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Oral N-AcetylCysteine in the Treatment of Obsessive-Compulsive Disorder: a systematic review of the clinical evidence

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~~TÍTULO DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Oral N-Acetylcysteine in the Treatment of Obsessive-Compulsive Disorder: a systematic review of the clinical evidence

ORIENTADOR

Ricardo Jorge Silva Assunção Torres Moreira

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 13/03/2018

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Oral N-Acetylcysteine in the Treatment of Obsessive-Compulsive Disorder: a systematic review of the clinical evidence

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Abbreviations: ACC - anterior cingulate cortex; BAI - Beck Anxiety Inventory; CBT - cognitive-behavioral therapy; CGI-I - clinical global impression-severity; CSTC - cortico–striato–thalamo–cortical; dACC - dorsal anterior cingulate córtex; GOR - grade of recommendation; GSH – glutathione; LOE - level of evidence; mGluR2/3 - metabotropic glutamate receptors; MRI - magnetic resonance imaging; NAC - N-acetylcysteine; NACET - N-acetylcysteine ethyl ester; OCD - obsessive-compulsive disorder; OFC - orbitofrontal cortex; P.O. - *per os*; SRI - serotonin reuptake inhibitors; Y-BOCS - Yale-Brown Obsessive Compulsive Scale

Abstract

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions and/or compulsions. It is a leading cause of morbidity worldwide, as it can interfere with all aspects of life. Despite the adequate treatment trials, half of patients preserve residual or impairing symptoms and serotonin reuptake inhibitors (SRIs) are not free from adverse side effects.

This work aims to systematically review the current evidence available concerning the efficacy of N-acetylcysteine (NAC) in the treatment of OCD.

Nine articles and one poster were included in our systematic review. Three of the five case reports encompassed showed a marked improvement in Y-BOCS, one failed to prove the efficacy of NAC in the treatment of OCD and the other one reported contradictory results. Regarding the five randomized controlled trials (RCTs) included, three reported significant improvement in Y-BOCS in the NAC treated group and the other two showed no significant improvement. NAC has an optimal tolerability profile, even in higher doses, and the most frequently reported adverse events were gastrointestinal.

Despite the degree of evidence being D, in our opinion the potential of NAC is underestimated.

Considering its exceptional tolerability profile, the use as an add-on agent should be contemplated, on an ad hoc basis.

Keywords: N-acetylcysteine; obsessive-compulsive disorder; nutraceutical

1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions and/or compulsions.[1] Obsessions are recurrent, persistent, distressing thoughts, mental images, or impulses that are experienced as intrusive and unwanted. Patients with OCD try to neutralize the anxiety and discomfort from the obsessions with compulsions. Compulsions are repetitive behaviors or mental acts that a person with OCD feels the urge to do in response to an obsessive thought. In fact, performing compulsions when obsessions recur, leads to reinforcement and repetitive behavior, due to the transitory relief of stress.[2]

OCD is a leading cause of morbidity worldwide with 1.1%–1.8% annual prevalence [1] and 2%–3% lifetime prevalence.[3] It is a potentially disabling psychiatric disorder that can interfere with all aspects of life, such as work, school, and personal relationships. The age at onset is bimodal, with peaks in late childhood or early adolescence and early adulthood.[4]

Converging lines of evidence link OCD to abnormalities in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), striatum, and thalamus.[5,6] Orbitofrontal cortex is functionally divided into two parts[7]: the lateral OFC is hyperactivated (during symptom provocation[8,9] and proportionally to OCD symptom severity[10]) and the medial OFC is hypoactivated (inversely correlated with symptom severity).[14] The dorsal anterior cingulate cortex (dACC) has also been implicated, proved not only by functional neuroimaging [11,12] and treatment studies [13], but also by the decrease in OCD symptoms after anterior cingulotomy.[14,15]

At the neurocircuit level, a combination of neuroimaging, neuropsychological and treatment studies have provided substantial evidence that the pathophysiology of OCD entails abnormal functioning along cortico–striato–thalamo–cortical (CSTC)

pathways.[2,10,16–18] Activity in this circuit was elevated in the basal state, accentuated during symptom provocation[19–21] and nearly normal with successful treatment.[22,23]

At a neurotransmission level, serotonin seems to have an important role in the pathophysiology of OCD, essentially due to the discovery of serotonin reuptake inhibitors (SRIs) efficacy in the treatment of OCD.[24] In fact, brain imaging studies reported that certain regions in the brain have reductions in serotonin availability.[25–27] However, as mentioned above, only about half patients respond to treatment with SRIs[28], concluding that an explanation based only on serotonin deficit couldn´t completely illustrate the pathophysiology of this disease.

