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Alternative use of the cough drug - N-acetylcysteine in psychiatry: a review of recent clinical trials

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Abstract

Introduction and purpose

N-acetylcysteine (NAC) is one of the more popular drugs, widely available in pharmacies, used to treat wet cough. NAC's diverse mechanism of action has drawn the attention of researchers for its great potential in the treatment of many conditions. Indeed, it has been noted that administration of NAC allows indirect modulation of the central nervous system, which may be important in the treatment of psychiatric diseases. The following review focuses on recent reports of NAC's potentially beneficial effects on psychiatric conditions such as depression, schizophrenia, obsessive-compulsive disorder, and addiction.

Description of the state of knowledge

Based on studies conducted on animals (rats), a positive effect of NAC has been proven, observing a reduction in the severity of depressive symptoms. Based on the above data, more and more human studies are being conducted, where the effect of NAC on the symptoms of various mental conditions is being investigated. In recent years, the antioxidant, anti-inflammatory and neurotransmitter function modulating effects of NAC on the brain have been proven, with significant potential in the treatment of mental illness.

Conclusions

The potential impact of NAC on the treatment of mental illness is a rapidly developing topic in recent years. On the basis of available scientific data, partial reduction of symptoms of mental illnesses through the use of NAC has been confirmed. It is a very promising drug, which in this indication requires additional studies to unequivocally confirm its beneficial effects on the functioning of the central nervous system.

Key words

N-acetylcysteine; glutathione; depression; schizophrenia; obsessive-compulsive disorder; addictions.

Introduction

N-acetylcysteine (NAC) is an acetylated precursor, a naturally occurring amino acid - L-cysteine, and is commonly known as one of the expectorant drugs used to treat bronchitis associated with the common cold. It exhibits mucolytic activity - it cleaves disulfide bonds in the glycoproteins of mucous secretions present in the respiratory tract, thus destabilizing their structure and reducing their viscosity. The secretion thus formed is more easily removed. In the above-mentioned indication, NAC is most often administered orally (*per os*, p.o.), but due to the first-pass effect through the liver, its bioavailability is very low (about 10%). Usually used at a dose of 600 mg per day for no more than 5 days, it provides relief from wet cough by facilitating expectoration of lingering respiratory secretions. Larger doses of NAC have found use in treating poisoning from one of the most popular painkillers - paracetamol. As an antidote to paracetamol, NAC binds and inactivates the toxic metabolites of paracetamol and allows the body to maintain normal levels of glutathione - a naturally occurring tripeptide

with antioxidant and detoxifying properties - thus protecting the liver from damage. For this purpose, it is administered intravenously (*in venam*, i.v.) in much higher doses of up to 30 g. (1)

Research into the mechanism of action of mucolytics has provided new insights into their mode of action. This is because the antioxidant properties of some drugs practiced in the treatment of cough have been proven. Thus, in addition to a direct effect on the dilution of thick mucus and improvement of mucociliary transport, mucolytics have an indirect effect, affecting the elimination of free radicals, which play an important role in the pathogenesis and maintenance of inflammation in many respiratory diseases, such as cystic fibrosis, idiopathic pulmonary fibrosis or acute respiratory distress syndrome (ARDS). The resulting effect thus determines the anti-inflammatory effect, accelerating the healing process. (2)

Mechanism of action

The likely array of positive consequences of NAC is attributed to its effect on increasing levels of glutathione, the main endogenous antioxidant (antioxidant) found in the human body. The effectiveness of glutathione supplementation is limited by the hydrolysis of this compound in the liver and intestines, so the increase in glutathione concentration is primarily possible indirectly. The positive effect of glutathione is determined, among other things, by neutralizing and removing reactive forms of oxygen and nitrogen - free radicals (oxidants). Under physiological conditions, free radicals are formed as a result of aerobic respiration processes and have a bactericidal, bacteriostatic function and are involved in signal transduction in the cell. Inflammatory processes, metabolism of certain drugs, ultraviolet radiation, stress and tobacco use cause rapid and uncontrolled formation of free radicals. Occurring in excess, they instantly react with cellular structures and - causing unwanted effects - gradually lead to increasing oxidative stress, i.e. degenerative processes in the body. Free radicals most often damage the walls of blood vessels and contribute to cardiovascular diseases such as atherosclerosis. In addition, they also commonly attack the brain, which, according to researchers, can underlie the occurrence of psychiatric (depression, schizophrenia, obsessive-compulsive disorder) and neurodegenerative diseases (Alzheimer's disease, Parkinson's disease). Radicals in the body are also the cause of DNA degradation, so they are also responsible for premature aging processes and induce the occurrence of autoimmune diseases and cancer. Eliminating excess free radicals, referred to as "scavenging," allows the body to maintain a balance between radicals and antioxidants, which

