intervention yielded a 11.9%, 24.1%, and 23.7% decrease in negative symptoms compared to placebo, respectively. Although differences between the studies are extensive in terms of baseline negative symptoms, phase of illness, and antipsychotic treatment, these mean changes are somewhat comparable to what would be considered treatment response. No benefit was shown in positive symptom reduction across studies. These findings indicate a potential niche for NAC in targeting negative symptoms in patients with schizophrenia.

Certainty assessment from the GRADE analysis was used to inform the findings from the limited literature available. Interpretations of the aggregated effect size for the outcome differences were hampered by the lack of reporting in the Sepehrmanesh et al[23] study as previously discussed. Although the low level of certainty in the associated benefits of NAC is characterized here, the refractory nature of negative and cognitive symptoms in schizophrenia makes a compelling case for NAC utility in select patients. As current standards of care have little to no benefit on these symptom domains, small improvements from NAC supplementation may translate to significant improvements in functional capacity that may be deemed meaningful to patients or caregivers.

Post hoc analysis[24] of the data published by Berk and colleagues[21] attempted to further inform NAC's impact on cognitive symptoms. Among a sample of 58 patients randomized to placebo or NAC, working memory was significantly improved from baseline to end point in the NAC-treated group. However, these findings were not correlated with functioning, and no improvement was seen in the assessments of attention span and executive functioning; the sample was a combined cohort of patients with schizophrenia or bipolar disorder with psychotic symptoms from 2 similarly designed studies. Due to the limited findings and heterogeneity of study participants, this publication has few clinical applications.

Additional analysis[25] has proposed the potential for stage-specific employment of NAC. Data from Berk and colleagues[21] was stratified by duration of illness, showing that patients with schizophrenia of 20 or more years' duration had lower scores in all PANSS scores with significant differences reported for the total and PANSS positive scores. Notably, significant improvement in the Social and Occupational Functioning Assessment Scale (SOFAS) was shown when accounting for the use of NAC and longer duration of illness. Although the absolute change in SOFAS was small, any improvement in functioning in this cohort of patients with a longer duration of schizophrenia may yield meaningful outcomes in maintenance of patient independence, ability to accomplish activities of daily living, or level of care and support required.

Among the 3 randomized trials reviewed, the Berk et al[21] publication is likely the best reflection of adverse drug events with NAC. Sparse reporting of this in the outpatient study by Sepehrmanesh et al[23] and the inpatient study by Farokhnia et al[22] add inconsistency to our aggregated analysis of reported side effects. Indigestion was more commonly reported with NAC than placebo (39% vs 31%) as was diarrhea (25% vs 17%). These unpleasant events may promote nonadherence to NAC among a population with predisposed risk factors for nonadherence. However, reported adverse events in the placebo groups were consistently similar across studies, and there were no reports of adverse events resulting in patient morbidity or mortality. The low risk of harm from serious adverse drug events adds to the support for NAC use in patients who can tolerate this supplementation.

Review of NLM's clinical trials database yielded 4 clinical trials focused on supplementation of NAC in patients with schizophrenia and included or planned to include assessment of PANSS or cognitive function scores, had results pending or posted, and were not associated with the literature already reviewed. The NAC in Early Phase Schizophrenia Spectrum Psychosis trial[26] assessed NAC 1800 mg in the morning and 900 mg at night for 28 weeks of total therapy. Results posted in June 2017 include data on 41 of the 61 patients enrolled and did not yield differences in positive, negative, or cognitive symptom score reduction. As of December 2018, the Treatment of Cognitive and Negative Symptoms in Schizophrenia with N-acetylcysteine trial[27] is currently recruiting 40 participants to be randomized to either placebo or NAC 1200 mg twice daily for 8 weeks. The Pilot Trial of Acute N-acetylcysteine Effects on Working Memory and Other Cognitive Functions in Schizophrenia[28] included 28 participants randomized to NAC 1200 mg twice daily for 3 days then once daily for 2 days or matching placebo with subsequent crossover for the remaining 5 days. No statistical analyses were reported. A trial[29] of sodium benzoate and/or N-acetylcysteine added to treatment as usual in patients with early schizophrenia spectrum disorder had not yet started recruiting at the time of this review but will randomize 64 patients to sodium benzoate 1 g daily and/or NAC 1 g twice daily or placebo for 12 weeks. Additionally, a published protocol[30] was also gathered that outlined a double-blind, randomized, controlled trial targeting negative symptoms in patients with documented clozapine-resistant schizophrenia.

Reviewing product formulation is necessary when considering NAC initiation. Prescription liquid products that may be administered orally are available. These may prove difficult to administer for patients who manage their own medications as compared to an oral tablet and may not be covered by insurance outside of use for acetaminophen toxicity. An effervescent prescription tablet is also available but is often costlier than the liquid preparations, is only available in 500 and 2500 mg tablets, and is indicated for the treatment of acetaminophen toxicity. There are nonprescription, oral, over-the-counter options that may be more reasonable to use and provide significant cost savings for institutions willing to vet the manufacturer and product quality. The studied twice-daily dosing regimen represents a consideration for adherence concern in patients who manage their own medications.

