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Assoc. Prof. Nursu Cakin Memik, Assoc. Prof. Ozlem Yildiz Gundogdu & Prof. Umit Tural

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Review

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Use of N-acetylcysteine in Obsessive-Compulsive and Related Disorders

Nursu Cakin Memik[1], Ozlem Yildiz Gundogdu[1], Umit Tural[2]

ABSTRACT:

Use of N-acetylcysteine in obsessive-compulsive and related disorders

Information on the use of N-acetylcysteine (NAC) in neuropsychiatric disorders has increased in recent publications. Although there are positive reports on the use of NAC in obsessive-compulsive and related disorders (OCRD), such data have not yet been validated. This article aims to review the research, case series and case reports that have been published about the use of NAC in OCRD. Research papers and case reports on the use of NAC in OCRD published within the last five years have been reviewed using the search engines of "Pubmed" and "Medline Central" databases. The search was performed by matching the terms "obsessive-compulsive disorder (OCD)", "trichotillomania (TTM)", "nail biting", "skin picking", "hoarding disorder", and "body dysmorphic disorder" with "N-acetylcysteine". The search identified 4 papers on TTM, 3 papers on nail biting behavior, 1 paper on OCD and 1 paper on skin-picking behavior. Three of these papers were double-blind, placebo-controlled studies and four were case reports/series. The results of 2 papers out of the 7 that we reviewed showed that there was no difference between NAC and placebo, while 5 papers reported that the response to the NAC therapy was positive. We did not find any papers on the use of NAC in either hoarding disorder or body dysmorphic disorder. NAC is thought to be a promising psychopharmacologic agent in OCD, which is defined under OCRD due to its common etiology, similar clinical features and similar response to treatment, as well as in TTM, skin picking and nail biting. The effectiveness of glutamatergic modulators on repetitive behaviors or OCD has increased interest in NAC. Although there are a few studies in the area, many research projects are being planned, with some already in progress (www.clinicaltrials.gov), a fact that emphasizes the importance of NAC in OCRD treatment. NAC has been used in a broad spectrum of conditions such as paracetamol intoxication, doxorubicin cardiotoxicity, ischemia-reperfusion-induced injury of the myocardium, acute respiratory distress syndrome, bronchitis, chemotherapy intoxication and heavy metal intoxication. In recent years, there has been an increase in the number of studies exploring the use of NAC in neuropsychiatric disorders such as schizophrenia, autism, bipolar disorder and OCRD. In this review, we have seen that the results of studies assessing the efficacy of NAC in psychiatric disorders are promising; however, there is a need for further studies to evaluate its mechanism of action, appropriate dose range and duration of treatment.

Keywords: obsessive-compulsive and related disorders, obsessive-compulsive disorder, trichotillomania, skin picking, nail biting, glutamate, N-acetylcysteine

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[1]Assoc. Prof., Kocaeli University, School of Medicine, Department of Child and Adolescent Psychiatry, Kocaeli - Turkey
[2]Prof., Kocaeli University, School of Medicine, Department of Psychiatry, Kocaeli - Turkey

Corresponding author:
Dr. Nursu Çakın Memik,
Kocaeli Üniversitesi, Tıp Fakültesi Hastanesi, Morfoloji Binası, Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Anabilim Dalı, Kocaeli - Turkiye

Phone: +90-262-303-8636

E-mail address:
nursucakinmemik@gmail.com

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INTRODUCTION

Given that NAC acts on glutamatergic transmission, glutathione, neurotrophin, apoptosis, mitochondrial function, and inflammation systems, research has been initiated recently on its action in neuropsychiatric disorders[1]. Clinical trials have reported that glutamatergic modulators may be effective on repetitive or compulsive behavior disorders[2-4]. For this reason, NAC has been considered as a single or additional drug therapy to be used in psychiatric disorders, and its use has increased in recent years[5]. NAC's efficacy has been investigated in cocaine, cannabis and nicotine addiction, Alzheimer's and Parkinson's diseases and disorders in the compulsive spectrum, with positive results being obtained[1]. Double-blind, placebo-controlled studies have shown that NAC is effective especially for treating bipolar depression, schizophrenia, substance use, pathological gambling, and repetitive behaviors seen in autistic spectrum disorders[6-19].

