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In Adult Patients with Obsessive Compulsive Disorder (OCD), is the Amino Acid N-Acetyl Cysteine (NAC) Effective in Reducing Severity of OCD?

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In adult patients with Obsessive Compulsive Disorder (OCD), is the amino acid N-Acetyl Cysteine (NAC) effective in reducing severity of OCD?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "In adult patients with Obsessive Compulsive Disorder (OCD), is the amino acid N-Acetyl Cysteine (NAC) effective in reducing severity of OCD?"

STUDY DESIGN: Review of three English language primary studies, published between 2015-2017.

DATA SOURCES: Three randomized controlled trials (RCTs) were found using PubMed-NCBI. These studies analyzed the effectiveness in reducing the severity of OCD in adults with OCD.

OUTCOME MEASURED: The main outcome measured was a reduction of OCD severity after taking N-Acetyl Cysteine. Outcomes were measured using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Participants answered a 67 part questionnaire about their everyday habits. From the questionnaire, the interviewer generated a list of target OCD symptoms. The target symptoms were then used in 19 interview style questions asking about the severity of each symptom. The severity of those symptoms range from 0-4, with 4 being the highest severity. Questions 1-10 were added together for a Y-BOCS final score, based on the patient's responses.

RESULTS: There was an overall reduction of symptoms from the beginning to end of each trial. However, the placebo group had a similar reduction in symptoms, which made the results statistically insignificant. In the study conducted by Costa et al. 6 of 16 patients in the NAC group versus 5 of 19 patients in the control group had a significant reduction in Y-BOCS score (P=0.40). In the results of the study by Paydray et al. 11 of 22 in the NAC group and 8 of 22 in the control group had a significant reduction in Y-BOCS score (P=0.54). In the study conducted by Sarris et al. 4 of 20 patients in the NAC group versus 4 of 15 in the control group had a significant reduction in Y-BOCS score (P=0.15).

CONCLUSION: The results of the RCTs remain inconclusive as to whether NAC is an effective medication for reducing the severity of OCD in adults. NAC as an alternative treatment to current medications for OCD remains affordable and tolerable, indicating further research is needed for its efficacy.

KEY WORDS: Obsessive Compulsive Disorder, N-acetylcysteine

INTRODUCTION

Obsessive Compulsive Disorder (OCD) is a psychiatric disorder in which a person has intrusive thoughts, ideas, or urges (obsessions) that can force him/her to perform repetitive activities or rituals (compulsions) to relieve the sense of anxiety associated with those thoughts, ideas, or urges.[1-3] To be diagnosed with OCD, a person can have obsessions, compulsions, or both, and his/her symptoms are not attributable to another disorder and must cause clinically significant stress, according to the DSM-V.[3] While symptoms can vary, OCD can be categorized into four characteristic groups: cleaning, symmetry, forbidden or taboo thoughts, and harm.[3] Cleaning encompasses the fear of contamination, which causes the person to have sanitation rituals such as washing his/her hands multiple times. Symmetry comprises of repeating, ordering, and counting compulsions.[3] Forbidden or taboo thoughts involve beliefs that are not acceptable to society such as aggressive or sexual obsessions and compulsions.[3] Harm revolves around thoughts or images about others or himself/herself getting hurt; he/she will continually verify that harm won't occur.[3] Quality of life and psychosocial performance are severely reduced in persons with OCD. Anxiety and task completion are time consuming and debilitating, demanding more than an hour of time per day.[1,3]

OCD affects approximately 2.3% of the U.S. population as a lifelong disorder, while 1.3% of the U.S. population is affected for a 12-month period.[3] Males are more affected in adolescence while females are more affected as adults.[3] Individuals with existing disorders such as schizophrenia, schizoaffective, Tourette's, bipolar, or eating disorders have a higher prevalence of OCD.[3] Seventy-six percent of people with OCD have a comorbid anxiety disorder.[3]

While the current cost is unknown, in 1990 OCD was estimated to cost 8.4 billion dollars.[4] This includes direct costs of services and medications, but also indirect costs such as loss of productivity and unemployment. In 1990 the estimated indirect costs totaled 74%, or 6.2 billion dollars, of the total yearly cost of OCD.[5] In 2005 the total cost increased to 10.6 billion dollars, with indirect costs not calculated.[4] In a nationwide survey conducted between 2003 and 2010, 728,644 healthcare visits per year were by people diagnosed with OCD.[6] Visits varied from medication changes to psychotherapy, with a range of psychiatrists, primary care physicians, and other specialties treating these patients.[6]

