THE EFFECT OF PAROXETINE ON HEART RATE VARIABILITY IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: The impacts of antidepressant pharmacotherapies on cardiovascular risk are unclear. We completed a systematic review with meta-analysis to assess the effect of paroxetine on heart rate variability (HRV) in patients with major depressive disorder (MDD).
Methods: The searches were accomplished via EMBASE, MEDLINE/PubMed (using the National Library of Medicine), Cochrane Library, CINAHL, Scopus, and Web of Science databases. We included non-blind, single, or double-blind randomized control trials in patients older than 18 diagnosed with MDD. Paroxetine needs to be enforced as a chronic therapeutic medication. We included individual studies that investigated resting HRV.
Results: We documented 402 studies, only following screening and eligibility phases; only six were included (five studies in the meta-analysis). No significant change was noticed for the SDNN index: subtotal=8.23 [CI: -2.17, 18.63], p=0.12, I2=54% (*very low* quality of evidence). A significant change was distinguished for the LF index: subtotal=0.74 [CI: 0.33, 1.15], p=0.0004, I2=0% (low quality of evidence). A significant alteration was perceived for the HF index: subtotal=0.33 [CI: 0.06, 0.6], p=0.02, I2=0% (low quality of evidence).
Conclusion: Meta-analysis demonstrated that paroxetine could advance HRV in MDD patients. Nevertheless, our supposition is founded only on statistical analysis and the very low quality of evidence breakdown reinforces the necessity for further studies to confirm or reject this theory.

Keywords: Cardiovascular risk; Heart rate variability; Major depressive disorder; Paroxetine.

INTRODUCTION

Major depressive disorder (MDD) is a severe and recurrent medical condition that negatively affects psychological systems, leading to persistent sadness and loss of interest (Brewer *et al*., 2023). This psychiatric disorder has had increased attention over the last 15 years. MDD affects how a person thinks and behaves. Consequently, it is linked with a large amount of emotional and physical problems, including schizophrenia, bipolar disorder, autism spectrum disorder (Ardesch *et al*., 2023), cardiovascular diseases (Krittanawong *et al*., 2023), and diabetes (Cao *et al*., 2023). An earlier review stated that subjects with cardiovascular diseases have more MDD than the general public (Hare *et al*., 2014).

In this way, one of the 17 Sustainable Development goals published by the United Nations is to safeguard healthy lives and to promote well-being for all (https://sdgs.un.org/goals/goal3). The scientific research literature has indicated that MDD treatment is an appropriate technique to lessen physical and emotional illness (Ardesch *et al*.,

2023; Krittanawong *et al*., 2023; Cao *et al*., 2023; Hare *et al*., 2014), promoting greater well-being and healthier lives. Amongst the most prevalent MDD pharmacotherapies included are paroxetine (Yoshimura *et al*., 2022), venlafaxine (Kim *et al*., 2022), nortriptyline (Mowla *et al*., 2006), fluoxetine (Adjei *et al*., 2023) and amitriptyline (Suryanto *et al*., 2021). All the stated pharmacotherapies are currently prescribed for such MDD patients.

Instead, we need to be cautious when evaluating the cardiovascular adverse effects of each medication. For example, a systematic review (Tarchi *et al*., 2023) suggested that it is obligatory to better and deeply explore the relationship between selective serotonin reuptake inhibitors and sexual dysfunction. This needs to be clarified because of the methodological limitations and heterogeneity of the current studies. Additionally, another study (Gutlapalli *et al*., 2022) highlighted that venlafaxine increases cardiovascular risk attributable to fatal cardiac arrhythmias in post-myocardial infarction MDD patients. Yet, this supposition was disallowed based on their data.

Heart rate variability (HRV) is a non-invasive technique that estimates cardiovascular risk (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Wang *et al*. (2023) enforced HRV for occurrences of type 2 diabetes. The authors suggested that autonomic dysfunction leads to the development of type 2 diabetes. Kaze *et al*. (2023) accompanied Wang *et al*. (2023) and evaluated HRV and its association with the risk of incident stroke in subjects with type 2 diabetes. Taken together, HRV may offer reliable evidence for the likely risks of these antidepressant medications (Maki *et al*., 2023).

Founded on the evidences mentioned above, we emphasize the following points: Is paroxetine able to influence resting HRV? Is there a risk for MDD patients undergoing

paroxetine treatment? Consequently, we executed a systematic review and meta-analysis to estimate the effects of paroxetine on HRV in patients identified with MDD.

METHODS

The study is a post-hoc nature of the review process, since it was not possible to predict how meta-analysis would be conducted during the review protocol elaboration.

Registration

The review was described according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) (Page *et al*., 2021) and is registered in the PROSPERO database (CRD42023394513).

Search strategy and study selection

The searches were completed via EMBASE, MEDLINE/PubMed (by means of the National Library of Medicine), Cochrane Library, CINAHL, Scopus, and Web of Science databases with the submission of the keywords "heart rate variability" OR "HRV" OR "heart rate variation" OR “heart rate complexity” OR "SDNN" OR "RMSSD" OR "autonomic function" OR "autonomic reactivity" OR "HR-variability" OR “autonomic regulation” OR “autonomic activity" AND "Paroxetine, cis-(+)-Isomer" OR "Paroxetine, cis-(-)-Isomer" OR "Seroxat" OR "Aropax" OR "Paroxetine Hydrochloride Anhydrous" OR "Paroxetine Hydrochloride Hemihydrate" OR "Paxil" OR "BRL 29060" OR "BRL29060" OR "BRL-29060" OR "Paroxetine Hydrochloride" OR "Paroxetine Maleate" OR "Paroxetine Acetate" OR "FG7051" OR "FG-7051" OR "FG 7051". We only included manuscripts written in English.

All articles approved were exported to the Rayyan QCRI program (Qatar Computing Research Institute, Qatar) to eliminate duplicates. The Rayyan program screened the studies by reading the title and abstract. The suitability stage was finalized by two autonomous

reviewers (CMO and ASC) reading their entire articles. Another reviewer was invited to give a decision (VEV) if there was a discrepancy concerning a particular study.

The studies were required to originate from peer-reviewed scientific journals, which were published from the start of the database until June 2023. We counted in non-blind, single or double-blind randomized control trials (RCTs), studies comparing paroxetine with other pharmacotherapies or placebo; we omitted cohort studies, cross-over design, references that evaluated psychiatric disorders other than MDD or two diagnoses, studies with patients older than 18 years diagnosed with MDD. Paroxetine was necessary as a chronic treatment, and patients needed to be diagnosed with MDD. Furthermore, we only included studies that considered resting HRV.

