Effects of 12-month, double-blind N-acetyl cysteine on symptoms, cognition and brain morphology in early phase schizophrenia spectrum disorders

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ABSTRACT

Background: Currently approved medications for schizophrenia are relatively ineffective for negative symptoms and cognitive impairment. N-Acetyl Cysteine (NAC) is a neuroprotective agent that improved general symptoms, cognitive impairment and negative symptoms in some but not all studies, but failed to improve positive symptoms in patients with schizophrenia. Progressive brain mass loss (PBML) has been consistently observed in early phase schizophrenia. NAC mitigates the deleterious effects oxidative stress, inflammation and glutamatergic excitotoxicity and these three pathological processes are hypothesized to contribute to PBML.
Methods: In this study, we assessed the effects NAC (3600 mg/day) in a 52-week, double-blind, placebo controlled trial on symptoms, and cognition in early phase schizophrenia spectrum disorders (N = 60). In the context of the clinical trial, we explored the effects of NAC on brain morphology.
Results: NAC significantly improved (time × group) PANSS total (F = 14.7, p < 0.001), negative (F = 5.1, p = 0.024) and disorganized thought (F = 13.7, p < 0.001) symptom scores. NAC failed to improve PANSS positive symptoms and BACS cognitive scores. In preliminary analyses, baseline right (r = −0.48, p = 0.041) and left (r = −0.45, p = 0.018) total cortical thickness, and thickness in other cortical regions, were associated with NAC related improvement in PANSS total scores, but NAC, as compared to placebo, did not significantly impact brain morphology over the study treatment period.
Conclusions: These results replicate some but not all previous findings of NAC efficacy. Preliminary results suggest that NAC's symptom effects may be related to structural integrity, but NAC failed to demonstrate treatment effects on longitudinal measures of brain morphology.
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1. Introduction

Existing pharmacologic treatments for schizophrenia spectrum disorders, primarily first- and second-generation antipsychotic drugs (APDs), decrease psychotic symptoms but are relatively ineffective for negative symptoms and cognitive impairment (Buchanan et al., 2010). Negative and cognitive symptoms are core features of schizophrenia and contribute to the marked functional deficits and poor quality of life associated with this illness (Breier et al., 1991; Green, 1996; Green et al., 2004; Nuechterlein et al., 2004). In addition, the approved APDs have relatively similar mechanisms of action that involve modulation of key neurotransmitters such as dopamine and serotonin (Horacek et al., 2006), suggesting that therapeutic targets with novel mechanisms may be required to improve negative symptoms and cognitive impairment. Another shortcoming of exiting treatments for schizophrenia is their lack of disease modification. Progressive brain mass loss (PBML), demonstrated by reductions in cortical thickness, total gray and white matter volumes, and hippocampal volume is a hallmark pathophysiological finding in schizophrenia with particularly pronounced effects during the early stages of the illness (Andreasen et al., 2011; Arango et al., 2012; Cannon et al., 2015; Gogtay et al., 2004; Hulshoff Pol and Kahn, 2008; Hummer et al., 2016; Pantelis and Wood, 2009; Pantelis et al., 2005; Peters et al., 2010; van Haren and Kahn, 2016; Whitford et al., 2006). The causes of PBML are not known but oxidative stress (Keshavan et al., 1993), inflammation (Muller et al., 2015) and glutamatergic excitotoxicity (Olney et al., 1991; Tsai and Coyle, 2002) are among the leading hypotheses to account for it. There are no treatments

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that have proven to slow or halt PBML which represents an area of important unmet medical need.

N-acetyl cysteine (NAC) is a neuroprotective agent (O. Dean et al., 2011) with three novel mechanisms of action. First, it mitigates the deleterious effects of oxidative stress by contributing the precursor molecule cysteine for glutathione synthesis and thereby increasing glutathione levels during oxidative stress (Dringen and Hirrlinger, 2003). Second, NAC decreases neuro-inflammation by attenuating pro-inflammatory cytokine levels (Chen et al., 2008; Nascimento et al., 2010) that may damage neurons and glia (Beumer et al., 2012; Garcia-Bueno et al., 2014; Muller et al., 2015).Third, NAC regulates glutamatergic function by promoting intra- and extracellular glutamate exchange through the cysteine-glutamate antiporter (Baker et al., 2002). Thus, NAC has actions that align with key pathophysiological hypotheses of schizophrenia and potential causes of PBML,

In two double-blind, placebo-controlled trials in chronic schizophrenia, NAC demonstrated significant efficacy for total and negative symptoms, but not positive symptoms (Berk et al., 2008; Farokhnia et al., 2014). A recent third NAC trial, however, failed to demonstrate positive and negative symptom improvement (Conus et al., 2018). In addition, NAC has been shown to improve mismatch negativity (Lavoie et al., 2008) and low-level auditory processing (Retsa et al., 2018), which are measures of pre-attentive information processing and may be linked to cognitive impairment (Lavoie et al., 2008). Two recent NAC trials reported improvement in the cognitive domains of processing speed, which was related to negative symptoms (Conus et al., 2018), and working memory (Rapado-Castro et al., 2017). NAC has been consistently found to be safe and well tolerated in schizophrenia studies (Berk et al., 2008; Farokhnia et al., 2014).