OCD is believed to be caused by a combination of genetic and environmental factors. There is increased incidence throughout families. Factors such as trauma, major life events, premenstrual periods, and postpartum periods correlate to patients with new diagnoses or exacerbations of OCD.[3] Research suggests that OCD involves the cortico-striato-thalamo-cortical (CSTC) circuit, the orbitofrontal cortex, and the ventromedial striatum within the brain.[3] In these regions, there is dysregulation and increased levels of the neurotransmitter, glutamate.[3] Excess glutamate causes hyperactivity and oxidative stress which correlates to symptoms found in OCD patients.[3] OCD typically has a gradual onset in the third decade of life and can consist of wide range of obsessions and/or compulsions. Standard methods used to treat OCD include selective serotonin reuptake inhibitors (SSRIs), clomipramine, cognitive behavioral therapy, and atypical antipsychotics.[1,2,7] Other medications include riluzole, memantine, topiramate, lamotrigine, and NAC.[2]

NAC is a prodrug of cysteine that acts to modulate the glutamate-cysteine antiporter within the CSTC circuit, orbitofrontal cortex, and the ventromedial striatum.[8] As mentioned above, OCD patients have been found to have excess glutamate within glial cells.[8,9] By providing

NAC, extracellular cysteine levels are increased, allowing the antiporter on glial cells to exchange extracellular cysteine for intracellular glutamate.[1] The excess glutamate then leaves the cell and binds with inhibitory receptors on neighboring neurons, preventing synaptic release of glutamate.[9] A glutamate decrease within glial cells indirectly reduces oxidative stress these cells undergo, thereby reducing cellular damage.[8,9] Additionally, cysteine is a component of glutathione, an antioxidant that directly removes reactive oxygen species and nitrogen species from glial and neuronal cells.[1,9] By providing the prodrug, NAC, levels of glutathione are increased, allowing for increased removal of reactive oxygen species that would otherwise damage the cells.[1,8,9]

There is no cure for patients with OCD. However, there are multiple therapies aimed at reducing the symptoms the patients experience. This paper evaluates three double-blind, randomized controlled trials comparing the efficacy of NAC as an oral medication for reducing the severity of OCD.

OBJECTIVE

The objective of this selective evidence based medicine review is to determine whether or not "In adult patients with Obsessive Compulsive Disorder (OCD), is the amino acid N-Acetyl Cysteine (NAC) effective in reducing severity of OCD?"

METHODS

Specific search criteria were used to obtain three studies for this review. The studies all were randomized, double-blind, placebo controlled clinical trials that used non-pregnant adults 18-70 years old with OCD. Additional criteria included use of the Y-BOCS scale to measure reduction in OCD after a trial of NAC. One of the studies selected patients with a Y-BOCS score of $\geq$21 while another study selected patients that scored $\geq$16 on the Y-BOCS.[2,8] The third study

chose patients that scored ≥16 on the total Y-BOCS but also chose patients if they scored ≥10 for the presence of only compulsions.[1] All of the studies used a titrated dose of NAC, with two studies reaching a daily dose of 3000mg, and one study reaching a daily dose of 2000mg.[1,2,8] One study did not allow patients to have previously taken any psychotropic medications six weeks prior to the study. The other studies had more leniency with allowing stable medications to be taken throughout the trial.[1,2,8] One study also had patients taking fluvoxamine in both the experimental and control groups during the course of the trial.[2] All three studies were double-blind randomized control trials that used visual and taste matched placebos to the NAC.[1,2,8] They all measured the reduction in severity of OCD using the Y-BOCS.

To obtain this data, the key words "Obsessive Compulsive Disorder" and "N-acetylcysteine" were used. All of the data sources were published in English and were found by the author via PubMed-NCBI. Selection was based on clinical question relevance and whether the outcomes presented in each study were patient oriented evidence that matters (POEMs). Inclusion criteria for this review consisted of randomized controlled double-blind studies that were published after 2013. Exclusion criteria for this review were patients under 18 years old or pregnant.[1,2,8] The studies used for this review presented the statistics for Control Event Rate (CER), Experimental Event Rate (EER), Relative Benefit Increase (RBI), Absolute Benefit Increase (ABI), and Number Needed to Treat (NNT). Additionally, a p-value of <0.05 was considered statistically significant for the results of each trial. The demographics of each study are presented in Table 1.

