In this edition of our newsletter, we highlight a recent article by Jacob Schor, ND, FABNO in which he discusses the utilization of N-Acetylcysteine as an adjunctive treatment for Schizophrenia.

N-Acetylcysteine is a widely known and utilized therapeutic agent with a wide spectrum of clinical applications and benefits:

- Acetaminophen toxicity and acute liver failure: the number one cause of acute liver failure in the United States.
- Influenza: whose victims are primarily aging individuals—three quarters of all flu-related deaths occur in the elderly
- Chronic obstructive pulmonary disease: the fourth-leading cause of death in the United States (includes emphysema and chronic bronchitis)
- Helicobacter pylori: the bacterial culprit behind stomach ulcers, and a potentially lethal pathogen closely linked to malignant gastric cancer, the second most frequent cause of cancer death worldwide
- Long relegated to infrequent use in unusual circumstances, the amino acid-derived compound N-acetyl cysteine (NAC) has drawn increased scientific attention
- NAC replenishes levels of the intracellular antioxidant glutathione (GSH), which is often deficient with advancing age and in chronic illness
- NAC also regulates expression of scores of genes in the pathways that link oxidative stress to inflammation
- These dual effects give NAC a unique role in the prevention and treatment of many common diseases, both acute and chronic
- NAC can protect against avian influenza and more common seasonal flu symptoms
- NAC reduces the frequency and duration of attacks of chronic obstructive pulmonary disease (COPD) and may slow the clinical course of idiopathic pulmonary fibrosis (IPF)
- NAC protects tissues from the effects of exercise-induced oxidative stress, adding value and safety to your workout
- NAC improves insulin sensitivity in people with some of the most difficult-to-treat metabolic disorders
- NAC blocks cancer development at virtually every step in the process, and through multiple mechanisms, making it an important cancer chemopreventive agent
- NAC fights the stomach infection Helicobacter pylori on two fronts, inhibiting the organism’s growth while reducing production of inflammatory cytokines that can lead to gastritis and cancer
Biotics offers a number of formulations which incorporate NAC:

**NAC (N-Acetyl-L-Cystine)**

**ADB5-Plus 90 tab**

**Bio-Detox Packs ACTIVATES AMPK!**

**Bio-Multi Plus 90T**

**BioProtect 90C ACTIVATES AMPK!**

**BioProtect Plus Activates AMPK! NEW!!**

**GSH-Plus NOW WITH AN NPN!**

**MCS CANADA (Metabolic Clearing Support)**

**Nutri-Clear NEW ADVANCED FORMULATION**

Regards,

Rob Lamberton

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Contributing Writer / Advisory Board Member:

[Nutricula: The Science of Longevity Journal](#)

[Healthy Organic Woman Magazine](#)
N-acetylcysteine as Adjunctive Treatment for Schizophrenia

Study finds benefits greater for participants with long-term illness

By Jacob Schor, ND, FABNO

About the Author

Jacob Schor ND, FABNO, is a graduate of National College of Naturopathic Medicine, Portland, Oregon, and now practices in Denver, Colorado. He served as president to the Colorado Association of Naturopathic Physicians and is now on the board of directors of both the Oncology Association of Naturopathic Physicians and the American Association of Naturopathic Physicians. He is recognized as a fellow by the American Board of Naturopathic Oncology. He serves on the editorial board for the International Journal of Naturopathic Medicine, Naturopathic Doctor News and Review (NDNR), and Integrative Medicine: A Clinician's Journal. In 2008, he was awarded the Vis Award by the American Association of Naturopathic Physicians. His writing appears regularly in NDNR, the Townsend Letter, and Natural Medicine Journal.

Reference

Rapado-Castro M, Berk M, Venugopal K, Bush Al, 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;3(57):69-75.

Design
A double-blind, placebo-controlled trial to investigate whether duration of illness was a factor in modulating the response to N-acetylcysteine (NAC).

**Participants**

The study included 121 participants who were randomized to receive placebo (n=62) or N-acetylcysteine (NAC; n=59) for 24 weeks. Participants were required to meet diagnostic criteria for schizophrenia (DSM-IV) and have either a Positive and Negative Symptom Score (PANSS) of ≥55 (range is 30 to 100) or a Clinical Global Impression-Severity (CGI-S) score ≥3 (range is 1 to 7). Both inpatients and outpatients were eligible. Participants needed to be currently taking an antipsychotic agent. Individuals who were taking a mood stabilizer (eg, lithium, valproate, carbamazepine) were excluded, as were those currently taking drugs known to prevent glutathione depletion (500+ mg of NAC per day, 200+ μg of selenium per day, or 500+ IU of vitamin E per day).

**Study Medication and Dosage**

Participants received 2 NAC (500 mg) capsules 2 times a day (for a total of 2 g a day) or matching placebo capsules.

**Outcome Measures**

Participants were assessed at baseline using a structured clinical interview (Mini International Neuropsychiatric Interview [MINI], DSM-IV) using various psychological assessment tools. Blinded investigators, who were all experienced clinicians, performed the assessments.

