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**Master of Science Thesis**

# Assessment of the reporting quality of randomized controlled trials for agomelatine in the treatment of major depressive disorder published from 2000 to 2019 using the CONSORT statement

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# Αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών για την αγομελατίνη στη θεραπεία της μείζονος καταθλιπτικής διαταραχής που δημοσιεύθηκαν από το 2000 έως το 2019 με τη χρήση της δήλωσης CONSORT

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# Contents

# Abstract

**Introduction:** Agomelatine is indicated for the treatment of Major Depressive Disorder (MDD) for over a decade. However, no studies have been conducted to assess the reporting quality of Randomized Controlled Trials (RCTs) in the treatment of MDD with agomelatine.

**Objective:** Assessment of the reporting quality of RCTs for agomelatine in the treatment of MDD published from 2000 to 2019 using the CONSORT 2010 statement.

**Methods:** Research of PubMed for RCTs referring to the treatment of MDD with agomelatine, from January 01 2000 until August 31 2019, was conducted on September 01 2019. The full texts of the trials were assessed using the CONSORT checklist. The reporting of the checklist's items was evaluated and graded. Scores were calculated for each trial and item and comparisons were made.

**Results:** The overall compliance for the 20 eligible RCTs was 84,1%. Compliance for each item ranges widely from 25% to 100%. Between pre-CONSORT and post-CONSORT groups, items 8a, 8b, 9, 10 and 11a showed a statistically significant increase in reporting during time and a statistically significant improvement in reporting objectives (p-value= 0.025) was also found.

**Conclusions:** The reporting quality of RCTs for agomelatine in the treatment of MDD is suboptimal and further improvement is necessary to assess their validity.

**Key words:** agomelatine, major depressive disorder, s20098, MDD, CONSORT, randomized, controlled, trials, RCTs.

# Περίληψη

**Εισαγωγή:** Η αγομελατίνη χρησιμοποιείται για τη θεραπεία της μείζονος καταθλιπτικής διαταραχής για περισσότερο από μία δεκαετία. Ωστόσο, δεν έχουν διεξαχθεί μελέτες για την αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών στη θεραπεία της μείζονος καταθλιπτικής διαταραχής με αγομελατίνη.

**Στόχοι:** Αξιολόγηση της ποιότητας αναφοράς τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών της αγομελατίνης στη θεραπεία της μείζονος καταθλιπτικής διαταραχής, οι οποίες δημοσιεύθηκαν από το 2000 έως το 2019 με τη χρήση της δήλωσης CONSORT.

**Μέθοδοι:** Κατά τη διάρκεια της 01 Σεπτεμβρίου 2019 διεξήχθη έρευνα στη διαδικτυακή βάση δεδομένων PubMed για δημοσιεύσεις τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών σχετικά με τη θεραπεία της ΜΚΔ με αγομελατίνη, από τη 01 Ιαν 2010 έως τις 31 Δεκ 2018. Τα πλήρη κείμενα των επιλεγμένων μελετών αξιολογήθηκαν χρησιμοποιώντας ως εργαλείο τη λίστα ελέγχου της δήλωσης CONSORT. Η ορθή αναφορά για κάθε ένα από τα στοιχεία της λίστας ελέγχου αξιολογήθηκε και βαθμολογήθηκε. Υπολογίστηκαν οι βαθμολογίες για κάθε μελέτη και για κάθε στοιχείο και πραγματοποιήθηκαν συγκρίσεις.

**Αποτελέσματα:** Η συνολική συμμόρφωση για τις 20 τυχαιοποιημένες ελεγχόμενες κλινικές δοκιμές, οι οποίες πληρούσαν τις απαραίτητες προϋποθέσεις και συμπεριλήφθηκαν στη μελέτη ήταν 84,1%. Η συμμόρφωση για κάθε στοιχείο κυμαίνεται ευρέως από 25% έως 100%. Μεταξύ των ομάδων προ-CONSORT 2010 και μετά-CONSORT 2010, τα στοιχεία 8α, 8β, 9, 10 και 11α παρουσίασαν στατιστικά σημαντική αύξηση της επιτυχούς αναφοράς τους κατά τη διάρκεια του χρόνου, καθώς επίσης βρέθηκε και στατιστικά σημαντική βελτίωση στην επιτυχή αναφορά των στοιχείων με την πάροδο του χρόνου (p-value = 0.025).

**Συμπεράσματα:** Η ποιότητα αναφοράς των τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών για την αγομελατίνη στη θεραπεία της ΜΚΔ ήταν ανεπαρκής και κρίνεται απαραίτητη η περαιτέρω βελτίωσή τους, με σκοπό την αξιολόγηση της εγκυρότητάς τους.

**Λέξεις κλειδιά:** αγομελατίνη, μείζων καταθλιπτική διαταραχή, s20098, ΜΚΔ, τυχαιοποιημένες ελεγχόμενες κλινικές μελέτες, CONSORT.

# Introduction

Major depressive disorder (MDD) is a recurrent, persistent and seriously impairing mental condition associated with substantial symptom severity (significant somatic as well as psychiatric symptoms), diminished role functioning-quality life [1] and is considered as one of the leading causes of disability worldwide [2]. With an estimated 350 million people affected globally, depressive disorders are a major contributor to the overall global burden of disease [3].

The global point prevalence of major depressive disorder is 4.7% (4.4-5.0%) and the annual incidence is 3.0% (2.4-3.8%) [4]. MDD occurs about twice as often in women than it does in men [5] and affects one in six adults in their lifetime [6] [7]. MDD occurs in 7% of the general older population and it accounts for 5.7% of YLDs among those over 60 years old [8]. Rates of major depressive disorder appear to be higher in older women than in older men, but with the gender gap somewhat narrower in this age group, particularly among the oldest old, than the two-fold difference seen across the rest of the adult lifespan [9] [10].

Major depressive disorder is one of the most common psychiatric disorders in the US (about 16.2 million Americans - 6.7% of the total population- have experienced at least one episode of MDD) [11]. MDD has been shown to impose a substantial economic burden on all levels of society. The economic burden of MDD was estimated at 210.5 billion in the US. While approximately half of the amount was due to direct medical costs, the other half was attributable to indirect costs related to absenteeism, presentism and suicide, further underscoring the toll that MDD imposes on a patient's life [12]. In Europe, in every year over a third of the total EU population suffers from mental disorders, while major depressive disorder is one of the most frequent (6.9%) [13] [14].

