Postgraduate Program

"Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics"

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
Σχολή Επιστημών Υγείας
Πανεπιστήμιο Θεσσαλίας

Πρόγραμμα Μεταπτυχιακών Σπουδών

«Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική»

Master of Science Thesis

Assessment of the reporting quality of randomized controlled trials for vortioxetine in the treatment of major depressive disorder published from 2010 to 2018

Angos Pavlos

Αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών για τη βορτιοξετίνη στη θεραπεία της μείζονος καταθλιπτικής διαταραχής που δημοσιεύθηκαν από το 2010 έως το 2018

Άγγος Παύλος

Τριμελής Επιτροπή
Ιωάννης Στεφανίδης, Καθηγητής
Ηλίας Ζιντζαράς, Καθηγητής
Χρυσούλα Δοξάνη, PhD

Larisa 2019

Contents

Abstract

Introduction: After the publication of the CONSORT 2010 statement, no studies have been conducted to assess the reporting quality of randomized controlled clinical trials (RCTs) in the treatment of Major Depressive Disorder with Vortioxetine.

Objective: To investigate the current situation of the reporting quality of RCTs in leading medical journals with the CONSORT 2010 statement as criteria for the RCTs published from 2010 to 2018.

Methods: Thorough research of online biomedical databases for publications of RCTs referring to the treatment of MDD with vortioxetine, from Jan 01 2010 until Dec 31 2018, was conducted on Jan 10 2019. Non-randomised or non-controlled trials, post-hoc analyses, follow-up and side-studies, reviews and meta-analyses were excluded. Trials reported as animal, in vitro or case studies were also excluded. The full texts of the eligible trials were assessed using the CONSORT checklist as a tool. The proper reporting of each one of the checklist's 37 items was evaluated and graded as either "yes" or "no" depending on whether it had been reported. Scores were calculated for each trial and each item and comparisons were conducted.

Results: 324 publications were evaluated. 165 were excluded by title, 106 by abstract, 38 by review of the full text. Most common exclusion reasons were irrelevance to the topic and non-randomised or non-controlled designs of trials. 15 trials were eligible for inclusion in the study. Mean compliance to the CONSORT list of the included trials was 84,5%. 12 out of the 15 trials had successful overall reporting (>80%) score. Items best reported were 1b, 2a, 2b, 3a, 4a, 5, 6a, 12a, 13a, 14b, 17a and 19, with a reporting score of 100%. Items most poorly reported (<70%) were 13b, 3b, 8b, 8a, 11a, 20, 6b, 10.

Conclusions: The reporting quality of the included RCTs for vortioxetine in the treatment of major depressive disorder was suboptimal, even for key aspects of trial methodology. Better reports in terms of completeness and transparency, will help the scientific community evaluate their validity and reach safe decisions concerning the treatment of MDD.

Key words: vortioxetine, major depressive disorder, MDD, CONSORT, randomised, controlled, trials, RCTs.

Περίληψη

Εισαγωγή: Μετά τη δημοσίευση της δήλωσης CONSORT 2010, δεν έχουν διεξαχθεί μελέτες για την αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών (RCTs) στη θεραπεία της μείζονος καταθλιπτικής διαταραχής (ΜΚΔ) με βορτιοξετίνη.

Στόχοι: Να διερευνηθεί η τρέχουσα κατάσταση της ποιότητας αναφοράς των RCT σε κορυφαία ιατρικά περιοδικά με τη δήλωση CONSORT 2010 ως κριτήριο για RCTs που δημοσιεύτηκαν από το 2010 έως το 2018.

Μέθοδοι: Στις 10 Ιανουαρίου 2019 διεξήχθη διεξοδική έρευνα σε διαδικτυακές βιοϊατρικές βάσεις δεδομένων για δημοσιεύσεις RCT σχετικά με τη θεραπεία της ΜΚΔ με βορτιοξετίνη, από τη 01 Ιαν 2010 έως τις 31 Δεκ 2018. Οι μη τυχαιοποιημένες ή μη ελεγχόμενες μελέτες, οι post-hoc αναλύσεις και οι μετα-αναλύσεις αποκλείστηκαν. Οι μελέτες που αναφέρονται σε ζώα, in vitro ή μελέτες περιπτώσεων εξαιρέθηκαν επίσης. Τα πλήρη κείμενα των επιλεγμένων μελετών αξιολογήθηκαν χρησιμοποιώντας τη λίστα ελέγχου CONSORT ως εργαλείο. Η ορθή αναφορά για κάθε ένα από τα 37 στοιχεία της λίστας ελέγχου αξιολογήθηκε και βαθμολογήθηκε ως "ναι" ή "όχι" ανάλογα με το αν είχε αναφερθεί. Οι βαθμολογίες υπολογίστηκαν για κάθε μελέτη και πραγματοποιήθηκαν συγκρίσεις.