In addition to the serotonin transporter system, there is growing evidence that disrupted neurotransmission of glutamate, the main neurotransmitter within the CSTC, is implicated in the pathogenesis of OCD.[29,30] Research has shown significantly higher levels of glutamate in the cerebral spinal fluid and several sections of the brain, namely orbitofrontal cortex and caudate[31–33], suggesting a role of glutamatergic hyperactivity and it´s consequent excitotoxicity and oxidative stress, in the pathophysiology of OCD.[29,33–35]

Oxidative stress is attested by lipid peroxidation and alterations to antioxidant systems in serum samples of these patients.[36–38] Symptom severity, as measured by Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, seems to be correlated with increased levels of oxidative stress.[35,37,39]

As OCD is a phenotypically heterogeneous disorder with a broad range of symptomatic expression[40], there has been increasing interest in identifying more uniform subtypes with distinct patterns of co-morbidities and outcomes.[41]

American Psychiatric Association practice guidelines recommend cognitive-behavioral therapy (CBT) that involves exposure and response prevention, and

serotonin reuptake inhibitors (SRIs) as safe and effective first-line treatments for OCD. Despite the adequate treatment trials, 40% to 60% of patients preserve residual or impairing symptoms [42] and SRIs are not free from adverse side effects. The severity and nature of adverse reactions associated with the use of SRIs, particularly in the required higher doses, can often lead to treatment discontinuation. SRIs can lead to adverse effects such as anxiety, insomnia, nausea, diarrhea, headache, constipation, dizziness, sedation, decreased libido and sexual dysfunction.[43–45] In addition to this, current antidepressant treatments need an extended waiting period, usually several weeks or even months, until the onset of symptom improvement.[46]

Consequently, the investigation for more targeted pharmacologic agents and new augmentation strategies are crucial.

Regarding this matter, in 2006, Lafleur and colleagues[47] found promising results with the use of N-acetylcysteine (NAC). In addition to these results, the excellent tolerability profile and low-cost of NAC, raised a large expectation around this pharmacological agent. It cannot be obtained through diet, therefore, supplements are the only source.

NAC is an acetylated precursor of the amino acid cysteine and has been widely used for its recognized ability as an antioxidant, by its metabolic contribution to glutathione (GSH) synthesis, in the treatment of acetaminophen overdose and as a mucolytic.[48]

With oral administration, NAC is almost entirely converted to cysteine in the liver, which is mostly turned into GSH. Nevertheless, the remaining cysteine enters the systemic circulation and crosses the blood-brain barrier.[48] Reaching the brain, cysteine is oxidized to cystine. Extracellular cystine is exchanged by intracellular glutamate by the cystine–glutamate antiporter (or x(c)-system), located mainly on glial cells in the

brain[49], thereby regulating extracellular glutamate levels and promoting cystine entry to the cell.[50] Inside the cell, cystine can be reduced to cysteine, which is the limiting reagent for GSH assembly.[53]

NAC might exert its therapeutic effect on OCD through two main mechanisms.

First, NAC participates in the general antioxidant activities by its metabolic contribution to GSH production by providing an additional concentration of cysteine.[53,54] Increased availability of GSH, scavenges toxic by-products of glutamatergic and dopamine metabolism, reducing oxidative and nitrosative stress, and thus cell damage.[55] (Figure 1)

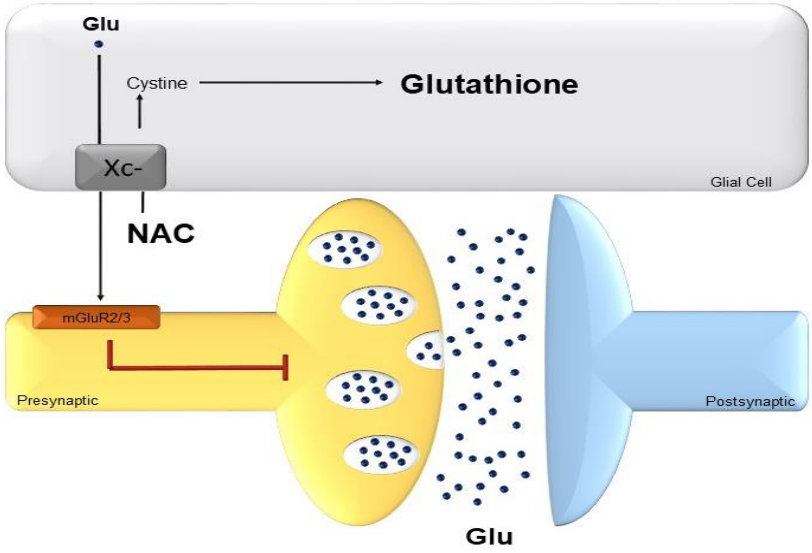

Figure 1: Mechanism of action of NAC. When inside the brain, cysteine is oxidized to cystine. Extracellular cystine is exchanged by intracellular glutamate (Glu) by the cystine–glutamate antiporter (or x(c)-system), thereby regulating extracellular glutamate levels and promoting cystine entry to the cell. Inside the cell, cystine can be reduced to cysteine, which is the limiting reagent for GSH assembly. Non-vesicular glutamate in extracellular space, activates group II metabotropic glutamate receptors (mGluR2/3). These receptors negatively modulate the glutamatergic neurotransmission and excitotoxicity.