quickly react with radicals, converting excess radicals into inactive derivatives or lowering their concentration. In this way, oxidative homeostasis is maintained. (3)

Administration of NAC leads to a change in the concentration of L-cysteine in the body and allows modulation of the levels of neurotransmitters such as glutamate and dopamine. Glutamate is the predominant form of glutamic acid under physiological conditions, which is a component of glutathione described earlier. L-cysteine enhances neuronal regulation and regulates the flow of glutamate both inside and outside of cells through the use of a special transporter located preferentially on glial cells in neural tissue. The available amount of L-cysteine can adequately regulate glutamate levels, which, among other things, affects the proper functioning of the central nervous system (CNS), coordinating memory processes and learning skills. In addition, NAC affects dopaminergic metabolism and regulates dopamine levels, which is promising in the context of addiction therapy. (4)

NAC is also characterized by anti-inflammatory properties. NAC has been shown to reduce the levels of cytokines associated with inflammatory processes: interleukin-6 (IL-6), interleukin-1 (IL-1β) and tumor necrosis factor (TNF-α). Modulation of the inflammatory response pathway may be indirectly linked to the antioxidant effects discussed earlier. Oxidative stress and changes in the levels of pro-inflammatory cytokines often underlie psychiatric disorders, so it has been hypothesized that the potential of NAC in psychiatry could be exploited. (5,6)

Psychiatry

Due to its documented antioxidant properties, modulating glutamate function and anti-inflammatory effects, NAC has become a focus of research for its effects on the CNS. A number of preclinical and clinical studies have examined the correlation of NAC administration with its effects on the course of psychiatric disorders such as schizophrenia, depression, obsessive-compulsive disorder and substance abuse disorders. The increase in research interest has opened the floodgates for alternative therapies to help some mental illnesses. This work reviews the growing body of research evidence pointing to the promising properties of NAC. Preclinical and clinical studies on NAC conducted in recent years are summarized below. (7)

1. Depression

As one of the most common diseases worldwide, depression is a major cause of disability and inability to work. Patients rarely see a doctor, rarely receive adequate treatment, and the disease gradually limits their life activities The symptoms of depression can be

recurrent or chronic. The affected person loses enjoyment of life and takes a pessimistic view of his or her current situation. A volatile, irritable mood and indifference appear. Patients find it difficult to control their emotions, have difficulty in undertaking various activities; they lose their previous interests. They feel anxiety, a sense of hopelessness, have sleep disturbances, declines in libido or loss of appetite. (8)

The pathogenesis of depression involves a number of oxidative disorders, such as oxidative damage to erythrocytes, significant oxidative stress and elevated antioxidant enzyme activity in peripheral tissues. Standard antidepressant therapy results in a reduction of the elevated values. It has been suggested that NAC could benefit drug-resistant depression and induce antidepressant effects, partly as a result of alleviating oxidative stress by increasing glutathione levels. At the same time, NAC may exhibit anti-inflammatory properties and increase extracellular glutamic acid levels. (9)