Major depressive disorder (MDD) is a commonly occurring disorder in all countries where epidemiological surveys have been carried out [15]. In 1996 the WHO has ranked depression as the fourth leading cause of disability worldwide [16] and projects that, by 2020, it will be the second leading cause [17]. In 2008, WHO ranked major depression as the third cause of burden of disease worldwide and projected that the disease will rank first by 2030 [18].

Agomelatine, the compound under study, was discovered and developed by Servier Laboratories Ltd (France) [19]. In 1997, following an application to the World Health Organization, s20098 was attributed the international non-proprietary name agomelatine in recognition of its innovative melatonergic profile, as compared with other antidepressants acting via monoaminergic mechanisms [20]. The antidepressant agomelatine has a mechanism of action quite different from any other antidepressant. It combines antagonist actions at serotonergic 5HT2C receptors with agonist actions at melatonergic MT1 and MT2 receptors. Neither mechanism alone has any evidence of efficacy in depression, but when combined in a single molecule, agomelatine has proven antidepressant actions [21] [22] [23]. In February 2009, the committee for medicinal products for human use of the European Medicines Agency provided marketing authorization for treating major depressive disorder [24] episodes in adults with agomelatine [25] and after one year agomelatine received and TGA approval for marketing in Australia in August 2010 [26].

In clinical research, randomized controlled trials (RCTs) are the gold standard for ascertaining the efficacy and safety of a treatment (healthcare interventions). RCTs are used to answer patient-related questions and are required by governmental regulatory bodies as the basis for approval decisions. The quality of an RCT depends on an appropriate study question and study design, the prevention of systematic errors and the use of proper analytical techniques. All of these aspects must be attended to in the planning, conductance, analysis, and reporting of RCTs. RCTs must also meet ethical and legal requirements. RCTs cannot yield reliable data unless they are planned, conducted, analyzed, and reported in ways that are methodologically sound and appropriate to the question being asked. The quality of any RCT must be critically evaluated before its relevance to patient care can be considered [27].

In 1996, the urgency for improving RCTs, led two separate initiatives by interested researchers and editors to the development of the first CONSORT guidelines [28]. The guidelines included a checklist and flow chart for trial participants. Primarily directed toward simple parallel trials, the guidelines were rapidly adopted by many journals and editorial groups. These included The Lancet, BMJ, JAMA, Annals of Internal Medicine, Obstetrics and Gynecology, the Vancouver Group, and the Council of Science Editors. CONSORT, like science itself, is a work in progress, and its development remains an iterative process [29]. Examination of the use of the first proposed flow chart [30] [31] led to its revision in the second edition (2001) [32] [33]. As new evidence emerges, the CONSORT committee continues to revise the guidelines as needed. The Consort statement revised again in 2010 [34] and over the past years, a number of CONSORT recommendations (updates and extensions) for the publication of RCTs have been developed and published [35] [36] [37].

The adoption of the CONSORT statement had a beneficial impact on the reporting quality of RCTs [38] and it is the guide for the assessment of the reporting quality of RCTs in many medical fields and subspecialties (hematology [39], surgery [40]). The assessment of reporting quality of RCTs for agomelatine in major depressive disorder has not yet been assessed based on the CONSORT (revised version 2010).

# Purpose

Randomized controlled trials (RCTs) are the gold standard for ascertaining the efficacy and safety of a treatment (healthcare interventions). The CONSORT statement is an evidence based approach to improve the quality of reporting of RCTs. Given the relative lack of reports evaluating studies in psychiatry and the apparent absence of such a study for the treatment of major depressive disorder with agomelatine, this thesis aims at assessing the reporting quality of RCTs concerning MDD treatment with agomelatine. The present study will evaluate RCTs published from January 01 2000 to August 31 2019, following the last Consolidated Standards of Reporting Trials - CONSORT statement revision checklist [41].

# Materials and Methods

Search Strategy

On September 01 2019, in order to identify the randomized controlled trials to be included in the present study, a comprehensive computerized search of English language publications listed in the electronic databases MEDLINE (via PubMed) was conducted. The search term used was “agomelatine”. The filters “article types”, “publication dates” and “species” were customized as “Randomized Controlled Trials”, “from 2000/01/01 to 2019/08/31” and “Humans” respectively.

Search results were first screened for eligibility by title, then by abstract and finally by full text review when deemed necessary. Screening of the articles and selection of eligible RCTs were conducted by one researcher - the author.

Eligibility Criteria

Inclusion criteria: Eligible for entry in the present study were randomized controlled trials (RCTs) comparing agomelatine with placebo or another active antidepressant as oral monotherapy for the treatment of adults (≥18 years old, no limitations regarding to gender and origin) with a primary diagnosis of major depressive disorder (MDD) according to standard operationalised diagnostic criteria (Feighner Criteria [42] [43] [44] , Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5 and ICD-10 [45]). Every RCT had to include a randomization procedure resulting in at least two arms with one of them serving as control. Only articles including final results of RCTs were eligible. Interim analyses were only included if results of the primary outcome were presented and the report of the final results had not yet been published before the end of the pre-specified time frame. Reports of trials regarding treating symptoms of MDD were also included. RCTs had to be published only in English language from January 01 2000 to August 31 2019.

Exclusion criteria: Non-eligible for entry in the present study were non-randomised and/or non-controlled trials, observational studies, side-studies, reviews, post-hoc analyses of RCTs, follow-up studies, cluster RCTs or other types of analyses/ reviews. Trials reported as “animal studies”, “in vitro studies”, “case studies”, “systematic reviews” or “genetic association studies” were also excluded. Reports of trials regarding treating symptoms of MDD or coping with side effects were excluded. Abstracts, editorials, meta-analyses, letters and other Post-hoc, subgroup and pharmacokinetic analyses were to be excluded only after reading the article, in order not to lose any additional published work, unidentified with PubMed.

From the records identified, duplications were removed and then, an initial screening was performed on the basis of title and the remaining articles were read in abstract and full text to apply the eligibility criteria and select the reports included in the analysis. References of the articles included in the analysis were screened in order not to lose any relative reports unidentified with the initial search. For all remaining articles, the full text of the article was obtained and reviewed.

Data Extraction

After the eligible RCTs were identified, thorough assessment of each one's complete report was conducted. The revised CONSORT (2010) checklist [46] was used to evaluate the reporting completeness of the eligible RCTs. From the total of 20 eligible RCTs, 10 were conducted until 2010, when the revise CONSORT 2010 version was published and 10 after 2010.

