The Interface

GETTING A KNACK FOR NAC: N-Acetyl-Cysteine

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

N-acetyl-cysteine, N-acetylcysteine, N-acetyl cysteine, and N-acetyl-L-cysteine are all designations for the same compound, which is abbreviated as NAC. NAC is a precursor to the amino acid cysteine, which ultimately plays two key metabolic roles. Through its metabolic contribution to glutathione production, cysteine participates in the general antioxidant activities of the body. Through its role as a modulator of the glutamatergic system, cysteine influences the reward-reinforcement pathway. Because of these functions, NAC may exert a therapeutic effect on psychiatric disorders allegedly related to oxidative stress (e.g., schizophrenia, bipolar disorder) as well as psychiatric syndromes characterized by impulsive/compulsive symptoms (e.g., trichotillomania, pathological nail biting, gambling, substance misuse). While the dosages, pharmacological strategies (monotherapy versus augmentation), and long-term risks are not fully evident, NAC appears to be a promising, relatively low-risk intervention. If so, NAC might be an ideal treatment strategy for a variety of psychiatric conditions in both psychiatric and primary care settings.

KEY WORDS

Antioxidants, NAC, N-acetylcysteine, N-acetyl-cysteine, N-acetyl-L-cysteine

INTRODUCTION

In this edition of The Interface, we discuss N-acetyl-cysteine, or NAC, a precursor to the amino acid cysteine. Through cysteine, NAC plays a notable metabolic role in the body's general antioxidant activities as well as in regulating the glutamatergic system (i.e., reward/reinforcement). Because of these functions, NAC may have a therapeutic influence on psychiatric syndromes that are either characterized by oxidative stress or impulsivity/compulsivity. In this article, we will review the basic characteristics of NAC, describe its metabolic pathway, and review available clinical case reports and studies of NAC in the field of psychiatry. Although the explicit role of NAC in various psychiatric syndromes as well as its long-term safety are not patently clear, this compound may have a promising future as either a monotherapy or an augmentation strategy in both psychiatric and primary care settings.

A PRIMER ON N-ACETYL-CYSTEINE PHARMACEUTICAL GRADE NAC

N-acetyl-cysteine, N-acetylcysteine, N-acetyl cysteine, and N-acetyl-L-cysteine are all designations for the same compound, which is collectively referred to as NAC. Pharmaceutical-grade NAC is primarily used in medical settings for respiratory conditions (i.e., as a mucolytic agent, Mucomyst™), to manage acetaminophen overdoses, and to prevent radio-contrast-induced nephropathy.[1] More recent investigations have explored the use of NAC in various psychiatric disorders.[1] NAC is available as an oral solution as well as intravenous and inhaled preparations.[2] The half-life of NAC is approximately 5.6 hours, and 30 percent of the drug is renally excreted.[2] With regard to side effects, oral or inhaled NAC has been associated with drowsiness, stomatitis, clamminess, rhinorrhea, and hemoptysis.[2] While side effects are generally mild, there are rare reports of renal stone formation during NAC treatment.[3] According to the United States Food and Drug Administration (FDA), NAC is a category B pregnancy risk.[2]

OVER-THE-COUNTER NAC

In addition to prescription availability, NAC is commercially accessible as an over-the-counter product and has been safely used as a supplement in humans for years (NAC is relatively rare in food).[4,5] Commercial NAC is available in 500-mg tablets and capsules, 600-mg tablets and capsules, 750-mg capsules, and 1000-mg tablets.[6]

THE METABOLIC ROLES OF NAC

NAC is an acetylated variant and precursor of the amino acid, L-cysteine.[7] Through the role of cysteine, NAC metabolically contributes to two key physiological functions: 1) antioxidant activity and 2) the regulation of the glutamatergic system.

Antioxidant activity. With regard to antioxidant activity, the cysteine component of NAC combines with glutamate and glycine, all of which are precursors in the production of glutathione.[8] In the production of glutathione, cysteine is the rate-limiting step.[5] Glutathione, in turn, is a major endogenous antioxidant.[3] In fact, it is the most generic cellular antioxidant in the body.[8] Because of its antioxidant activity, glutathione is essential for the immune system to exert its full potential. While glutathione is commercially available, its oral bioavailability remains controversial.[9] Therefore, its precursor, NAC, has been a more promising avenue to pursue in clinical investigations.[9]

In terms of clinical implications, oxidative stress has been empirically associated with a number of psychiatric disorders,[10] including schizophrenic[11] and bipolar, depressive, and anxiety disorders.[12] Therefore, NAC may be a useful intervention for these psychiatric disorders—a postulation that is now being supported by preliminary research.