Several limitations of the existing literature are present that should be noted for interpretation of this review and the GRADE analysis reported. Significant heterogeneity in antipsychotic treatment, stage of illness, treatment setting, and severity of baseline PANSS symptoms are present between studies. Inconsistency of data reporting has been noted in the outcome findings from the publication by Sepehrmanesh and colleagues[23] and in the prevalence of adverse drug event reporting in the publications by Sepehrmanesh et al[23] and Farokhnia et al.[22] Although reduction in negative symptoms was consistently reported across studies, these findings were not correlated with functional improvement in the randomized trials, a more meaningful patient outcome. Due to data reporting, results from the 3 randomized trials could not be aggregated to assess effect size of the intervention on outcomes. Therefore, the certainty assessment of GRADE was used as an objective method of characterizing the quality of existing literature and its findings.

Corroborating evidence suggests some benefit of NAC treatment on negative symptoms in short-to-medium-length treatment trials. The common dose studied has been 1000 mg twice daily although this is not standardized across all trials, and no study has evaluated a dose response relationship or optimal effectiveness dose. Although certainty in the findings of benefit is low, NAC may have unique benefits in specific subgroups of patients with schizophrenia. Further research is investigating NAC targeting negative symptoms in clozapine-resistant patients, which should yield further insight. GRADE assessment of the current evidence indicates a low certainty of benefit for negative symptoms with standard use of NAC in patients with schizophrenia. However, a trial of this low-risk intervention may be warranted in patients with resistant negative symptoms and subsequent impaired functioning despite being on appropriate antipsychotic therapy as they may experience additional benefit in this symptom domain.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). Arlington (VA): American Psychiatric Association; 2013.
2. Bobes J, Arango C, Garcia-Garcia M, Rejas J. Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. J Clin Psychiatry. 2010;71(3):280-6. DOI: 10.4088/JCP.08m04250yel. PubMed PMID: 19895779.
3. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJM, Birnbaum ML, et al. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am J Psychiatry. 2017;174(3):216-29. DOI: 10.1176/appi.ajp.2016.16050503. PubMed PMID: 27919182; PubMed Central PMCID: PMC6231547.
4. Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull. 2010;36(1):94-103. DOI: 10.1093/schbul/sbp130. PubMed PMID: 19955388.
5. Saarni SI, Viertiö S, Perälä J, Koskinen S, Lönnqvist J, Suvisaari J. Quality of life of people with schizophrenia, bipolar disorder and other psychotic disorders. Br J Psychiatry. 2010;197(5):386-94. DOI: 10.1192/bjp.bp.109.076489. PubMed PMID: 21037216.
6. Barnes TRE, Leeson VC, Mutsatsa SH, Watt HC, Hutton SB, Joyce EM. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. Br J Psychiatry. 2008;193(3):203-9. DOI: 10.1192/bjp.bp.108.049718. PubMed PMID: 18757977; PubMed Central PMCID: PMC2576506.
7. Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease—a non-systematic review of epidemiology, possible causes, and interventions. Front Psychiatry. 2014;5:137. DOI: 10.3389/fpsyt.2014.00137. PubMed PMID: 25309466.
8. Laursen TM, Wahlbeck K, Hällgren J, Westman J, Ösby U, Alinaghizadeh H, et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. PLoS One. 2013;8(6):e67133. DOI: 10.1371/journal.pone.0067133. PubMed PMID: 23826212; PubMed Central PMCID: PMC3691116.
9. Ackenheil M. Differing response to antipsychotic therapy in schizophrenia: pharmacogenomic aspects. Dialogues Clin Neurosci. 2004;6(1):71-7. PubMed PMID: 22034253.
10. Buchanan RW. Persistent negative symptoms in schizophrenia: an overview. Schizophr Bull. 2007;33(4):1013-22. DOI: 10.1093/schbul/sbl057. PubMed PMID: 17099070; PubMed Central PMCID: PMC2632326.
11. Goff DC. Drug development in schizophrenia: are glutamatergic targets still worth aiming at? Curr Opin Psychiatry. 2015;28(3):207-15. DOI: 10.1097/YCO.0000000000000152. PubMed PMID: 25710242.
12. Moghaddam B, Javitt D. From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology. 2012;37(1):4-15. DOI: 10.1038/npp.2011.181. PubMed PMID: 21956446.
13. Emiliani FE, Sedlak TW, Sawa A. Oxidative stress and schizophrenia. Curr Opin Psychiatry. 2014;27(3):185-90. DOI: 10.1097/YCO.0000000000000054. PubMed PMID: 24613987; PubMed Central PMCID: PMC4054867.
14. Kinon BJ, Chen L, Ascher-Svanum H, Stauffer VL, Kollack-Walker S, Zhou W, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. Neuropsychopharmacology. 2010;35(2):581-90. DOI: 10.1038/npp.2009.164. PubMed PMID: 19890258; PubMed Central PMCID: PMC3055392.
15. Lavoie S, Murray MM, Deppen P, Knyazeva MG, Berk M, Boulat O, et al. Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology. 2008;33(9):2187-99. DOI: 10.1038/sj.npp.1301624. PubMed PMID: 18004285.
16. Carmeli C, Knyazeva MG, Cuénod M, Do KQ. Glutathione precursor N-acetyl-cysteine modulates EEG synchronization in schizophrenia patients: a double-blind, randomized, placebo-controlled trial. PLoS One. 2012;7(2):e29341. DOI: 10.1371/journal.pone.0029341. PubMed PMID: 22383949; PubMed Central PMCID: PMC3285150.
17. Retsa C, Knebel J-F, Geiser E, Ferrari C, Jenni R, Fournier M, et al. Treatment in early psychosis with N-acetyl-cysteine for 6 months improves low-level auditory processing: pilot study. Schizophr