Obsessive compulsive and related disorders (OCRD) are defined in the DSM-5[20]. Obsessive compulsive disorder (OCD) as an Axis-I diagnosis, body dysmorphic disorder, hoarding disorder, trichotillomania (TTM), skin picking disorder (excoriation), substance/medication-induced OCRD, OCRD due to another medical condition, other specified OCRD, and unspecified OCRD diagnoses are all listed under the heading OCRD[20]. OCD is an anxiety disorder characterized by obsessions that are defined as repetitive and continuous thoughts, impulses or fantasies which come from time to time involuntarily, are experienced as inconvenient and cause a certain anxiety or trouble, as well as compulsions that are defined as repetitive behaviors or cognitive actions the individual cannot resist from committing as a reaction to the obsession or due to his/her rules that have to be strictly followed[21]. The common aspect of the disorders included in OCRD is committing repetitive behaviors or cognitive acts to remove cognitive preoccupation and discomfort[20]. Their common etiology, similar clinical features and similar responses to treatment resulted in the grouping of these disorders within the same spectrum[3,22-25].

N-Acetylcysteine (NAC)

NAC is a natural amino acid that modulates glutamate metabolism and acts as an antioxidant[26]. It is an acetaldehyde form of the amino acid cysteine that is contained in food and synthesized by the body. Cystine is formed through oxidation of two cysteine molecules. The metabolism of cystine is the same as that of cysteine. NAC is less toxic and less susceptible to oxidation than cysteine and dissolves in water more easily[27]. L-cysteine is known to have little effect on glutathione levels in the brain as it undergoes metabolism when taken orally[28-30]. Since glutathione is rapidly hydrolyzed in the liver and intestinal system and has very little blood-brain barrier permeability, it also does not cause an increase in glutathione levels when taken orally. Due to these properties of NAC, it is more convenient for oral or parenteral use than cysteine or glutathione[31]. NAC can be used intravenously, orally or through inhalation[32]. It has been shown in animal studies that NAC can pass the blood-brain barrier and cause an increase in glutathione[33-35]. NAC has been used for many years in the treatment of contrast nephropathy or acetaminophen intakes in high or toxic doses[1,36,37]. It has been reported that NAC was absorbed rapidly when taken orally, and its peak concentration (t_{max}) was reached in 1.4±0.7 hours with a mean half-life ($t_{1/2}$) of 2.5±0.6 hours[38]. It was also reported that its bioavailability increased with dose and its peak concentration was 16 µmol/l for a 600 mg dose and 35 µmol/l for a 1200 mg dose[39]. After oral intake, NAC is known to pass from the gastrointestinal system to the liver, where it fully transforms into cysteine; it is then eliminated through the kidneys[5,40]. Cysteine that is not converted to glutathione is capable of crossing the blood-brain barrier[41].

NAC is tolerated well, has mild side effects, and studies have often reported that its side effects are

not any different than those of placebo[9,6]. This information was also supported by a review that assessed 46 placebo-controlled studies involving 4000 subjects who used NAC orally[40]. It was stated that NAC did not lead to serious side effects even at a dose of 8000 mg/day[42]. NAC was reported to be superior to other pharmacologic agents as it did not have serious side effects[37]. Its most frequently seen side effects are said to be nausea and flatulence; it can also cause exacerbation in asthma if used intravenously. For this reason, it is recommended to use NAC carefully in asthma patients[43]. Drowsiness, nausea, vomiting, tachycardia, rhinorrhea, stomatitis, and hemoptysis are also mentioned among its side effects[5,32]. Although it has been reported in some animal studies that the use of NAC at very high doses causes pulmonary hypertension, no such side effect has been seen in studies performed on humans[44]. While NAC has antiepileptic properties at low doses, it may increase the likelihood of an epileptic attack at high doses[45,46].