The CONSORT checklist is a set of 25 items (amounting to 38, when sub-items are calculated separately, including the flow diagram), that should be included in an optimally written RCT report. Every article was thoroughly inspected for the fulfillment of each one of the 38 items on the checklist. The interpretation of the CONSORT checklist items was done according to the "CONSORT 2010 Explanation and Elaboration" document [47]. In the case of item 1b concerning the abstract of the report, the "CONSORT for reporting randomised trials in journal and conference abstracts" extension document was taken into reference [48]. In the case of item 19 concerning the harms of the report, the "CONSORT for reporting randomised trials in journal and conference abstracts" extension document was taken into reference [49]. Thus, a total CONSORT score for each article was obtained with maximum probable total CONSORT score being equal to 38.

The items in the checklist were investigated in terms of whether they were reported or not [50]. Following the relevant guidelines, items were considered to be properly reported when complete and clear information about them was provided in the RCT report. This was termed a positive response and was assigned the value of 1. No information was considered a negative response and was given the value of 0. Alternatives responses (partial, ambiguous or indirect reporting of an item) in addition with unclear responses to each question were also considered a negative response (Table 1).

The items of the CONSORT checklist are divided into groups corresponding to the respective parts of an RCT report (title and abstract [51], introduction, methods, results and discussion). A positive response for a certain item was only accepted when information about it was provided in the corresponding part of the report. The only exceptions to this rule were the items listed under the checklist title "Other Information"; if properly reported, these items were considered to be fulfilled no matter what part of the article they were reported in.

Data Analysis

A descriptive statistical analysis of all evaluated articles was conducted. All relevant studies were checked for compliance with the statement by assessing the fulfillment of the 38 CONSORT 2010 items. In order to assess adherence to the CONSORT checklist items, the number and proportion of reports describing each of the 38 items were calculated. The number and proportion of these items by the RCTs published in a journal were calculated. The sum of the scores was converted to a percentage value for each trial, each item, each section, and the total of the CONSORT checklist. For each article, the quality of its reporting was determined by the total number of items it included in the 38-item checklist.

In order to detect reporting differences over time, studies were grouped by publication date (2 groups: 2000-2010 and 2011-2019). Frequencies for each reporting item of the checklist were calculated for pre-CONSORT 2010, post-CONSORT 2010 and combined period group of articles. Finally, the checklists' items were separated into five groups according to the sections of the published article (title/abstract/introduction, methods, results, discussion and other information) in order to calculate the compliance of the checklist items in each of the 5 groups and examine differences in compliance among publication dates (75% compliance with the checklist, overall and by time period) and to calculate the percentage of the items that were reported in at least 75% of the articles in overall and by item group. Comparison between >75% compliance among different time periods was calculated using the chi-square test.

Data were analyzed using Microsoft Excel 2016. Data were processed, frequencies were calculated and statistical tests were performed using IBM SPSS v25 statistics package, provided by University of Thessaly. A two-sided level of 0.05 (P-value) was set as a threshold of statistical significance.

| Item | | | | | | | | | | | RCTs | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | # | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| **Title and abstract** | | | | | | | | | | | | | | | | | | | | | | |
| | 1 a | 10 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| | 1 b | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Introduction** | | | | | | | | | | | | | | | | | | | | | | |
| **Background and objectives** | 2 a | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 2 b | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Methods** | | | | | | | | | | | | | | | | | | | | | | |
| **Trial Design** | 3 a | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 3 b | 7 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 0 |
| **Participants** | 4 a | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 4 b | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Interventions** | 5 | 18 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| **Outcomes** | 6 a | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 6 b | 10 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| **Sample size** | 7 a | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | 7 b | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Randomization sequence generation** | 8 a | 14 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 8 b | 14 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Rnd Allocation mech.** | 9 | 15 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Implementation** | 10 | 15 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Blinding** | 11a | 16 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 11b | 17 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 |
| **Statistical Methods** | 12a | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 12b | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Results-diagram** | 13 | 16 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| **Participant flow** | 13a | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 13b | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Recruitment** | 14a | 17 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 14b | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Baseline data** | 15 | 17 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Numbers analyzed** | 16 | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Outcomes and estimation** | 17a | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | 17b | 14 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 |
| **Ancillary analyses** | 18 | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Harms** | 19 | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Discussion** | | | | | | | | | | | | | | | | | | | | | | |
| **Limitations** | 20 | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Generalisability** | 21 | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Interpretation** | 22 | 20 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Other Information** | | | | | | | | | | | | | | | | | | | | | | |
| **Registration** | 23 | 8 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 |
| **Protocol** | 24 | 8 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 |
| **Funding** | 25 | 18 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Consort Score** | 38 | | 22 | 30 | 31 | 34 | 25 | 36 | 34 | 27 | 28 | 32 | 34 | 34 | 37 | 33 | 35 | 36 | 31 | 35 | 32 | 33 |

**Table 1: Items reported per RCT**

# Results

Search Results

The search in PubMed yielded 489 potentially eligible articles that were screened for eligibility. Of those, 329 articles were excluded by title, 123 were excluded by abstract while 37 required full text review to be conclusively defined as ineligible. In total 469 articles were excluded from the study. The screening strategy and reasons for exclusion are summarized in Figure 1.