Glutamatergic regulation. In addition to its role as a general antioxidant, NAC supplies cysteine as a front-end substrate for the glutamatergic system. In this important second metabolic role, NAC influences or modulates the glutamatergic system.[13] The glutamatergic system is related to reward-seeking repetitive behaviors (i.e., reward, reinforcement, and relapse).[13,14] These processes may contribute to psychiatric syndromes characterized by impulsive/compulsive behaviors, such as substance abuse and gambling. These two distinct metabolic pathways and their corresponding roles are outlined in Figure 1.

STUDIES OF NAC IN PSYCHIATRY

At the present time, rigorous studies on the efficacy of NAC in various psychiatric conditions are limited. However, there have been several clinical investigations of NAC, including case reports, open-label pilot studies, and double-blind placebo-controlled trials.

Schizophrenia. In a randomized, double-blind, crossover study of patients with schizophrenia, Lavoie et al[15] found that NAC, administered at 2g/day for 60 days, improved mismatch negativity. In another study of schizophrenic patients (N=84), Berk et al[16] undertook a randomized, double-blind, placebo-controlled trial and found that NAC, administered at 1g twice daily for 24 weeks, was a moderately effective augmentation strategy and resulted in improvement in the study scales assessing positive and negative symptoms as well as overall functioning.

Bipolar disorder. In another study by Berk et al,[17] NAC was administered to 75 depressed bipolar patients at 1gm twice daily for 24 weeks, in combination with medication as usual. In this randomized, double-blind, placebo-controlled trial of NAC as an augmentation strategy, the investigators noted significant improvements in the study scales assessing mood, global functioning, and social/occupational functioning.

Cocaine dependence. In an open-label study of 23 cocaine-dependent outpatients, Mardikian et al[18] examined the efficacy of NAC (dosed at 1200mg per day, 2400mg per day, and 3600mg per day) over a four-week study period. In terms of response, 70 percent of participants either significantly reduced or discontinued their use of cocaine.

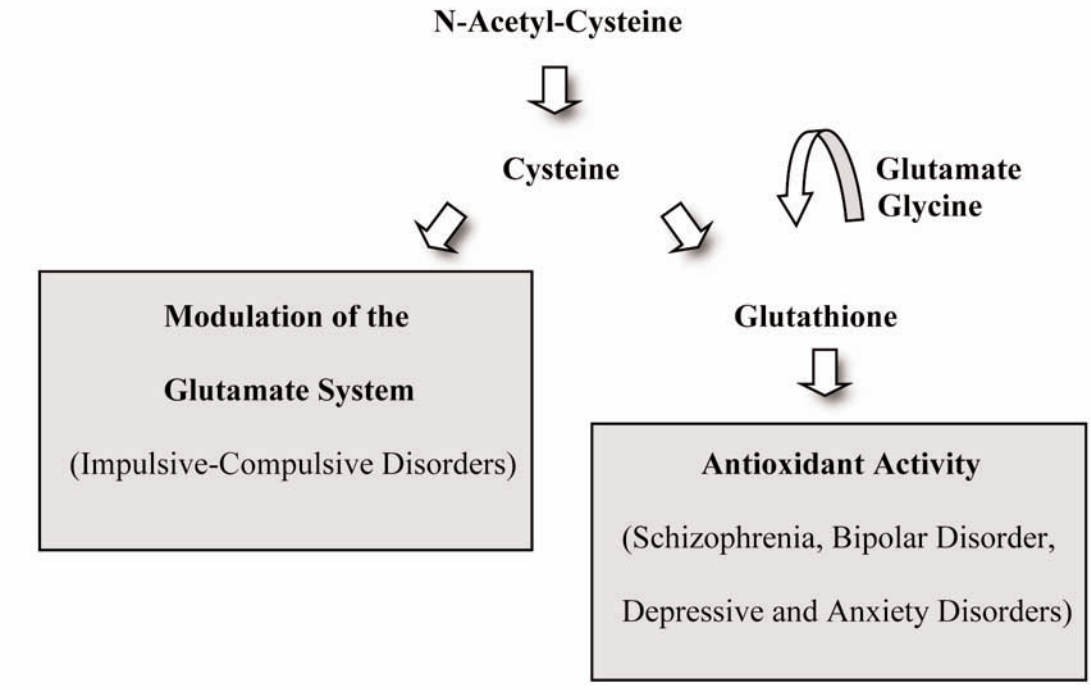

FIGURE 1. N-Acetyl-Cysteine and Its Postulated Metabolic Functions[5,10]

In a double-blind, placebo-controlled, cross-over study, LaRowe et al[19] examined the efficacy of NAC in 13 cocaine-dependent participants over a three-day period. Participants received a total dosage of 2400mg. During treatment with NAC, there were trends for a greater reduction in withdrawal symptoms and cocaine craving.