Αποτελέσματα: Αξιολογήθηκαν 324 δημοσιεύσεις. 165 εξαιρέθηκαν από τον τίτλο, 106 από την περίληψη, 38 από την αξιολόγηση του πλήρους κειμένου. Οι πιο συνηθισμένοι λόγοι αποκλεισμού ήταν η μη-σχέση με το θέμα και οι μη-τυχαιοποιημένες ή μη-ελεγχόμενες μελέτες. 15 μελέτες επιλέχθηκαν για συμπερίληψη στη μελέτη. Η μέση συμμόρφωση με τη λίστα CONSORT των μελετών που συμπεριλήφθηκαν ήταν 84,5%. 12 από τις 15 μελέτες είχαν συνολική βαθμολογία επιτυχούς (> 80%) αναφοράς. Στοιχεία που αναφέρθηκαν καλύτερα ήταν τα 1b, 2a, 2b, 3a, 4a, 5, 6a, 12a, 13a, 14b, 17a και 19, με βαθμολογία αναφοράς 100%. Στοιχεία που αναφέρθηκαν χειρότερα (<70%) ήταν 13b, 3b, 8b, 8a, 11a, 20, 6b, 10.

Συμπεράσματα: Η ποιότητα αναφοράς των RCT που συμπεριλήφθηκαν για τη βορτιοξετίνη στη θεραπεία της ΜΚΔ ήταν ανεπαρκής, ακόμη και για βασικές πτυχές της μεθοδολογίας. Καλύτερες αναφορές όσον αφορά στην πληρότητα και στη διαφάνεια θα βοηθήσουν την επιστημονική κοινότητα να αξιολογήσει την εγκυρότητά τους και να λάβει ασφαλείς αποφάσεις σχετικά με τη θεραπεία της ΜΚΔ.

Λέξεις κλειδιά: βορτιοξετίνη, μείζονα καταθλιπτική διαταραχή, ΜΚΔ, τυχαιοποιημένες ελεγχόμενες κλινικές μελέτες, CONSORT.

Introduction

Psychiatric disorders account for 22,8% of the global burden of diseases [1]. The leading cause of this disability is major depressive disorder (MDD), which has substantially increased since 1990, largely driven by population growth and ageing [2]. With an estimated 350 million people affected globally, the economic burden of depressive disorders in the USA alone has been estimated to be more than US$210 billion, with approximately 45% attributable to direct costs, 5% to suicide-related costs, and 50% to workplace costs [3].

Major depressive disorder (MDD) in older adults is also a growing public health concern as the global population ages. The United Nations estimates that 16.9% of the world's population was aged 55 or older in 2015.1 By 2050, this is projected to exceed 27% of the global population [4]. Global estimates suggest that MDD affects almost 7% of the individuals aged 60 years or older worldwide and accounts for 5.7% of years lived with disability [5]. Trends are similar in the United States; in 2012, 14% of the US population was over 65 and 26% was over 55 years of age [6]. By 2030, more than 20% of Americans are expected to be over 65 years old [7].

Two analyses of nationally representative samples recently found that Americans aged 55 years or older had 12-month prevalence of MDD between 4.0% and 5.6% [8,9]. When MDD prevalence was stratified by 10-year age intervals within this older US population, the highest prevalence was found in the subgroup aged 55 to 64 years (6.2% and 7.4%), and declined in older age groups [8,9]. The 12-month prevalence was also found to be higher for women than for men [8,9].

Vortioxetine, the compound under study, was approved in 2013 in the US for the treatment of adults with MDD and in the European Union for the treatment of a major depressive episode (MDE) in adults. The mechanism of action of vortioxetine is related to its multimodal activity, which combines 2 pharmacological actions: direct modulation of receptor activity and inhibition of the serotonin (5-HT) transporter. In addition to inhibiting the 5-HT transporter, vortioxetine is an antagonist at 5-HT3, 5-HT7, and 5-HT1D receptors; a partial agonist at 5-HT1B receptors; and an agonist at 5-HT1A receptors [10-12].

Randomized controlled trials (RCTs), when appropriately designed, conducted, and reported, represent the gold standard for evaluating healthcare interventions. However, randomized trials can yield biased results if they lack methodological rigor. To accurately assess a trial,

readers of a published report require complete, clear, and transparent information on its methodology and findings. Unfortunately, assessments frequently fail because authors neglect to provide clear and complete descriptions of such critical information [13].

Reporting quality assessment is therefore the first stage in a critical literature review. In 1996, the Consolidated Standards for Reporting of Trials (CONSORT) group produced the CONSORT statement, an evidence-based approach to help improve the quality of reporting RCTs. The group published a revised statement in 2001. The methodological factors included in the CONSORT statement were selected due to empirical evidence indicating their importance.

The CONSORT statement has been supported by a growing number of medical and healthcare journals and editorial groups, including the International Committee of Medical Journal Editors (ICMJE), the Council of Science Editors (CSE), and the World Association of Medical Editors (WAME) [14]. Subsequently, the expanding body of methodological research reported the refinement of CONSORT 2010. Over the past 16 years, a number of CONSORT recommendations (including updates and extensions) for the publication of RCTs have been developed.

Since their introduction, the quality of published RCTs has improved significantly in journals endorsing the CONSORT criteria. For example, analyses of the cardiothoracic and general surgery literature indicate substantial improvements in the reporting of RCTs after the CONSORT criteria were endorsed by their principal journals [15].