Second, NAC modulates glutamatergic neurotransmission. The release of non-vesicular glutamate to extracellular space caused by NAC, activates group II metabotropic glutamate receptors (mGluR2/3). These receptors are predominantly

presynaptic and negatively modulate the glutamatergic neurotransmission and excitotoxicity.[36,60] (Figure 1)

The present work aimed to provide a systematic review of the current evidence available concerning the efficacy of NAC in the treatment of OCD.

2. Methods

A systematic review focusing on the efficacy of NAC on OCD was performed in accordance with PRISMA criteria.[58]

2.1. Search Strategy

An online literature search for publications regarding NAC in the treatment of OCD was conducted, until September 2017, in PUBMED, COCHRANE and SCIENCE DIRECT databases. The search algorithm included search terms - "N-acetylcysteine","acetylcysteine" or "NAC" AND "obsessive compulsive disorder".

2.2. Eligibility Criteria

The inclusion criteria were: (1) clinical trials and case reports studying the use of NAC in the treatment of OCD in adult and pediatric populations, (2) studies investigating the therapeutic effect of NAC as either a stand-alone or adjunctive treatment, (3) articles written in English.

We excluded studies that (1) investigated an OCD-related disorder, as described by DSM-5, (2) did not involve humans, (3) were systematic reviews.

2.3. Study Selection and Data Collection Process

Studies were screened and selected by two reviewers. First, all titles and abstracts were read, and the inclusion and exclusion criteria were applied. Second, the articles

considered for inclusion after selection by title/abstract reading were read fully, and the inclusion and exclusion criteria were applied again. The data collected from each study were: type of study, number of patients enrolled and mean age, co-morbidities of participants and concomitant medication, dose and duration of NAC treatment, outcome measures with respective baseline and endpoint scores.

Table 1
Levels of evidence

Level	Description
1a	SR or meta-analysis of RCTs with homogeneity or Cochrane review with favorable findings
1b	Prospective high-quality RCT (medium sized with N between 50 and 100 or large sized with N over 100 and/or higher validity trials based on adequate follow-up, intent to treat analysis, baseline similarity, equal treatment and dropout rates)
2a	SR of cohort (prospective, nonrandomized) studies with homogeneity
2b	Individual cohort (prospective, nonrandomized) study or low-quality RCT (small sized with N less than 50 and/or lower validity trials based on adequate follow-up, intent to treat analysis, baseline similarity, equal treatment and dropout rates)
3a	SR of case–control (retrospective) studies with homogeneity
3b	Individual case–control (retrospective) study
4	Open label trials, case series or reports
5	Expert opinion without critical appraisal or based on physiology or bench research

RCT: Randomized controlled trial; SR: Systematic review

Table 2
Grade of recommendation

Grade	Description
A	At least one level 1a study or two level 1b studies
B	At least one level 1b, 2a, or 3a study, or two level 2b or 3b studies
C	At least one level 2b or 3b study, or two level 4 studies
D	Level 5 evidence, or troublingly inconsistent or inconclusive studies of any level, or studies reporting no improvements
N	No studies identified

2.4. Level of evidence ratings

We provide a grade of recommendation (GOR) for the use of NAC in OCD based on the level of evidence (LOE) for each study. Using a well-established scale[59], each

study was individually assessed to determine the LOE, ranging from level 1 to 5 (Table 1). After assessing all identified studies, a GOR ranging from A (solid evidence) to D (limited, inconsistent or inconclusive evidence) was assigned (Table 2).

3. Results

3.1. Search and Study Selection

A total of 250 articles were identified by our query. Of these, 240 were excluded because they were review articles, were not performed in humans or included patients with OCD related disorders. Therefore, nine articles and one poster were included in our systematic review. Five of the included articles are double-blind, placebo-controlled trials, and the other 5 are case reports.