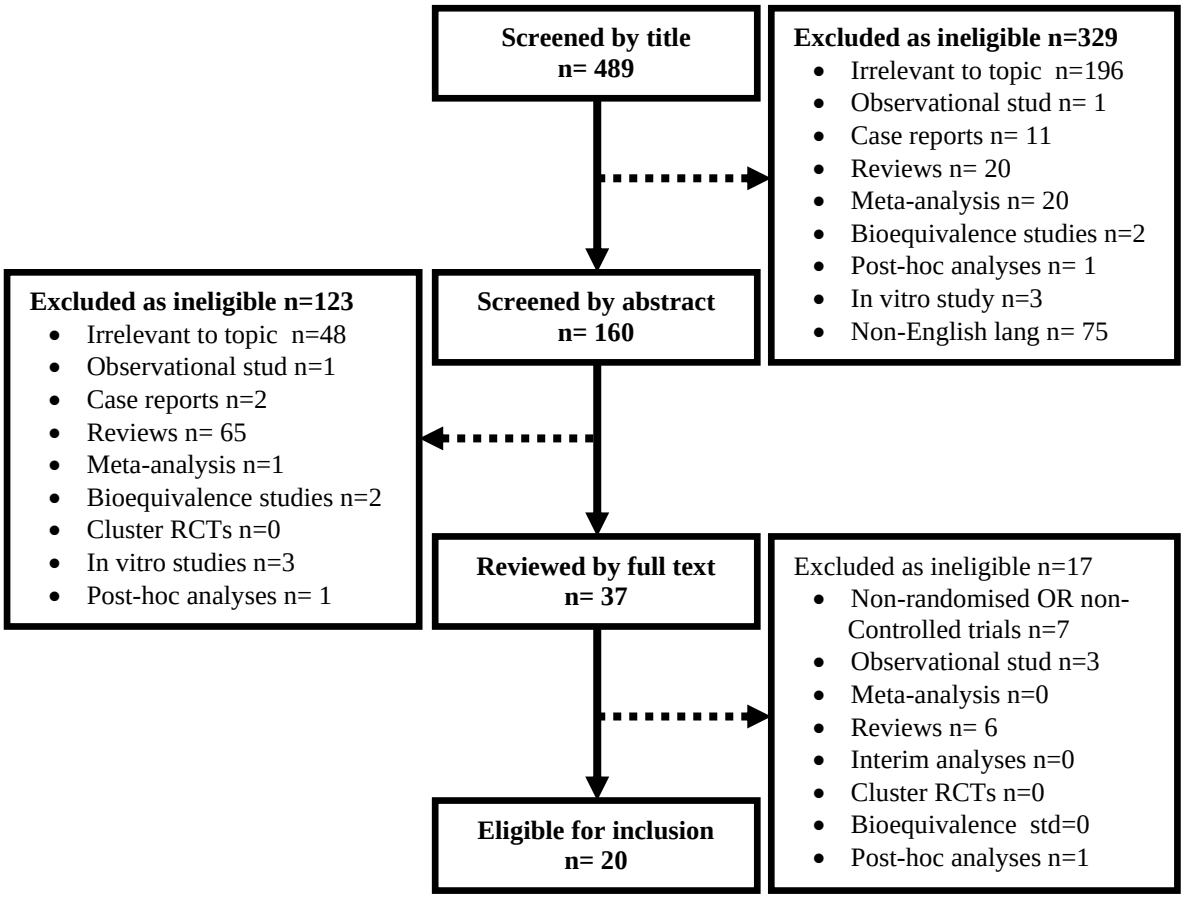


**Figure 1: Summary of the screening strategy and reasons for exclusion at each step.**

Eligible Trials

Finally, 20 RCTs were deemed eligible to be included in the present study. 5 RCTs were published in Journal of Clinical Psychiatry, 3 in European Neuropsychopharmacology, 3 in Journal of Clinical Psychopharmacology, 3 in International Clinical Psychopharmacology, 2 in International Journal of Neuropsychopharmacology, 1 in Asian Journal Psychiatry, 1 in Journal of Affective Disorders, 1 in Human Psychopharmacoly: Clinical and Experimental and 1 in Pharmacopsychiatry. The control group received placebo in 8 RCTs and another pharmaceutical substance in 12 RCTs. 15 trials had 2 study arms while 5 trials had more than 2 study arms. All RCTs were blinded and multicenter. A full list of these RCTs is provided in the Appendix.

Reporting Quality Results

**1)** The overall compliance for the 20 included randomized controlled trials was 84,1%. 17 RCT reports included adequate information of about at least 75% of applicable items. Compliance for each item is summarized in Table 2.

| Item | | Number of RCTs applicable | Number of RCTs reported | Proportion |
|---|---|---|---|---|
| **Title and Abstract** | | | | |
| **1a** | | 20 | 10 | 50% |
| **1b** | | 20 | 20 | 100% |
| **Introduction** | | | | |
| **2a** | Background and objectives | 20 | 20 | 100% |
| **2b** | | 20 | 20 | 100% |
| **Methods** | | | | |
| **3a** | Trial design | 20 | 20 | 100% |
| **3b** | | 20 | 7 | 35% |
| **4a** | Participants | 20 | 20 | 100% |
| **4b** | | 20 | 20 | 100% |
| **5** | Interventions | 20 | 18 | 90% |
| **6a** | Outcomes | 20 | 20 | 100% |
| **6b** | | 20 | 10 | 50% |
| **7a** | Sample size | 20 | 5 | 25% |
| **7b** | | 20 | 20 | 100% |
| **8a** | Randomization | 20 | 14 | 70% |
| **8b** | | 20 | 14 | 70% |
| **9** | Rnd. Allocation mech. | 20 | 15 | 75% |
| **10** | Implementation | 20 | 15 | 75% |
| **11a** | Blinding | 20 | 16 | 80% |
| **11b** | | 20 | 17 | 85% |
| **12a** | Statistical methods | 20 | 20 | 100% |
| **12b** | | 20 | 20 | 100% |
| **Results** | | | | |
| **13** | Participant Flow Diagram | 20 | 16 | 80% |
| **13a** | Participant Flow | 20 | 20 | 100% |
| **13b** | | 20 | 20 | 100% |
| **14a** | Recruitment | 20 | 17 | 85% |
| **14b** | | 20 | 20 | 100% |
| **15** | Baseline data | 20 | 17 | 85% |
| **16** | Numbers Analyzed | 20 | 20 | 100% |
| **17a** | Outcomes and estimation | 20 | 20 | 100% |
| **17b** | | 20 | 14 | 70% |
| **18** | Ancillary analysis | 20 | 20 | 100% |
| **19** | Harms | 20 | 20 | 100% |
| **Discussion** | | | | |
| **20** | Limitations | 20 | 20 | 100% |
| **21** | Generalisability | 20 | 20 | 100% |
| **22** | Interpretation | 20 | 20 | 100% |
| **Other Information** | | | | |
| **23** | Registration | 20 | 8 | 40% |
| **24** | Protocol | 20 | 8 | 40% |
| **25** | Funding | 20 | 18 | 90% |