Although the quality of reporting in RCTs in the medical sciences has been discussed, the quality of reporting in RCTs on the treatment of MDD with vortioxetine published in the English language has not yet been assessed following publication of the CONSORT statement (2010 version).

Purpose

Given the relative lack of report evaluating studies in psychiatry and the apparent absence of such a study for the treatment of MDD with vortioxetine, this thesis aims at assessing the reporting quality of RCTs concerning MDD treatment with vortioxetine. The thesis will be focused on RCTs published from 2010 to 2018, following the last CONSORT statement revision checklist [16] and will also provide recommendations for improving report evaluation in the future.

Materials and Methods

Search Strategy

On January 10 2019 we searched the Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, AMED, the UK National Research Register, and PSYNDEX from January 01 2010 until December 31 2018, with English language restriction. We used the search terms “depress*” OR “dysthymi*” OR “adjustment disorder*” OR “mood disorder*” OR “affective disorder” OR “affective symptoms” combined with “vortioxetine” OR “Lu AA21004”.

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 was conducted by the author.

Eligibility Criteria

Inclusion Criteria: Eligible for entry were double-blind, randomised controlled trials (RCTs) comparing vortioxetine with placebo or another active antidepressant as oral monotherapy for the acute treatment of adults (≥18 years old and of both sexes) with a primary diagnosis of major depressive disorder (MDD) according to standard operationalised diagnostic criteria (Feighner Criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, and ICD-10). The studies had to be published in English, from January 01 2010 until December 31 2018. They had to include a randomisation 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.

Exclusion Criteria: Non-eligible for entry were non-randomised and/ or non-controlled trials, post-hoc analyses of RCTs, follow-up studies, side-studies or other types of analyses/ reviews. Trials reported as “animal studies”, “in vitro studies”, “case studies”, or “systematic reviews” were also excluded.

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. Report evaluation was done according to the CONSORT 2010 statement using the CONSORT checklist as a tool. The CONSORT checklist is a set of 25 items (amounting to 37 when sub-items are calculated separately) that should be included in an optimally written RCT report.

Every article was thoroughly inspected for the fulfillment of each one of the 37 items on the checklist. The interpretation of the CONSORT checklist items was done according to the "CONSORT 2010 Explanation and Elaboration" document, which is available online along with the checklist on the CONSORT-statement website [17].

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 [18].

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. Partial, ambiguous or indirect reporting of an item was also considered a negative response (Table 1).

Moreover, the items of the CONSORT checklist are divided into groups corresponding to the respective parts of an RCT report (title and abstract, 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 Analyses

A descriptive statistical analysis of all evaluated articles was conducted. Data were analyzed using Microsoft Excel 2013. All relevant studies were checked for compliance with the statement by assessing the fulfillment of the 37 CONSORT items.

In order to assess adherence to the CONSORT checklist items, the number and proportion of reports describing each of the 37 items was calculated.

In addition, the number and proportion of these items by the RCTs published in a journal was 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 37-item checklist. For example, a RCT reporting 20 of the 37 items on the checklist would score 54.1%. Each item on the checklist was also evaluated by tabulating the number of RCTs that reported the item. For example, if 23 of 27 RCTs reported item 2a on the checklist, that item would score an overall compliance score of 85.2%.

It must be noted that for some RCTs, certain items might not have been applicable. For instance, item 11b requires the reporting of detailed information about the similarity of interventions in case blinding was applied. This item is deemed non-applicable in open-label trials.

Non-applicable items were not included in the denominator for the calculation of the respective percentages.

Item		RCTs															
		#	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15
Title and abstract																	
	1a	15	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
	1b	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Introduction																	
Background and objectives	2a	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	2b	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Methods																	
Trial design	3a	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	3b	15	1	1	0	0	0	0	1	0	1	0	1	1	0	0	0
Participants	4a	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	4b	15	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Interventions	5	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Outcomes	6a	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	6b	3						0			1		1				
Sample size	7a	15	0	1	1	1	1	1	1	1	1	0	1	1	1	0	1
	7b	15	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Rnd. Sequence generation	8a	15	1	1	0	1	1	1	1	0	0	1	1	1	0	0	0
	8b	15	0	0	0	1	1	1	1	0	0	1	0	1	0	0	0
Rnd. Allocation concealment mech.	9	15	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0
Implementation	10	15	1	1	1	1	1	1	1	0	1	0	0	1	1	0	0
Blinding	11a	15	1	1	1	1	1	1	1	0	1	0	0	1	0	0	0
	11b	15	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0
Statistical methods	12a	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	12b	15	1	0	1	0	1	0	1	1	1	1	1	1	1	1	1
Results																	
Participant flow	13a	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	13b	4						0	0				0	1			
Recruitment	14a	15	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
	14b	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Baseline data	15	15	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Numbers analysed	16	15	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
Outcomes and estimation	17a	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	17b	15	1	0	1	1	1	1	1	1	0	1	1	1	0	0	1
Ancillary analyses	18	12	1	1	1	0	0	0	1	1	0	1	1	1	1	1	1
Harms	19	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Discussion																	
Limitations	20	15	0	0	1	0	1	1	1	1	0	0	1	1	1	0	1
Generalisability	21	15	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1
Interpretation	22	15	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
Other information																	
Registration	23	15	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1
Protocol	24	15	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1
Funding	25	15	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1
CONSORT Score			89%	89%	89%	83%	89%	86%	97%	86%	78%	83%	89%	100%	66%	66%	80%

Table 1. Items reported per RCT.