Data Extraction

Data related to the author, study design, study participants features and intervention of the respective studies were extracted from primary studies and presented in Table 1. Absent data was requested by contacting the corresponding study authors. This stage was completed independently by two reviewers (CMO and ASC). When the author's correspondent did not respond, the Web Plot Digitizer® was enforced to extract the data presented in graphs. The HRV indices data were plotted as mean and standard deviations (SD). Values presenting with "standard error" or "confidence intervals" (CI) in the primary studies were converted to SD.

Assessment of the risk of bias

The analysis of bias was conducted using the Risk of Bias version 2 (RoB2) (Sterne *et al*., 2019) via the Review Manager program (RevMan 5.4.1). Risk of bias is a tool based on the domains. Its evaluation was split into six areas: "Randomization process", "Deviations from intended interventions", "Missing outcome data", "Measuring of the outcome", "Selection of the reported results" and "Overall bias". Our assumptions were founded on the

table developed by (Sterne *et al*., 2019), "Reviewers' judgment and criteria for judgment." Two independent authors completed the risk of bias analysis (CMO and ASC).

A further researcher (VEV) was referred to if there were any inconsistencies in their verdicts. The application of the Risk of Bias 2 (RoB 2) tool was performed on a per-outcome basis (HRV), as recommended by current guidelines (Sterne *et al*., 2019). This is important for a nuanced understanding and assessment of bias within the study.

The assessors of the Risk of Bias were trained with appropriate sessions (VEV, AAP, CMO, ASC and RDR).

The RoB 2 assessment was conducted automatically by trained researchers using an Excel tool to implement RoB2 available at:

https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2

The Excel tool provides algorithms developed to guide users to judgements about the risk of bias. The algorithm maps responses to questions onto a proposed risk-of-bias judgment and provides proposed judgements (full guidance available at https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). The researchers were guided to verify the algorithm' response and change if appropriate, however, the algorithms and researchers' decisions were coincident for all domains.

The Cochrane Handbook for Systematic Reviews of Interventions (Higgins *et al.,* 2011) was also used as a reference guide during the evaluation. A judgment of "high" indicated a high risk of bias, "low" indicated a low risk of bias, and "some concerns" indicated the presence of bias due to lack of information or uncertainty about the potential for bias. Thus, the outcome was categorized as having low or high risk of bias or some concerns.

GRADE (Levels of Evidence)

We enforced the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group (GRADE Working Group, 2004) to assess the

inevitability of the evidence. This analysis included the study design of randomized trials (strong evidence). We also considered study quality (detailed study methods and execution) and limitations in the strength of evidence analysis (Meader *et al*., 2014). We applied the GRADEpro GDT v4® (McMaster University, Ontario, Canada) to extend the summary of the findings table.

Outcome Measures

Resting HRV indices included the time and frequency domains. The time domains included the root-mean-square of differences between adjacent normal RR intervals (RMSSD) and the standard deviation of the NN intervals (SDNN). The frequency domains included the high (HF) and low (LF), and very low frequencies (VLF) in absolute and normalized units besides the mean total power (TP) (Task Force 1996).

Qualitative Analysis (Systematic Review)

A descriptive synthesis was instigated to designate detailed data on how each study was completed. The details for each study were presented in texts and tables. The results of the individual qualitative analysis per study were finalized by examining HRV indices for the intervention or control protocols.

Quantitative Analysis (Meta-Analysis)

After choosing all references, we estimated the possibility of meta-analysis. Post-hoc analyses were considered when no less than two references reported an outcome and combining references were statistically and methodologically similar. In an optimistic situation, we introduced the HRV indices. The evidence required to construct the meta-analysis was the pre-and post-intervention period. We performed a pairwise Meta-analysis so as to better understand the effect of paroxetine treatment by comparing post intervention data

between groups. We adopted the principle of extracting all data offered between protocols in pre- and post-paroxetine interference.

Heterogeneity was computed via the I^2 statistic, where a number greater than 50% indicates substantial heterogeneity between the tests (Higgins *et al*., 2002). For the "95% CI" and "Test for overall effect size" values, significant changes were expected for $p<0.05$ (or <5%). We enforced a random-effect model as this more conservative method allows the study heterogeneity to fluctuate beyond chance, providing other generalizable results (de Lima *et al*, 2018). All data were formed using the Review Manager Program (RevMan 5.4.1). This software provides a calculator to convert standard deviation and confidence intervals based on mean, standard deviation, sample size and p-value.

RESULTS

Description of studies

A total of 412 references were recognized through searches in the databases. After eliminating duplicates (n=6), 406 publications were screened for inclusion. Amongst the cited studies, 351 records were excluded after reviewing the title or abstract, and one study was excluded as it was completed using animals. We excluded 18 studies that did not assess MDD patients, seven reviews, five non-randomized designs, four references unrelated to paroxetine, three studies that did not evaluate the outcome of interest, three letters, two studies that were not published until June 2023, two references that did not analyze resting HRV, one Editorial, one study was written in a language other than English, one case report, one reference that evaluates acute effects of paroxetine and one study was not retrieved.

The remaining six papers were selected for full-text reading, risk of bias assessment, GRADE, and qualitative analysis (Rechlin *et al*., 1994; Roose *et al*., 1998; Yeragani *et al*., 2002 A; Yeragani *et al*., 2002 B; Davidson *et al*., 2005; Tian *et al*., 2016). The study

characteristics included are offered in Table 1. Five references (Rechlin *et al*., 1994; Roose *et al*., 1998; Yeragani *et al*., 2002 A; Yeragani *et al*., 2002 B; Tian *et al*., 2016) were nominated for the quantitative analysis (meta-analysis). The search procedure and selection phases followed the PRISMA protocol flow diagram shown in Figure 1.

The studies included in this review were published between 1994 and 2016 (Table 1). Four studies originated from the USA (Roose *et al*., 1998; Yeragani *et al*., 2002 A; Yeragani *et al*., 2002 B; Davidson *et al*., 2005), one from Germany (Rechlin *et al*., 1994), and one from China (Tian *et al*., 2016). Three studies were offered as double-masked, randomized, and controlled trials (Roose *et al*., 1998; Davidson *et al*., 2005; Tian *et al*., 2016), while three studies were presented as single-masked, randomized and controlled trial designs (Rechlin *et al*., 1994; Yeragani *et al*., 2002 A; Yeragani *et al*., 2002 B).

