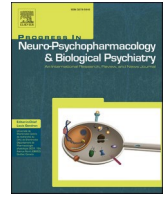




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## N-acetyl cysteine (NAC) augmentation in the treatment of obsessive-compulsive disorder: A phase III, 20-week, double-blind, randomized, placebo-controlled trial

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### ABSTRACT

**Objective:** Preliminary evidence has suggested that adjunctive N-acetylcysteine (NAC), an antioxidant precursor to glutathione, may reduce symptoms of obsessive-compulsive disorder (OCD). We conducted a 20-week, multi-site, randomized controlled trial to investigate the safety and efficacy of the adjunctive use of NAC in OCD.

**Methods:** The study was a phase III, 20-week, double-blind, randomized controlled trial across multiple sites in Australia investigating 2 g to 4 g per day of NAC (titrated according to response) in 98 participants with DSM-5 diagnosed OCD. Data were analysed using linear mixed effects models for the 89 participants who attended at least one follow-up visit.

**Results:** A modified intention-to-treat analysis of the primary outcome found no evidence that NAC reduced symptoms of OCD measured on the Yale-Brown Obsessive-Compulsive Scale, relative to placebo (mean difference at week 20 = 0.53, 95% compatibility interval = -2.18, 3.23;  $p = 0.70$ ; favouring placebo). There was also no evidence that NAC, compared to placebo, improved outcomes on the secondary measures including anxiety, depression, quality of life, functioning, or clinician/participant impression. NAC was well-tolerated with only mild gastrointestinal adverse events associated with the treatment.

**Conclusion:** We found no evidence supporting the efficacy of the adjunctive use of NAC in OCD.

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## 1. Introduction

Obsessive-compulsive disorder (OCD) is a chronic and disabling mental illness characterized by recurrent and intrusive thoughts, images or urges (obsessions) and repetitive behaviours or mental acts (compulsions) (American Psychiatric Association, 2013). Despite substantial evidence supporting the use of cognitive behavioural therapy, exposure and response prevention, and selective serotonin reuptake inhibitors (SSRIs) in the initial treatment of OCD, approximately 25% of OCD patients do not achieve an adequate treatment response to either of these first-line interventions (Hirschtritt et al., 2017; Katzman et al., 2014). Psychological therapies are also time-intensive and may be inaccessible to certain patient groups, whilst the high doses of SSRIs that are recommended for OCD patients carry risks of adverse effects (Bloch et al., 2010; Hirschtritt et al., 2017). Changing to clomipramine or augmentation of SSRIs with an antipsychotic provide further meaningful improvement in only around one-third of treatment-resistant patients and may also be poorly tolerated due to anticholinergic and metabolic adverse effects, respectively (Costa et al., 2017; Hirschtritt et al., 2017). Augmentation strategies for treating OCD that are safe and efficacious are thus needed.

Various glutamate-modulating drugs (e.g., memantine, riluzole, lamotrigine) have been examined as augmentation strategies or monotherapies for treating OCD (Marinova et al., 2017). This stems from evidence suggesting that glutamate signalling dysregulation may contribute to the pathophysiology of OCD (Marinova et al., 2017). *N*-acetyl cysteine (NAC) is a prodrug to the essential amino acid cysteine and has been used as a mucolytic agent for chronic obstructive pulmonary disease, as well as an antidote for paracetamol (acetaminophen) toxicity (Berk et al., 2013). NAC demonstrates glutamate-modulating and antioxidant properties through the regulation of cystine-glutamate antiporter activity as well as the biosynthesis of glutathione, an endogenous antioxidant (Berk et al., 2013). Given oxidative stress has also been implicated in the pathophysiology of OCD, there is promise in investigating the utility of NAC in the treatment of OCD (Maia et al., 2019).

Four randomized controlled trials (RCTs) have investigated the efficacy of NAC in adults with OCD (Afshar et al., 2012; Costa et al., 2017; Paydary et al., 2016; Sarris et al., 2015). In a 12-week trial, Afshar et al. (2012) ( $n = 48$ ) reported a 10.9-point decrease in total Y-BOCS score in the NAC group when compared with a 5.7-point decrease in the placebo group ( $p = 0.003$ ) (Afshar et al., 2012). Paydary et al.'s (2016) 10-week trial compared 200 mg/daily fluvoxamine plus placebo to 200 mg/daily fluvoxamine plus 2 g/daily of NAC in 44 individuals with OCD who had ceased psychotropic medications six weeks prior to the study (Paydary et al., 2016). The slope of treatment response was greater in the NAC augmentation group compared to the placebo augmentation group ( $p = 0.012$ ), although there was no clear evidence of benefit at the final study visit (Paydary et al., 2016). By contrast, Sarris et al. (2015) ( $n = 44$ ) and Costa et al. (2017) ( $n = 40$ ) had longer trial periods and larger NAC doses (16-week trials with a 3 g/day dosage) and found no evidence of benefit of NAC on total Y-BOCS scores by the study endpoint (Costa et al., 2017; Sarris et al., 2015). However, it should be noted that a significant effect was found in the Sarris et al. study, in favor of NAC, on the 'compulsions' subscale of the Y-BOCS at the Week-12 timepoint.

Given the inconsistent findings reported in earlier RCTs of NAC for OCD, additional studies using larger sample sizes are required. Further, as longer trial durations may be required for the potential benefits of NAC to become apparent (Yolland et al., 2020), studies with longer trial lengths are also needed. We therefore designed a phase III, 20-week, double-blind, randomized, placebo-controlled trial to investigate the efficacy of NAC (2 g to 4 g/day) as an augmentation agent in adults with DSM-5 diagnosed OCD. We hypothesized that participants who received NAC would have a greater reduction in total Y-BOCS score at the conclusion of the trial compared to those who received placebo. We additionally hypothesized similar benefits of adjunctive NAC over

placebo on secondary outcomes of mood, anxiety, functioning, clinical impression, and quality of life.

## 2. Methods

### 2.1. Trial design

This was a phase III, 20-week, randomized, double-blind, parallel-group, placebo-controlled trial. Participants were allocated to receive either NAC or placebo alongside their usual treatment in a 1:1 ratio. All participants underwent a four-week single-blinded placebo washout (only the participants were blinded) at the completion of the trial period (week-20 to week-24).

### 2.2. Participants

Eligibility criteria required participants to have: age between 18 and 75 years; a primary diagnosis of OCD (confirmed with the Structured Clinical Interview for the DSM-5; SCID-5); a Y-BOCS score  $\geq 16$ ; and the desire and capacity to consent to the study and follow its procedures. All participants were required to be on psychotropic medication for their OCD (and continue to do so throughout the trial; see Table S1 for permitted medications and dosage ranges). The dosages and duration of antidepressants were required to be stable i.e., taken for a minimum of eight weeks at consistent dose and within the recommended therapeutic range for OCD (Pittenger and Bloch, 2014; Sansone and Sansone, 2011). In cases where it was the participant's first antidepressant trial, a stable dosage for a minimum of 12 weeks was required.