One preclinical randomized controlled trial (RCT) examined Wistar rats in which depression was induced by removing the olfactory bulb, one of the most commonly used experimental models of depression. In this way, it is possible to induce certain depressive behaviors in the animals and relate them to similar symptoms found in humans. The rats were then given NAC at a dose of 2,000 mg/day for 12 weeks and subjected to forced swimming tests (the Porsolt test), which involves placing an experimental animal in a water-filled dish and measuring how long the animal remains motionless - antidepressants shorten this period. After 16 weeks (12 weeks of test drug administration and four weeks of follow-up - observation), a small but clinically significant improvement over placebo was proven. The results were tabulated with the Montgomery-Asberg Depression Rating Scale (MARDS), which is used in general psychiatry most often to assess the effect of antidepressants. Administration of NAC produced comparable effects to imipramine, which is considered the first fully effective antidepressant. Magnetic resonance imaging (MRI) spectroscopy showed significantly higher levels of glutamate-glutamine and N-acetylaspartate, making it clear which group of rats received NAC. Higher levels of the indicated transmitters indicate NAC administration-induced reduction of oxidative stress. (7,10,11)

A different result was obtained by conducting a human clinical trial, where the effect of NAC on depressive disorders occurring in adult cannabis users was analyzed. Participants in the study were administered NAC at a dose of 2400 mg/day for 12 weeks, after which they were followed clinically for 4 weeks. It was shown that NAC had no effect on depressive

symptoms as measured by the Hamilton Depression Rating Scale (HDRS) anxiety and depression scale, nor was it more effective than cessation of cannabis use. (7,12,13)

An analysis of several other RCTs evaluating adjunctive NAC therapy for the treatment of depression found that NAC led to significant improvements in functioning based on a scale used to mark mental health status and changes during treatment (Clinical Global Impression Scale, CGI-S) compared to placebo. However, other scales evaluated at the time (SLICE LIFE, SOFAS, LIFE-RIFT) did not prove clinically significant improvement in the assessment of depressive symptoms compared to placebo. (14)

As can be seen from the scientific data cited - studies show mixed results. Single studies show a beneficial effect of NAC on depressive symptoms, however, further long-term clinical studies on the effect of NAC on the course of depression are needed to confirm this effect and to recommend NAC in supportive therapy for depression.

2. Schizophrenia

Schizophrenia is a severe and chronic psychotic disorder that destabilizes basic mental functions. The clinical picture of schizophrenia is complex and leads to emotional incapacity and impoverished thinking. Lack of motivation and passivity in undertaking activities result in loss of aspirations and life goals. Gradually emerging mental ailments destructively affect the fulfillment of professional duties and social roles. Affected individuals feel a desire for seclusion, which entails a loss of interpersonal ties. This is often associated with feelings of unreality, and the totality of symptoms present significantly impairs functioning and distorts assessment of reality. (15)

Among the symptoms that form the core of schizophrenia, a distinction is made between positive, negative and cognitive symptoms. Positive (productive) symptoms are characterized by the presence of: hallucinations, primarily auditory; delusions, which are disturbances in the content of thinking; and catatonic agitation, which is characterized by excessive verbal and motor behavior. Negative (attritional) symptoms are characterized by a lack of feelings of pleasure, emotional deprivation and social isolation. Cognitive (cognitive) disorders are marked by the presence of memory deficits, concentration problems and problems with world perception. (16,17)

There are many hypotheses explaining the pathogenesis of schizophrenia. One of them is the glutamate theory, according to which the onset of the disease is caused by insufficient activity of the excitatory neurotransmitter glutamic acid, discussed earlier, and the malfunction of its N-methyl-D-aspartate (NMDA) receptors on neurons of the gamma-

aminobutyric acid system (GABA-ergic system). Reduced glutamic acid levels in schizophrenia patients have been confirmed by MRI studies. (7,18)

Currently, the mainstay of pharmacological treatment of schizophrenia is classical and atypical neuroleptics. The moderate efficacy of treatment, the broad profile of side effects, and thus the insufficient improvement in the lives of patients, have created difficulties in the effective pharmacotherapy of schizophrenia. Given the previously described mechanism of action of NAC and the pathogenesis of schizophrenia, attempts have been made to see if NAC can be a promising link in the treatment of this disorder.