3.2. Evidence of effectiveness of NAC

3.2.1. Case reports and case series (Table 3)

In 2005, Lafleur et al.[60] (N = 1; LOE 4), was the first to report the benefits of NAC in OCD. A significant improvement in OCD symptoms was described in a 58-year-old woman with treatment-resistant OCD, by adding NAC to fluvoxamine therapy. Previously, this patient had not improved with other drugs and only had a partial response with 300mg/day of fluvoxamine, therapy that she had been taking for the preceding 12 years. During the 13-week trial, the SSRI drug was maintained throughout the NAC treatment period. The dose used in this study was initiated at 600 mg *per os* (P.O.) daily and titrated upward to a total daily dosage of 3000mg over seven weeks and maintained at this dose for the remaining six weeks. During the trial, there was an improvement on Yale-Brown Obsessive Compulsive Scale score (Y-BOCS). In the first week, was noticed a serious reduction in symptom severity, a drop of 8 points on the Y-BOCS scale (from a baseline score of 32 to 24). At the end of the study, the Y-BOCS

score was reduced to 9, with an overall reduction of 22 points from the beginning of this therapeutic intervention. The patient continued treatment with the same dose of fluvoxamine and NAC, and after a 2-month follow-up visit improvements were consistent.

Posteriorly, in 2013, Van Ameringen et al.[61] (N = 6; LOE 4) failed to demonstrate the efficacy of NAC add-on therapy in adult patients with treatment-resistant OCD. In 5 of the six patients included in this study, no significant improvement of OCD symptoms was reported. The NAC treatment was started at 500 mg daily and was titrated up, depending on the clinical response and tolerability, to a mean dosage at the endpoint of 2800 mg/day. One patient was lost to follow-up after six weeks, and the other five completed 12 weeks of treatment. These five had been taking 3000 mg/day of NAC for 4 weeks at the study endpoint. The overall mean change from baseline score, as measured in Y-BOCS, was -1.3, with only one patient responding to NAC treatment (defined as a Clinical Global Impression-Severity (CGI-I) score of 2 and a 35% reduction in Y-BOCS, at the endpoint), with an overall reduction of 9 (Y-BOCS of 26 at baseline, 17 at endpoint).

Yazici et al.[62] (N = 1; LOE 4), in 2014, reported the recovery achieved by adding NAC to citalopram in a 15-year-old female with treatment-resistant OCD. The patient was supplemented with NAC, which was titrated from 600 mg to 2400 mg daily over six weeks and maintained for further 18 weeks, while treatment with 60 mg/day citalopram was continued. In 24 weeks, a significant drop in symptom severity was detected as measured by the Y-BOCS, with a baseline score of 37 reduced to 9. This is considered a "full response", according to Pallanti and Quercioli[42] response classification (decrease in YBOCS score greater than 35% and a CGI-S of 1 or 2).

More recently, in 2015, these authors have published a series of 5 case reports [63] (N = 5; LOE 4), also in pediatric age. All patients were initially treated with NAC 600 mg daily, as augmentation therapy. The NAC dosage was then titrated up, taking into consideration the clinical response and side effects, to a final dosage that varied from 1800 mg to 3000mg. Four of the 5 participants showed significant improvement with NAC augmentation therapy, after 24 weeks follow-up. Two experienced "full response", as defined above; the other two patients entered "remission", considered when Y-BOCS score is less than 16. The remaining patient, considered as a "non-responder", had a decrease in Y-BOCS score less than 25% and CGI-S of 4. The overall mean change in Y-BOCS from baseline was - 17.

Saraiva et al. (2015)[64] (N = 1; LOE 4) described a complete remission of all symptoms in a 44-year-old man with resistant OCD, after NAC (1200mg/day) augmentation to paroxetine and risperidone. No adverse side effects were reported.

3.2.2. Clinical Trials (Table 4)

To assess the efficacy and safety of NAC, as an augmentation treatment in patients with treatment-refractory OCD, Afshar et al.[65] (N =48; LOE 2b) performed a 12-week randomized, double-blind, placebo-controlled clinical trial. In this study, 48 adult patients, with mean age of 31 years, were randomized into two equal groups and treated with SRIs, at the same dose as in the pre-intervention, plus either placebo or NAC. The intervention group was supplemented with 2400mg NAC daily, which was titrated from 600 mg and doubled weekly considering the clinical improvement and tolerance. The effects of NAC in the reduction of Y-BOCS score were significant over time and in comparison with the placebo group. Likewise, significant improvement in symptom severity, as measured by mean Y-BOCS reduction, was noticed by the end of the eighth week to the end of the study. At study endpoint, the mean reduction in Y-

BOCS score was 11 in the NAC group and 6 in control group. Fifty-three percent of NAC-treated patients evidenced a clinical response at the end of the study, defined as a ≥35% reduction in Y-BOCS score, which was significantly higher than the control group (15%). Regarding side effects, NAC-treated participants experienced significantly higher rates of gastrointestinal adverse events.