Exclusion criteria included: extreme unmanageable OCD symptoms (Y-BOCS score of  $\geq 32$ ) and/or treatment-refractory OCD; a history of bipolar disorder, any psychotic disorder, or primary diagnosis of an obsessive-compulsive spectrum disorder/s (secondary diagnosis permitted; per SCID-5); severe depressive symptoms (defined as Structured Interview Guide for Hamilton Depression Rating Scale [SIGHD-17] score of  $\geq 24$ ); current substance use disorder/s (alcohol, and/or non-alcohol as per SCID-5); suicidal ideation SIGHD-17 score  $\geq 3$ ; allergy to NAC or use of medication with known or suspected negative interactions with NAC; a serious or unstable medical condition/s; current gastrointestinal ulcers; pregnancy or lactation. Treatment-refractory OCD was defined as inadequate responses to a minimum of three trials of serotonin reuptake inhibitors (SRIs), including clomipramine; one augmentation strategy (e.g. an antipsychotic or mood stabilizer); as well as engagement in adequate cognitive behavioural therapy specific for OCD (e.g. completion of an inpatient OCD program or minimum 15 sessions of outpatient exposure response prevention). Treatment-refractory criteria for the trial were formulated from the current literature at the time of protocol development and group consensus from the study psychiatrists experienced in OCD treatment.

Participants were withdrawn from the trial if they experienced a severe deterioration in their OCD symptoms (medical monitors were notified if there was a  $\geq 25\%$  increase in their Y-BOCS score from baseline); ceased taking the investigational product (IP) for 7+ days; underwent substantial treatment changes (for example, change in primary medication or entry into an inpatient OCD program); experienced serious adverse events (SAEs) warranting withdrawal as determined by the medical monitors on a case by case basis; or if a participant elected to withdraw from the trial at their own volition.

### 2.3. Intervention

Participants were randomly allocated to receive NAC capsules (500 mg per capsule) or placebo for the first 20 weeks of the trial. The NAC was sourced and encapsulated by BioCeuticals® in line with pharmaceutical Good Manufacturing Practices. Placebo capsules consisted of an inert substance (microcrystalline cellulose powder). Study medication was provided in bottles consisting of 120 capsules of NAC/placebo.

Participants commenced the treatment at a dose of two capsules twice per day (1000 mg NAC BID) for the first eight weeks of the trial. From Week-8, in cases of non-response, defined as  $\leq 35\%$  reduction in Y-BOCS score from baseline (Mataix-Cols et al., 2016), the dose was titrated to three capsules twice per day (1500 mg NAC BID), where tolerable. In cases of continued non-response in those who received an initial titration, the dose was further titrated to four capsules twice per day (2000 mg NAC BID) from Week-12, where tolerable. In the event of intolerable side effects, the participant was permitted to reduce the dose to the previous amount.

## 2.4. Procedures

The multi-site study was conducted at The Melbourne Clinic (TMC) Professorial Unit in Melbourne, Victoria (University of Melbourne); The Royal Brisbane and Women's Hospital in Brisbane, Queensland (University of Queensland; UQ) and NICM Heath Research Institute, Westmead, New South Wales (Western Sydney University; WSU). Recruitment and data collection occurred from November 2016 to July 2020. The study was registered on the Australian New Zealand Clinical Trial Registry (ANZCTR; ACTRN12616000847415) and approved by TMC Research Ethics Committee (project number 279), WSU Human Research Ethics Committee (project number H12181) and UQ Medical Research Ethics Committee (project number 2016001720) prior to recruitment. Funding to conduct the trial was provided by the National Health and Medical Research Council (NHMRC; GNT1104460).

The trial was advertised on Facebook, Google, local radio stations in Melbourne (Smooth FM, Gold FM) and Sydney (2SER), the Anxiety Recovery Centre of Victoria (ARCVic) website and community seminars, as well as brochures and posters displayed in various pharmacies and GP clinics (facilitated by TONIC Media Network). Referrals from clinicians affiliated with the three recruitment sites were also utilised.

Participants were pre-screened for the trial via telephone or by an online survey facilitated by REDCap (an electronic data capture tool hosted at The University of Melbourne) (Harris et al., 2009) which ascertained date of birth, postcode, current medications and therapies, OCD treatment history, medical history (including allergies), contraception methods and pregnancy/lactation status. Consent to be pre-screened was obtained verbally on the telephone or specified by the participant on the electronic survey. Participants meeting initial criteria were provided with the participant information and consent form and asked to review and discuss with their treating doctor/s. If willing to proceed with the trial, an appointment for the baseline screening visit was made where written informed consent was obtained. Demographic, medication, medical history, height, weight, and OCD treatment history information were collected. The Y-BOCS, NetSCID-5 and SIGHD-17 were administered by the research assistant to determine eligibility. Eligible participants completed the self-report questionnaires, had blood pressure measured, and were randomized into the trial.

Participants were assessed every four weeks for the following 24 weeks (unless withdrawn prior). They were reimbursed \$20 per attended visit to cover any costs incurred due to participation. Adequate trial medication was dispensed at each visit to accommodate the ensuing four weeks. Participants were asked to return remaining capsules at their next appointment so adherence for the previous month could be determined (by counting remaining capsules). All participants who completed the 24 weeks of the trial were offered three bottles of NAC (120 capsules per container, 500 mg NAC per capsule) with a letter thanking them for participating and advising to discuss with their treating doctor prior to commencing the samples. For those participants who were active in the trial ( $n = 10$ ) during COVID-19 restrictions (Mar-2020), visits were permitted to be completed via Telehealth (telephone call/Zoom).

## 2.5. Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio according to a computer-generated randomisation sequence generated by an independent third party. All participants and study staff were blinded to treatment allocation, except in the final four weeks of the study (single blinded). A pharmacologically inert 'forest berry flavouring' was used to obfuscate the scent of the NAC, and this was matched in the placebo capsules, which were also identical in shape and size to the NAC capsules. All data cleaning and preparation for analysis was completed blinded to treatment allocation.

## 2.6. Assessment scales

**The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) severity scale** – was the primary outcome measure used in the trial. The Y-BOCS is a 10-item, semi-structured, clinician administered instrument and is regarded as the gold standard for measuring the severity of both obsessive and compulsive symptoms. It is used extensively in OCD clinical trials (Fineberg et al., 2020; Goodman et al., 1989; Skapinakis et al., 2016). All research assistants completed Y-BOCS training with SBW, BV, ND and/or MB, clinicians with extensive experience in the assessment and treatment of OCD.

**Structured Clinical Interview for DSM-5 (SCID-5)** – a computerized version of the SCID-5 (NetSCID-5, created by Telesage (Brodey et al., 2016)) was used to confirm the diagnosis of OCD, screen for exclusionary disorders applicable to the study (psychotic disorder, bipolar disorder, current substance use disorder/s) and to determine the presence of comorbidities. A condensed version of the SCID-5 was administered using the following DSM-5 diagnostic modules: mood disorders, psychotic disorders, substance use disorders (alcohol, and non-alcohol), anxiety disorders, obsessive-compulsive and related disorders, and gambling disorder.

**Dimensional Obsessive-Compulsive Scale (DOCS)** – a self-reporting measure which captures thematic aspects of OCD symptoms as well as their perceived severity (Abramowitz et al., 2010). The DOCS assesses the following symptom dimensions: germs and contamination; responsibility for harm, injury, or bad luck; unacceptable obsessional thoughts; symmetry, completeness, and exactness.