Results

Search Results

The search yielded 324 potentially eligible articles that were screened for eligibility. Of those, 165 articles were excluded by title, 106 were excluded by abstract while 38 required full text review to be conclusively defined as ineligible. The screening strategy and reasons for exclusion are summarized in Figure 1.

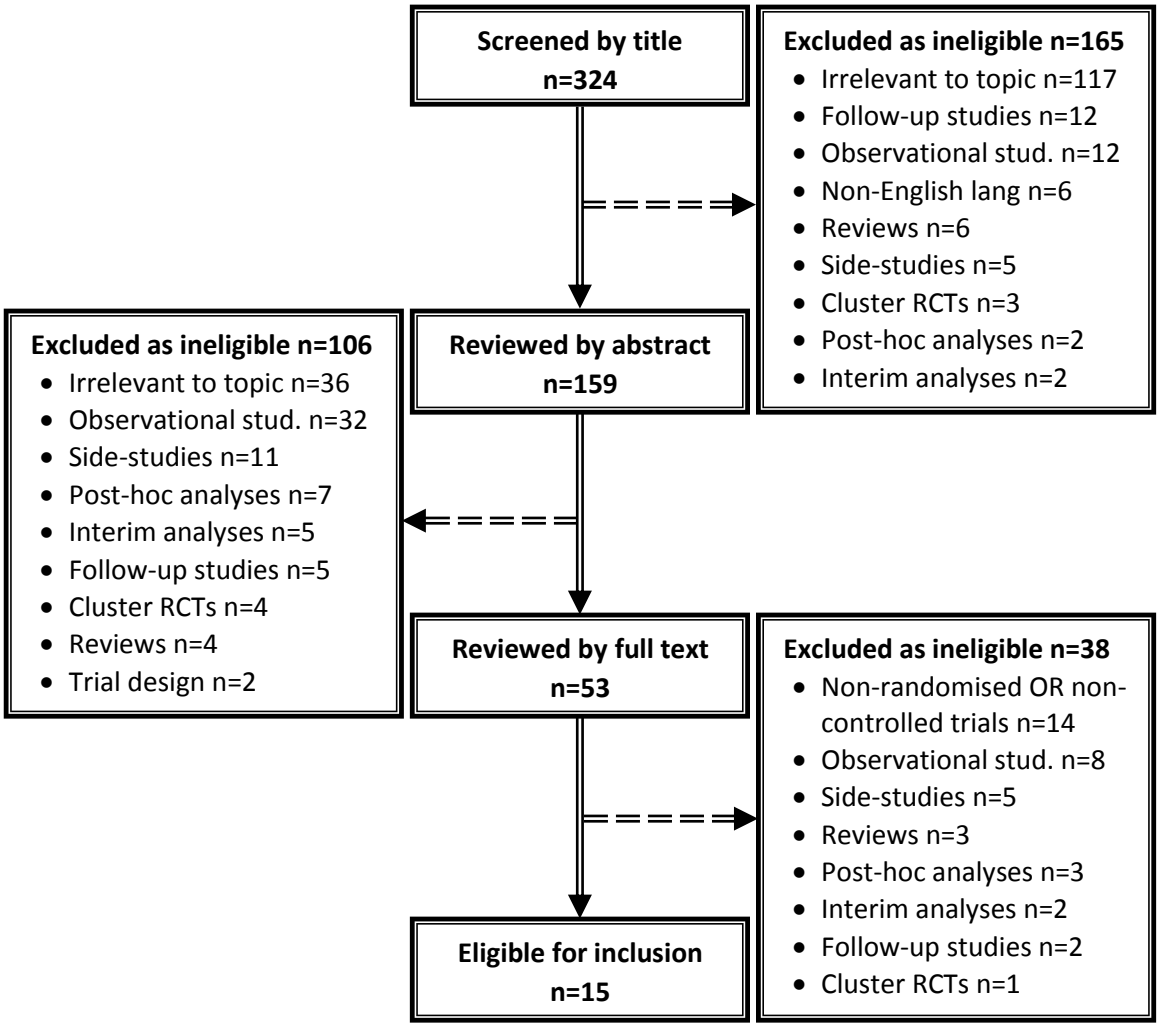

Figure 1. Summary of the screening strategy and reasons for exclusion at each step.

In total 309 articles were excluded from the study. Of those 153 were irrelevant to topic, 6 articles were written in a language other than English, 56 were observational studies, 21 were sub-studies or side-studies based on trials, 19 were trial follow-up studies, 14 were non-randomized and/ or non-controlled clinical trials, 13 were reviews, 12 were post-hoc analyses of trials, and 8 were cluster randomized trials.