In 2015, Sarris et al.[66] (N =44; LOE 2b) published the results of another randomized, double-blind, placebo-controlled clinical trial using a higher dose of NAC, 3000 mg/day (1500mg twice daily), in OCD patients (with ≥16 points in Y-BOCS score, at baseline). In this 16-week study, NAC was titrated from 1000 mg/day and elevated 1000 mg weekly. The mean age of the 44 study participants was 37 years with the majority (70.5%) taking psychotropic drugs, over half (56.8%) having SSRI and about one third (29,5%) were utilizing adjunctive therapies. In term of results, an apparent effect was emerging by week 12, however, at the endpoint, this study failed to show a significant time x treatment interaction for Y-BOCS total score. Despite this, a significant time x treatment interaction was described for the Y-BOCS compulsions subscale in NAC group, with a significant reduction detected at the twelfth week, although dissipated at the sixteenth. Overall, at week 16, 20% of NAC-treated patients evidenced a clinical response, defined as a ≥35% reduction in Y-BOCS score, compared with 27% in placebo group. NAC was well-tolerated with no differences in the total adverse events between the groups. Nevertheless, heartburn was the only clinical adverse event experienced in significantly higher rates in NAC group.

One year later, the same authors [67] explored this data further and released an analysis of potentially modifying factors, such as age, severity and duration of illness, OCD presentation type, baseline anxiety and depression score and the use of

antidepressant medications. They concluded that NAC is more effective in younger people with a shorter duration of OCD diagnosis.

Paydary et al. (2016)[68] (N =44; LOE 2b) performed a ten-week randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of NAC as an augmentation therapy compared to fluvoxamine monotherapy. In this work, 44 adult patients, with moderate to severe OCD (≥21 in Y-BOCS score), were randomized into two identical groups and treated with a SSRI (200mg/day of fluvoxamine), plus either placebo or NAC. All patients took fluvoxamine 100mg/day in the first four weeks and 200mg/day for the rest of the study. The NAC group was supplemented with 2000mg NAC daily (1000mg bid), which was titrated from 1000 mg (500 twice daily) and doubled in the first week. Results analysis revealed a significant time x treatment interaction for the Y-BOCS total score and the Y-BOCS obsession subscale score. The difference between mean scores of Y-BOCS total score, Y-BOCS obsession subscale score, and Y-BOCS compulsion subscale score was not significant between the two groups at each time point of the trial. Furthermore, 12 NAC-treated participants accomplished remission (Y-BOCS score at the endpoint ≤16), compared to 5 patients in the control group, which was almost significant (p=0.062). Regarding side effects, NAC-treated participants did not experience significantly higher rates of adverse events.

Ghanizadeh and colleagues (2017)[69] (N =34; LOE 2b) conducted a randomized, double-blind, placebo-controlled trial to evaluate the possible effects of NAC as an augmentation therapy compared to citalopram monotherapy in the treatment of children and adolescents (10 to 21 years) with OCD. In this 10-week trial, 34 patients were randomized into two groups to receive citalopram (20 to 40 mg/day) plus placebo or citalopram (20 to 40 mg/day) plus NAC (titrated up to 2400mg/day over six weeks). Results showed a significant decrease in the Y-BOCS score in the NAC-treated group

from the fourth week to the end of the trial. In fact, the Y-BOCS score decreased from 21 to 11 in the NAC group during this study. Also, the Y-BOCS score at the end of the trial was significantly different between the two groups. The mean difference of Y-BOCS score was not statistically different between the two groups, at each time point of the trial. The mean score of change for "resistance/control to compulsion"- the sum of items 9 and 10 scores of Y-BOCS - in NAC group was significantly higher compared to placebo. Regarding side effects, there was no statistical difference between groups.

The most recent randomized, double-blind, placebo-controlled trial evaluating the effectiveness of NAC as an SRI augmentation treatment was conducted by Costa et al. (2017)[70] (N =40; LOE 2b). In this trial, an adult treatment-resistant cohort of 40 patients, with a mean age of 38 years, was randomized to NAC (dose titrated from 1200mg/day to a maximum of 3000 mg/day over two weeks) and placebo. All participants were concomitantly taking at least an SRI, by international OCD treatment guidelines.[71,72] The obtained results demonstrated a non-significant difference in Y-BOCS scores between groups at the end of the study. A significant reduction in Y-BOCS score was noticed in NAC treated group over time. However, the control group showed an identical improvement. In a secondary analysis, patients treated with NAC had a significant reduction in anxiety, as measured by Beck Anxiety Inventory (BAI) score, compared to placebo group. The frequency of adverse events did not differ significantly between groups, except for "stomach/abdominal pain".