**Structured Interview Guide for the Hamilton Depression Rating Scale (SIGHD-17)** – A 17-item clinician administered instrument which assesses both psychological and physiological depressive symptoms (Williams, 1988).

**Beck Anxiety Inventory (BAI)** – a 21-item, self-reported questionnaire which assesses physiological and psychological symptoms of anxiety (Beck et al., 1988).

Other scales included The Sheehan Disability Scale (SDS) (Sheehan et al., 1996); Clinical Global Impression scale (CGI) and Patient Global Impression scale (PGI) (Guy, 1976; Mohebbi et al., 2018); World Health Organization Quality of Life – BREF (WHOQoL-BREF) (WHO, 1998); Barratt Impulsivity Scale-11 (BIS-11) (Patton et al., 1995). All the above measures were completed at each visit (baseline and follow-ups) except for the NetSCID-5 and BIS-11 (baseline only) and WHOQoL-BREF (baseline, Week-12 and Week-20 only). Side-effects and adverse events were described qualitatively by the participant at each follow-up visit. Side-effects were further assessed using the self-reported Systematic Assessment for Treatment Emergent Events (SAFTEE), a 55 item symptom checklist assessing the presence and severity of emerging side effects (Levine and Schooler, 1986). Seated blood pressure was measured at the end of each visit.

## 2.7. Sample size

A target sample size of 128 participants was specified in the protocol to provide 80% power to detect a difference of three-points on the Y-BOCS total score between the placebo and NAC groups at the final study



visit (Week-20), with a type-I error of 5%. A three-point difference on the Y-BOCS was chosen as the minimal clinically important difference as this is approximately equivalent to a 15% reduction in symptoms, similar to what has been reported in a meta-analysis of SSRI therapies for OCD (Bloch et al., 2010). The achieved sample size of 98 participants was less than this target sample size. The primary reason for the smaller than anticipated final sample size was due to COVID-19 related recruitment challenges in the latter stages of the study. When the power analysis was re-performed using the attained sample size a lower power of 70% was reached. Alternatively, a larger effect size of 3.5 points on the YBOCS would be required to maintain 80% power.

## 2.8. Statistical analysis

The analysis of primary and secondary outcomes was undertaken using linear mixed effects models (LMMs). These models include all available data (including study non-completers) and account for the non-independence of repeated measurements within participants. Models included fixed effects of baseline outcome score, time, treatment, and a time x treatment interaction (Singer et al., 2003). Additionally, pre-specified baseline covariates - recruitment site, age, sex, and alcohol consumption (standard drinks/week) - were included in all models. Covariates - bodyweight and concurrent psychotherapy were pre-specified for inclusion but were dropped due to missing data. Smoking status (yes/no) was planned to be included but was dropped as the sample consisted almost exclusively of non-smokers ( $n = 95$ , 97%). The outcome of interest was the difference in outcome score at the final study visit (Week-20) between treatment groups, adjusted for baseline severity and covariates. Model fit was compared between models including time as continuous, log-transformed, and categorical variable using the Akaike Information Criterion. Linear time produced adequate fit and was used throughout. Random intercept and slope terms were included in each model. LMMs were fit using R package *lme4* (Bates et al., 2007). Cohen's  $d$  effect sizes were calculated using the pooled standard deviation at baseline.

For the primary outcome we additionally performed a sensitivity analysis to assess the influence of informative, or 'missing not at random', missing data on the assessed treatment effect. Informative missing data occurs when missingness is related to the true value of the outcome, for instance if participants discontinue the trial due to perceived treatment inefficacy or worsened symptoms. For this sensitivity analysis, we used a pattern mixture model in which intercepts and slopes were estimated separately for study completer and non-completer strata and the results are combined in a proportionally weighted average (Hedeker and Gibbons, 1997). Additionally, we performed a sensitivity analysis for the effect of compliance, including only participants who had treatment or placebo compliance of more than 75%, and a sensitivity analysis excluding participants receiving antipsychotic medications ( $n = 4$ ).

Treatment response was defined as a  $\geq 35\%$  reduction in Y-BOCS as well as a CGI-I rating of 1 ("very much improved") or 2 ("much improved") at study endpoint (Mataix-Cols et al., 2016). We additionally used the criteria of Jacobson and Truax (1992) to evaluate the proportion of participants with 'reliable' and 'clinically significant' change at study endpoint. A change  $\geq 10$  points on the Y-BOCS constituted a reliable change and a final total Y-BOCS score  $\leq 14$  constituted a clinically significant change (Fisher and Wells, 2005). Fitted values from the primary LMM were used to evaluate the latter treatment response criterion.

For secondary outcome scales DOCS, BAI, and SIGHD-17 scale items were not completed (skipped or missed) on only a few occasions ( $< 1\%$  of responses). Prior to calculating summary scores for these scales, we performed single imputation using predictive mean matching to fill these missed items (R package *mice*) (Buuren and Groothuis-Oudshoorn, 2010). Secondary outcomes which were ordinally scored (quality of life [WHOQoL-BREF item 1], CGI, and PGI) were modelled using Bayesian

mixed effects ordered probit models (Bürkner and Vuorre, 2019). Although not specified a-priori, we chose to use Bayesian models for these outcomes as they easily allow for inclusion of random effects (Bürkner and Vuorre, 2019). Secondary outcomes were not adjusted for multiple comparisons and should be considered exploratory. All statistical analyses were performed using R version 4.1.0 (Team, 2013) and plots were produced using *ggplot2* (Wickham, 2016). The analysis code and results are available in the supplementary material.

## 3. Results

A total of 963 individuals inquired about the trial, of whom 575 were pre-screened via phone or online survey, and 118 were assessed in baseline appointments. Twenty were excluded from the trial during the baseline visit, leaving a total of 98 participants who were randomized (see CONSORT chart; Fig. 1). A total of 89 of these participants (44 in the NAC group and 45 in the placebo group) provided any outcome data after randomisation and were included in the analysis. There were 29 (58%) study completers in the NAC group and 29 (60%) in the placebo group. Overall study adherence was good and there was no significant difference in adherence between NAC (median = 93%, IQR = 10) and placebo (median = 89%, IQR = 17) groups. In participants who remained in the study until at least Week-8, there was weak evidence that more participants were titrated to a higher dose in the NAC group ( $n = 33$ , 83%) than the placebo group ( $n = 26$ , 67%;  $p = 0.17$ ).

### 3.1. Sample characteristics

Treatment arms were well-balanced on demographic and clinical characteristics (Table 1), although there were more females in the treatment group ( $n = 34$ , 77%) than the placebo group ( $n = 26$ , 58%). Most participants (85%) were born in either Australia or New Zealand. The median age was 32 years. Most participants (65%) had completed post-high school education (i.e., a diploma or tertiary study). In terms of clinical characteristics, the mean Y-BOCS score at baseline was 23.0 and the median OCD duration was seven years. Concurrent pharmacotherapies used by the participants is displayed in Supplementary Table 1. The most common medications for OCD were fluoxetine ( $n = 25$ , 26%), escitalopram ( $n = 15$ , 15%), sertraline ( $n = 13$ , 13%), fluvoxamine ( $n = 10$ , 10%) and paroxetine ( $n = 10$ , 10%). There were six participants taking antipsychotics (6%) and none taking a glutamate-modulating agent. Most participants (67%) met criteria for a comorbid psychiatric disorder on the SCID-5, the most common being recurrent major depressive disorder (51%) and generalized anxiety disorder (21%).