Studies exploring the effects of NAC have reported that it has an inhibiting effect on the glutamatergic system, diminishes oxidative stress, is effective in the inflammatory system, results in neutrophile inhibition, has vasodilating and mucolytic effects and a protective effect on the kidneys[47-51]. After being taken, NAC turns into cystine and acts as a substrate for the cystine-glutamate antiporter system contained in the glial cells, which determines the extracellular glutamate level[51]. When cystine enters glial cells, glutamate is released into the extracellular synaptic area, and when glutamate increases in the extracellular synaptic area, the inhibitor metabotropic glutamate receptors in glutamatergic nerve endings are stimulated. Group II metabotropic glutamate receptors are located in the presynaptic area of neurons in many regions of the brain such as the cortex, amygdala, hippocampus, and striatum[53]. The Group II metabotropic glutamate receptors have an important role in modulating the release of vesicular glutamate[54]. As a result of the stimulation of presynaptic glutamate receptors by glutamate, a decrease occurs in the release of glutamate[2,9,26,55,56]. For this reason, the use of drugs such as NAC, which reduces the glutamate level, in treating psychiatric diseases seems promising[57]. The impact of NAC on compulsive behaviors is thought to occur when it causes a decrease in glutamate in the nucleus accumbens[2,9,55,56,58-61]. Additionally, NAC is thought to protect glial cells from glutamate toxicity, because an elevated glutamate level reduces glutathione and this increases glial cell vulnerability through oxidative damage[55]. An excessive increase in glutamate level and dysfunctional cystine transport into glial cells are seen in many neurologic and psychiatric disorders[62]. It has been shown in preclinical studies that NAC protects glial cells against glutamate toxicity, decreases the glutamate level, and increases glutathione[63-65].

In addition to its effect on glutamate release, NAC also has antioxidant properties[42,65]. It is known that in many mental disorders, oxidative balance is impaired, antioxidants diminish and free radicals increase. NAC is reported to contribute to the establishment of this balance[1]. NAC increases the level of cysteine, which is the rate-limiting substrate in the synthesis of glutathione, the most important antioxidant of the brain[42,66]. After being taken, NAC turns into cystine and, as cystine enters into the cells, glutamate shuttles out of the cells through the cystine-glutamate antiporter system located in the glial cells. The cystine inside the cells transforms into cysteine[1]. NAC is thought to have a positive impact on the function of glial cells by increasing cysteine and glutathione in the glial cells[67]. Glutathione neutralizes reactive oxygen and nitrogen species from the cell through both direct and indirect scavenging and maintaining the oxidative balance in the cell[68]. In addition to providing cysteine for glutathione production, NAC is known to scavenge oxidants directly, particularly through the reduction of the hydroxyl radical, OH, and hypochlorous acid[69]. NAC is reported to be effective also on the oxidative stress that results from a mitochondrial function disorder[70,71]. Oxidative stress has been empirically associated

with a number of psychiatric disorders, including OCRD. NAC, which is characterized by a good bioavailability, is a precursor of the major endogenous antioxidant glutathione production, a property which makes NAC valuable.

Animal studies have reported that NAC is effective on cocaine-seeking behavior and mediates the behavioral counterparts of animal cravings by increasing activity of the cystine-glutamate antiporter system and restoring extracellular glutamate concentrations in the nucleus accumbens[56,72]. NAC has been found to decrease cocaine-seeking behavior and cocaine-related withdrawal symptoms[9].