Table 3
Case reports and case series

Study	Study design	N	Mean Age	Co-morbidities	Dosage	Duration	Concomitant medication	Outcome measure	Baseline score	End point score	Results	Evidence of efficacy
Lafleur et al. 2005 [60]	Case report	1	58	Recurrent MDD (in remission at the time of the trial)	3000mg daily, titrated from 600 mg over 6 weeks	13 weeks	Fluvoxamine (300mg/d)	Y-BOCS	32	9	Marked improvement in Y-BOCS	4
Yazici et al. 2014 [62]	Case report	1	15		2400mg daily, titrated from 600mg over 6 weeks	24 weeks	Citalopram (60mg/d)	Y-BOCS	37	9	Marked improvement in Y-BOCS	4
Yazici et al. 2015 [63]	Case Series	5	11	MDD[b,d]; Epilepsy[d]	1800-3000mg daily, titrated from 600mg	24 weeks	Citalopram (60mg/d) and Aripiprazole (20mg/d)[a1] Clomipramine (150mg/d) and Aripiprazole (30mg/d)[b1] Clomipramine (150mg/d)[c1] Citalopram (60mg/d)[d1] Fluoxetine (30mg/d)[e1]	Y-BOCS, CGI-S	39[a] 39[b] 37[c] 39[d] 34[e]	13[a] 35[b] 23[c] 23[d] 9[e]	Marked improvement in Y-BOCS in 4 of the 5 patients	4
Saraiva et al. 2015 [64]	Case Report	1	44	NR	1200mg/d	NR	Paroxetine (60mg/d) and Risperidone (2mg/d)	NR	NR	NR	Complete remission of all symptoms	4
Van Ameringen et al. 2012 [61]	Case Series	6	54	Tourette's syndrome [a2]; MDD [a2; b2; f2]; dysthymia [a2; f2] ; skin picking [f2] ; trichotillomania [f2] ; ADHD [f2] ; MDE[c2] ; panic disorder with agoraphobia[d2]; social phobia [d2] ; generalised anxiety disorder [d2] ; substance abuse [d2]	Mean of 2800 mg/d, titrated from 500mg (5 patients had been taking 3000mg/d for 4 weeks at study endpoint)	12 weeks	All patients were taking 2 or more psychotropic agents	Y-BOCS, CGI-S	31 [a2] 29 [b2] 26 [c2] 34 [d2] 31 [e2] 25 [f2]	32 [a2] 36 [b2] 17 [c2] 30 [d2] 28 [e2] 25 [f2]	Only 1 met response criteria	4

Abbreviations: a1: case 1 from Yazici et al. 2015; b1: case 2 from Yazici et al. 2015; c1: case 3 from Yazici et al. 2015; d1: case 4 from Yazici et al. 2015; e1: case 5 from Yazici et al. 2015; NR: not reported; a2: case 1 from Van Ameringen et al. 2012; b2: case 2 from Van Ameringen et al. 2012; c2: case 3 from Van Ameringen et al. 2012; d2: case 4 from Van Ameringen et al. 2012; e2: case 5 from Van Ameringen et al. 2012; f2: case 1 from Van Ameringen et al. 2012; ADHD: Attention deficit hyperactivity disorder; MDD: major depressive disorder; MDE: major depressive episode; NAC: N-acetylcysteine; CGI-S: Clinical Global Impressions severity

Table 4
Clinical Trials

Study	Study design	N	Age -Mean -Range	Co-morbidities	Dosage	Duration -With titration -Without titration	Concomitant medication	Outcome measure	Mean Baseline score	Mean End point score	Results	Evidence of efficacy
Afshar et al. 2012 [65]	RDBPCT	48(39)	31 18-45	NR	2400mg daily, titrated from 600mg	12 weeks 9 weeks	SRI ONLY*	Y-BOCS, CGI-S and CGI-I	28	17	Significant improvement in Y-BOCS	2b
Sarris et al. 2015 [66]	RDBPCT	44(34)	37 18-70	56.8% had a DSM-IV diagnosed comorbid psychiatric disorder	3000mg daily titrated from 1000mg	16 weeks 13 weeks	70.5 % psychotropic drugs; 56.8% SSRI; 29.5 % adjunctive therapies such as antipsychotics. [#]	Y-BOCS, CGI-S; CGI-I; HAM–A; MADRS; GHQ-28	27	22	No significant improvement in Y-BOCS; Significant reduction in Y-BOCS compulsions subscale score at week 12	2b
Paydary et al. 2016 [68]	RDBPCT	44(44)	33 18-60	Comorbid DSM-IV axis I disorders were exclusion criteria	2000mg daily titrated from 1000mg	10 weeks 9 weeks	Fluvoxamine ONLY (200mg/day) [+]	Y-BOCS	27	NR	Significant improvement in Y-BOCS total score and in Y-BOCS obsession subscale score	2b
Ghanizadeh et al. 2017 [69]	RDBPCT	34(29)	16 10-21	NR	2400mg daily titrated from 600mg	10 weeks 4 weeks	Citalopram ONLY (20 to 40 mg/day) [+]	Y-BOCS; PedsQL™ 4.0	21	11	Significant improvement in Y-BOCS score	2b
Costa et al. 2017 [70]	RDBPCT	40(35)	38 18-65	OCD only 22.5%	3000mg daily titrated from 1200mg	16 weeks 14 weeks	At least an SRI* SRI ONLY 25% SRI+ antipsychotic 37.5% SSRI+clomipramine12.5 % SRI+other [&]25%	Y-BOCS; BAI; BDI; BABS; DY-BOCS	26	21	No Significant improvement in Y-BOCS score but significant reduction in BAI score	2b