### 3.2. Primary outcome (total Y-BOCS)

Response to treatment over time is displayed in Fig. 2 and Table 2 for the primary outcome total Y-BOCS score. In the LMM analysis, the mean difference between NAC and placebo groups at Week20 was estimated to be 0.53 points (95% compatibility interval [CI] = - 2.18, 3.23;  $p = 0.70$ ), favouring placebo. This was equivalent to a standardized effect size (Cohen's  $d$ ) of 0.13 (95% CI = -0.55, 0.81).

Results were not meaningfully changed in the pattern mixture model assessing the influence of informative missing data on the results (mean difference [MD] = 0.62, 95% CI = -2.21, 3.46;  $p = 0.66$ ), nor in the model excluding participants taking antipsychotic medication (MD = 0.14, 95% CI = -2.67, 2.94;  $p = 0.92$ ). Similarly, results were not meaningfully changed when restricting the study to those with high ( $>75\%$ ) adherence to treatment or placebo (MD = 1.11, 95% CI = -2.06, 4.28,  $p = 0.49$ ).

Using the criteria of Mataix-Cols et al. (2016) in study completers only, there were four treatment responders in the NAC group (13.8%) compared to nine (31.0%) in the placebo group (risk ratio [RR] = 0.44, 95% CI = 0.13, 1.20;  $p = 0.13$ ). Using the treatment response criteria of Jacobson and Truax in the full sample, there were four treatment



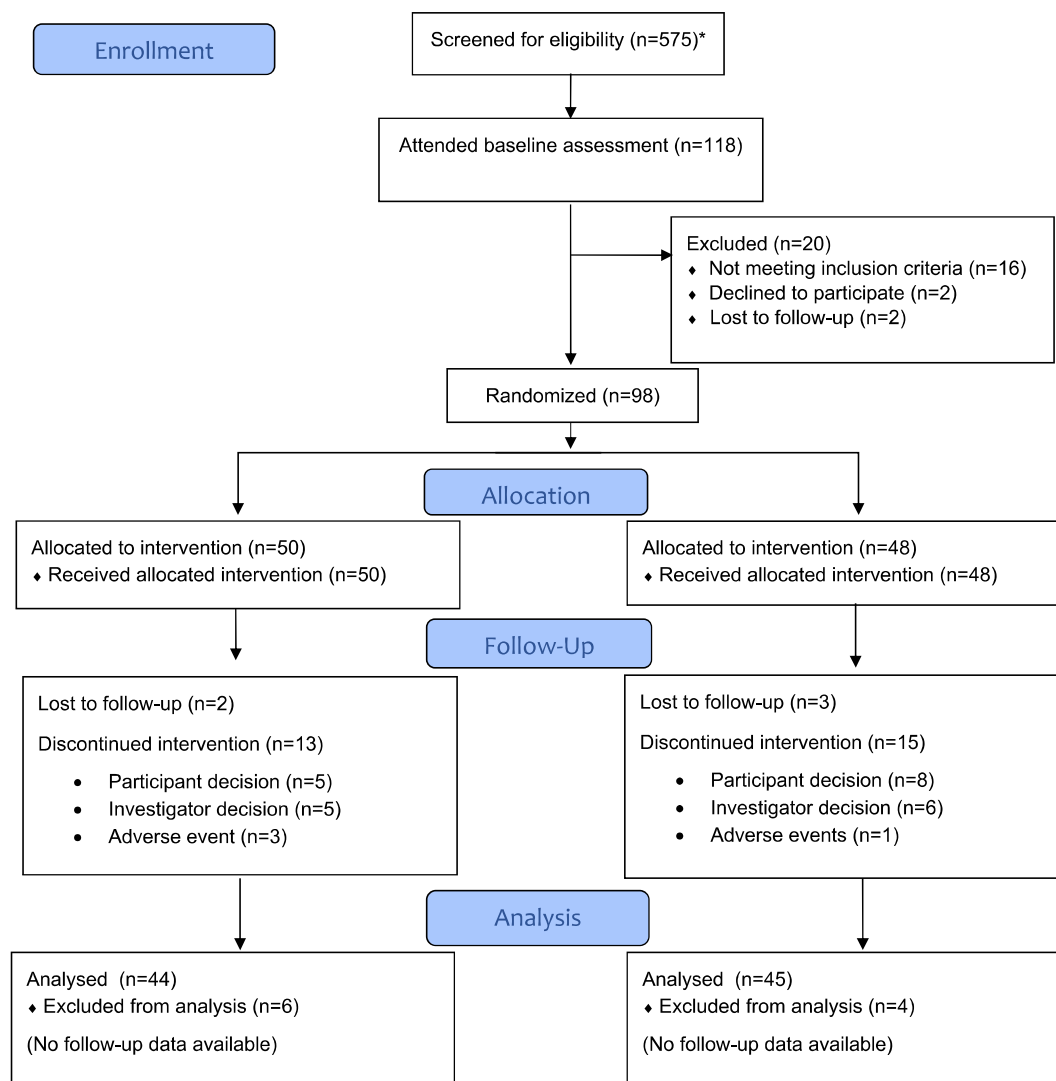


Fig. 1. Consort flow diagram.

\*Primary reasons that screened participants did not continue to baseline assessment were: loss to follow-up, unstable medical conditions, not receiving medication for OCD, meeting criteria for treatment refractory OCD, declined participation, did not want to receive placebo, and did not wish to use contraception.

responders in the NAC group (9.09%) compared to 6 (13.3%) in the placebo group (RR = 0.68, 95% CI = 0.18, 2.23;  $p = 0.53$ ).

At Week-24, following the four-week single-blinded placebo washout, a between-group  $t$ -test provided weak evidence that total YBOCS score was higher in the group which had received NAC compared to the placebo group (MD = 1.95, 95% CI = -1.65, 5.55;  $p = 0.28$ ).