Eligible Trials

Finally, 15 RCTs were deemed eligible to be included in the present study. A full list of these RCTs is provided in the Appendix.

Reporting Quality Results

The overall compliance for the 15 included randomised controlled trials was 84,5% of applicable items. 12 RCT reports (80%) included adequate information of about at least 80% of applicable items. Compliance figures for each item are summarized in Table 2.

The different CONSORT items have been variedly reported in the 15 RCTs. Compliance for each item ranges widely from 25% of trials to even 100% of trials (where the item is applicable).

Reporting was particularly succesful (in >95% of RCTs) for the following items:

- Item 1b - *Structured summary of trial design, methods, results, and conclusions*: Reported correctly in 15 out of 15 trials (100%).
- Item 2a - *Scientific background and explanation of rationale*: Reported correctly in 15 out of 15 trials (100%).
- Item 2b - *Specific objectives or hypotheses*: Reported correctly in 15 out of 15 trials (100%).
- Item 3a - *Description of trial design (such as parallel, factorial) including allocation ratio*: Reported correctly in 15 out of 15 trials (100%).
- Item 4a - *Eligibility criteria for participants*: Reported correctly in 15 out of 15 trials (100%).
- Item 5 - *The interventions for each group with sufficient details to allow replication, including how and when they were actually administered*: Reported correctly in 15 out of 15 trials (100%).
- Item 6a - *Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed*: Reported correctly in 15 out of 15 trials (100%).

Item		Number of RCTs applicable	Number of RCTs reported	Proportion
Title and abstract				
1a		15	14	93%
1b		15	15	100%
Introduction				
2a	Background and objectives	15	15	100%
2b		15	15	100%
Methods				
3a	Trial design	15	15	100%
3b		15	6	40%
4a	Participants	15	15	100%
4b		15	14	93%
5	Interventions	15	15	100%
6a	Outcomes	15	15	100%
6b		3	2	67%
7a	Sample size	15	12	80%
7b		15	14	93%
8a	Rnd. Sequence generation	15	9	60%
8b		15	6	40%
9	Rnd. Allocation concealment mechanism	15	11	73%
10	Implementation	15	10	67%
11a	Blinding	15	9	60%
11b		15	12	80%
12a	Statistical methods	15	15	100%
12b		15	12	80%
Results				
13a	Participant flow	15	15	100%
13b		4	1	25%
14a	Recruitment	15	14	93%
14b		15	15	100%
15	Baseline data	15	14	93%
16	Numbers analysed	15	14	93%
17a	Outcomes and estimation	15	15	100%
17b		15	11	73%
18	Ancillary analyses	12	11	92%
19	Harms	15	15	100%
Discussion				
20	Limitations	15	9	60%
21	Generalisability	15	13	87%
22	Interpretation	15	14	93%
Other information				
23	Registration	15	12	80%
24	Protocol	15	13	87%
25	Funding	15	13	87%

Table 2. Compliance figures per item.

- Item 12a - *Statistical methods used to compare groups for primary and secondary outcomes*: Reported correctly in 15 out of 15 trials (100%).
- Item 13a - *For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome*: Reported correctly in 15 out of 15 trials (100%).
- Item 14b - *Why the trial ended or was stopped*: Reported correctly in 15 out of 15 trials (100%).
- Item 17a - *For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)*: Reported correctly in 15 out of 15 trials (100%).
- Item 19 - *All important harms or unintended effects in each group*: Reported correctly in 15 out of 15 trials (100%).

On the contrary, successful reporting was relatively to particularly low (in <70% of RCTs) for the following items:

- Item 13b - *For each group, losses and exclusions after randomisation, together with reasons*: Reported correctly in 1 out of 4 applicable trials (25%). Although most trials were succesful in reporting item 13a - *For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome*, the same was not true for item 13b. Theoretically, this item applies to cases of losses and exclussions after randomisation, yet still even in the cases applicable, the succesful reporting rate was particularly problematic.
- Item 3b - *Important changes to methods after trial commencement (such as eligibility criteria), with reasons*: Reported correctly in 6 out of 15 applicable trials (40%). Again reporting in this item proved to be problematic. Theoretically, there could be no change in methods after trial commencement, yet highly unlikely, but even in this case method was not reported as unchanged throughout the trial.
- Item 8b - *Type of randomisation; details of any restriction (such as blocking and block size)*: Reported correctly in 6 out of 15 applicable trials (40%). Although item 8a proves to have a slightly better reporting rate, it was not a common thing for researchers to report the type of randomisation used, and/ or just mention a computerized randomisation technique, without further information.
- Item 8a - *Method used to generate the random allocation sequence*: Reported correctly in 9 out of 15 applicable trials (60%).
- Item 11a - *If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how*: Reported correctly in 9 out of 15 applicable trials (60%).

Similaringly, reporting of blinding among researchers or care providers was poorly mentioned. Most reports were aout participants' blinding procedures.