Regarding the diagnostic criteria, Tian *et al*. (2016) followed the 17-item Hamilton Depression Scale (HAMD-17) (Hamilton *et al*., 1960) and Self-rating Depression Scale (SDS) (Zung *et al*., 1965) while Davidson *et al.* (2005) Roose *et al*. (1998), Yeragani *et al*. (2022 A) and Yeragani *et al*. (2022 B) followed the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria (DSM-IV) and Rechlin *et al*. (1994) followed the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III).

There were no inconsistencies concerning mean age: 60±20 years (Davidson *et al*., 2005); 60.4±10.5 years - paroxetine group and 60.8±13.4 years - nortriptyline group (Yeragani *et al*., 2002 A); 60.4±10.5 years (Yeragani *et al*., 2002 B); 60.2±9.7 years (Tian *et al*., 2016); 58±11 years (Roose *et al*., 1998), except Rechlin *et al*. (1994) that studied younger patients (43±9.5 years old).

Concerning inclusion and exclusion criteria, Davidson *et al*. (2005) excluded patients with a history of psychosis or bipolar disorder, alcohol or other substance abuse three months prior to the study, hypertensive subjects (>140/90 mmHg), pregnant or lactating, patients

with an electrocardiogram or laboratory abnormalities, not fluent in English language, patients that had taken psychotropic drugs 14 days before the study and no patients received medicines for heart diseases. Rechlin *et al*. (1994) omitted patients with heart and cerebral diseases, diabetes, polyneuropathy, and alcoholism.

Roose *et al*. (1998) included patients with ischemic heart disease. They excluded patients presenting with myocardial infarction three months before the study, patients with a baseline QTc interval ≥ 460 ms, and those receiving drugs with class 1 antiarrhythmic activity or warfarin.

Tian *et al*. (2016) similarly included patients with ischemic heart disease. They excluded patients with allergic disorders, infected patients, autoimmune disease, rheumatic heart disease, endocrine disease, severe liver disease, renal failure, history of drug abuse, or had been prescribed with an anti-inflammatory or immunosuppressant drug except aspirin three weeks prior to the myocardial infarction.

Yeragani *et al*. (2002A) and Yeragani *et al*. (2022B) assessed the same sample with ischemic heart disease. They excluded outpatients whose myocardial infarction occurred three months before their recruitment, patients who presented a baseline QTc ≥460 ms, unstable or crescendo angina, or patients who received medications with class I antiarrhythmic activity or warfarin.

Regarding intervention, the patients from Davidson *et al.* (2005) study received paroxetine for three weeks at initial doses of 10 mg. The doses were increased to 20, 30, and 40 mg/day every four to five days. The control group received venlafaxine 37.5 mg and increased it to 75, 150, and 225 mg/day. Yeragani *et al*. (2002A) and Yeragani *et al*. (2002B) studied the same sample, and patients younger than 65 years received an initial paroxetine dose of 20 mg/day for the initial three weeks; older patients started at 10 mg/day for the first week, and the medication was increased to 20 mg/day for the next two weeks. At the end of

three weeks, if patients did not present a 50% reduction in HAMD scores, the paroxetine dose was increased to 30 mg and, if required to 40 mg at the end of the fifth week. The control group was treated with nortriptyline, which began at 25 mg and increased to 50 mg by the third day. On the seventh day, the plasma levels were measured, and the dose was adjusted to reach a plasma nortriptyline level between 304 and 456 nmol/L. The notion was to necessitate the dose within the therapeutic range of 190–570 nmol/L (50–150 ng/mL).

In the Tian *et al*. (2016) study, the dose of paroxetine or fluoxetine was 10 mg/day initially and increased to 20 mg/day. In contrast, the control did not receive antidepressant treatment for eight weeks. Rechlin *et al*. (1994) treated patients with 20 mg/day of paroxetine in 14 days, whereas the control group was treated with 150 mg/day of amitriptyline in 14 days. In Roose *et al*. (1998) study, the initial dose of paroxetine was 20 mg/day for the first three weeks, while for patients greater than or equal to 65 years, paroxetine started at 10 mg/day for the first week and increased to 20 mg for weeks two and three. If the patient did not meet the response criteria at the end of week three, the paroxetine dose was increased to 30 mg at week four and, if necessary, to 40 mg at the end of week five. The control group was prescribed nortriptyline, which commenced at 25 mg for the first two days and increased to 50 mg on day three. On day seven, the plasma level was judged, and the dose was adjusted to achieve a nortriptyline plasma level between 304 and 456 nmol/L (80-120 ng/mL) if required. This level was targeted to increase patients' probability of achieving a nortriptyline plasma level within the therapeutic range of 190 to 570 nmol/L (50-150 ng/mL).

Qualitative analysis

Davidson *et al*. (2005) achieved an analysis of variance for repeated measures and reported no significant effect of paroxetine on HRV. However, they demonstrated a lessening in the beat-to-beat interval changes during deep breathing and respiratory sinus arrhythmia.

Yeragani *et al*. (2002 A) appraised patients awake, sleeping, and through 20 hours. The authors reported a more profound HRV reduction of nortriptyline in MDD patients and ischemic heart disease. In this situation, it was advised that paroxetine might be a safer treatment in patients with myocardial infarction owing to its weaker impact on HRV.

Yeragani *et al*. (2002 B) fixated on nonlinear HRV analysis in the identical population. Also, their results suggested a significant decrease in the chaotic response of their heart period time series, perhaps attributable to the vagolytic effect of nortriptyline in MDD patients with myocardial infarction. Likewise, they suggested that paroxetine may be a safer option in MDD patients with ischemic heart disease.

Tian *et al*. (2016) equated MDD patients with ischemic heart disease treated with paroxetine, fluoxetine, and no pharmacotherapies. Both fluoxetine and paroxetine increased HRV.

According to Rechlin *et al*. (1994), paroxetine was suitable for MDD patients with autonomic dysfunction as they observed no effect of this drug on HRV throughout standard dosages.

Additionally, Roose *et al*. (1998) recommended that selective serotonin reuptake inhibitors are safer than tricyclic antidepressants for supervision of depressed patients with heart disease.

Analysis of the Risk of Bias

The risk of bias in the six detailed studies was not similar. The risk of biased results is summarized in Figure 2. Further facts about the risk of bias in the involved outcomes are reported in the supplementary file, Risk of bias (Supplementary Material 1 Risk of bias) rulings about each risk of bias item for every included study.

Randomization Process

The outcome required events for generating the randomization sequence, and the outcome reported precise methods regarding allocation.

Deviation from Intended Interventions

Participants blinding and its events were partially reported. The outcomes were not evaluated through blinded assessors of outcomes. Appropriate analysis used to estimate the effect of assignment to intervention was appropriate. There was not a potential for a substantial impact on the result of the failure to analyze participants in the group to which they were randomized.