Res. 2018;191:80-6. DOI: 10.1016/j.schres.2017.07.008. PubMed PMID: 28711476.
18. Kinon BJ, Chen L, Ascher-Svanum H, Stauffer VL, Kollack-Walker S, Zhou W, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. Neuropsychopharmacology. 2010;35(2):581-90. DOI: 10.1038/npp.2009.164. PubMed PMID: 19890258; PubMed Central PMCID: PMC3055392.
19. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. Lancet Psychiatry. 2018;5(8):664-77. DOI: 10.1016/S2215-0366(18)30050-6. PubMed PMID: 29602739.
20. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6. DOI: 10.1136/bmj.39489.470347.AD. PubMed PMID: 18436948; PubMed Central PMCID: PMC2335261.
21. Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. Biol Psychiatry. 2008;64(5):361-8. DOI: 10.1016/j.biopsych.2008.03.004. PubMed PMID: 18436195.
22. Farokhnia M, Azarkolah A, Adinehfar F, Khodaie-Ardakani M-R, Hosseini S-M-R, Yekehtaz H, et al. N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: a randomized, double-blind, placebo-controlled study. Clin Neuropharmacol. 2013;36(6):185-92. DOI: 10.1097/WNF.0000000000000001. PubMed PMID: 24201233.
23. Sepehrmanesh Z, Heidary M, Akasheh N, Akbari H, Heidary M. Therapeutic effect of adjunctive N-acetyl cysteine (NAC) on symptoms of chronic schizophrenia: a double-blind, randomized clinical trial. Prog Neuropsychopharmacol Biol Psychiatry. 2018;82:289-96. DOI: 10.1016/j.pnpbp.2017.11.001. PubMed PMID: 29126981.
24. Rapado-Castro M, Dodd S, Bush AI, Malhi GS, Skvarc DR, On ZX, et al. Cognitive effects of adjunctive N-acetyl cysteine in psychosis. Psychol Med. 2017;47(5):866-76. DOI: 10.1017/S0033291716002932. PubMed PMID: 27894373.
25. Rapado-Castro M, Berk M, Venugopal K, Bush AI, Dodd S, Dean OM. Towards stage specific treatments: effects of duration of illness on therapeutic response to adjunctive treatment with N-acetyl cysteine in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2015;57:69-75. DOI: 10.1016/j.pnpbp.2014.10.002. PubMed PMID: 25315856.
26. National Library of Medicine. N-acetyl-cysteine (NAC) in early phase schizophrenia spectrum psychosis (NACPSY). National Institutes of Health [cited 2018 May 23]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01354132?term=n-acetylcysteine&cond=Schizophrenia&rank=6&view=results
27. National Library of Medicine. Treatment of cognitive and negative symptoms in schizophrenia with N-acetylcysteine (NAC2). National Institutes of Health [cited 2018 May 23]. Available from: https://clinicaltrials.gov/ct2/show/NCT02505477?term=n-acetylcysteine&cond=Schizophrenia&rank=3
28. National Library of Medicine. A pilot trial of acute N-acetylcysteine effects on working memory and other cognitive functions in schizophrenia (NAC). National Institutes of Health [cited 2018 May 23]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT01232790?term=schizophrenia&cond=n-acetyl+cysteine&rank=1
29. National Library of Medicine. Sodium benzoate and/or N-acetylcysteine added to TAU in patients with early schizophrenia spectrum disorder. National Institutes of Health [cited 2018 May 23]. Available from: https://clinicaltrials.gov/ct2/show/NCT03510741?term=schizophrenia&cond=n-acetyl+cysteine&rank=5
30. Rossell SL, Francis PS, Galletly C, Harris A, Siskind D, Berk M, et al. N-acetylcysteine (NAC) in schizophrenia resistant to clozapine: a double blind randomised placebo controlled trial targeting negative symptoms. BMC Psychiatry. 2016;16(1):320. DOI: 10.1186/s12888-016-1030-3. PubMed PMID: 27629871.