In preclinical studies performed on animals experimentally induced with schizophrenia, NAC was shown to improve mitochondrial dysfunction and apoptosis, reduce oxidative stress and inflammation, and enhance neurogenesis. (18,19) Based on studies in animal models of schizophrenia, it has been suggested that NAC administration could modulate inflammatory processes in the nervous system by repairing damaged neurons. In addition, it would make it possible to increase (pathologically reduced) glutathione levels in the cerebrospinal fluid of patients with schizophrenia. At present, literature data on the effects of NAC in alleviating schizophrenia symptoms are fragmentary. One RCT evaluating the efficacy of NAC in the adjunctive therapy of schizophrenia observed no clinically significant effect on positive or negative symptoms of schizophrenia after eight weeks of NAC administration at a dose of 1000-3600 mg/day. However, a significant advantage of NAC over placebo in alleviating positive and negative symptoms of schizophrenia was noted for longer administration of NAC (24 weeks). The use of the Positive and Negative Syndrome Scale (PANSS) for schizophrenia was used to evaluate the results. As a result, it was found that the effects of NAC appeared slowly and were therefore not noticeable after eight weeks of therapy. (20-22)

Another RCT in patients treated with NAC tested the efficacy of NAC as an adjunctive treatment in addition to standard antipsychotic therapy. For a period of 24 weeks, patients took NAC twice daily at a dose of 1,000 mg. Of the 140 participants, 84 patients completed the study. Clinically significant improvement was observed based on the PANSS scale compared to placebo. (20,23)

A smaller clinical trial involved a group of 46 schizophrenic patients who were treated concurrently with risperidone, a second-generation antipsychotic drug that is a first-line therapy for schizophrenia. One of the patient groups evaluated in the study was taking NAC in addition to risperidone, while the other was taking a placebo. The dose of NAC for the first week of the study was 1,000 mg/day and was gradually increased over a period of seven

weeks until the dose reached 2,000 mg/day. After eight weeks, compared to study participants taking placebo, the group receiving NAC achieved statistically significant improvement in overall, including negative symptoms of schizophrenia. (24,25)

Researchers conducting another clinical trial found improved neuronal signaling in people with schizophrenia taking NAC. Neuronal signaling enhances the intercommunication of neurons, which allows different areas of the brain to connect, then effectively process the information provided and perform tasks. The effect was evident by electroencephalography (EEG) even before any clinical improvement - changes in the brain may precede the clinically detectable effects of NAC, which may underscore the possible utility of this EEG as a biomarker of treatment efficacy in future studies. (26)

The clinical trials that have been conducted demonstrate the effect of NAC on symptoms occurring in the course of schizophrenia. However, confirmation of the therapy's effectiveness requires more long-term studies.

3. Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is manifested by the occurrence of recurrent, intrusive thoughts and/or activities, and the attempt to refrain from them is associated with anxiety and increasing fear. Intrusive thoughts (obsessions) occur against the patient's will, but are treated as the patient's own thoughts; they often concern embarrassing or absurd things. Intrusive activities (compulsions) manifest themselves in the constant repetition of certain tasks; the patient is not infrequently aware of the pointlessness of the activities performed, but they are partly unavoidable and difficult to resist. Among the compulsions, the most common are repeatedly checking the closing of doors, recurring hand washing, arranging objects and striving for self-imposed order. The aforementioned activities are a response to growing insecurity and a kind of alleviation of the emerging feelings of anxiety. (27)

The occurrence of OCD has been linked to abnormalities in glutamic acid metabolism in the glutamatergic system and hyperactivity in the corticospinal-thalamocortical area of the brain, which is responsible for regulating emotions and impulsive and compulsive behavior. Patients with a diagnosis of OCD have been found to have impaired glutamate levels and the presence of oxidative stress. Given NAC's mechanism of action, the possible therapeutic potential for future treatment of the condition has been noted. Preclinical and clinical studies conducted have tested the effect of NAC in modulating glutamate levels and alleviating oxidative stress, thereby minimizing OCD symptoms. Experimental animal studies have proven the effective effect of NAC in the context of reducing animal behavior consistent with

OCD symptoms in humans. The doses of NAC used in the cited study ranged from 1800-3000 mg/day. Study results ranged from no effect to clinically significant improvement. (27,28)

The available scientific literature is limited and evidences only a few RCTs examining NAC in the treatment of OCD. The studies tested the efficacy of NAC both as monotherapy and as adjunctive treatment along with selective serotonin reuptake inhibitors (SSRIs). The diagnostic tool used to assess outcomes was the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which is the most widely used scale to assess the nature and severity of OCD symptoms. Compared to placebo, NAC did not result in significant clinical improvement in most cases; however, two studies observed a 35% reduction in presenting symptoms on the Y-BOCS scale. (7)

Current scientific data indicate that the extent of NAC's effects may be too small to justify its use in OCD therapy, but longer-term studies in the future are required to assess the effects of NAC on the symptoms of the disease in the perspective of long-term therapy.