**Table 2: Compliance figures per item.**

**2)** Compliance for each item ranges widely from 25% to 100% of trials (Figure 2):

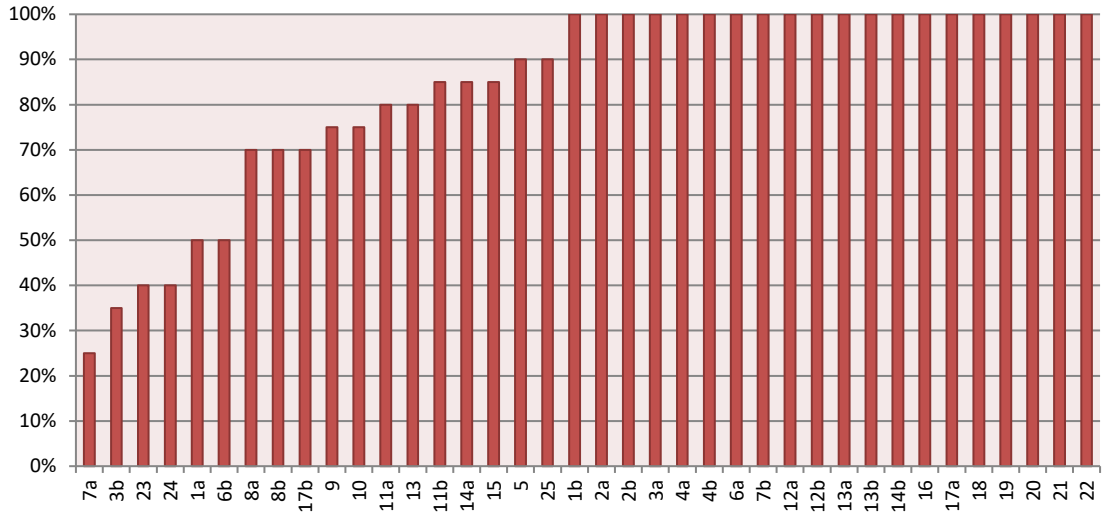


**Figure 2: Compliance per item**

- Reporting was successful (100% of RCTs) for the following items: Item 1b: *Structured summary of trial*, Item 2a: *Scientific background and explanation of rationale*, Item 2b: *Specific objectives or hypotheses*, Item 3a: *Description of trial design*, Item 4a: *Eligibility criteria for participants*, Item 4b: *Settings and locations where the data were collected*, Item 6a: *Completely defined pre-specified outcome measures*, Item 7b: *When applicable, explanation of any interim analyses and stopping guidelines*, Item 12a: *Statistical methods used to compare groups for outcomes*, Item 12b: *Methods for additional analyses*, Item 13a: *For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome*, Item 13b: *Losses and exclusions after randomization, together with reasons*, Item 14b: *Why the trial ended/stopped*, Item 16: *For each group, number of participants included in each analysis and whether the analysis was by original assigned groups*, Item 17a: *For each outcome, results for each group, and the estimated effect size and its precision*, Item18: *Results of any other analyses performed*, Item 19: *All important harms or unintended effects in each group*, Item 20: *Trial limitations*, Item 21: *Generalisability of the trial findings*, Item 22: *Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence*.

- On the contrary, reporting was particularly low (<50% of RCTs) for the following items:
    - Item 7a: *How sample was determined* (25%): This part of the trial design of each RCT was poorly mentioned.
    - Item 3b: *Important changes to methods after trial commencement with reasons* (35%): Reporting of this part of the trial design proved to be poorly reported. Theoretically, there could be no change in methods after trial commencement, but even in this case method was not reported as unchanged throughout the trial.

- Item 23: *Registration number and name of trial registry* (40%): Reported correctly in 8 out of 20 trials. By registering a randomized trial, authors typically report a minimal set of information and obtain a unique trial registration number. If authors had not registered their trial they should explicitly state this and give the reason. Covert redundant publication of clinical trials can also cause problems, particularly for authors of systematic reviews when results from the same trial are inadvertently included more than once.
- Item 24: *Where the full trial protocol can be accessed* (40%): Reported correctly in 8 out of 20 trials. A protocol for the complete trial is important because it pre-specifies the methods of the randomized trial, such as the primary outcome (see item 6a). Having a protocol can help to restrict the likelihood of undeclared post hoc changes to the trial methods and selective outcome reporting (see item 6b). Elements that are important for inclusion in the protocol for a randomized trial.

**3)** The different CONSORT items have been variedly reported in RCTs (Figure 3).

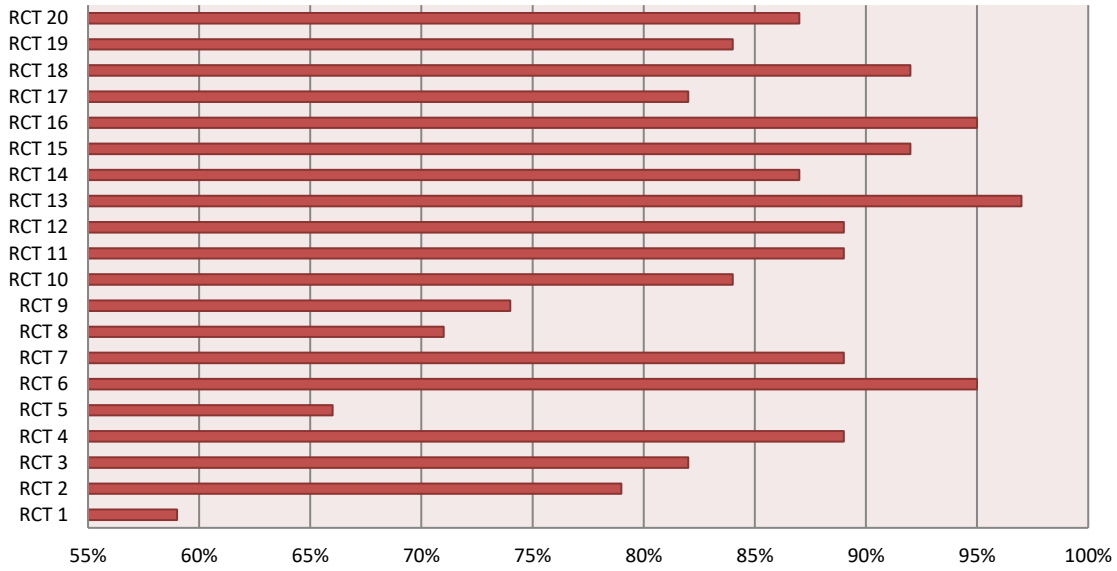


**Figure 3: Compliance per RCT**

**4)** Of a total of 20 articles, 10 were published in the period 2000-2010 and in 10 the period 2011-2019. The percentages of articles reporting each item by publishing period is shown at Table 3.