Missing outcome data

The outcome had the whole outcome data and no losses were included for statistical analysis. Sample loss was related to patients' health status.

Measurement of the outcome

We noted totally appropriate outcome measurement. Assessors were aware of the intervention received by study participants.

Selection of the reported result

No outcome was provided with all HRV outcomes necessary to fully comprehend HRV.

Overall Bias

The outcome presented at least one additional bias.

Quantitative Analysis

For the SDNN, LF, and HF results, we levied a random effect and mean difference (MD) model to quantify their effect sizes. The black diamond dimension here characterizes the 95% CI (Figures 3, 4 & 5). A negative effect indicates reduced values in the intervention group compared to the control (Amitriptyline, Nortriptyline, or Fluoxetine).

No significant alteration was distinguished for the SDNN index. In the “Test for overall effect,” we discovered a subtotal=8.23 [CI: -2.17, 18.63], p=0.12, and heterogeneity=54% (Figure 3). The GRADE quality of evidence for this result was *very* low (Table 2).

A significant change was noticed in the LF index. In the "Test for overall effect," we revealed a subtotal=0.74 [CI: 0.33, 1.15], p=0.0004, and heterogeneity=0% (Figure 4). The GRADE quality of evidence for this result was low (Table 2).

A significant modification was identified for the HF index. In the “Test for overall effect,” we revealed a subtotal=0.33 [CI: 0.06, 0.6], p=0.02, and heterogeneity=0% (Figure 4). The GRADE quality of evidence for this result was low (Table 2).

DISCUSSION

Our systematic review was led to investigate the effects of paroxetine on HRV in MDD patients. As the key results, we stated that:

1) Analysis of the risk of bias demonstrated unclear/high risk regarding patients’ blinding and outcome assessors’ blinding in five studies (83.3%);

2) Meta-analysis specified that SDNN was not significantly influenced by paroxetine, but it revealed that paroxetine significantly improved LF and HF and;

3) Quality of evidence for SDNN was *very low*, while it was low for LF and HF.

The mechanism of drug actions for paroxetine, venlafaxine, nortriptyline, fluoxetine, and amitriptyline increases the synaptic serotonin concentrations. Consequently, these pharmacological components alleviated the symptoms of MDD. These include mood alterations, persistent feelings of sadness or loss of interest, and other psychological impairments (Shrestha *et al*., 2022). Moreover, previous evidence suggests that serotonin

affects the autonomic nervous system (Haynes 2020). Besides, it was designated that paroxetine would permit weaker autonomic effects compared to other antidepressants (Davidson *et al*., 2005; Yeragani *et al*., 2002 A; Yeragani *et al*., 2002 B). This is the reason for implementing a systematic review to comprehend better the role of paroxetine on HRV in MDD patients.

When we assessed random sequence generation and allocation concealment, we recognized that three references elucidated this point (Yeragani *et al*., 2002 A; Yeragani *et al*., 2002 B; Roose *et al*., 1998). Nevertheless, three studies could not explain how the subjects were allocated and if they were randomly divided into groups (Davidson *et al*., 2005; Rechlin *et al*., 1993; Tian *et al*., 2016). This is a significant issue in investigating systematic changes between the group's baseline profile, as it permits us to detect any factor that disturbs the subjects or any error regarding the selection of the study members (Tripepi *et al*., 2010).

One study clarified how patients' and outcome assessors' blinding was completed (Roose *et al*., 1998). Patients' blinding reduces the risk of knowing which treatment was applied rather than the treatment itself, influencing HRV. The detailed account observed in Roose *et al*. (1998) study may safeguard that the groups received similar diagnostic investigations, attention, and adjunct interventions (Higgins *et al*., 2022). Still, the other references were unsuccessful (Davidson *et al*., 2005; Rechlin *et al*., 1993; Tian *et al*., 2016; Yeragani *et al*., 2002 A; Yeragani *et al*., 2002 B).

Furthermore, we understood that two references offered the whole outcome data and no missing outcome data was stated (Rechlin *et al*., 1993; Tian *et al*., 2016), whereas in one study, the authors did not clarify the degree of sample loss (Yeragani *et al*., 2002 A). Yeragani *et al*. (2002 B), Davidson *et al*. (2005), and Roose *et al*. (1998) elucidated sample loss between the study onset and study conclusion. This detail advances the prospect that the paroxetine effect estimation was biased (Higgins *et al*., 2022).

Two references were free of selective HRV outcomes reporting (Rechlin *et al*., 1993; Yeragani *et al*. (2002 A). Davidson *et al*. (2005) did not present RMSSD, SDNN, LF, HF, or LF/HF indices, while in the Roose *et al*. (1998) study, RMSSD and frequency domain HRV indices were missing, Tian *et al*. (2016) did not state the RMSSD index and it was also absent in the Yeragani *et al*. (2002 B) study. It is possible that there was a range of outcomes to be stated based on a selection of a subset of the original HRV indices recorded to be contained within the references examined. Our concern is that non-significant data could be withdrawn from the study (Higgins *et al*., 2022).

The SDNN index is the standard deviation of all normal RR intervals and is prejudiced by both sympathetic and parasympathetic branches of the autonomic nervous system (Vanderlei *et al*., 2008). Our quantitative analysis could not detect a significant effect of paroxetine on SDNN in MDD patients. Amongst the references that estimated the SDNN, we noticed a high risk of bias in Roose *et al*. (1998) study when analyzing attrition bias owing to incomplete outcome data, as there was a transformation regarding sample size between paroxetine and nortriptyline groups. The equivalent was detected in Yeragani *et al*. (2002 B); this is since 90% of patients treated with paroxetine completed the trial, and only 65% completed the nortriptyline trial.

When studying the quality of evidence for the SDNN index, we detected severe inconsistencies as a result of substantial heterogeneity (I^2=54%). The greater the heterogeneity, the greater the questioning concerning the result's validities (Delgado-Rodríguez M and Sillero-Arena, 2018). The lack of detailed information regarding the placebo was a situation that negatively influenced publication bias. Also, a serious point was highlighted concerning inaccuracy. The high 95% confidence interval (-2.17, 18.63) impacted the GRADE levels of evidence analysis. Taken together, the inevitability was *very* low for the SDNN index.