The purpose of this study is to assess the therapeutic effects of NAC on total, negative, and positive symptoms, cognitive impairment and functioning in schizophrenia spectrum disorders. We will focus on the cognitive domains of processing speed and working memory in attempts to replicate earlier results (Conus et al., 2018; Rapado-Castro et al., 2017). We will also explore the effects of NAC on cortical thickness, total cortical gray and white matter volumes and hippocampal volume in the context of the clinical trial. These morphological indices were chosen because they are consistently reported as linked to the pathophysiology of schizophrenia and to demonstrate progressive changes in PBML studies as noted above. Lastly, safety and tolerability of NAC will be evaluated. Several noteworthy components of the study design were included, such as enrollment of only early phase patients who were within three years since illness onset. An early stage population may be more likely to achieve benefits from neuroprotective treatments because their illness is still actively evolving. Also, a 52-week treatment period was employed which may provide information about the durability of potential therapeutic effects. Finally, oral bioavailability of NAC is relatively low (4% to 10%) (Coles et al., 2018; Olsson et al., 1988) and we therefore elected to use a higher dose (3600 mg/day) than previously studied in schizophrenia.

2. Experimental/materials and methods

2.1. Site and subjects

The study was conducted at the Prevention and Recovery Center for Early Psychosis (PARC), which is part of Indiana University School of Medicine (IUSM) and the Eskenazi Health System. PARC provides full clinical services and is an active research clinic for young people (ages 16 to 30 years) in the early stages of a psychotic illness.

Subjects provided written consent and the research was approved by the IU Institutional Review Board. Subjects had a DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective or psychosis not otherwise specified, as determined by the Structured Clinical Interview for DSM-IV-TR (SCID-I/P Patient Edition) (First et al., 2002) and corroborated by family informants and medical records. Subjects were male or

female, between 16 and 35 years of age, and within three years of the first onset of a non-affective, non-substance use-induced psychosis. First onset was operationally defined as first emergence of psychotic symptoms coupled with evidence of seeking treatment. Antipsychotic drug cumulative doses prior to study enrollment and during the trial were represents as chlorpromazine equivalent doses (Woods, 2003). Exclusionary criteria included IQ < 70, current substance use disorders, pregnancy, serious medical disorders and inability to provide informed consent.

2.2. Study design and medication

The study design consisted of a 52-week, double-blind, 1:1 randomization to placebo or NAC (3600 mg/day). Study medication was added to stable doses of antipsychotic medications and administered twice per day in identical capsules. NAC was initiated at 600 mg/day and then increased over the first four weeks until a maximum dose of 3600 mg/day was achieved. NAC has been added to antipsychotic medications in previous studies without evidence of serious adverse events (Berk et al., 2008; Farokhnia et al., 2014). Subjects were maintained on the same antipsychotic agent for the duration of the trial unless a switch to a different agent was clinically indicated. Antipsychotic dose adjustments were permitted to maximize the clinical outcomes and subject retention. Compliance with study medications was assessed by pill counts at each visit. Adjunctive psychiatric medications that were deemed clinically necessary, such as mood stabilizers and antidepressants, were permitted. The study medication, both active compound and placebo, was produced by Vesta Pharmaceuticals, Inc., Indianapolis, Indiana, under Good Manufacturing Practice conditions. Compounds were contained in capsules identical for weight, shape, diameter, and thickness. Ongoing stability and microbial quality testing was completed by Advanced Botanical Consulting & Testing, Inc., Tustin, California, throughout the course of the study.

2.3. Assessments and schedule of events

Symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) with total score and three sub-scale scores defined by Marder et al. (1997) reflecting positive, negative and disorganized thought symptoms. Reliability on the PANSS was established with intra-class correlations between 0.85 and 0.93. Clinical Global Impression – Severity (CGI) (Guy, 1976) was used to quantify illness severity. These measures were administered at baseline and weeks 4, 12, 24, 36 and 52. Cognition was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). The BACS is a widely employed assessment battery that assesses 4 domains of cognition, including verbal memory, working memory, processing speed, and reasoning/problem solving. Developed as a brief and effective tool for assessing cognitive change in schizophrenia, the composite score has high test-retest reliability in both individuals with schizophrenia and healthy controls (ICCs N 0.80). In addition, the BACS was also selected due to it clear functional relevance, as evidenced by correlations between the composite score and measures such as independent living skills (r = 0.45), performance of everyday living skills (r = 0.56), and interview-based assessments of cognition (r = 0.48) (Keefe et al., 2006). The BACS and its four domains have also been shown to be sensitive to treatment effects (Bowie et al., 2012). The two cognitive domains that were improved by NAC in previous studies were working memory and processing speed which are both included in the BACS (Conus et al., 2018; Rapado-Castro et al., 2017) and will be a focus to attempt to replicate in this study. All BACS scores were corrected for norms based upon age and gender of participants (Keefe et al., 2004). Functioning was assessed with the Personal and Social Performance scale (PSP) (Morosini et al., 2000). Both the BACS and PSP were administered at baseline, and weeks 24 and 52. Symptom and neurocognitive raters were all masters- or doctoral-level clinicians with extensive