Between pre-CONSORT 2010 and post-CONSORT 2010 period groups, some items showed a statistically significant increase in reporting during time (Table 3):
Item 8a: *Method used to generate the random allocation sequence* ($p=0,003<0.05$)
Item 8b: *Type of randomization* ($p=0,003<0.05$)
Item 9: *Mechanism used to implement the random allocation sequence* ($p=0,010<0.05$)
Item 10: *Who generated the random allocation sequence, who enrolled patients, and who assigned participants to interventions* ($p=0,010<0.05$)
Item 11a: *If done, who was blinded after assignment to interventions and how* ($p=0,025<0.05$).

| Data Item | Combined 2000-2019 (n=20) | pre-CONSORT 2010 (n=10) | post-CONSORT 2010 (n=10) | P-value |
|---|---|---|---|---|
| **Title and abstract** | | | | |
| **1a** | 0,50 | 0,60 | 0,40 | 0,371 |
| **1b** | 1,00 | 1,00 | 1,00 | 1,000 |
| **Introduction** | | | | |
| **2a** | 1,00 | 1,00 | 1,00 | 1,000 |
| **2b** | 1,00 | 1,00 | 1,00 | 1,000 |
| **Methods** | | | | |
| **3a** | 1,00 | 1,00 | 1,00 | 1,000 |
| **3b** | 0,35 | 0,30 | 0,40 | 0,639 |
| **4a** | 1,00 | 1,00 | 1,00 | 1,000 |
| **4b** | 1,00 | 1,00 | 1,00 | 1,000 |
| **5** | 0,90 | 0,90 | 0,90 | 1,000 |
| **6a** | 1,00 | 1,00 | 1,00 | 1,000 |
| **6b** | 0,50 | 0,40 | 0,60 | 0,371 |
| **7a** | 0,25 | 0,20 | 0,30 | 0,605 |
| **7b** | 1,00 | 1,00 | 1,00 | 1,000 |
| **8a** | 0,70 | 0,40 | 1,00 | **0,003** |
| **8b** | 0,70 | 0,40 | 1,00 | **0,003** |
| **9** | 0,75 | 0,50 | 1,00 | **0,010** |
| **10** | 0,75 | 0,50 | 1,00 | **0,010** |
| **11a** | 0,80 | 0,60 | 1,00 | **0,025** |
| **11b** | 0,85 | 0,90 | 0,80 | 0,531 |
| **12a** | 1,00 | 1,00 | 1,00 | 1,000 |
| **12b** | 1,00 | 1,00 | 1,00 | 1,000 |
| **Results** | | | | |
| **13** | 0,80 | 0,80 | 0,80 | 1,000 |
| **13a** | 1,00 | 1,00 | 1,00 | 1,000 |
| **13b** | 1,00 | 1,00 | 1,00 | 1,000 |
| **14a** | 0,85 | 0,70 | 1,00 | 0,060 |
| **14b** | 1,00 | 1,00 | 1,00 | 1,000 |
| **15** | 0,85 | 0,70 | 1,00 | 0,060 |
| **16** | 1,00 | 1,00 | 1,00 | 1,000 |
| **17a** | 1,00 | 1,00 | 1,00 | 1,000 |
| **17b** | 0,70 | 0,70 | 0,70 | 1,000 |
| **18** | 1,00 | 1,00 | 1,00 | 1,000 |
| **19** | 1,00 | 1,00 | 1,00 | 1,000 |
| **Discussion** | | | | |
| **20** | 1,00 | 1,00 | 1,00 | 1,000 |
| **21** | 1,00 | 1,00 | 1,00 | 1,000 |
| **22** | 1,00 | 1,00 | 1,00 | 1,000 |
| **Other information** | | | | |
| **23** | 0,40 | 0,30 | 0,50 | 0,361 |
| **24** | 0,40 | 0,20 | 0,60 | 0,068 |
| **25** | 0,90 | 0,80 | 1,00 | 0,136 |

**Table 3: Numbers and percentages of items reported by 75% or more of the articles by reporting group**

| Checklist items/period | 2000-2019 N(%) | 2000-2010 N(%) | 2011-2019 N(%) |
|---|---|---|---|
| **Overall (38)** | 29 (76,3) | 24 (63,1) | 31 (81,5) |
| **Title/abstract/introduction (4)** | 3 (75) | 3 (75) | 3 (75) |
| **Methods (17)** | 12 (70,5) | 9 (52,9) | 14 (82,3) |
| **Results (11)** | 10 (90,9) | 8 (72,7) | 10 (90,9) |
| **Discussion (3)** | 3(100) | 3 (100) | 3 (100) |
| **Other information (3)** | 1 (33,3) | 1 (33,3) | 1 (33,3) |

**Table 4: Numbers and percentages of items/period reported by 75% or more of the articles by reporting group**

**5)** The numbers and percentages showing the checklist items that was reported by 75% or more of the articles by period and by group is shown at Table 4 and Figure 4.

- 29 checklist items (76,3%) were reported from 75% or more of the articles published from 2000 to 2019, 24 (63,1%) the period 2000-2010 and 31 (81,5%) 2011 to 2019, showing a trend of increase in reporting CONSORT items after its revision.

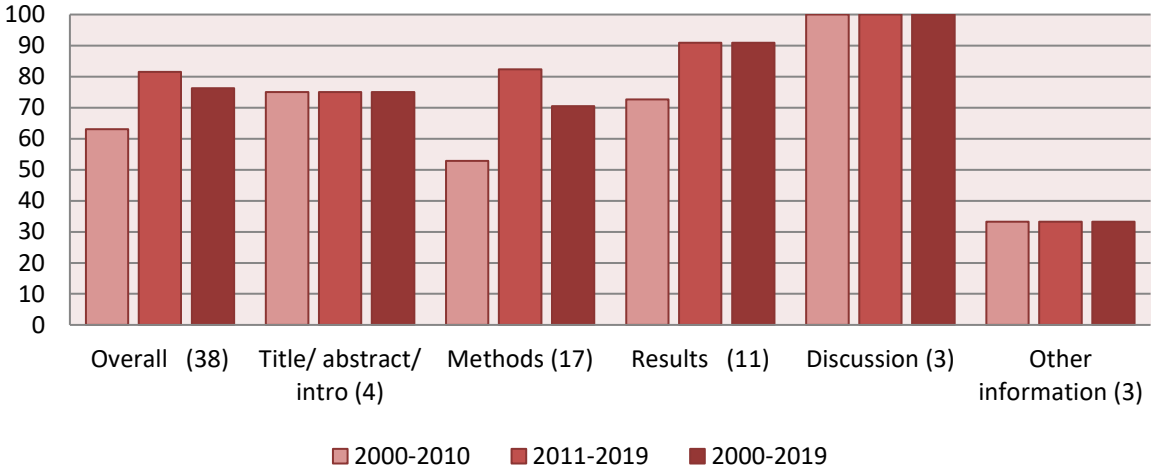


**FIgure 4: Percentage of items reported in >75% of the articles by period and by group**

- The >75% compliance with CONSORT by time period was: overall: 17 (85%), 2000-2010: 6 (60%) and 2011-2019: 10 (100%) expressing a statistically significant difference in compliance among the different time periods (p-value= 0.025) (Table 5 and Figure 5).