- Item 20 - *Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses*: Reported correctly in 9 out of 15 applicable trials (60%). Almost half of the trials failed to report their limitations clearly, according to the CONSORT statement.
- Item 6b - *Any changes to trial outcomes after the trial commenced, with reasons*: Reported correctly in 2 out of 3 applicable trials (67%). Although aplicable to only 3 of the trials, this item was not reported as "unchanged", even when not applicable.
- Item 10 - *Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions*: Reported correctly in 10 out of 15 applicable trials (67%). This part of the trial design was poorly reported and in some cases inadequetly mentioned.

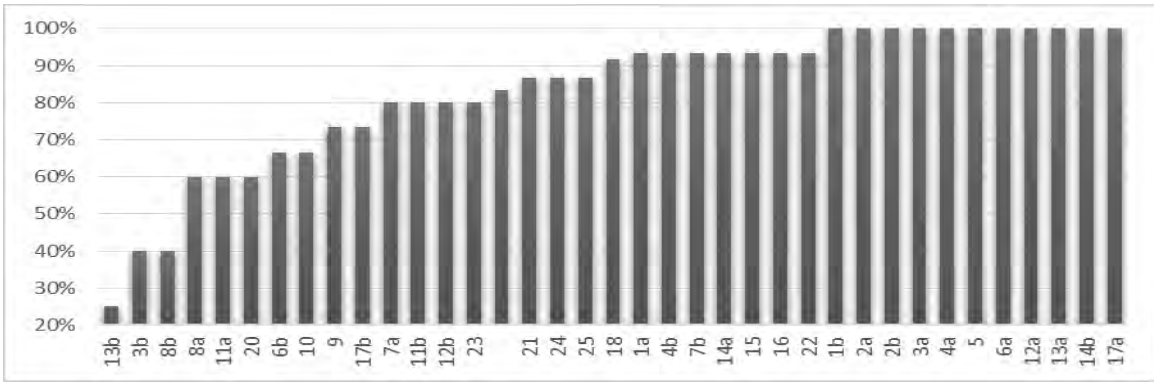

Figure 2. Compliance per applicable item.

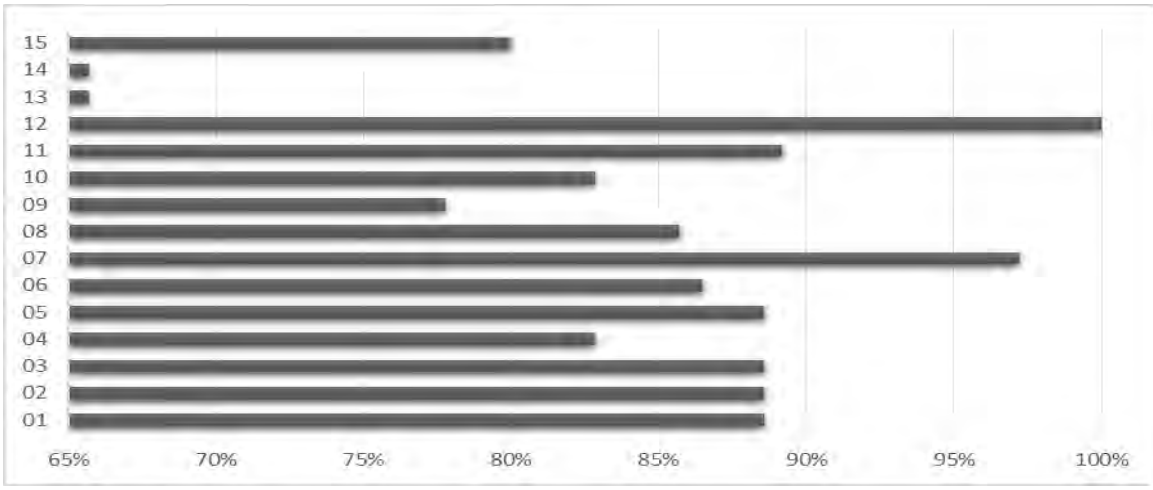

Figure 3. Compliance per RCT.

Discussion

It is widely accepted that the search for new drugs but also decision-making in every aspect of modern medicine should be based on high-quality evidence. In this context, randomized controlled trials have increasingly been relied upon as the optimal way of reaching safe conclusions regarding an intervention [19]. RCTs are the most rigorous method of establishing a cause-effect relationship between an intervention and an outcome [20]. Nevertheless, the scientific value of RCTs may be compromised by bias arising from flaws and deficiencies in various methodological aspects of the trial such as in randomisation, handling of allocated arms, and assessment of outcomes or data analysis [21]. The evaluation of the methodological quality of a trial is connected with the quality of the reporting of its design, conduct and analysis [22].

Over the years, scales and checklists have been developed in order to appraise the quality of RCT reports [23,24]. The CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials, offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. In addition, extensions of the CONSORT Statement have been developed to give additional guidance for RCTs with specific designs, data and interventions. Even after 8 years of implementation of the CONSORT statement, it has not yet been fully adopted in the preparation and the reporting of RCTs, notably in the psychiatric community.