Besides glutamate, NAC is reported to be effective on the dopaminergic system[1]. Increased activity of the cystine-glutamate antiporter system results in increased activation of metabotropic glutamate receptors on inhibitory neurons and facilitates vesicular dopamine release. Dopamine is a pro-oxidant, forming hydrogen peroxide and free radicals through auto-oxidation and normal metabolism, and dysregulation of dopamine signaling is thought to be a major contributor to neurotoxicity[68,73,74].

With its mucolytic action, NAC is used in the treatment of acetaminophen intoxication, doxorubicin cardiotoxicity, cardiac ischemia-

Table 1: Summary of trials/case reports that were reviewed

Author, Publication year	Diagnosis	Type of trial	Duration of trial	Subject/ case	Subject age segment	Sample size	NAC Dose/ day	Result
Bloch et al., 201336	TTM	Double-blind, placebo-controlled	12 weeks	Children, adolescents	8-17 (14.0±2.4)	39	2400mg	No statistically significant difference between NAC and placebo.
Grant et al., 200958	TTM	Double-blind, placebo-controlled	12 weeks	Adults	18-65 (34.3±12.1)	50	1200-2400mg	Response to treatment with NAC (56%) is significantly higher than placebo (16%)
Rodrigues-Barata et al., 2012111	TTM	Case report	6 months	Adults	23	-	1200mg	Response to treatment
			3 months	Adolescents	19	-	1200mg	Response to treatment
Odlaug et al., 20073	TTM, nail biting	Case report / Letter to editor	-	Adults	28	-	1200mg	Response to treatment
	TTM		-	Adults	40	-	2400mg	Response to treatment
	Skin picking		-	Adults	52	-	1800mg	Response to treatment
Lafleur et al., 200655	OCD	Case report / Letter to editor	12 weeks	Adults	58	-	3000mg	Response to treatment
Berk et al., 2009122	Nail biting	Series of cases	7 months	Adults	46	-	2000mg	Response to treatment
			4 months	Adults	44	-	2000mg	Response to treatment
			28 weeks	Adults	46	-	-	Response to treatment
Ghanizadeh et al. 2013115	Nail biting	Double-blind, placebo-controlled	2 months	Children, adolescents	6-18 (9.28±2.81 for NAC group) (10.76±3.14 for placebo group)	42	800mg/day	Response to treatment with NAC is significantly higher than placebo at month 1. Response is no different than placebo at month 2.

reperfusion injury, acute respiratory distress syndrome, bronchitis, chemotherapy intoxication, AIDS, heavy metal intoxication and mental disorders[32]. The mechanism of action of such a widely used agent is still not clear.

Glutamatergic modulators such as NAC are thought to be useful in repetitive or compulsive disorders[2,55]. On www.clinicaltrials.gov, it is also seen that a large number of studies on the use of NAC in OCRD have been planned, conducted, and finalized. Oxidative stress and dysregulation of glutamate are common across psychiatric disorders. There are similarities across OCRD with alterations to oxidative biology, and changes in glutamate-dependent long term potentiation. The efficacy of NAC on both of these systems makes it of clinical interest[68]. The low cost of NAC, its ease of administration, and its limited adverse effects are all compelling reasons to investigate its role in psychiatric disorders further. For this reason, we reviewed and discussed the published clinical trials and case reports on the use of NAC in OCRD.

METHOD

Research papers and case reports on the use of NAC in OCRD published within the last five years were reviewed using the search engines of Pubmed and Medline Central databases. Studies published between 2009 and 2013 were included in the assessment. The search was performed by matching the terms "OCD", "TTM", "nail biting", "skin picking", "hoarding disorder", and "body dysmorphic disorder" with "N-acetylcysteine". There was no limitation with respect to the age groups involved in the trials. Papers published in languages other than Turkish or English were not included in the assessment.

RESULTS

The results of 7 papers on the use of NAC in OCRD were evaluated. It was seen that there was 1 paper on OCD, 4 papers on TTM, 3 papers on nail biting disorder, and 1 paper on skin-picking disorder; there were no papers on hoarding disorder or body dysmorphic disorder. The results of the papers included in the study are summarized in Table 1.