Table 1 - Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Costa, 2017 (1)	RCT	39	18-65	Patients with OCD diagnosis, based on the Diagnostic and Statistical Manual-IV (DSM-IV), who failed to respond to ≥1 previous treatment and had a total Y-BOCS ≥16, or ≥12 on the compulsions Y-BOCS scale. Other medications such as mood stabilizers, stimulants, sedatives, and hypnotics were allowed if they were stable for 1 month. Antipsychotics and clomipramine were allowed if they were prescribed 2 months prior and stable one month.	Presence of any psychotic disorder, liver disease, asthma, previous psychosurgery, current drug abuse/dependence, suicide risk, comorbidities preventing use of protocol medications, previous exposure to NAC, pregnancy, lactation, or women without reliable birth control methods.	4	NAC, 1200mg/day x1wk, 2400mg/day x1wk, 3000mg/day x14wks. Patients also continued regimen of medications prescribed before the RCT.
Paydray, 2016 (2)	RCT	46	18-60	Patients who met the DSM-IV Text Revision criteria of mod-severe OCD, scoring >21 on Y-BOCS who did not receive psychotropic medications 6wks prior to study.	Suicidal ideation, seizures, substance dependence, IQ<70, comorbid DSM-IV axis 1 disorders, neurological, cardiac, renal, hepatic, or other serious medical illness, psychosurgery, head trauma, pregnancy, breastfeeding	2	NAC, 1000mg/day x1wk, 2000mg/day x9 wks. Patients also had fluvoxamine 100mg/day x4wks, 200mg/day x6wks.
Sarris, 2015 (8)	RCT	35	18-70	Patients who fulfill the DSM-IV text revision criteria, scoring ≥16, without any treatment for the past 4 weeks if this is the 2nd medication they are trying, or 12 weeks if this is the 1st medication they are trying. Females were required to use effective contraception if of childbearing age and sexually active.	Current engagement in a psychological program, a clinically unstable medical disorder, bipolar I disorder, epilepsy, schizophrenia, asthma, or recent gastrointestinal ulcers, pregnancy, breastfeeding, consumption of ≥250mg NAC, 100 mg selenium, or 500 IU Vitamin E.	1	NAC, 1000mg/day x1wk, 2000mg/day x1wk, 3000mg/day x14wks. Patients also continued regimen of medications prescribed before the RCT.

OUTCOMES MEASURED

The outcome measured, a reduction in the severity of OCD, was a POEM. It was obtained using the self-reported Y-BOCS. The exam begins with a 67 part questionnaire that patients fill out. Based on the responses from the questionnaire, the interviewer creates a list of target symptoms.[10] The interviewer then uses the target symptoms to ask 19 additional interview-style questions, where the patient rates his/her symptoms on a scale of 0-4.[10,11] The higher the number, the higher the severity. Based on the patient's responses, questions 1-10 are added together for a total Y-BOCS score.[10,11] Questions 11-19 are excluded from the total score because they are considered investigational.[11]

RESULTS

In the study conducted by Costa DLC, Diniz JB, Requena G, et al., there were 39 patients age 18-65 originally included in the trial, with 22 allocated to the control group, and 17 allocated to the experimental group.[1] A modified intention-to-treat analysis was conducted because two patients (one from the placebo group and one from the experimental group) dropped out before week three, which were excluded from the analysis.[1] Two other patients from the placebo group dropped out before the end of the trial, but their missing data was imputed using the last observation carried forward.[1] The dropout rate between the two groups was not significant, indicating congruence between the groups throughout the trial (NAC= 1 of 17, placebo= 3 of 22; $p=0.43$).[1] This study is generalized to male and non-pregnant female adults but limited to patients with treatment-resistant OCD. The experimental group received NAC 1200mg/day for one week, 2400mg/day for the next week, and 3000mg/day for the following 14 weeks.[1] The experimental group was given a taste and visually matched placebo. All patients in the study were also taking an SSRI that they were stable on before starting the study; mood stabilizers,

stimulants, sedatives, and hypnotics had to be stable for at least one month; antipsychotics and clomipramine had to be stable for at least two months.[1] Y-BOCS were administered every week for the first three weeks and then every two weeks until the end of the 16 week trial.[1]