### 3.3. Secondary outcomes

The effect of NAC treatment on secondary outcomes is displayed in Table 2. There was no evidence that NAC improved symptoms on the Y-BOCS obsession (MD = 0.06, 95% CI = -1.33, 1.44;  $p = 0.94$ ) or compulsion subscales (MD = 0.60, 95% CI = -0.91, 2.10;  $p = 0.43$ ), favouring placebo in each instance. There was weak or no evidence that NAC improved symptoms on the total DOCS (MD = -1.08, 95% CI = -5.55, 3.39;  $p = 0.63$ ), total BAI (MD = -1.78, 95% CI = -5.61, 2.04;  $p = 0.36$ ), total SIGHD-17 (MD = -0.81, 95% CI = -2.64, 1.03;  $p = 0.39$ ), or global impairment on the SDS (MD = -1.04, 95% CI = -4.05, 1.97;  $p = 0.49$ ). For ordinal scaled outcomes, there was no evidence that NAC improved symptoms on the CGI-S (standardized mean difference [SMD] on latent variable scale = 0.16, 95% CI = -0.77, 1.08; favouring placebo), CGI-I (SMD = 0.26, 95% CI = -0.34, 0.85; favouring placebo),

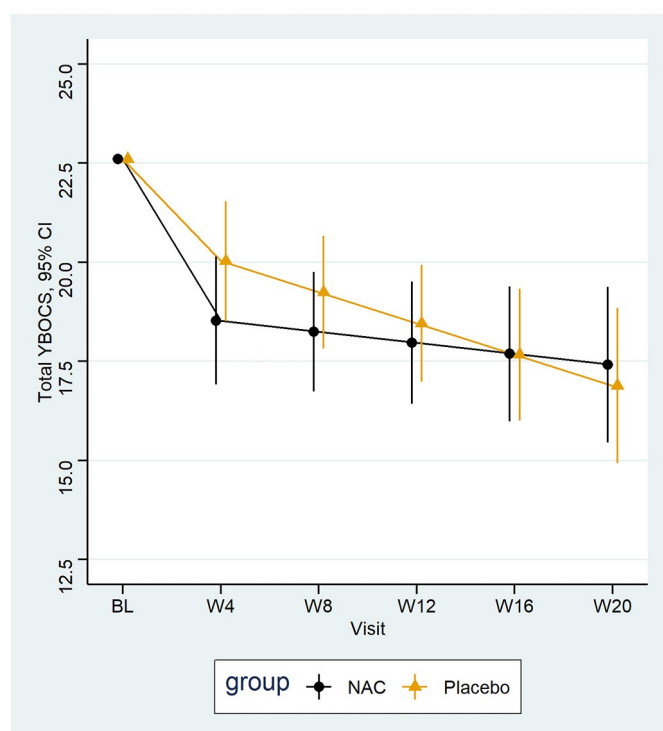
PGI-S (SMD = 0.25, 95% CI = -0.50, 1.02; favouring placebo), PGI-I (SMD = -0.16, 95% CI = -0.91, 0.59; favouring NAC) or quality of life on the WHOQoL-BREF (SMD = -0.50, 95% CI = -1.61, 0.61; favouring placebo) (Table 2). The results for the ordinally scaled outcomes using weaker, less informative priors were not materially different (Supplementary Table 2).

### 3.4. Safety

Risk of adverse events in each treatment group are displayed in Fig. 3. NAC treatment was associated with an increased risk of nausea (risk difference [RD] = 16%; 95% CI = -1%, 33%), acid reflux (RD = 16%, 95% CI = 0%, 32%), and changes in bowel habits (RD = 16%, 95% CI = 2%, 30%). NAC was associated with decreased risk of skin changes/rash (RD = -16%, 95% CI = -23%, -2%) and physical fatigue/lethargy (RD = -12%, 95% CI = -23%, -2%). There was no evidence that NAC influenced systolic or diastolic blood pressure (see Fig. S1 and Fig. S2). As most NAC participants were titrated to a higher dose (83%), we were unable to investigate whether adverse events were more frequent in this subgroup. Three serious adverse events (SAEs) occurred during the trial. Two of these concerned participants in the placebo group – one a suicide attempt via polypharmacy overdose, the second a shoulder dislocation

**Table 1**  
Participant demographic and clinical characteristics.

Characteristic	NAC (n = 44)	Placebo (n = 45)
Age, median (IQR)	31.5 (20.8)	32.0 (21.0)
Country of birth, n (%)		
Australia/New Zealand	39 (88.6)	37 (82.2)
Other	5 (11.4)	8 (17.8)
Sex, n (%)		
Male	10 (22.7)	19 (42.2)
Female	34 (77.3)	26 (57.8)
Education, n (%)		
High school early leaver	2 (4.55)	5 (11.1)
Graduated high school	11 (25.0)	13 (28.9)
College certificate/diploma	10 (22.7)	8 (17.8)
Graduate/postgraduate degree	21 (47.7)	19 (42.2)
Employment, n (%)		
Full time	13 (31.0)	14 (31.8)
Part time	11 (26.2)	10 (22.7)
Student	7 (15.9)	7 (15.6)
Unemployed	8 (19.0)	7 (15.9)
OCD chronicity (years), median (IQR)	9 (14)	6 (15)
Comorbid psychiatric diagnosis, n (%)		
Yes	31 (70.5)	29 (64.4)
No	13 (29.5)	16 (35.6)
Prior failed medication trials		
1	20 (45.5)	23 (51.1)
2	11 (25.0)	11 (24.4)
3+	13 (29.5)	11 (24.4)



**Fig. 2.** Estimated marginal means at each follow-up visit by treatment group ( $n = 89$ ).

Estimated marginal means are calculated with baseline outcome score, age and alcohol intake at the sample mean, and averaged over sex and recruitment site.

in the context of Ehlers Danlos Syndrome. The third SAE involved a participant in the NAC group who was treated for an acute episode of ischemic colitis in hospital after experiencing constipation, abdominal pain, and rectal bleeding. This SAE was deemed unrelated to the trial given the participant's past history of constipation.

At Week-24, following the four-week single-blinded placebo washout, there was no clear evidence of greater risk of adverse events in

the group that had received NAC compared to the placebo group. There was, however, some evidence of greater risk of sleep difficulties (NAC: 3, Placebo: 11; RD = -32%, 95% CI = -54%, -9%), drowsiness (NAC: 4, Placebo: 11; RD = -28%, 95% CI = -51%, -5%), irritability (NAC: 3, Placebo: 3; RD = -24%, 95% CI = -45%, -2%), and trouble sitting still (NAC: 3, Placebo: 9; RD = -24%, 95% CI = -45%, -2%) in the placebo group compared to the group which had received NAC.

#### 4. Discussion

In this phase III, double-blind, multicentre RCT, we found no evidence that the use of NAC as an augmentation therapy improved OCD symptoms (as measured by the Y-BOCS), relative to placebo. Similarly, no evidence of a benefit on secondary outcomes such as mood, anxiety, functioning, or quality of life was noted. NAC was well-tolerated with only mild gastrointestinal adverse events associated with the treatment.

Our findings are in contrast with a recent meta-analysis summarising the results of five RCTs ( $N = 182$ ) which used NAC, in doses between 2 g and 3 g daily, for OCD (four using NAC adjunctively, one using NAC as either monotherapy or adjunctively) (Gadallah et al., 2020). The meta-analysis estimated that NAC produced a mean reduction in OCD symptoms on the Y-BOCS scale of 2.97 points (95% CI = 1.02, 4.93). There are several potential reasons for the divergence between this meta-analytic result and the present findings. Firstly, the sample size of the meta-analysis was modest. The largest included study in the meta-analysis included 44 participants, fewer than half of the participants included in the present trial (Paydary et al., 2016). The results of the meta-analysis may therefore be influenced by small study effects. Secondly, there may exist important differences in clinical characteristics between this and previous studies. For instance, most of our sample had a comorbid psychiatric diagnosis (67%), reflecting the presentations of OCD requiring psychotropic medications in real-world clinical practice. Previous trials including participants with depression as well as addiction and substance use disorders have found mixed findings regarding NAC's efficacy as an augmentation strategy (Ooi et al., 2018). The extensive psychiatric comorbidity in our sample may have influenced our findings, given the differences in the proposed neurobiology within the most common comorbid mental disorders in our sample (e.g., major depression, generalized anxiety), notwithstanding that NAC in theory might benefit such comorbidity (Fernandes et al., 2016). Information regarding comorbidity was not available from previous studies which identified treatment benefits in response to NAC (Afshar et al., 2012; Paydary et al., 2016), so whether this characteristic may modify treatment response is unclear. Finally, it is acknowledged that there are jurisdictional differences with the various studies; potentially reflecting the differences between the positive and null findings.