DISCUSSION

Obsessive-Compulsive Disorder (OCD)

OCD is a chronic mental disorder that progresses with obsession and compulsion symptoms and significantly impairs functioning[75]. OCD is among the top ten diseases that create the highest disability by lowering the individual's quality of life and causing loss of income[76,77]. Epidemiologic studies conducted in various societies and cultures show that the lifelong prevalence of OCD is between 2 and 3%[78]. The primary treatment of OCD is through cognitive behavioral therapies, which involve exposure and response prevention, and pharmacotherapy with clomipramine, serotonin reuptake inhibitors (SSRI) or dual reuptake inhibitors[79-82]. Since OCD symptoms are chronic and the drug therapies used can achieve only 30-40% recovery, research to find new therapies for OCD is still in progress[83-85]. There is a mention of glutamatergic dysfunction in the pathogenesis of OCD[49,55,56,72,86-92]. Chakrabarty et al. reported an increase in the level of glutamate in the cerebrospinal fluid of OCD patients not using medication[86]. In a case control study, it was seen that an of augmentation memantine, which is an antagonist for the N-Methyl D-Aspartate (NMDA) receptor, also produced a positive effect in OCD[93]. When Coric et al. reported the efficacy of NAC in riluzole-resistant OCD through reducing glutamate release and increasing its re-absorption from the synaptic gap, there was speculation that NAC could also be useful in OCD[2].

Many studies have reported that OCD involves increased oxidative stress, increased lipid peroxidation, changes in antioxidative enzyme systems and elevated cytokine levels prior to inflammation and that the extent of lipid peroxidation is associated with the severity of OCD symptoms[94-98]. All these results suggest that

NAC can be effective in treating OCD by reducing oxidative stress and inflammation[47,48].

Marble-burying behavior in mice is regarded as a model for OCD due to its behavioral similarity[99]. Like SSRIs, NMDA receptor antagonists also decrease marble-burying behavior in mice[99-101]. Based on this observation, Egashira et al. examined the effect of NAC on marble-burying behavior; mice were divided into groups and they were given fluvoxamine, mirtazapine, NAC and alpha-tocopherol, respectively. In the end, the marble-burying behavior was statistically significantly decreased with mirtazapine, fluvoxamine and NAC, but not with alpha-tocopherol, which is an antioxidant. This result was interpreted to show the effect of NAC on the marble-burying behavior occurring more through the glutamate system than because of its antioxidant property. It was also reported in this trial that giving NAC together with fluvoxamine did not result in an additive effect on the marble-burying behavior. This result was interpreted to show that NAC could be used as an alternative therapy rather than in a combination therapy[37].

Lafleur et al. (2006) reported about the recovery achieved by adding NAC to fluvoxamine therapy in a 58-year-old patient who had been hospitalized and treated five times previously, trying many drug therapies, who had experienced a partial recovery with fluvoxamine[55]. When we reviewed the literature, this was the only case report we found regarding the use of NAC in OCD[55]. This patient had not benefited from fluoxetine, clomipramine or alprazolam therapies previously, and she had been taking fluvoxamine 300 mg/day for 12 years but had only partially recovered. For this reason, augmentation therapy with NAC was chosen; 600 mg of NAC was started and the dose was increased to 3 g/day. A decrease was seen in her Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score from the first week, and this decrease continued for 12 weeks[55]. The researchers concluded that NAC could be effective in SSRI-resistant OCD[55].

Considering the biological aspects of OCD, it is seen that NAC might be beneficial, but there is only one case report in this area. Therefore, conducting further double-blind placebo-controlled studies will be useful.