Regarding the LF index, earlier evidence emphasized that it does not solely represent the sympathetic nervous system (Reyes del Paso *et al*., 2013). This index is predisposed by both sympathetic and parasympathetic autonomic branches (Billman *et al*., 2013). So, the HF index is affected by vagal nerve activity and respiratory rate (Vanderlei *et al*., 2008). Our meta-analysis presented that paroxetine meaningfully improved LF and HF. Both studies included in the meta-analysis (Yeragani *et al*., 2002A; Rechlin *et al*., 1993) detected that paroxetine increased these indices. Rechlin *et al*. (1993) offered a high risk of bias relating to blinding (performance and detection bias) since the authors did not mention patients' and outcome assessors' blinding. Also, the limitations of the Yeragani *et al*. (2022 A) study include the fact that the authors excluded subjects in the placebo group (after placebo lead-in), decreasing the sample for comparison. Still, the HRV indices values were similar, and there were no significant changes between pre- and post-placebo epochs.

Concerning the quality of evidence for the LF and HF indices, there were no serious concerns related to inconsistency because of the low heterogeneity (I^2=0%). We found no grave concerns related to imprecision because no large 95% confidence interval was observed in both references (Yeragani *et al*., 2002A; Rechlin *et al*., 1993). Alternatively, we identified publication bias since both references did not define patients' and outcome assessors' blinding. So, the certainty was low for the LF and HF indices.

A relevant issue to be addressed is the control groups examined in the studies. It would be unethical to treat diagnosed MDD patients with a placebo as it would deprive the MDD patients of access to a scientifically acknowledged therapy (Millum and Grady 2013). With this in mind, the selected references evaluated control groups treated with other pharmacotherapies. Davidson *et al*. (2005) used venlafaxine as a control, Roose *et al*. (1998), Yeragani *et al*. (2002 A), and Yeragani *et al*. (2002 B) used nortriptyline, Tian *et al*. (2016) treated the control group

with fluoxetine while one more group persisted for eight weeks under no pharmacological treatment at all. Rechlin *et al*. (1994) evaluated amitriptyline as a control.

In this scenario, it was unsurprising to detect improved HRV in MDD patients in the control group in some references. Tian *et al*. (2016) detected that fluoxetine improved HRV, while Yeragani *et al*. (2002 A) noticed a slight decrease in HRV following nortriptyline treatment. Even so, Davidson *et al*. (2005) reported that venlafaxine reduced HRV during respiratory sinus arrhythmia, Rechlin *et al*. (1994) observed that amitriptyline decreased HRV, Roose *et al*. (1998) noted that HRV contracted after nortriptyline treatment and Yeragani *et al*. (2002 B) reported lessened chaotic HRV behavior in MDD patients treated with nortriptyline.

Considering that nortriptyline degenerated HRV in MDD patients with ischemic heart disease (Yeragani *et al*. 2002 A; Yeragani *et al*. 2002 B), we theorize that this pharmacotherapy increases cardiovascular risk in this population. So, in this case, paroxetine may be a benign choice in patients with myocardial infarction, possibly owing to its weaker antimuscarinic effects.

Some relevant points need to be highlighted. The studies designated provided a very small sample size. We encourage further clinical trials to increase this variable. Also, we noted high heterogeneity for SDNN meta-analysis, which could negatively influence quantitative analysis.

Another limitation in this review are the differences in inclusion and exclusion criteria proposed by the selected references. For instance, Davidson *et al*. (2005) and Rechlin *et al*. (1994) excluded patients with cardiac abnormalities while Roose *et al*. (1998), Yeragani *et al*. (2002A), Yeragani *et al*. (2022B) and Tian *et al*. (2016) included patients with ischemic heart disease. Moreover, we mention the weak statistical power of the meta-analysis by reason of the specific characteristics of the selected trials.

In our analysis, we draw attention to the lack of research literature and studies in languages other than English.

We also acknowledge the post-hoc nature of the review process and analyses as a major limitation in the manuscript. The meta-analysis that produced the results was not described in a pre-specified analysis plan, this is because with meta-analysis it is possible to only conduct after study selection. Considering that the absence of a clear statistical plan in the protocol influences the selection of the reported results in clinical trials evaluation (Sterne et al., 2019), it may have implications for the results.

In conclusion, our meta-analysis specified that paroxetine may improve HRV in patients with MDD. Nevertheless, our inference is founded on statistical analysis alone. Moreover, owing to the low quality of the studies included no conclusion can be formatted and we suggest additional studies with higher levels of evidence to support this theory.

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TABLES LEGEND

Table 1. Description of the characteristics of the study population of articles by author and year, sample, age (years), intervention, control and outcomes.

Table 2. Levels of evidence analysis.

FIGURE LEGENDS

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Figure 2. Cochrane risk of bias tool per outcome.

Figure 3. Meta-analysis for overall effects of paroxetine on SDNN HRV index in MDD patients. HRV: Heart rate variability; SDD: Standard deviation of the NN intervals.

Figure 4. Meta-analysis for overall effects of paroxetine on LF HRV index in MDD patients. HRV: Heart rate variability; LF: Low frequency.

Figure 5. Meta-analysis for overall effects of paroxetine on HF HRV index in MDD patients. HRV: Heart rate variability; HF: High frequency.

Table 1. Description of the characteristics of the study population of articles by author and year, sample, age (years), intervention, control and outcomes.

Author/ Years	Study Design	Sample	Age (years)	Intervention	Control	Outcomes
Davidson et al, 2005	Double-blind, randomized and controlled trial.	49 subjects entered the trial (n = 25 PAR, n = 24 VEN-XR).	60±20 years.	Treatment was administered for 3 weeks, at initial doses of PAR 10 mg. Every 4 to 5 days, the doses of PAR were increased to 20, 30, and then 40 mg/day.	Treatment was administered for VEN-XR 37.5 mg and for VEN-XR to 75, 150, and then 225 mg/day.	In patients with major depressive disorder PAR at 40 mg/day possess concentration-dependent mild to moderate NE reuptake inhibiting effects, consistent with that previously reported. At 40 mg/day, there was no suggestion of altered HRV. VEN-XR, at daily doses of 225 mg, is associated with substantial NET and SERT inhibition and reduced vagal control of HRV.

