CNS Spectrums

www.cambridge.org/cns

Letter to the Editor

Cite this article: Naguy A, and Naguy C (2021). N-acetyl-cysteine in schizophrenia—there is more than meets the eyes! *CNS Spectrums* **26**(5), 446–447.
https://doi.org/10.1017/S1092852920001583

Received: 14 May 2020
Accepted: 02 June 2020

Author for correspondence:
Ahmed Naguy,
Email: ahmednagy@hotmail.co.uk

CAMBRIDGE UNIVERSITY PRESS

N-acetyl-cysteine in schizophrenia—there is more than meets the eyes!

Ahmed Naguy[1] and Camellia Naguy[2]

[1]Child/Adolescent Psychiatrist, Al-Manara CAP Centre, Kuwait Centre for Mental Health (KCMH), Shuwaikh, State of Kuwait, and [2]Private Psychiatric Practice, Alexandria, Egypt

Dear Editor,

N-acetylcysteine (NAC) is an acetylated derivative of cysteine, a sulfur-containing amino acid that has been long used as antidote for paracetamol overdose and commonly as a mucolytic.

NAC is a widespread, inexpensive nutraceutical sold over-the-counter and comes in different formulations. As complementary/alternative medicine (CAM) products are currently in vogue, NAC use in psychiatric practice is nowadays rife and trend of utilization is on the rise to address a multitude of indications with varying degrees of evidence-base. Efficacy, widespread availability, high tolerability, safety, and lack of abuse potential render NAC an appealing addition to the psychopharmacological armamentarium. Recently, heaps of data from neuroscience accrue speaking to the idea of a pluripotent molecule with an attractive composite mode of action that gained a foothold in psychopharmacotherapy.[1,2]

Given the unmet clinical needs in schizophrenia pharmacotherapy particularly, exploring novel agents with qualitatively distinctive mechanisms of action is a pressing desideratum. Herein, we would try to shed some light on the promising therapeutic potential of NAC in schizophrenia spectrum disorders while examining the extant evidence.

NAC is a precursor to the antioxidant glutathione. It has been demonstrated to attenuate both glutamergic and dopaminergic dysregulation, modulate neurotropic and inflammatory pathways, ameliorate mitochondrial dysfunction, inhibit oxidative stress, and protect against apoptosis—all lie at the core of etiopathogenesis of schizophrenia.[3,4] This portfolio might translate clinically into neuro-protective and pro-cognitive actions.[5]

NAC has an excellent safety profile; an oral dose as high as 10× 2800 mg was evaluated for safety in a clinical study with no major adverse effect reported. Mild gastrointestinal symptoms were the most common adverse effects reported in clinical trials.[6] One downside of NAC, although it does cross blood–brain barrier, might be the relative low bioavailability. One promising avenue of research may be to explore derivatives of NAC, such as N-acetylcysteine amide, which has been reported in preclinical studies to have higher permeability through cellular and mitochondrial membranes with increased central nervous system bioavailability compared to NAC.

A suggested dosing regimen (Naguy, Personal Communication): 600 mg bid × 7 days, then 1200 mg bid × 4 weeks, and then 3000 mg/d (divided as 1800 mg am and 1200 mg nocte with 10 hs apart).

We could locate three systematic reviews and meta-analyses in literature attesting to the efficacy of NAC in schizophrenia. Chen et al[7] included only two double-blind, placebo-controlled trials and found adjunctive NAC may be efficacious in reducing negative and general symptoms of schizophrenia. A meta-analysis by Zheng et al[8] that included three randomized control trials with 307 participants (NAC: 153 and placebo: 154) showed that NAC significantly improved total symptom scores in schizophrenia. Yolland et al[9] conducted a systematic review yielding seven studies meeting study criteria (randomized, placebo-controlled trials assessing specific psychotic and cognitive symptoms in patients with schizophrenia or first-episode psychosis); all had low risk of bias. Among the 440 patients, mean duration of illness was 6.4 years; NAC (600–3600 mg/d) or placebo was added to stable antipsychotic regimens. No benefits for any symptoms were noted at ≤8 weeks. However, at ≥24 weeks and at the studies' final timepoints, NAC was associated with large and significant beneficial effects on total and negative symptoms, but not on positive symptoms or general ones (a mix of positive, negative, cognitive, and mood symptoms). In the three studies measuring cognitive changes, NAC showed moderately positive effects on working memory (but not processing speed).