Furthermore, the data gathered in the study was provided as dichotomous data, allowing for the calculations demonstrated in Table 2 below. Successful reduction in symptoms was considered a reduction in $\geq$25% in Y-BOCS score from week zero to week sixteen.[1] From the beginning to end of the trial, the NAC group had an average reduction of 4.3 points (25.6$\pm$4.4 to 21.3$\pm$8.1) while the placebo group had an average reduction of 3 points (24.8$\pm$3.8 to 21.8$\pm$6.0).[1] In the experimental group, 6 of 16 patients met the criteria for successful reduction in the Y-BOCS score, while 5 of 19 patients in the placebo group met the criteria for a successful reduction in the Y-BOCS score (P=0.40).[1] For every eight patients that are treated with NAC, one patient will have a reduction of $\geq$25% on the Y-BOCS. This trial had a small treatment effect.

Table 2: Efficacy of NAC in Reducing Severity of OCD Compared to Placebo

Study	**CER**	**EER**	**RBI**	**ABI**	**NNT**
Costa[1]	0.26	0.40	0.54	0.14	8
Paydray[2]	0.36	0.50	0.39	0.14	8
Sarris[8]	0.27	0.20	0.54	-0.07	-14

In the study led by Paydray K, Akamaloo A, Ahmadipour A, et al., 22 patients were included in each the experimental and control group with ages ranging from 18-60.[2] The data were presented as intention-to-treat analysis, meaning each subject was kept in the group to which he/she was originally assigned. The difference between Y-BOCS scores in each group did not differ significantly (NAC= 27.04$\pm$4.39, placebo= 25.81$\pm$3.83; P=0.32).[2] This study was generalized to male and non-pregnant female adults with OCD. The experimental group received

1000mg/day of NAC for the first week, and 2000mg/day for the remaining nine weeks.[2] The control group was given a placebo in place of the NAC for the same length of time.[2] Both groups were also given 100mg/day of fluvoxamine for the first four weeks and 200mg/day for the remaining six weeks.[2] Patients included in this study did not receive psychotropic medications six weeks prior to starting the NAC or placebo and fluvoxamine.[2]

The Y-BOCS was administered at week zero, four, eight, and ten.[2] Similar to the first study, a reduction in Y-BOCS score $\geq$25% was considered successful treatment.[2] In the results of the trial, both groups had patients with reduced severity of OCD. Of the 22 patients in the NAC group, 11 achieved successful treatment outcomes while 8 of 22 within the placebo group had successful treatment.[2] Comparing these results, there was no significant difference in reduction of symptoms (P=0.54).[2] The data was presented as dichotomous data, which allowed for the calculations shown in Table 2. This trial had a small treatment effect. For every eight patients that are treated with NAC, one patient will have a reduction of $\geq$25% on the Y-BOCS.

The final study from Sarris J, Oliver G, Camfield DA, et al. included 20 patients in the experimental group and fifteen patients in the placebo group, ranging from 18-70 years old.[8] This study was generalized to male and non-pregnant female adults and limited to patients with OCD. In this study, the experimental group received 1000mg/day for the first week, 2000mg/day the second week, and 3000mg/day for the following 14 weeks.[8] Patients were allowed to remain on prior medications if they were stabilized for at least four weeks before starting the trial or 12 weeks if this was the patient's first OCD treatment.[8] Compliance was measured by how consistently the patient took the NAC; a consumption rate of 75% or greater was considered compliant.[8] The Y-BOCS was administered at baseline and every four weeks until the end of the trial at week 16. Treatment was considered successful if there was a decrease in Y-BOCS score

of ≥35%.[8] Over the course of the trial, there were more patients by percentage in the control group that had Y-BOCS symptom reduction. Collectively the NAC group had an average reduction of 5.42 points (25.65±5.06 to 20.23±8.86).[8] The placebo group had an average reduction of 4.50 points (25.87±4.70 to 20.82±8.29).[8] Of the 20 patients in the NAC group, 4 patients were considered responders to treatment; of the 15 patients in the placebo group, 4 patients were considered responders (P=0.15).[8] The data was presented in dichotomous form, allowing for the calculations presented in Table 2. This trial had a very poor treatment effect. For every 14 patients treated with NAC, its use will have a negative effect on one patient in reducing the severity of OCD.