Yeragani et al, 2002 A	Double-blind, randomized and controlled trial.	44 patients were included. Twenty-four patients were included in the paroxetine treatment study and 20 patients in nortriptyline study.	60.4±10.5 years in patients taking paroxetine and 60.8±13.4 years in patients taking nortrityline.	Patients aged less than 65 years received an initial dose of 20 mg/day of paroxetine for the first 3 weeks; older patients were started at 10 mg/day for the first week, and then the medication was increased to 20 mg/day for the next 2 weeks. At the end of 3 weeks, if patients did not show a 50% decrease in HAMD scores, the paroxetine dose was increased to 30 mg and, if necessary, to 40 mg at the end of week 5.	The nortriptyline dose was started at 25 mg and increased to 50 mg by day 3. On the seventh day, plasma level was measured and the dose adjusted to achieve a plasma nortriptyline level between 304 and 456 nmol/L. The idea was to have the dose within the therapeutic range of 190–570 nmol/L (50–150 ng/mL).	The findings of this study suggest a more profound vagolytic function of nortriptyline in patients with major depression and cardiac disease, suggesting PAR as a safer option.
Yeragani et al, 2002 B	Single-blind, randomized and controlled trial.	24 patients were included in the paroxetine treatment study and 20 patients in the nortriptyline study who had at least 20,000 s of awake data.	60.4 ± 10.5 years.	Initial dose of paroxetine of 20 mg per day for the first 3 weeks, whereas older patients were started at 10 mg per day for the first week and then the dose was increased to 20 mg/day for the next 2 weeks. At the end of 3 weeks, if they did not show a 50% decrease in HAMD scores,	The nortriptyline dose was begun at 25 mg, which was increased to 50 mg by day 3.	The findings of this study suggest a significant decrease in chaos of HP time series, probably due to the vagolytic effect of nortriptyline in patients with major depression and cardiac disease and thus between

				paroxetine was increased to 30 mg at week 4 and, if necessary, to 40 mg at the end of week.		the two drugs; paroxetine may be a safer choice especially in the patients with myocardial infarction. This may be likely due to the weaker antimuscarinic effects of paroxetine.
Tian et al, 2016	Double-blind, randomized and controlled trial.	67 AMID patients, 23 were randomly assigned treatment with paroxetine, 23 with fluoxetine, and the rest with no antidepressant treatment for 8 weeks.	60.2±9.7 years.	The dose of paroxetine was 10 mg/day initially and increased to 20 mg/day.	23 patients were treated with fluoxetine, and 21 with no antidepressant treatment for eight weeks. The dose of fluoxetine was 10 mg/day initially and increased to 20 mg/day within one week based on individual patient response.	This study suggests the benefit of using paroxetine to improve cardiac function in AMID patients and such effect associates with GRK2 reduction.
Rechlin et al, 1994	Single-blind, randomized and controlled trial.	24 patients	43±9.5 years	20 mg/d of paroxetine in 14 days	150mg/d of amitriptyline in 14 days.	According to the results of HRA, paroxetine is appropriate for patients who already suffer from autonomic

						dysfunction, because it has no effects on autonomic function in normal dosage.
Roose et al, 1998	Double-blind, randomized and controlled trial.	Ninety-two patients. Eleven patients who began the placebo phase were not randomized. Eighty-one patients were randomized to drug treatment. Patients were either taking active parox- etine in the morning and nortriptyline placebo at night or taking paroxetine placebo in the morning and active nortriptyline at night.	58±11 years.	The initial dose of paroxetine was 20 mg/d for the first 3 weeks, whereas for patients 65 years and older paroxetine was started at 10 mg/d for the first week and increased to 20 mg for weeks 2 and 3. If at the end of week 3 the patient did not meet criteria for response, defined as a 50% reduction in baseline HRSD score and total HRSD score of 8 or less, the paroxetine dose was increased to 30 mg at week 4 and, if necessary, to 40 mg at the end of week 5.	The nortriptyline dose was begun at 25 mg for the first 2 days and increased to 50 mg on day 3. On day 7, a plasma level was measured and the dose adjusted, if nec- essary, to achieve a nortriptyline plasma level between 304 and 456 nmol/L (80-120 ng/mL). This level was targeted to in- crease the likelihood that patients would achieve a nortriptyline plasma level within the therapeutic range of 190 to 570 nmol/L (50-150 ng/mL).	The results of this study contribute important new information to the evaluation of risk, and are consistent with other data that suggest that SSRIs are safer than TCAs in the treatment of depressed patients with heart disease.

Legend: *PAR (Paroxetine), VEM-XR (Venlafaxine XR), Norepinephrine (NE), heart rate variability (HRV), Norepinephrine transporter (NET), serotonin transporter (SERT), Hamilton Rating Scale for Depression (HAMD), heart period (HP), Self-rating Depression Scale (SDS), acute myocardial infarction with depression (AMID), G protein-coupled receptor kinase-2 (GRK2), selective serotonin reup- take inhibitor (SSRIs), tricyclic antidepressants (TCAs), Heart rate analysis (HRA)

Table 2

Author(s):
Question: Paroxetina compared to controle for HRV
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paroxetina	control	Relative (95 % CI)	Absolute (95 % CI)		
Standard deviation of RR interval (follow-up: mean 42 days; assessed with: ms; Scale from: 20 to 120)												
3	randomised trials	very serious[a,b,c,d]	very serious[e]	not serious	serious[f]	publication bias strongly suspected[g]	85	87	-	MD **8.23 ms higher** (2.17 lower to 18.63 higher)	⨁◯◯◯ Very low	
Low frequency (follow-up: mean 42 days; assessed with: Hz2; Scale from: 0.5 to 6)												
2	randomised trials	serious[h,i]	not serious	not serious	not serious	publication bias strongly suspected[h,i]	36	32	-	MD **0.74 Hz2 higher** (0.33 higher to 1.15 higher)	⨁⨁◯◯ Low	
High frequency (follow-up: mean 42 days; assessed with: Hz2; Scale from: 0.4 to 5)												
2	randomised trials	serious[h,i]	not serious	not serious	not serious	publication bias strongly suspected[h,i]	36	32	-	MD **0.33 Hz2 higher** (0.06 higher to 0.6 higher)	⨁⨁◯◯ Low	