Our findings for the primary outcome measure do align with two previous trials (Costa et al., 2017; Sarris et al., 2015). However, we did not replicate the significant finding in the 'compulsions' Y-BOCS subscale at Week-12 in our previous trial (though this finding may have been a type-I error as the effect dissipated by the study endpoint) (Sarris et al., 2015). Our findings on the secondary outcome measures largely align with the secondary outcomes reported in previous trials, except for the finding that NAC produced a reduction in anxiety in the Costa et al. (2017) study, which involved a treatment resistant sample. Nor do our results align with the finding in Ghanizadeh et al. (2017), which found that NAC improved quality of life in a sample of children and adolescents (Ghanizadeh et al., 2017).

The 2 g to 4 g dose of NAC used in this study was generally well-tolerated with all three reported SAEs not deemed directly related to the trial. Nausea, acid reflux, and changes in bowel habits were reported more frequently in the NAC group compared to placebo. One previous trial, using 2.4 g/day NAC in an OCD sample, reported mild diarrhea in 16.7% of the NAC group compared to zero in the placebo group ( $p = 0.0047$ ) (Afshar et al., 2012). Another trial, using 2 g/day NAC in a clinically depressed sample, found gastrointestinal problems in 33.9% of

**Table 2**  
Effect of treatment on primary outcome and secondary outcomes.

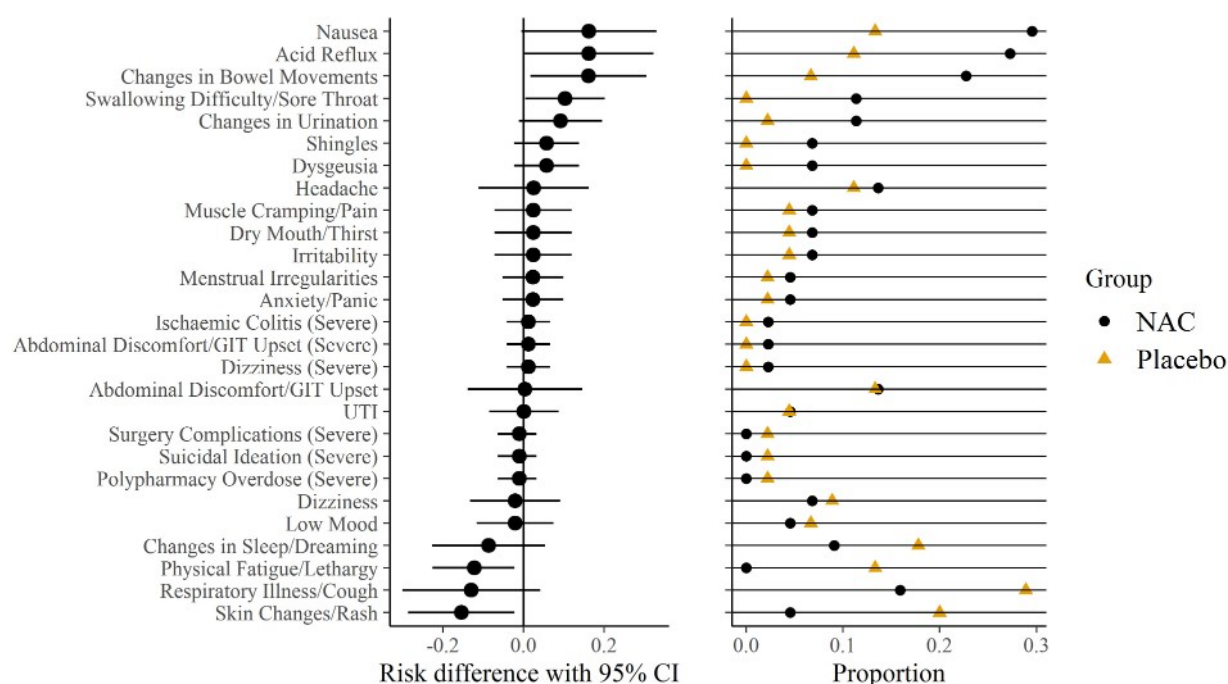
Psychological outcome	Baseline, mean (SD)		Week 20, mean (SD)		Adjusted mean difference at week-20 (95% CI); p value <sup>a</sup>	Cohen's d (95% CI) <sup>1</sup>
	NAC (n = 44)	Placebo (n = 45)	NAC (n = 29)	Placebo (n = 29)		
Y-BOCS total	23.1 (3.96)	22.1 (3.95)	17.6 (5.65)	15.8 (7.02)	0.525 (−2.18, 3.23); <i>p</i> = 0.70	0.132 (−0.549, 0.814)
Y-BOCS obsessions	11.3 (2.30)	10.4 (2.31)	8.55 (3.21)	7.93 (3.65)	0.057 (−1.33, 1.44); <i>p</i> = 0.94	0.024 (−0.571, 0.618)
Y-BOCS compulsions	11.9 (2.03)	11.6 (2.35)	9.08 (2.80)	7.86 (3.93)	0.598 (−0.908, 2.10); <i>p</i> = 0.43	0.273 (−0.415, 0.960)
DOCS total	28.3 (11.2)	25.7 (11.0)	19.0 (10.2)	16.9 (10.1)	−1.08 (−5.55, 3.39); <i>p</i> = 0.63	−0.097 (−0.500, 0.305)
BAI total	16.9 (10.3)	16.5 (11.3)	5.79 (6.52)	9.5 (7.53)	−1.78 (−5.61, 2.04); <i>p</i> = 0.36	−0.165 (−0.521, 0.189)
SIGHD total	9.59 (5.58)	8.89 (5.97)	6.14 (4.68)	7.14 (4.02)	−0.807 (−2.64, 1.03); <i>p</i> = 0.39	−0.140 (−0.459, 0.189)
SDS global impairment	14.6 (6.69)	12.1 (6.44)	7.89 (6.01)	8.21 (4.92)	−1.04 (−4.05, 1.97); <i>p</i> = 0.49	−0.156 (−0.609, 0.296)
<i>Ordinally scaled outcomes</i>						<i>Adjusted SMD at week-20 (95% CI)<sup>a,2</sup></i>
CGI-S	4.09 (0.520)	3.96 (0.638)	3.54 (0.881)	3.28 (0.882)	0.161 (−0.774, 1.08)	
PGI-S	2.88 (0.586)	2.76 (0.679)	2.50 (0.694)	2.32 (0.612)	0.254 (−0.502, 1.02)	
CGI-I	–	–	3.21 (0.995)	2.93 (1.16)	0.262 (−0.335, 0.845)	
PGI-I	–	–	2.72 (1.16)	2.82 (1.22)	−0.159 (−0.913, 0.593)	
Quality of life	3.47 (0.984)	3.47 (0.968)	3.64 (0.911)	3.79 (0.833)	−0.496 (−1.61, 0.607)	

BAI = Beck Anxiety Inventory; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; DOCS = Dimensional Obsessive-Compulsive Scale; PGI-I = Patient Global Impression – Improvement; PGI-S = Patient Global Impression – Severity; SDS = Sheehan Disability Scale; SIGHD = Structured Interview Guide for the Hamilton Depression Rating Scale; SMD = standardized mean difference; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

<sup>a</sup> Adjusted for age, sex, recruitment site, baseline score (where applicable), and baseline alcohol intake.