Apart from psychopathology, NAC was shown to have a moderate positive effect on akathisia in a randomized control trial after 24 weeks of treatment. If replicated these findings suggest that NAC may be effective as a neuroprotective strategy for akathisia and other extrapyramidal syndromes. Moreover, NAC supplementation has been shown to significantly decrease haloperidol-induced TD in rat models.[10]

Interestingly, NAC has been recently found to potentially prevent glucose metabolic disturbance by reshaping the structure of gut microbiota. This finding has been echoed in another study comparing NAC and metformin for metabolic and hormonal profiles in women with

polycystic ovary syndrome, where NAC outperformed metformin with better tolerability. These might open new venues to tackle antipsychotic-related metabolic syndrome.[11]

Recent preclinical study using a neurodevelopmental model of schizophrenia suggested that NAC may have promising effects in early stages of schizophrenia, at-risk mental state and prodroma phases preventing conversion to schizophrenia.[12]

NAC adjuventia of 600 mg/d has also been reported to help in TR schizophrenia.[13]

All-in-all, add-on NAC treatment in schizophrenia might span different symptom domains especially recalcitrant negative and cognitive domains, confer neuroprotection in early stages, halt progression of prodroma, mitigate antipsychotic neuro-metabolic derangements, and help with neuroleptic-resistant stages. It is an art rather than a science![14]

Disclosures. The authors do not declare any competing interests, financial affiliations, or conflicts within the past 36 months.

Ethical Approval. Ethics committee approval is not normally required in our institute for short communications.

References

1. Minarini A, Ferrari S, Galletti M, et al. N-acetylcysteine in the treatment of psychiatric disorders: current status and future prospects. *Expert Opin Drug Metab Toxicol*. 2017;**13**(3):279–292.
2. Nocito Echevarria MA, Andrade Reis T, Ruffo Capatti G, et al. N-acetylcysteine for treating cocaine addiction—a systematic review. *Psychiatry Res*. 2017;**251**:197–203.
3. Moodliar S, Naguy A. What's around the corner in the niche of psychopharmacotherapy of major depressive disorder? *Asian J Psychiatr*. 2019;**46**:13–14.
4. Dean O, Giorlando F, Berk M. N-acetylcyteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *J Psychiatry Neurosci*. 2011;**36**(2):78–86.
5. McCaddon A, Hudson PR, L-methylphonate, methylcobalmin, and N-acetylcysteine in the treatment of alzheimer's disease-related cognitive decline. *CNS Spectr*. 2010;**15**(1 Suppl 1)2–5.
6. BerK M, Jeavons S, Dean OM, et al. Nail-biting stuff? The effect of N-acetyl cysteine on nail-biting. *CNS Spectr*. 2009;**14**(7):357–360.
7. Chen AT, Chibnall JT, Nasrallah HA. Placebo-controlled augmentation trials of the antioxidant NAC in schizophrenia: a review. *Ann Clin Psychiatry*. 2016;**28**(3):190–196.
8. Zheng W, Zhang QE, Cai DB, et al. N-acetylcysteine for major mental disorders: a systematic review and meta-analysis of randomized controlled trials. *Acta Psychiatr Scand*. 2018;**137**(5):391–400.
9. Yolland CO, Hanratty D, Neil E, et al. Meta-analysis of randomised controlled trials with N-acetylcysteine in the treatment of schizophrenia. *Aust NZ J Psychiatry*. 2019;**54**(5):453–466
10. Salem H, Nagpal C, Pigott T, et al. Revisiting antipsychotic-induced akathisia: current issues and prospective challenges. *Curr Neuropharmacol*. 2017;**15**(5):789–798.
11. Zheng J, Yuan X, Zhang C, et al. N-Acetylcysteine alleviates gut dysbiosis and glucose metabolic disorder in high-fat diet-fed mice. *J Diabetes*. 2019;**11**(1):32–45.
12. Miyake N, Miyamoto S. Effectiveness of N-acetylcysteine in the treatment of schizophrenia. *Nihon Shinkei Seishin Yakurigaku Zasshi*. 2016;**36**(2):29–35.
13. Bulut M, Savas HA, Altindag A, et al. Beneficial effects of N-acetylcysteine in treatment-resistant schizophrenia. *World J Biol Psychiatry*. 2009;**10**(4 Pt2):626–628.
14. Koola MM. Antipsychotic-minocycline-acetylcysteine combination for positive, cognitive, and negative symptoms of schizophrenia. *Asian J Psychiatr*. 2019;**40**:100–102.

https://doi.org/10.1017/S1092852920001583 Published online by Cambridge University Press