CI: confidence interval; **MD:** mean difference

Explanations

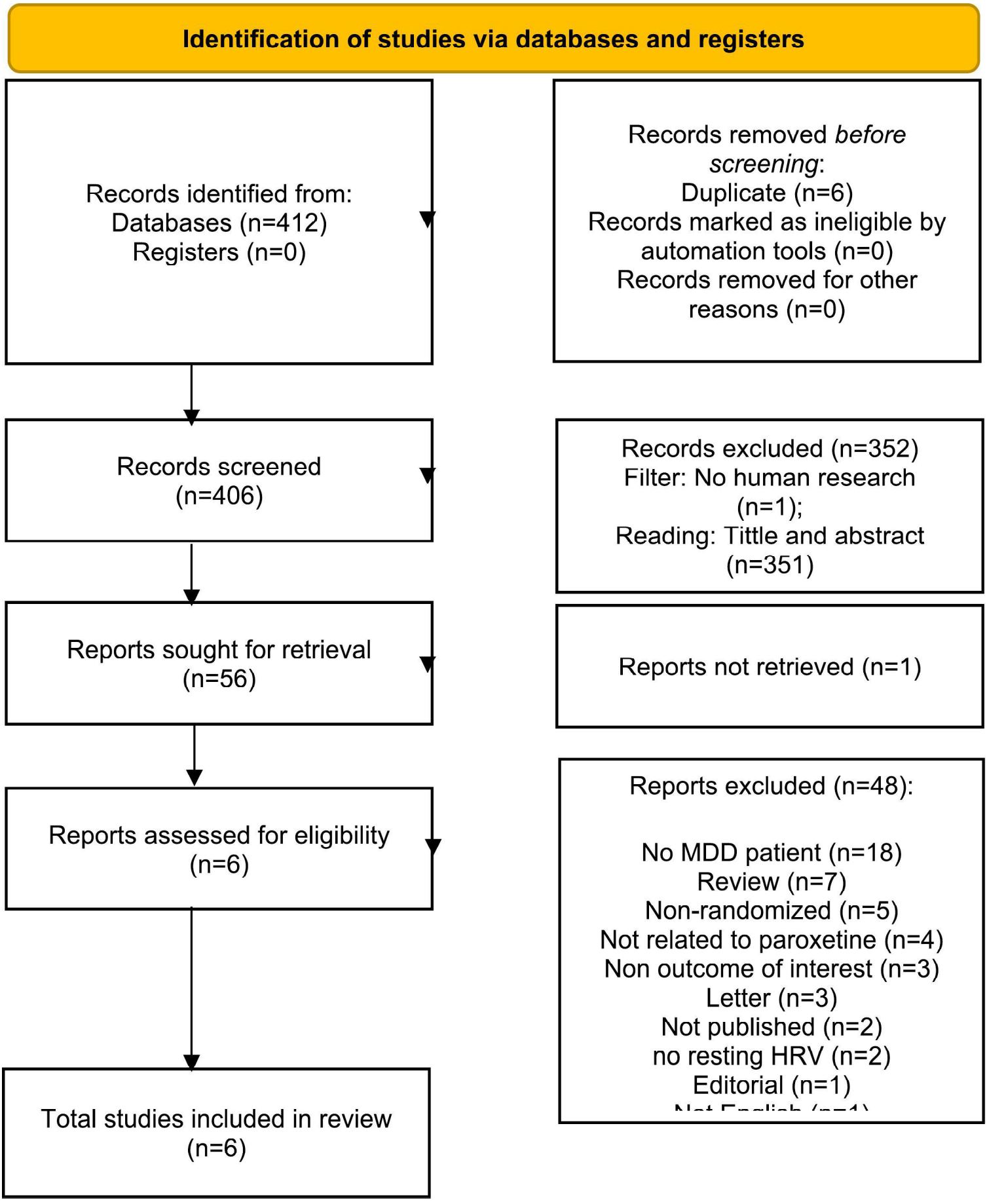
a. Incomplete outcome data (attrition bias)
b. Selective reporting (reporting bias)
c. Small number of patients were studied
d. The control group remained with no antidepressant treatment instead of placebo.
e. High heterogeneity: I2=54%
f. High Confidence interval: -2.17; 18.63.
g. The placebo period was not detailed.
h. The authors did not mention patients' blinding.
i. The authors did not mention outcome assessors' blinding.

Conflict of interest

"Dear Editor, we declare no conflict of interest."

Highlights

- We executed a systematic review and meta-analysis to estimate the effects of paroxetine on heart rate variability in patients identified with major depressive disorder.
- Analysis of the risk of bias evidenced unclear/high risk regarding patients' blinding and outcome assessors' blinding in five studies (83.3%);
- Meta-analysis specified that SDNN was not significantly influenced by paroxetine, but it exposed that paroxetine significantly improved LF and HF and;
- Quality of evidence for SDNN was very low, while it was low for LF and HF.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Databases (n=412)
Registers (n=0)
Records removed *before screening*:
Duplicate (n=6)
Records marked as ineligible by automation tools (n=0)
Records removed for other reasons (n=0)
Records screened
(n=406)
Records excluded (n=352)
Filter: No human research (n=1);
Reading: Tittle and abstract (n=351)
Reports sought for retrieval
(n=56)
Reports not retrieved (n=1)
Reports assessed for eligibility
(n=6)
Reports excluded (n=48):
No MDD patient (n=18)
Review (n=7)
Non-randomized (n=5)
Not related to paroxetine (n=4)
Non outcome of interest (n=3)
Letter (n=3)
Not published (n=2)
no resting HRV (n=2)
Editorial (n=1)
Total studies included in review
(n=6)