| Number of RCTs with compliance <75% per time period | | |
|---|---|---|
| 2000-2010 | 2011-2019 | 2000-2019 |
| 4 | **0** | **3** |
| Number of RCTs with compliance >75% per time period | | |
| 2000-2010 | **2011-2019** | **2000-2019** |
| 6 | 10 | 17 |

**Table 5: Numbers of RCTs with compliance < 75% and >75% by reporting group**

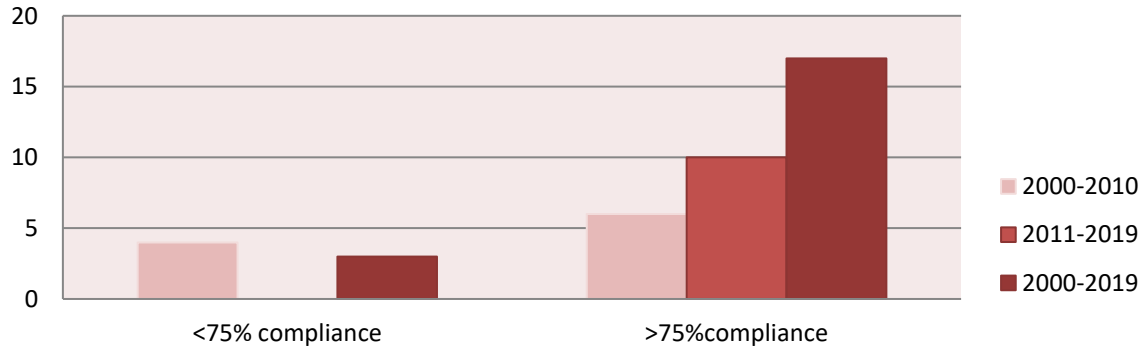


**FIgure 5: compliance among different time periods**

# Discussion

The aim of evidence-based medicine is to increase the use of high quality clinical research in clinical decision making [52] [53]. The best scientific evidence is considered to be a randomized controlled clinical trial [54]. RCT data are considered the gold standard for evaluating efficacy in clinical research and constitute evidence for medical treatment [55]. In 1992, a team of scientists published findings of a study comparing recommendations by experts with results of meta-analyses of randomised controlled trials for treating myocardial infarction (MI) [56] and nowadays RCTS are increasingly popular [57]. There have been quality indicators defined for RCTs, and these indicators should be considered in both design and reporting of RCTs. These quality indicators include internal and external validity and one of them is CONSORT 2010 statement. Using this checklist, investigators will provide precise details about the design, conduct, and analysis of their trial. A principal advantage of such reporting is that all readers will have uniform and standardized information to review, unaffected by the writing nuances of authors and the policies of editors. This will give readers essential information about what happened during the trial, especially around issues affecting a trial's internal validity [58].

The overall compliance (CONSORT 2010 statement) for the 20 included randomised controlled trials was 84,1%. The wide range of frequencies of reporting items across the sum of articles indicate that the reporting RCTs of agomelatine for the treatment of MDD are suboptimal. These results are in accordance with previous RCT report evaluating studies in oncology hematology and other medical fields [59] [60] [61].

Compliance for each item ranges widely from 25% to 100% of trials. Most information given, about the methodology and results of RCTs, was clear enough to enable readers to have an objective aspect of the quality of these trials. However, significant efforts should be made by authors and journals, for a further enhancement of compliance with about 50% of the CONSORT items. For example, inadequate trial registration and poor protocol reporting, as presented in the results, could also result in reporting bias.

CONSORT was not meant to be used as a quality assessment instrument. Rather, the content of CONSORT focuses on items related to the internal and external validity of trials. Many items not explicitly mentioned in CONSORT should also be included in a report, such as information about approval by an ethics committee, obtaining informed consent from participants, and, where relevant, existence of a data safety and monitoring committee. There is no evidence that reporting integrity implies methodological integrity and poor reporting is not necessarily associated with flawed design or conduct of a trial [62]. For example, reporting of the item 3b: important changes to methods after trial commencement with reasons (35%), proved to be poorly reported. Theoretically, there could be no change in methods after trial commencement, but even in this case, method was not reported as unchanged throughout the trial. However, proper reporting of RCTs is of major importance since it influences decision-making while systematic reviews and meta-analyses are based on data derived from reports [63].

Between pre-CONSORT 2010 and post-CONSORT 2010 period groups, some items showed a statistically significant increase in reporting during time. The >75%

compliance with CONSORT by time period was: overall: 17 (85%), 2000-2010: 6 (60%) and 2011-2019: 10 (100%) expressing a statistically significant difference in compliance among the different time periods (p-value= 0.025). These results showed that journals, such as Journal of clinical Psychiatry and Journal of clinical Psychopharmacology, have improved levels of compliance in their trial reports, since the revised CONSORT 2010. Journal editors, reviewers and authors should be encouraged to adhere to the CONSORT statement when reporting on RCTs and/or reviewing the reports of RCTs, in order to ensure high-quality trials. This thesis is the first attempt of assessment of the reporting quality of randomized controlled trials for agomelatine in the treatment of major depressive disorder using the CONSORT statement and further studies are needed to confirm the present results.

# Limitations

This study was conducted by a single researcher, the author. The search was restricted to literature from one database (PubMed) and eligible RCTs had to be published only in English language (non-English articles: 75 out 489 potentially eligible articles).

The evaluation of each CONSORT 2010 item was a rather complex procedure since no exact criteria exist as to what constitutes a positive or negative response. All possible precautions were taken on behalf of the researcher to eliminate selection and measurement bias, for example thorough studying of the existing scientific literature about major depressive disorder and understanding of the principles of conduction of medical reviews and comprehensive studying of the Consolidated Standards for Reporting of Trials (CONSORT), including updates, extensions and the “CONSORT Explanation and Elaboration” document.