Trichotillomania (TTM)

TTM is a hard-to-treat chronic disorder that leads to noticeable hair loss due to repetitive hair pulling and effects all the areas of functioning of the individual adversely[20]. The lifelong prevalence of TTM is known to range between 1 and 3%[102,103]. This chronic disorder often starts between ages 11 and 13 and progresses for a lifetime with fluctuations[104,105]. A meta-analysis where the treatment methods used in TTM were reviewed reported that cognitive behavioral therapy, and habit-reversal training in particular, were the most effective treatment methods[106]. SSRIs, although known to be no different than placebo in terms of efficacy, seem to be the most widely used pharmacological agents in treating TTM[43,105,106]. There are also studies that report the use of clomipramine, naltrexone, olanzapine and pimozide in TTM[43,106-110]. In a double-blind placebo-controlled study by Grant et al. (2009) with 50 adults (25 patients in the placebo group and 25 in the NAC group), NAC was used to treat TTM at doses between 1200 and 2400 mg/day for 12 weeks. NAC's effect started to be seen after week 9; 16% of TTM patients on placebo and 56% of those on NAC responded to the treatment (much, very much improved). As a result of this study, NAC was found to be greatly efficacious (1.2)[58]. Grant et al. reported that in their study, they found a 40.9% improvement in TTM with NAC based on the Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) and a 56% improvement (much, very much improved) based on the Clinical Global Impression Scale (CGI), and they compared their results with those of previous studies. They stated that in previous studies there was an 8.4% improvement with drug therapy based on MGH-HPS, a 41.5% improvement with the combination of drug therapy and cognitive behavioral therapy and decrease of between 34.8 and 66.4% in the MGH-HPS scores with cognitive

behavioral therapy alone. They concluded that the results obtained with NAC were important in TTM treatment[58]. Moreover, the authors stated that absence of a response to NAC therapy in 44% of TTM cases could be linked to the presence of subtypes of TTM, underlying genetic differences or the influence of comorbid psychiatric disorders on the treatment or the presence of neuropathophysiologic abnormalities[58]. Although 56% improvement was seen in the TTM symptoms in their study, no statistically significant difference was achieved by the treatment in the patients' quality of life or functioning as compared to the placebo group[58]. Grant et al. linked this result to the fact that the study had a short duration, the intensity of symptoms was low, the time required for hair growth was long and it would take time before the effects of the treatment would be reflected in functioning and quality of life[58].

In their 12-week double-blind placebo-controlled study on children and adolescents aged 8-17, Bloch et al. (2013) reported that the effect of NAC used at a dose of 2400 mg/day on TTM was not different from that of placebo[36]. The results of the study by Grant et al. evaluating the efficacy of NAC in adults with TTM and those of Bloch et al. studying children with TTM differed from each other in that the efficacy of NAC was significant in adults with TTM but not so in children. This observation can hypothetically be linked to a number of factors. To be able to generalize the results and to reveal the efficacy of NAC in treating children with TTM, there is a need for further placebo-controlled studies.

There are also case reports on the use of NAC in TTM. One of these cases involved a 23-year-old female patient who displayed hair regrowth in the second month of treatment with NAC at a dose of 1200 mg/day. The other case involved a 19-year-old female patient who showed hair regrowth in the third month of NAC treatment at a dose of 1200 mg/day with no apparent side effects[3,111]. There are also case reports indicating that a 28-year-old female patient with nail biting and TTM showed recovery from both behaviors with 1200 mg/day of NAC, and a 40-year-old female patient recovered from her hair-pulling behavior with 2400 mg/day of NAC[3].

There obviously is a need for studies where the duration of dealing with TTM is long, NAC is used in higher doses and cognitive behavioral therapies are added to the treatment. Making use of clinical symptoms, cognitive tests, neuroimaging and pharmacogenetic assessments and increasing research by including these fields will improve the results in TTM treatment.