4. Addictions

As a key component of NAC, cysteine plays an important role in modulating glutamatergic receptors, which are located in areas of the brain responsible for the development of addiction. By affecting receptor modulation, NAC may enable the restoration of normal glutamatergic neurotransmission pathways, thereby preventing the development of addiction. Chronic oxidative stress, leading to damage in the CNS, also contributes to the risk of addiction - NAC as a potent antioxidant may prevent such degenerative processes. The lack of effective treatment for addiction has prompted researchers to continue their search for safe and effective addiction therapy. (3-4)

4.1. Nicotine addiction

In one of the first clinical trials conducted to study the correlation of NAC's effects on nicotine addiction therapy, cigarette smoking addicts were administered NAC at a dose of 2,400 mg per day for 4 weeks. Participants in the clinical trial recorded the number of cigarettes smoked daily, and recorded the intensity of nicotine withdrawal symptoms weekly. Compared to placebo, smokers reported a gradual reduction in the number of cigarettes smoked, with no effect of NAC on withdrawal symptoms. The promising results of the study resulted in further development of research on NAC in the mentioned indication. Another study tested combination therapy of NAC together with varenicline, an adjunctive drug for smoking cessation. Using a dose of 1200 mg of NAC twice daily significantly reduced the number of cigarettes smoked after four weeks of therapy. (29) However, a 12-week RCT

involving 34 participants showed no difference in the frequency of cigarettes smoked compared to placebo, using a dose of 3,000 mg of NAC per day. (30) A similar result - no significant differences - was achieved in another RCT, where 48 study participants took 2400 mg of NAC per day for two weeks. (31)

NAC's antioxidant properties - increasing glutathione levels and modulating the glutamatergic system - may reverse the neuroplastic changes associated with nicotine addiction and help people quit smoking. However, the studies presented here prove different data. Thus, the effect of NAC may be determined by the appropriate dose and/or length of therapy provided; thus, further ongoing studies are needed to confirm the efficacy of NAC.

4.2. Cocaine addiction

The first clinical study examining the effect of NAC on cocaine addiction treatment involved 13 healthy, cocaine-dependent individuals. At the time, the effect of NAC on symptoms resulting from cocaine withdrawal was studied. Over the course of three days of hospitalization, study participants were administered a dose of 600 mg of NAC every six hours at the onset of cocaine withdrawal symptoms. It was shown that after 14 hours, there was an alleviation of withdrawal symptoms. After the end of NAC dosing, the reduction in appetite for cocaine consumption persisted for another 24 hours. (32)

Studies conducted in subsequent years, however, did not confirm a significant change in cocaine craving reduction relative to placebo. However, those who had already achieved abstinence showed a prolonged time to cocaine relapse and a dose-dependent reduction in cocaine craving, suggesting a potential effect of NAC in preventing relapse in those who had stopped using cocaine. (33,34)

Summary

The continuing development of medicine is making it possible to open the floodgates to new, alternative approaches to treating conditions where existing treatments are proving ineffective. One example is the increased interest in NAC, which is commonly used over-the-counter as a drug to relieve a wet cough, turns out to be a compound with a much more complex mechanism of action. Its brain function-modifying effects have the potential to be applied to the treatment of diseases in the field of psychiatry. Scientific data prove the positive effects of NAC on selected conditions; however, many of the clinical trials conducted do not support the benefits of the compound. NAC's growing popularity is no accident, however, and its promising properties need to be confirmed in further studies.

Authors contributions

Joanna Cieszkowska: Conceptualization, Writing - rough preparation, Methodology, Investigation, Project administration

Marta Czubala: Formal Analysis, Visualisation

Julia Czerwik: Software, Resources, Writing – review and editing.

Joanna Dmochowska: Supervision, Data curation

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All authors declare that they have no conflicts of interest.

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