Additionally, there appears to arise a pattern of failing in reporting items in the CONSORT checklist, particularly in the items 3b - *Important changes to methods after trial commencement (such as eligibility criteria), with reasons* and 6b - *Any changes to trial outcomes after the trial commenced, with reasons*, where it becomes obvious that changes to methods or outcomes can only be ascertained when the authors do report them. In case of changes not reported, a negative response cannot be confirmed unless the study protocol is available. For these items, the evaluation focuses on whether adequate reasons were provided when a change was indeed reported.

Limitations

This study was conducted by a single researcher, the author, making it inherently prone to selection and measurement bias. All possible precautions were taken on behalf of the researcher to eliminate those risks. Thorough studying of the existing medical and biomedical literature about major depressive disorder, 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.

The evaluation of each item was a rather complex procedure since no exact criteria exist as to what constitutes a positive or negative response, so each item was broken down into component elements derived from the documents. A positive response was accepted only when all of the component elements were met. Major depressive disorder and the use of relevant rating scales by the included trials 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.

Conclusions

This thesis has evaluated the reporting quality of randomised controlled trials for the treatment of major depressive disorder published between January 2010 and December 2018. The reports of 15 eligible trials were reviewed using the CONSORT 2010 statement as an assessment tool.

The results indicate that the reporting of vortioxetine and MDD RCTs is suboptimal. Some of the CONSORT checklist items are only reported in a minority of RCTs. Rather alarming is the fact that crucial methodological aspects for a RCT are underreported. Details about randomization, blinding, trial setup and timeframe are most often omitted. Information concerning harms, funding sources and protocol access are also frequently withheld. Summaries are also far from being written in a manner that best provides the reader with all the necessary information. Nevertheless, some CONSORT items seem to be adequately reported in most of the trials: those referring to the scientific background, nature of interventions, eligibility criteria, statistical methods, baseline patient characteristics, interpretation of results. However, these better reported items seem to represent more theoretical aspects of the trial.

These results are in accordance with previous RCT report evaluating studies in oncology and other medical fields. Peron et al. in their systematic review of oncologic RCT reporting [23] found poor compliance with many of the (pre-2010 revision) CONSORT items. As in the present study, some of the lowest compliance percentages were observed for items pertaining to randomization and blinding. The same holds true for a study by Ziogas & Zintzaras concerning RCTs about hematologic malignancies [25].

It should be noted that reporting integrity does not necessarily imply methodological integrity and poor reporting is not necessarily associated with flawed design or conduct of a trial [26,27]. 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 [26,28].

Bearing the above in mind, the present study concluded that the reporting quality of the included RCTs for vortioxetine in the treatment of major depressive disorder was suboptimal, even for key aspects of trial methodology. Major depressive disorder is a condition affecting millions of people, in urgent need for the discovery of novel and more effective treatments. In this effort, randomised controlled clinical trials will once

again serve as the optimum way of verifying the safety and efficacy of new therapies. Better reports in terms of completeness and transparency, will help the scientific community evaluate their validity and reach safe decisions.

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.

Acknowledgements

The author would like thank the members of the supervising committee, Prof Stefanidis Ioannis, Prof Zintzaras Elias and Dr Doxani Chrysa, for their tutoring, their intellectual support and their educative contribution during the dissertation of this thesis. Also Mr Mprotsis Theodoros and Mrs Kalogianni Katerina for their technical and administrational support. Finally Dr Provatas Antonios and Dr Latter Kyran for their moral support and intuitive suggestions.

Appendix

1. Alvarez, E., et al., A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol, 2012. 15(5): p. 589-600.
2. Baldwin, D.S., H. Loft, and M. Dragheim, A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). Eur Neuropsychopharmacol, 2012. 22(7): p. 482-91.
3. Katona, C., T. Hansen, and C.K. Olsen, A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. Int Clin Psychopharmacol, 2012. 27(4): p. 215-23.
4. Boulenger, J.P., H. Loft, and I. Florea, A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. J Psychopharmacol, 2012. 26(11): p. 1408-16.
5. Henigsberg, N., et al., A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. J Clin Psychiatry, 2012. 73(7): p. 953-9.
6. Boulenger, J.P., H. Loft, and C.K. Olsen, Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. Int Clin Psychopharmacol, 2014. 29(3): p. 138-49.
7. McIntyre, R.S., S. Lophaven, and C.K. Olsen, A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol, 2014. 17(10): p. 1557-67.
8. Jacobsen, P.L., et al., A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. J Clin Psychiatry, 2015. 76(5): p. 575-82.
9. Mahableshwarkar, A.R., et al., A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. J Clin Psychiatry, 2015. 76(5): p. 583-91.
10. Mahableshwarkar, A.R., et al., A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. Psychopharmacology (Berl), 2015. 232(12): p. 2061-70.
11. Mahableshwarkar, A.R., et al., A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder. Neuropsychopharmacology, 2015. 40(8): p. 2025-37.
12. Wang, G., et al., Comparison of vortioxetine versus venlafaxine XR in adults in Asia with major depressive disorder: a randomized, double-blind study. Curr Med Res Opin, 2015. 31(4): p. 785-94.
13. Liebowitz, M.R., et al., Vortioxetine versus placebo in major depressive disorder comorbid with social anxiety disorder. Depress Anxiety, 2017. 34(12): p. 1164-1172.
14. Nishimura, A., et al., Randomized, double-blind, placebo-controlled 8-week trial of the efficacy, safety, and tolerability of 5, 10, and 20 mg/day vortioxetine in adults with major depressive disorder. Psychiatry Clin Neurosci, 2018. 72(2): p. 64-72.
15. Inoue, T., et al., Randomized, 8-week, double-blind, placebo-controlled trial of vortioxetine in Japanese adults with major depressive disorder, followed by a 52-week open-label extension trial. Psychiatry Clin Neurosci, 2018. 72(2): p. 103-115.