Nail-Biting Behavior

Nail-biting behavior, which leads to functional impairment and uneasiness, is defined as "biting nails beyond the free edge with nail margin below the soft tissue border"[112,113], often beginning in adolescence[3]. Nail biting is a common condition affecting both genders[114]. The overall three-month prevalence of nail biting in community samples of children was found to be 22.3%[114]. Nail biting may involve physical consequences such as gingivitis, pinworm infestation, giardia infections and changes in nail appearance. Mental disorders often accompany nail biting, because it provokes reactions such as ridicule, embarrassment, warning and anger[115-117]. It has been reported that nail biting is often comorbid with other mental disorders, and 65% of those who bite their nails have an additional stereotypic behaviour[118,119]. In the DSM 5, nail-biting behavior is classified as a "body-focused repetitive behavior disorder" under the heading "other specified obsessive compulsive and related disorders"[20]. It is stressed that behavioral therapies such as habit reversal training have been commonly used for nail biting, but the results have not been satisfactory[120]. It has been reported that in a group of 30 children who were given habit reversal training for their nail-biting behavior, only 8 children stopped biting their nails[121]. There seem to be very few studies dealing with psychopharmacologic therapies used for nail biting problems[3,122]. A double-blind placebo-controlled study on nail biting found that clomipramine significantly reduced nail-biting behavior when compared to desipramine[123].

Odlaug et al. reported that in a 28-year-old female patient with nail-biting behavior and TTM, the symptoms of both disorders improved with 1200 mg/day of NAC[3]. They reported that this patient started nail biting at the age of 6; she spent 2-3 hours biting her nails, and although this caused bleeding in her fingers and injuries to her nail beds, she continued until she felt unbearable pain. When the patient did not get any benefit from bupropion and fluoxetine therapy, she was started on 600 mg/day of NAC; when no improvement was observed, the dose was raised to 1200 mg/day after 2 weeks, and some improvement was seen after a further 2 weeks. The improvement became apparent after 5 weeks. No serious side effects were reported with the NAC treatment[3].

Berk et al. (2009) reported that after they added NAC to the treatment of patients with bipolar disorders to determine the effect of NAC on their symptoms, there was a noticeable improvement in their nail biting behaviors[122]. The first in their series of cases was a 46-year-old female patient; she used 900 mg of lithium and 300 mg of quetiapine to treat to her bipolar disorder. When 2000 mg/day of NAC was added to her therapy, her nail biting behavior recovered within 2 weeks and the improvement continued in the 7th month. The second case involved a 44-year-old female patient being monitored because of her rapid cycling bipolar disorder, who used 15 mg/day of mirtazapine, fish oil, zinc, magnesium, vitamin B6 and valerian. Four months after the addition of 2000 mg/day of NAC, the patient stated that there was an apparent improvement in her nail-biting behavior. The authors reported the third case of a 46-year-old male patient who was being monitored for his bipolar disorder. An improvement was seen in his nail-biting behavior with NAC, but the researchers did not report whether or not he used any drugs for his bipolar disorder[122].

At the end of the double-blind placebo-controlled study conducted by Ghanizadeh et al. (2013) to determine the effect of NAC on nail-biting behavior in children and adolescents, the effect of NAC on nail biting was found to be no different than that of a placebo[115]. In their study, the measurement of nail length was used as the basic data and NAC was given at a dose of 800 mg/day. The patients were assessed three times during the study, once when they were enrolled and one and two months after the start of treatment, when their nail lengths were measured. The study included 42 individuals, 21 in the NAC group and 21 in the placebo group. Due to reasons such as non-compliance with the use of medication, failing to come for assessment interviews and withdrawing from the study due to side effects, only 14 people in the NAC group and 11 people in the placebo group were able to complete the study. An increased length of nails was found in both groups; in the measurements made after one month, the effect of NAC on nail growth was found to be statistically significantly different as compared to placebo, but this difference was seen to disappear after 2 months. It was reported that two patients in the NAC group left the study due to increased aggression, headache, agitation, and isolation[115]. The investigators concluded that reason for the effect of NAC on nail length being no different than that of the placebo could be that the patients in the NAC group might have cut their nails even though they were told not to do so. They also reported that the patients in the placebo group could have been affected by the fact that many of them had comorbid mental disorders and used psychopharmacologic agents for these mental disorders[115]. Evaluating the results of these studies and case reports, we can see that long-term placebo-controlled studies are needed to understand the effect of NAC on nail-biting behavior.