<sup>1</sup> Cohen's d is calculated using the pooled standard deviation at the baseline visit.

<sup>2</sup> Models are fit using Bayesian ordered probit regression. Priors on treatment effect coefficients are weakly sceptical; Normal (0, SD = 1). Standardized mean differences are in units of the latent continuous outcome variable. For all outcomes except for quality of life, standardized mean differences <0 indicate treatment benefit.



**Fig. 3.** Adverse events (*n* = 89).

The left part of the figure displays the difference in proportion (risk) of each adverse event reported throughout the trial. Positive risk differences indicate greater risk of the given adverse event in the NAC group (i.e., points on the right side of the line indicate increased risk in the NAC group). The right part of the figure displays the proportion of each adverse event in each group. Adverse events tagged with 'severe' are those with whose severity was reported as 'severe' by participants. All other adverse events were reported as of 'mild' or 'moderate' severity.

GIT = gastrointestinal tract; UTI = urinary tract infection.

the NAC group compared with 18.4% of the placebo group (*p* = 0.005) (Afshar et al., 2012; Berk et al., 2014).

The current study has several strengths, including its double-blind, randomized, placebo-controlled design, well defined inclusion/exclusion criteria, as well as a larger sample size and longer trial design compared to previous trials investigating the efficacy of NAC in OCD. However, several limitations must be noted. Firstly, there was considerable heterogeneity in the pharmacological and psychological

treatments that the sample participants were receiving. Given the limited sample size, we were unable to assess effect modification by the nature or class of these treatments. It may be, for instance, that NAC is efficacious if used with a particular class of medication but less so with others. A further limitation is that, though not meeting treatment refractory criteria, approximately half of the sample had trialed multiple (2+) pharmacotherapies. It is generally harder to display benefits of therapy in a population which may be at least partially treatment



resistant. However, it can be noted that the mean YBOCS baseline score was at the higher end of ‘moderate symptom severity’, and other similar OCD studies have had a higher pooled symptom severity level (which may provide greater potential of symptom reduction). Finally, it would have been ideal to have employed neuroimaging to assess the activity of glutamate and other relevant biomarkers or pharmacodynamic pathways in the brain. Additionally, the availability of relevant baseline markers such as glutathione levels or polymorphisms within pharmacologically relevant genes would have allowed the assessment of whether such features modified treatment response.

## 5. Conclusion

We found no evidence that the adjunctive use of NAC was effective in reducing OCD symptoms in this 20-week double-blind RCT. There was similarly no evidence of a benefit on secondary outcomes of mood, anxiety, functioning, and overall quality of life. Our findings are inconsistent with prior meta-analytic evidence which has supported the utility of NAC as a potential adjunctive agent in OCD. An updated meta-analysis, incorporating evidence from the present study, is required to reach conclusions about the efficacy of adjunctive NAC in OCD, and to identify any study or population subgroup features which may modify treatment response.

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## Author statement

JS conceptualised the study and oversaw all clinical trial activities. LC conducted the formal analysis and coordinated writing of the manuscript. All authors contributed equally to data curation, investigation, and methodology, and approved the final manuscript for submission.

## Conflict of interest & acknowledgements

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## Data availability

Data will be made available on request.

## Appendix A. Supplementary data

Supplementary tables and figures and analysis code and results to this article can be found online at <https://doi.org/10.1016/j.pnpbp.2022.110550>.

## References

- Abramowitz, J.S., Deacon, B.J., Olatunji, B.O., Wheaton, M.G., Berman, N.C., Losardo, D., Hale, L.R., 2010. Assessment of obsessive-compulsive symptom dimensions: development and evaluation of the dimensional obsessive-compulsive scale. *Psychol. Assess.* 22 (1), 180–198. <https://doi.org/10.1037/a0018260>.
- Afshar, H., Roohafza, H., Mohammad-Beigi, H., Haghighi, M., Jahangard, L., Shokouh, P., Hafezian, H., 2012. N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: a randomized, double-blind, Placebo-Controlled Trial. *J. Clin. Psychopharmacol.* 32 (6).
- American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)* Arlington. American Psychiatric Publishing, VA, p. 1000.
- Bates, D., Sarkar, D., Bates, M.D., Matrix, L., 2007. The lme4 package. *R package version* 2 (1), 74.
- Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. *J. Consult. Clin. Psychol.* 56 (6), 893–897. <https://doi.org/10.1037//0022-006x.56.6.893>.
- Berk, M., Malhi, G.S., Gray, L.J., Dean, O.M., 2013. The promise of N-acetylcysteine in neuropsychiatry. *Trends Pharmacol. Sci.* 34 (3), 167–177.
- Berk, M., Dean, O.M., Cotton, S.M., Jeavons, S., Tanious, M., Kohlmann, K., Malhi, G.S., 2014. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. *J. Clin. Psychiatr.* 75 (6), 628–636. <https://doi.org/10.4088/JCP.13m08454>.
- Bloch, M.H., McGuire, J., Landeros-Weisenberger, A., Leckman, J.F., Pittenger, C., 2010. Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. *Mol. Psychiatry* 15 (8), 850–855. <https://doi.org/10.1038/mp.2009.50>.
- Brodey, B.B., First, M., Linthicum, J., Haman, K., Sasiela, J.W., Ayer, D., 2016. Validation of the NetSCID: an automated web-based adaptive version of the SCID. *Compr. Psychiatry* 66, 67–70. <https://doi.org/10.1016/j.comppsy.2015.10.005>.
- Bürkner, P.-C., Vuorre, M., 2019. Ordinal regression models in psychology: a tutorial. *Adv. Methods Pract. Psychol. Sci.* 2 (1), 77–101.
- Buuren, S.V., Groothuis-Oudshoorn, K., 2010. Mice: multivariate imputation by chained equations in R. *J. Stat. Softw.* 1–68.
- Costa, D.L.C., Diniz, J.B., Requena, G., Joaquim, M.A., Pittenger, C., Bloch, M.H., Shavitt, R.G., 2017. Randomized, double-blind, placebo-controlled trial of N-acetylcysteine augmentation for treatment-resistant obsessive-compulsive disorder. *J. Clin. Psychiatr.* 78 (7), e766–e773. <https://doi.org/10.4088/JCP.16m11101>.
- Fernandes, B.S., Dean, O.M., Dodd, S., Malhi, G.S., Berk, M., 2016. N-acetylcysteine in depressive symptoms and functionality: a systematic review and meta-analysis. *J. Clin. Psychiatr.* 77 (4), 0–0.