Efficacy measures were repeated every 2 weeks for the first 8 weeks or on the day of study termination if the participant withdrew prior to 8 weeks. After 8 weeks, evaluations were every 4 weeks until 24 weeks, when the treatment was stopped. Postdiscontinuation follow-up was held 4 (±2) weeks after completion to determine any change in participant status.

Duration of the illness at baseline was grouped into <10 years, 10-20 years, and >20 years and compared with outcome measures. Data from this same study cohort was first published in 2008.¹

**Key Findings**

Initial analysis of these data in 2008 reported that subjects treated with NAC improved more than placebo-treated subjects over the study period in PANSS total (P=0.009), PANSS negative (P =0.018), and PANSS general (P=0.035). Improvements were also reflected in CGI-S (P=0.004), and CGI-Improvement (P=0.025) scores. No significant change on the PANSS positive subscale was seen. NAC treatment also was associated with an improvement in akathisia (P=0.022) in the first published study. Effect sizes at endpoint were consistent with moderate benefits.
In this current paper analyzing the same data but comparing duration of illness with outcome, “an interaction between treatment group and duration was consistently found for positive symptoms [PANSS positive subscale: F2, 60=6.578; \( P=0.003 \) and PANSS total: F2, 60=4.308; \( P=0.018 \)] and functional variables (CGI): F2, 58=4.647; \( P=0.013 \), Global Assessment of Functioning Scale (GAF): F2, 59=5.848; \( P=0.005 \) and the Social and Occupational Functioning Assessment Scale (SOFAS): F2, 21=3.964; \( P=0.035 \).” In other words, the longer the patients had suffered from schizophrenia, the more improvement they experienced taking NAC.

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These changes were not what the investigators had predicted. Their assumption was that the effects of NAC would be greater in patients with more recent disease onset. The results were the opposite: The longer the history of illness, the greater the response.

**Practice Implications**

These results are a pleasant and welcome surprise.

The hypothesis of this study was that people with early stages of schizophrenia would derive more benefit from NAC; this idea was proven wrong. Instead, it seems that the longer participants had suffered from schizophrenia, the greater their benefit from taking NAC. We should note that these benefits only apply to the symptoms of the illness. NAC did not change the “extrapyramidal adverse events associated with treatment” (ie, the movement disorders from long-term use of treatment medications); it only improved the symptoms of schizophrenia itself.

About 1.1% of the general population suffers from schizophrenia, but it is long known that schizophrenia runs in families. Risk of the disease increases to 10% for people who have a first-degree relative with schizophrenia. For an identical twin of a person with schizophrenia, the risk increases to 40% to 65%.

NAC is derived from the amino acid cysteine and is widely available over the counter as a nutritional supplement promoted for its antioxidant properties. NAC is well-tolerated and safe; it has been widely used internationally for decades. NAC is used as an antidote for acetaminophen overdose and has been approved for this purpose by the FDA since 1985, given either orally or intravenously.

NAC is also used as a mucolytic agent in chronic obstructive pulmonary disease and cystic fibrosis, to protect the kidneys from damage from the contrast agents used in imaging studies, and as a preventive agent for atrial fibrillation. NAC can be used to prevent and treat seasonal
influenza virus infection.\textsuperscript{10} It is also used to favorably affect ovulatory dysfunction in women with \textit{PCOS}.

There has been growing evidence over the past 10 years that NAC is also useful in treating psychiatric and neurological disorders. It appears to moderate pathophysiological processes that are involved in a range of psychiatric and neurological disorders, including oxidative stress, neurogenesis and apoptosis, mitochondrial dysfunction, neuroinflammation, and dysregulation of glutamate and dopamine.\textsuperscript{11} NAC reverses the neuroadaptation and metaplasticity induced by cocaine addiction.\textsuperscript{12} The neuroadaptation theory of addiction suggests that exposure to drugs of abuse induces adaptive molecular and cellular changes in the brain that mediate addiction-related memories. Compared to other types of memories, addiction-related memories develop quickly and last for an extremely long time; the cellular and molecular processes that mediate addiction-related memories are exceptionally adept and efficient.\textsuperscript{13}

In the last few years numerous reports have been published regarding the use of NAC to treat a range of psychiatric or neurological conditions, including schizophrenia; bipolar disorder; skin picking; trichotillomania; obsessive-compulsive disorder; autism; gambling; addiction to nicotine, cannabis, cocaine, and methamphetamine; epilepsy; amyotrophic lateral sclerosis; neuropathy; and traumatic brain injury.\textsuperscript{14-15}

In a systematic review of NAC use in psychiatry and neurology published in August 2015, Deepmala et al evaluated and graded the level of evidence for the use of NAC in treating psychiatric and neurological disorders as it stood at the time. For now, this review article, particularly the summary tables, should stand as our go-to reference in these matters.\textsuperscript{16} The amount of NAC used in these trials typically ranged from 2.0 to 2.4 grams of NAC per day, administered orally and divided into 2 doses.

For those of us trained in naturopathic medicine back when NAC was used solely as a mucolytic agent, this new range of applications is quite fascinating.

This current paper by Rapado-Castro now suggests NAC may be of even greater utility after long-term psychiatric debility. This is even more fascinating, as NAC may provide benefit in conditions that we once might have thought too longstanding and too deeply ingrained to be ameliorated.

\textbf{References}