Trichotillomania. Odlaug and Grant[13] reported two cases of trichotillomania that responded to treatment with NAC. In the first case, a 28-year-old man with both nail-biting and trichotillomania responded after four weeks of treatment with NAC, at a dose of 1200mg/day. In the second case, a 40-year-old woman with trichotillomania responded after 10 weeks of treatment with NAC, at a dose of 2400mg/day.

In a 12-week, double-blind, placebo-controlled trial, Grant et al[20] examined the effectiveness of NAC on 50 patients with trichotillomania. NAC was dosed between 1200 and 2400mg/day. Compared with controls, patients taking NAC experienced a significant reduction in hair-pulling symptoms.

Pathological gambling. In a study of 27 pathological gamblers, Grant et al[21] undertook an open-label, eight-week, pilot study with NAC. In this study, the mean effective dose of NAC was approximately 1500mg/day. At the end of the study, 60 percent of participants met the criteria for response.

Smoking. In a four-week placebo-controlled study of nicotine-dependent smokers, Knackstedt et al[22] examined the effectiveness of NAC, which was administered at 2400mg/day. Participants taking NAC generally reported a reduction in the number of cigarettes smoked.

Pathological nail biting. In addition to the case described by Odlaug and Grant, Berk et al[23] described three cases of individuals who were in a bipolar disorder treatment protocol and responded to treatment with NAC for pathological nail biting. In the first case, a 46-year-old woman ceased nail biting after two weeks of treatment with NAC, dosed at 1000mg twice per day. In the second case, a 44-year-old woman reported the discontinuation of nail biting after four months of treatment with NAC, dosed at 1000mg twice daily. In the last case, a 46-year-old man reported a meaningful reduction in nail biting after exposure to NAC for 28 weeks (no dosage was indicated in this last case report).

Pathological skin picking. Odlaug and Grant[13] reported the case of a 52-year-old woman with pathological skin picking who responded to treatment with NAC, dosed at 1800mg/day, at Week 4 of exposure.

Animal studies. According to preliminary studies in animals, NAC may be effective in the treatment of heroin addiction[24] as well as in

reducing the adverse effects of alcohol.[25]

POTENTIAL RESEARCH CONFOUNDS WITH ANTIOXIDANTS

In addition to unresolved questions about the genuine bioavailability of antioxidants,[7,9] studies of these compounds may be plagued by a number of other potential confounds, as well. These include the presence of antioxidants that already exist in the body, making the benefits of administered antioxidants difficult to verify; the existence of contaminants in many natural substances; varying quality and grade of antioxidants;[26] and varying study doses as well as small studies.[7]

A CLINICAL PERSPECTIVE

Despite limited case reports and studies and our general caveats with regard to research confounds with antioxidants, NAC appears to be promising in a number of psychiatric syndromes—particularly those associated with oxidative stress (e.g., schizophrenia and bipolar disorder) and impulsive/compulsive symptoms (e.g., trichotillomania, pathological nail biting, gambling, and substance misuse). Because of the reported positive treatment outcomes, the high prevalence of these disorders in both psychiatric and primary care settings, and the low risk and good tolerability of NAC, the use of NAC as either a monotherapy or an augmentation strategy with conventional psychotropic medications seems to be a reasonable consideration. Only further research will clarify the ultimate effectiveness of NAC, the dosages that are most beneficial for a given psychiatric condition, the necessary duration of treatment, and any unforeseen risks with continuous long-term administration of the compound.

CONCLUSION

Via the generation of cysteine, NAC is a precursor to the general body antioxidant, glutathione, and plays a role in the regulation of the glutamatergic system (i.e., the regulation of reward, reinforcement, and relapse). In these roles, NAC may be a useful monotherapy or augmentation strategy for psychiatric disorders related to oxidative stress (e.g., schizophrenia and bipolar disorder) and/or psychiatric syndromes characterized by impulsive/compulsive symptoms (e.g., trichotillomania, nail biting, pathological hair pulling, substance misuse, and gambling). Preliminary case reports and clinical trials appear promising. Only further research will clarify appropriate dosing ranges, duration of treatment, and any unforeseen risks with long-term NAC administration. At present, NAC appears to be a compound worth watching—one that may, in the future, play a valuable role in both psychiatric and medical settings.

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