Skin-Picking Disorder

Although excoriation is a problem that has existed before, it was defined for the first time in the DSM-5 under the title OCRD[20]. It has been reported that skin-picking disorder often starts after acne, which is a dermatologic problem, but it continues after solving the acne problem[124,125].

Although skin-picking behavior is considered normal to some extent, it is considered as a problematic behavior when it becomes repetitive, ritual or impulsive, causes tissue damage or leads to functional impairment and tension[126]. Although individuals agree that their skin-picking behavior is illogical, they describe an intrusive picking thought or urge that they cannot resist[126]. Some patients report that their skin picking behavior can last for hours[127]. It has been reported that an individual with a skin-picking disorder engages in this behavior for several hours a day, thus missing, or coming late to, work, school or other activities[125,127-131]. Of two studies dealing with skin-picking behavior, one found its prevalence to be 2% in people with skin diseases and the other study that it was found in 3.8% of students[126,125]. Community sample studies report that the prevalence of excoriation ranges between 1.4 and 5.4%[132,133]. Although fewer than 20% of the patients with skin-picking disorder have been reported to seek treatment, new treatment methods are still being researched because of excessive distortion occurring in functionality[128,130]. Treatments for skin picking disorder include cognitive behavioral therapies such as habit reversal training and psychopharmacologic agents such as SSRIs, naltrexone, and NAC[124,134,135]. It is reported that the prevalence of comorbid disorders that are classified under OCRD, such as body dysmorphic disorder and TTM, together with skin-picking disorder is high[124].

A controlled study carried out to reduce skin-picking behavior reported a noticeable decrease in the severity of picking seen with fluoxetine[136]. In a study by Odlaug et al. (2007) assessing 5 patients with TTM, nail biting and skin picking being given NAC therapy, two of the patients did not respond to the NAC therapy[3]. The authors reported the case of a 52-year-old female patient showing a noticeable recovery with NAC therapy who had picked the skin on her arms and legs since the age of 15, especially skin areas that were not smooth. She could not control her picking behavior and felt relaxed after she picked her skin. Skin infections occurring after picking required antibiotic therapy. She was started on 1200 mg/day of NAC to decrease her skin-picking behavior. There was a 50% improvement at the end of the first week and she had a full recovery from her skin-picking behavior with 1800 mg/day[3].

CONCLUSION

The results derived from the seven publications that were reviewed can be summarized as follows:

1. In view of all the research data and case reports, it is obvious that there is a need for controlled studies on the use of NAC and other glutamate modulators in OCRD.
2. Considering that individuals' quality of life and functioning are adversely effected from OCRD, it seems important to specify the treatment options that can be used.
3. NAC is superior to other agents that act on glutamate because it has few side effects and low costs.
4. In view of all the results, studies on the use of NAC in OCRD seem to be promising.

There is a need for a large number of studies to be conducted on NAC's mechanism of action and its use in neuropsychiatric diseases. It seems important to study areas such as the use of NAC as a single or additional therapy in neuropsychiatric disorders, duration of treatment, drug dose intervals and results of long-term use. Oxidative stress and dysregulation of glutamate have been associated with a number of psychiatric disorders, such as addiction, Alzheimer's and Parkinson's diseases, bipolar depression, schizophrenia, substance use, pathological gambling, and OCRD. The efficacy of NAC on oxidative balance and modulation of glutamate metabolism makes it a compound worth pursuing. While there are studies with positive results, these suffer from methodological problems and need to be repeated, NAC can be considered as a promising drug for neuropsychiatric disorders, but it should be further investigated.

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