Abbreviations: RDBPCT: randomized, double-blind, placebo-controlled trial; SRI: Serotonin Reuptake Inhibitor; SRI: Serotonin reuptake inhibitor; *: The SRI drug is not specified; [#]: stable treatment regimen for a minimum of 4weeks of current treatment and a minimum of 12 weeks if it was their first OCD treatment; HAM–A: Hamilton Anxiety Rating Scale; MADRS: Montgomery– Asberg Depression Rating Scale; GHQ-28: General Health Questionnaire; (CGI–S, CGI–I): Clinical Global Impression Scales–Severity and –Improvement; PedsQL™ 4.0: Pediatric Quality of life Inventory; [+]: initiated with the study; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BABS: Brown Assessment of Beliefs Scale; DY-BOCS: Dimensional Y-BOCS; [&]: mood stabilizers, sedatives, hypnotics, other antidepressants, and stimulants

4. Discussion

In a field where current treatments are limited, have suboptimal efficiency and an extensive spectrum of side effects, the search for alternatives is essential. Some authors suggest that NAC, due to its antioxidant effects and glutamatergic neurotransmission modulation, may be a promising pharmacological treatment for OCD. We systematically reviewed all published studies (in English) up to date assessing the efficacy of NAC in OCD, including clinical trials, case series and case reports.

Since the first case report in 2006 [60], five clinical trials, 2 case reports, and 2 case series have been published. All case reports and case series demonstrated a marked improvement in symptoms with NAC augmentation therapy, except that carried out by Van Ameringen et al.[61] This failure could be attributable to some factors. First, the shortest duration of NAC intake at the maximum dose (4 weeks), compared to Lafleur et al.[60] (7 weeks), Yazici et al.[62] (18 weeks) and Yazici et al.[63] (at least 22 weeks). Second, half of the participants (3 out of 6) also had at least one comorbid diagnosis, other than depression. To corroborate this hypothesis, the responder patient had a history of only one comorbid disorder, which was a previous episode of major depressive disorder. Depression is highly prevalent during the natural course of OCD. Third, although all patients reported full compliance with treatment, one cannot be entirely sure that this is true, as they had to purchase and consume the correct dose of NAC on their own. The authors have not objectively verified the adherence to an adequate treatment regimen. In the other studies, similar problems could have also occurred. However, compliance may have been more accurate since the patient in the Lafleur et al. case report [60] was at the inpatient unit throughout the treatment and the other two studies were conducted on children under parental care.

On the other hand, several factors may have contributed to an overestimation of the effect of NAC in the studies mentioned above. For example, the patient of Lafleur et al.[60] was hospitalized during the treatment period, receiving supportive psychotherapy, which was not a formal or manual driven cognitive-behavioral treatment plan but may have positively influenced the results. It is also important to note that in “case 1” of Yazici et al.[63], the introduction of NAC was made only after four weeks of the increase of citalopram and this drug could have elicited its full response during the study.

In Saraiva et al.[64] no obsessive symptom rating scale was used. The "classification" of the symptomatic improvement was based on the patient's interview and report.

The five clinical trials included in this review showed non-consensual results; 3 of them proclaimed NAC as a promising therapy in OCD patients. After the full analysis of their methodologies, we could delineate some aspects that can justify their differences.

In Afshar et al.[65], Paydary et al.[68] and Ghanizadeh et al.[69] the concomitant medication used during NAC supplementation was composed of only one drug, in particular, an SRI. The other two studies used different concomitant psychotropic drugs between participants and in Sarris et al.[66] NAC was used in monotherapy in 29.5% of patients.