DISCUSSION

When comparing the total point decrease among the experimental groups and control groups, the experimental group had a greater average point reduction in all three trials. However, the difference between the experimental and control groups based on p-values was calculated to be insignificant each time. Placebo groups should not have had a significant reduction in Y-BOCS scores alongside the NAC group. In one trial, there were actually more patients in the control group than the NAC group that had decreased Y-BOCS scores.[8] These results make the effectiveness of NAC in patients with OCD difficult to assess.

Aside from its possible role in reducing OCD severity, NAC is most commonly known for its use in reversing acetaminophen toxicity. With its role in the glutaminergic system and its antioxidant effects, it has been shown to be beneficial in chronic diseases such as chronic obstructive pulmonary disease, contrast induced nephropathy, idiopathic pulmonary fibrosis, and influenza.[12] More importantly, there has been efficacy among patients taking NAC with mental health disorders.[12] In studies of patients with schizophrenia, bipolar disorder, and nail-biting,

there was a reduction of disease specific symptoms. However, the schizophrenia, bipolar disorder, and nail-biting studies all lasted 24 weeks, whereas two trials reviewed in this paper lasted 16 weeks and one trial lasted ten weeks.[1,2,8,12] An extended study may have shown more beneficial outcomes for patients with OCD, as NAC demonstrated benefit in other mental disorders when used for a longer time period. A longer duration may have also decreased the number of responders among the placebo groups.

In addition to duration of trials, there were other limitations. Each of the studies used sample sizes of less than 50 patients.[1,2,8] Once patients were split in half for an experimental group and control group, 25 or less patients used NAC during each of the trials. While the studies were double-blind and placebo controlled, limited sample sizes can increase error margin. Also, compliance with medications could have influenced the results. One trial reported a compliance threshold of 75% of pills taken throughout the 16 week study.[8] This means that patients would still be considered compliant even if they missed up to four weeks of treatment. The other trials did not state compliance thresholds that patients were required to meet.

In addition, two of the studies allowed patients to continue taking psychotropic medications such as SSRIs and antipsychotics.[1,8] While those medications were stabilized prior to initiating the trial of NAC, drug interactions were not specifically studied in these trials. Previous medications the patients were taking could have modified the effect of NAC.

In regard to NAC's tolerability, very few adverse outcomes were reported throughout the three trials. The only significant adverse outcomes were stomach/abdominal pain and heartburn.[1,8] Other adverse effects that were reported occurred in both the experimental and placebo groups thus making them nonsignificant. NAC's tolerability, in addition to its wide availability over the counter and relatively cheap cost make its use more desirable. NAC can be

found for around $10-20 for a 120 count of 600mg tablets.[13] However, these benefits do not prove useful for OCD patients when the data suggests it is not effective in reducing OCD symptom severity when compared to a placebo. Further studies need to be conducted to evaluate reduction in Y-BOCS score among patients taking NAC.

CONCLUSION

The evidence for whether the amino acid NAC is effective in reducing the severity of OCD in adults is inconclusive. Among the three RCTs used in this review, it was found that patients' Y-BOCS scores decreased. However, these results are insignificant because the placebo group in each trial also had a decrease in Y-BOCS score. Two trials needed to treat eight patients before seeing benefit in one patient. The third trial, based on the percentage of patients in the NAC and control groups that met criteria for OCD symptom severity, indicated that one patient would have a negative effect for every 14 patients that were treated with NAC.

It would be worthwhile to investigate the use of NAC for OCD further due to its reduction in symptoms that occurred, benefits in other mental health disorders, its tolerability, and minimal cost. Future studies could include longer trial duration, more participants, or higher dosages of NAC. Additionally, exploring NAC as monotherapy or dual therapy with one consistent medication may provide significant results. This would eliminate one of the limitations of the study that allowed patients to take other medications, possibly decreasing the efficacy of NAC.

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