- Fineberg, N.A., Hollander, E., Pallanti, S., Walitz, S., Grunblatt, E., Dell'Osso, B.M., Menchon, J.M., 2020. Clinical advances in obsessive-compulsive disorder: a position statement by the International College of Obsessive-Compulsive Spectrum Disorders. *Int. Clin. Psychopharmacol.* 35 (4), 173–193. <https://doi.org/10.1097/YIC.0000000000000314>.
- Fisher, P.L., Wells, A., 2005. How effective are cognitive and behavioral treatments for obsessive-compulsive disorder? A clinical significance analysis. *Behav. Res. Ther.* 43 (12), 1543–1558.
- Gadallah, A.-H.A., Ebada, M.A., Gadallah, A., Ahmed, H., Rashad, W., Eid, K.A., Alkanj, S., 2020. Efficacy and safety of N-acetylcysteine as add-on therapy in the treatment of obsessive-compulsive disorder: a systematic review and meta-analysis. *J. Obsess.-Compulsive and Related Disorders* 25, 100529.
- Ghanizadeh, A., Mohammadi, M.R., Bahraini, S., Keshavarzi, Z., Firoozabadi, A., Alavi Shostari, A., 2017. Efficacy of N-acetylcysteine augmentation on obsessive compulsive disorder: a multicenter randomized double blind placebo controlled clinical trial. *Iran. J. Psychiatry* 12 (2), 134–141.
- Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Charney, D.S., 1989. The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. *Arch. Gen. Psychiatry* 46 (11), 1006–1011.
- Guy, W., 1976. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education, and Welfare, Public Health Service.
- Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* 42 (2), 377–381.
- Hedeker, D., Gibbons, R.D., 1997. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol. Methods* 2 (1), 64.
- Hirschtritt, M.E., Bloch, M.H., Mathews, C.A., 2017. Obsessive-compulsive disorder: advances in diagnosis and treatment. *JAMA* 317 (13), 1358–1367. <https://doi.org/10.1001/jama.2017.2200> %J JAMA.
- Jacobson, N.S., Truax, P., 1992. Clinical Significance: A Statistical Approach to Defining Meaningful Change in Psychotherapy Research.
- Katzman, M.A., Bleau, P., Blier, P., Chokka, P., Kjernisted, K., Van Ameringen, M., McGill, U., 2014. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatr.* 14 (1), S1. <https://doi.org/10.1186/1471-244X-14-S1-S1>.
- Levine, J., Schooler, N.R., 1986. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol. Bull.* 22 (2), 343–381.
- Maia, A., Oliveira, J., Lajnef, M., Mallet, L., Tamouza, R., Leboyer, M., Oliveira-Maia, A. J., 2019. Oxidative and nitrosative stress markers in obsessive-compulsive disorder: a systematic review and meta-analysis. *Acta Psychiatr. Scand.* 139 (5), 420–433. <https://doi.org/10.1111/acps.13026>.
- Marinova, Z., Chuang, D.-M., Fineberg, N., 2017. Glutamate-modulating drugs as a potential therapeutic strategy in obsessive-compulsive disorder. *Curr. Neuropharmacol.* 15 (7), 977–995. <https://doi.org/10.2174/1570159X15666170320104237>.
- Mataix-Cols, D., de la Cruz, L.F., Nordsletten, A.E., Lenhard, F., Isomura, K., Simpson, H. B., 2016. Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder. *World Psychiatry* 15 (1), 80.
- Mohebbi, M., Dodd, S., Dean, O., Berk, M., 2018. Patient centric measures for a patient centric era: agreement and convergent between ratings on the Patient Global Impression of Improvement (PGI-I) scale and the Clinical Global Impressions-Improvement (CGI-S) scale in bipolar and major depressive disorder. *Eur. Psychiatr.* 53, 17–22.
- Ooi, S.L., Green, R., Pak, S.C., 2018. N-acetylcysteine for the treatment of psychiatric disorders: a review of current evidence. *Biomed. Res. Int.* 2018, 2469486. <https://doi.org/10.1155/2018/2469486>.
- Patton, J.H., Stanford, M.S., Barratt, E.S., 1995. Factor structure of the Barratt impulsiveness scale. *J. Clin. Psychol.* 51 (6), 768–774. [https://doi.org/10.1002/1097-4679\(199511\)51:6<768::aid-jclp2270510607>3.0.co;2-1](https://doi.org/10.1002/1097-4679(199511)51:6<768::aid-jclp2270510607>3.0.co;2-1).
- Paydary, K., Akamaloo, A., Ahmadipour, A., Pishgar, F., Emamzadehfard, S., & Akhondzadeh, S. (2016). N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. *J. Clin. Pharm. Ther.*, 41(2), 214–219. doi:<https://doi.org/https://doi.org/10.1111/jcpt.12370>.
- Pittenger, C., Bloch, M.H., 2014. Pharmacological treatment of obsessive-compulsive disorder. *Psychiatr. Clin. North Am.* 37 (3), 375–391. <https://doi.org/10.1016/j.psc.2014.05.006>.
- Sansone, R.A., Sansone, L.A., 2011. SNRIs pharmacological alternatives for the treatment of obsessive compulsive disorder? *Innov. Clin. Neurosci.* 8 (6), 10–14.
- Sarris, J., Oliver, G., Camfield, D.A., Dean, O.M., Dowling, N., Smith, D.J., Ng, C.H., 2015. N-acetyl cysteine (NAC) in the treatment of obsessive-compulsive disorder: a 16-week, double-blind, randomised, Placebo-Controlled Study. *CNS Drugs* 29 (9), 801–809. <https://doi.org/10.1007/s40263-015-0272-9>.
- Sheehan, D.V., Harnett-Sheehan, K., Raj, B.A., 1996. The measurement of disability. *Int. Clin. Psychopharmacol.* 11 (Suppl. 3), 89–95. <https://doi.org/10.1097/00004850-199606003-00015>.
- Singer, J.D., Willett, J.B., Willett, J.B., 2003. *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. Oxford university press.
- Skapinakis, P., Caldwell, D.M., Hollingworth, W., Bryden, P., Fineberg, N.A., Salkovskis, P., Lewis, G., 2016. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 3 (8), 730–739. [https://doi.org/10.1016/S2215-0366\(16\)30069-4](https://doi.org/10.1016/S2215-0366(16)30069-4).
- Team, R.C., 2013. *R: A Language and Environment for Statistical Computing*. Vienna, Austria.
- WHO, 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *The WHOQOL Group. Psychol. Med.* 28 (3), 551–558. <https://doi.org/10.1017/s0033291798006667>.
- Wickham, H., 2016. *ggplot2: Elegant Graphics for Data Analysis*. Springer.
- Williams, J.B., 1988. A structured interview guide for the Hamilton depression rating scale. *Arch. Gen. Psychiatry* 45 (8), 742–747. <https://doi.org/10.1001/archpsyc.1988.01800320058007>.
- Yolland, C.O., Hanratty, D., Neill, E., Rossell, S.L., Berk, M., Dean, O.M., Harris, A.W., 2020. Meta-analysis of randomised controlled trials with N-acetylcysteine in the treatment of schizophrenia. *Austr. & New Zealand J. Psychiatr.* 54 (5), 453–466.