Apparently, the existence of comorbidities may mitigate the therapeutic effects of NAC in OCD. In Sarris et al.[66] almost 60% of patients had a comorbid psychiatric disorder, and in Costa et al.[70] only 22.5% suffered only from OCD. It would be important to know the specific psychiatric comorbidities. Nevertheless, some clinical trials did not record any information about comorbidities in their participants. The clinical trials in which patients have the higher mean age are the same that have not

achieved significant positive outcomes. However, we have to keep in mind that older patients may also be the ones with longer disease duration. Hence, this factor, and not the age itself, can be the real modifying factor for NAC efficacy. This possibility was suggested in a post hoc analysis of the clinical trial conducted by Sarris et al.[67]

In the clinical trial of Sarris et al.[66] a 75% tablet consumption rate was considered to be the minimum threshold for compliance. Therefore, the low response rate reported could be attributable to the suboptimal patient compliance. These differences could also be explained by the fact that to achieve maximum NAC effect it would require a treatment duration over than 16 weeks. Considering the titration phase, these study periods did not reflect the duration of full NAC dose.

We may not forget that OCD has a heterogeneous neurobiology nature. Therefore, the efficacy of NAC could be limited to a subset of people with polymorphisms in glutamate genes. Additionally, the necessary NAC dose to perform its neurobiological functions could be different for a subset of patients.

Ghanizadeh et al.[69] and Sarris et al.[66] demonstrated a higher reduction in compulsions compared to obsessions. However, Paydary et al.[68] showed the opposite results. For this reason, efforts must be made to explore whether NAC may exert a preferential effect on compulsions or obsessions.

Future clinical trials need to address some important methodological issues to provide more definitive answers regarding the benefits of NAC for OCD. For example, there is a crucial need for larger samples to detect moderate or small effect sizes. Additionally, trials may also need longer follow-up times, as it is not clear the NAC latency time for efficacy and if this effect can be maintained over time. It would be important to sustain the follow-up for some time after discontinuation of NAC, in order

to detect symptom relapsing. Dose-finding studies are still a need, as it remains to be demonstrated if higher doses correlate with greater efficacy.

Future research with magnetic resonance imaging (MRI) or functional MRI brain imaging would also be important, in order to understand in more detail what are the specific effects of NAC in brain activity that contribute to reduce symptoms in some patients and, consequently, expand the knowledge of the pathophysiology of this disease.

The beneficial effects of NAC could also be limited by its low bioavailability. Therefore esterification of the carboxyl group of NAC to produce N-acetylcysteine ethyl ester (NACET) would enhance its lipophilicity and, consequently, its pharmacokinetics[73]. In this way, NACET could be employed in future clinical trials as it holds the potential to be more effective than NAC.

As we expected, NAC used in doses ranging from 1200 mg to 3000 mg, has proved an optimal tolerability profile and the most frequently reported adverse events were gastrointestinal. This information is in accordance with previous research using NAC for other diseases. In fact, De Rosa et al.[74] showed that doses up to 8000 mg/day are not known to cause any clinically significant adverse reaction.

Regarding the level of evidence of the studies included in this systematic review, and the fact that some of these studies have not proven the efficacy of NAC in the treatment of OCD, we consider that the GOR for using this pharmacological agent in the treatment of OCD is D.

5. Conclusion

We would expect NAC to have a beneficial effect on OCD symptoms due to what is known about the pathophysiology of OCD. However, up to now, there are contradictory results.

It must be taken into consideration that the two RCTs that have not showed positive results tend to be the ones with more confounding variables, such as the use of different concomitant psychotropic drugs or the existence of other psychiatric comorbidities.

In this way, despite the degree of evidence being D, our opinion is that the potential value of NAC is being underestimated. Considering the level of disability caused by resistant OCD, and the exceptional tolerability profile of NAC, its use as an add-on agent should be contemplated, on an ad hoc basis. Furthermore, the only relevant side effect associated with NAC, diarrhoea, may also have clinical utility, as it can counterbalance constipation caused by other psychopharmaceuticals commonly used in OCD treatment.

It is essential to consider further studies to better elucidate the potential role of NAC in the treatment of OCD. These studies should preferentially be RCTs with larger number of participants and proper time of follow up. Additionally, it would also be important to have a better characterization of the participants included in the study, namely the mean age, mean duration of disease and symptom dimensions. Other aspects that can interfere with the efficacy of NAC in the treatment of OCD are the presence of other psychiatric diseases, concomitant treatments (pharmacological and non pharmacological) and adherence to prescribed therapies. These variables should also be evaluated in future studies.

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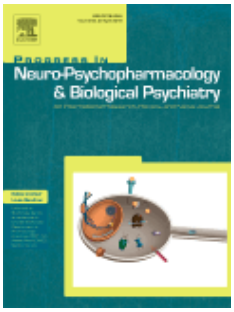

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