Major depressive disorder and the use of relevant rating scales (included in RCTs) could not be assessed by the author, to eliminate selection bias. Ambiguity in reporting or misplaced reporting of certain items in the included RCTs posed an extra factor of measurement bias. Data were extracted and analyzed only by the author.

# Conclusions

This thesis evaluated the reporting quality of randomised controlled trials for the treatment of major depressive disorder with agomelatine published between January 10 2000 and August 31 2019. The reports of 20 eligible RCTs were reviewed using the CONSORT 2010 statement as an assessment tool.

A well-designed and well-reported RCT should meet all of the criteria of the CONSORT statement. The wide range of frequencies of reporting items across the sum of articles indicate that the reporting RCTs of agomelatine for the treatment of MDD are suboptimal.

The overall compliance for the 20 included randomized controlled trials was 84,1% of applicable items. Compliance for each item ranges widely from 25% to 100% of trials. 17 out 20 RCTs reported >75% compliance with the CONSORT items, 15 reported >80% and only 5 out 20 (25%) RCTs reported compliance >90%. Among the most frequently recorded items the following ones are included: structured summary of trial, scientific background and explanation of rationale with specific objectives and hypotheses, eligibility criteria for participants, harms or unintended effects and trial limitations. On the contrary, reporting was particularly low (<50% of RCTs) for the following items: sample determination (25%), changes to methods after trial commencement (35%), registration number and name (40%) and protocol reporting (40%). Details about randomization, blinding and trial setup were sometimes omitted.

Between pre-CONSORT 2010 and post-CONSORT 2010 period groups, some items showed a statistically significant increase in reporting during time: method used to generate the random allocation sequence, type of randomization, mechanism used to implement the random allocation sequence, who generated the random allocation sequence, who enrolled patients, and who assigned participants to interventions and who was blinded after assignment to interventions and how ($p<0.05$). These results highlight the improvement of reporting of RCTs after the revision of the CONSORT checklist in 2010.

It should be noted that 24 (63,1%) the period 2000-2010 and 31 (81,5%) 2011 to 2019, showing a trend of increase in reporting CONSORT items after its revision and the >75% compliance with CONSORT 2010 by time period expressed a statistically significant difference in compliance among the different time periods (p-value= 0.025). This suggests that there is good evidence in the literature that the adoption of CONSORT 2010 statement improves the quality of conduct and reporting of trials in journals. As new methods of treatment are evolving, substantial obedience of their RCT reports to CONSORT statement is obliged in order to assess effectively their validity. Broader recommendations of CONSORT statement by medical journals would also contribute to plainly improved reporting quality.

Major depressive disorder, one of the most common mental disorders, is a significant medical condition affecting millions of people worldwide and the discovery of novel and more effective treatments is necessary. In this effort, randomised controlled clinical trials will once again serve as the optimum way of verifying the safety and efficacy of new pharmaceutical and genetic therapies. According to the above, the

present thesis concluded that the reporting quality of the included RCTs for agomelatine in the treatment of MDD is suboptimal. The knowledge gained from this study should be viewed as an opportunity for improved adherence and increased awareness of the CONSORT statement. Higher quality reports in terms of completeness and transparency will help the scientific community evaluate their validity, improve RCT interpretation, minimize biased conclusions and reach safe decisions about treatment effectiveness and efficacy of MDD.

## Conflict of Interest Statement

The author certifies that he has no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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# Appendix

List of articles – RCTs included in th present study:


1. Loo H, Hale A et al. Determination of the dose of agomelatine, a melatonergic agonist and selective 5HT2c antagonistic, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int Clin Psychopharmacol. 2002;17:239-247.
2. Kennedy SH, Emsley R et al. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. Eur Neuropsychopharmacol. 2006;16:93-100.
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5. Kennedy SH, Rizvi S, Fulton K, Rasmussen J et al. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. J Clin Psychopharmacol 2008 28: 329–333.
6. Goodwin GM, Emsley R et al. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009;70:1128-37.
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8. Zajecka J, Schatzberg A et al. Efficacy and safety of agomelatine in the treatment of major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2010;30:135-44.
9. Stahl SM, Fava M et al. Agomelatine in the treatment of major depressive disorder: an 8-week, multicenter, randomized, placebo-controlled trial. *J Clin Psychiatry* 2010;71:616-26.
10. Hale A, Corral RM et al. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. *Int Clin Psychopharmacol* 2010;25:305-14.
11. Quera-Salva MA, Hajak G et al. Comparison of agomelatine and escitalopram on nighttime sleep and daytime condition and efficacy in major depressive disorder patients. *Int Clin Psychopharmacol* 2011;26:252-62.
12. Heun, R, Ahokas, A et al. The efficacy of agomelatine in elderly patients with recurrent major depressive disorder: a placebo controlled study. J Clin Psychiatry 2013 74(6), 587–594.
13. Corruble E, de Bodinat C et al. Efficacy of agomelatine and escitalopram on depression, subjective sleep and emotional experiences in patients with major depressive disorder: a 24-wk randomized, controlled, double-blind trial. Int J Neuropsychopharmacol 2013;16:2219-2234.

14. Shu L, Sulaiman AH et al. Comparable efficacy and safety of 8 weeks treatment with agomelatine 25‐50 mg or fluoxetine 20‐40 mg in Asian out-patients with major depressive disorder. Asian J Psychiatr. 2014;8:26‐32.
15. Kennedy SH, Avedisova A et al. A placebo-controlled study of three agomelatine dose regimens (10mg, 25mg, 25-50mg) in patients with major depressive disorder. Eur. Neuropsychopharmacol. 2014 24, 553–563.
16. Montgomery SA, Nielsen RZ et al. A randomised, double blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin-noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine. Hum. Psychopharmacol Clin Exp. 2014 29 (5), 470–482.
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20. Yu YM, Gao KR et al. Efficacy and safety of agomelatine vs paroxetine hydrochloride in Chinese Han patients with major depressive disorder: a multicentre, double-blind, noninferiority, randomized controlled trial. J Clin Psychopharmacol. 2018 Jun;38(3):226-233.

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | |
| | 2b | Specific objectives or hypotheses | |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | |
| Participants | 4a | Eligibility criteria for participants | |
| | 4b | Settings and locations where the data were collected | |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | |
| Sample size | 7a | How sample size was determined | |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | |
| | 11b | If relevant, description of the similarity of interventions | |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | |

| | | | |
|---|---|---|---|
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | |
| | 14b | Why the trial ended or was stopped | |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

# References


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