References

1. GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. Lancet 2015; 386: 2145–91.
2. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1603–58.
3. WHO. Depression: fact sheet. Geneva: World Health Organisation, 2017. http://www.who.int/mediacentre/factsheets/fs369/en/. Accessed Jan 11, 2019.
4. United Nations Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2015 Revision. Custom data acquired via website http://esa.un.org/unpd/wpp/DataQuery/. Accessed Jan 2, 2018.
5. WHO Mental Health in the Elderly. 2015. http://www.who.int/mediacentre/factsheets/fs381/en/. Accessed Nov 9, 2018.
6. United States Census Bureau. 2012 National Population Projections. 2012. https://www.census.gov/population/projections/data/national/2012.html. Accessed Nov 24, 2018.
7. Colby S, Ortman J. Projections of the size and composition of the U.S. population: 2014 to 2060, current population reports, P25-1143, U.S. Census Bureau, Washington, DC; 2014.
8. Reynolds K, Pietrzak RH, El-Gabalawy R, Mackenzie CS, Sareen J. Prevalence of psychiatric disorders in U.S. older adults: findings from a nationally representative survey. World Psychiatry. 2015; 14(1): 74–81.
9. Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML. High occurrence of mood and anxiety disorders among older adults: the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2010; 67(5): 489–496.
10. Bang-Andersen B, Ruhland T, Jorgensen M, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine
11. (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J Med Chem. 2011; 54(9): 3206–3221.
12. Mork A, Pehrson A, Brennum LT, et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. J Pharmacol Exp Ther. 2012; 340(3): 666–675.
13. Westrich L, Pehrson A, Zhong H, et al. In vitro and in vivo effects for the multimodal antidepressant vortioxetine (Lu AA21004) at human and rat targets. Int J Psychiatry Clin Pract. 2012; 16(S1): 47.
14. Schulz KF, Altman DG, Moher D, for the CONSORT Group (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials for the CONSORT Group. BMJ 340: c332: 698–702.
15. Halpern SH, Darani R, Douglas MJ, Wight W, Yee J (2004) Compliance with the CONSORT checklist in obstetric anaesthesia randomised controlled trials. Int J Obstet Anesth 13: 207–214.
16. Erin NK, Robert MS, Nader P, Aaron SD (2011) Standards for reporting randomized controlled trials in neurosurgery. J Neurosurg 114: 280–285.
17. Schulz KF, Altman DG, Moher D, for the CONSORT Group (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel-group randomized trials. BMJ 340: c869.
18. CONSORT Transparent Reporting of Trials. http://www.consort-statement.org/. Accessed Jan 23 2019.
19. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, Schulz KF and the CONSORT Group, 2008. CONSORT for reporting randomised trials in journal and conference abstracts. Lancet: 371:281-283.

20. Sibbald B, Ronald M, 1998. Understanding controlled trials. Why are randomized controlled trials so important? BMJ, 316:201.
21. Jüni P, Altman D & Egger M, 2001. Assessing the quality of controlled clinical trials. BMJ, 323(7303):42–46
22. Huwiler-Müntener K, Jüni P, Junker C & Egger M, 2002. Quality of Reporting of Randomized Trials as a Measure of Methodologic Quality. JAMA, 287(21): 2801-2804.
23. Andrew E, 1984. Method for assessment of the reporting standard of clinical trials with roentgen contrast media. Acta Radio1 Diag 25:55-58
24. Péron J, Pond GR, Gan HK, Chen EX, Almufti R, Maillet D, You B, 2012. Quality of reporting of modern randomized controlled trials in medical oncology: a systematic review. J Natl Cancer Inst. 104(13): 982-9.
25. Ziogas DC & Zintzaras E, 2009. Analysis of the quality of reporting of randomized controlled trials in acute and chronic myeloid leukemia, and myelodysplastic syndromes as governed by the CONSORT statement. AnnEpidemiol,19(7):494-500
26. Toulmonde M, Bellera C, Mathoulin-Pelissier S, Debled M, Bui B, Italiano A, 2011. Quality of randomized controlled trials reporting in the treatment of sarcomas. J Clin Oncol., 29(9):1204-9.
27. Devereaux PJ, Choi PT, El-Dika S, Bhandari M, Montori VM, Schünemann HJ,...& Guyatt GH, 2004. An observational study found that authors of randomized controlled trials frequently use concealment of randomization and blinding, despite the failure to report these methods. J Clin Epidemiol 57:1232–1236.
28. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M,...&Klassen TP, 1998. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet. 352(9128):609-13.