Figure 1

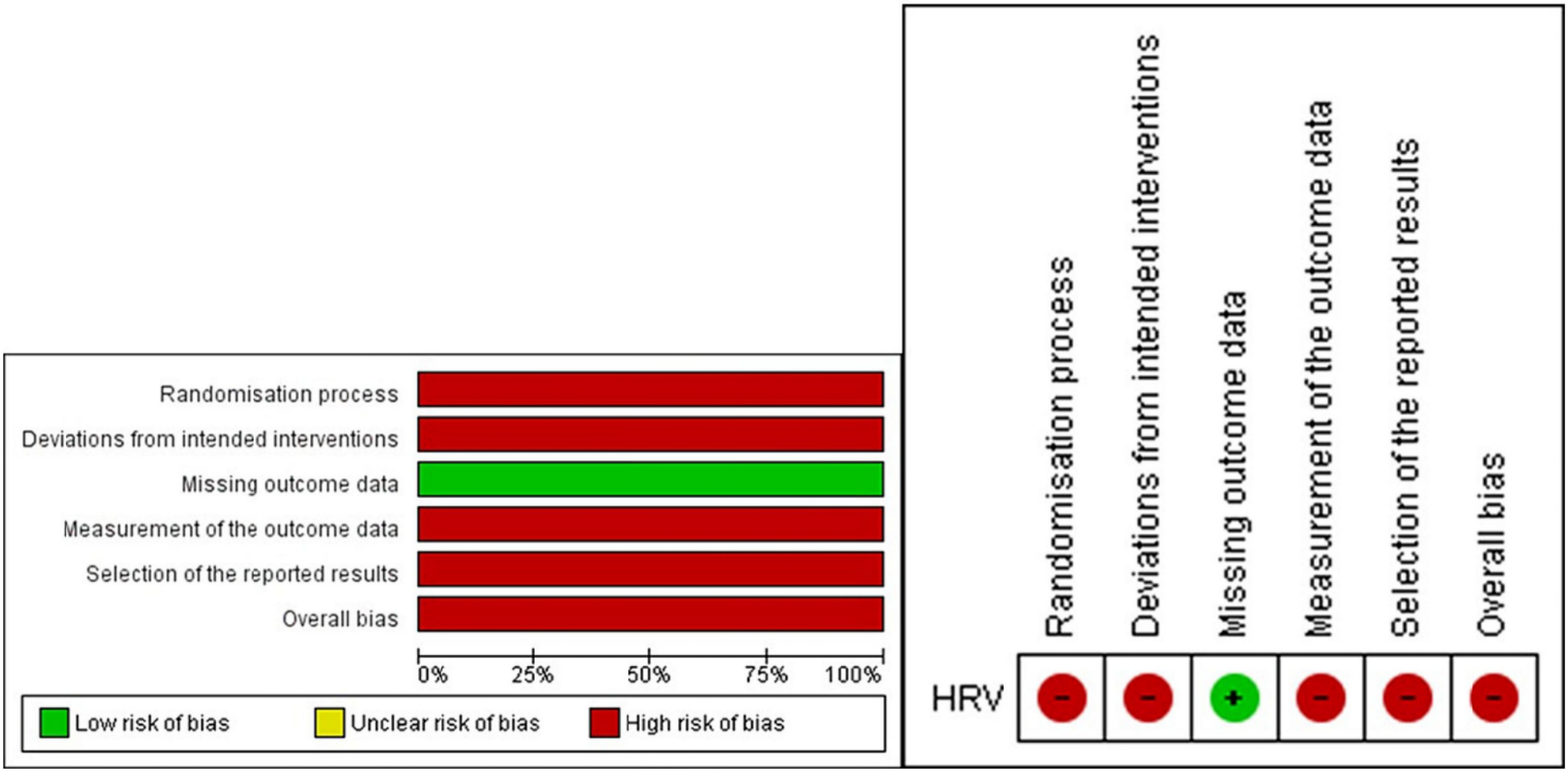
Randomisation process
Deviations from intended interventions
Missing outcome data
Measurement of the outcome data
Selection of the reported results
Overall bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias
HRV
Randomisation process
Deviations from intended interventions
Missing outcome data
Measurement of the outcome data
Selection of the reported results
Overall bias

Figure 2

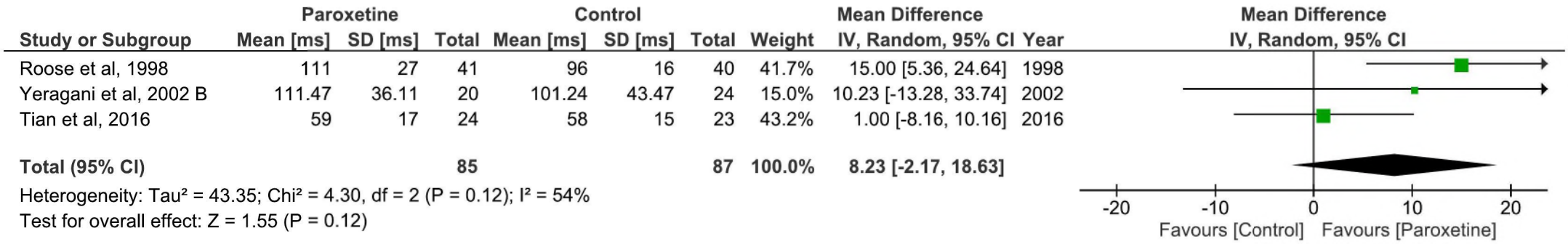
Paroxetine
Control
Mean Difference
Mean Difference
Study or Subgroup
Mean [ms]
SD [ms]
Total
Mean [ms]
SD [ms]
Total
Weight
IV, Random, 95% CI
Year
IV, Random, 95% CI
Roose et al, 1998 111 27 41 96 16 40 41.7% 15.00 [5.36, 24.64] 1998
Yeragani et al, 2002 B 111.47 36.11 20 101.24 43.47 24 15.0% 10.23 [-13.28, 33.74] 2002
Tian et al, 2016 59 17 24 58 15 23 43.2% 1.00 [-8.16, 10.16] 2016
Total (95% CI) 85 87 100.0% 8.23 [-2.17, 18.63]
Heterogeneity: Tau² = 43.35; Chi² = 4.30, df = 2 (P = 0.12); I² = 54%
Test for overall effect: Z = 1.55 (P = 0.12)
-20
-10
0
10
20
Favours [Control]
Favours [Paroxetine]

Figure 3

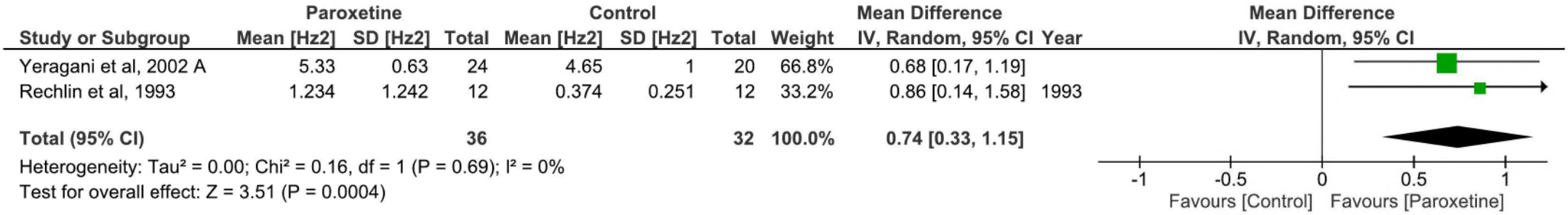
Paroxetine
Control
Mean Difference
Mean Difference
Study or Subgroup
Mean [Hz2]
SD [Hz2]
Total
Mean [Hz2]
SD [Hz2]
Total
Weight
IV, Random, 95% CI
Year
IV, Random, 95% CI
Yeragani et al, 2002 A 5.33 0.63 24 4.65 1 20 66.8% 0.68 [0.17, 1.19]
Rechlin et al, 1993 1.234 1.242 12 0.374 0.251 12 33.2% 0.86 [0.14, 1.58] 1993
Total (95% CI) 36 32 100.0% 0.74 [0.33, 1.15]
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0004)
-1
-0.5
0
0.5
1
Favours [Control]
Favours [Paroxetine]

Figure 4

Study or Subgroup	Paroxetine Mean [Hz2]	Paroxetine SD [Hz2]	Paroxetine Total	Control Mean [Hz2]	Control SD [Hz2]	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Yeragani et al, 2002 A	4.59	0.94	24	4.1	1.08	20	20.0%	0.49 [-0.11, 1.09]	
Rechlin et al, 1993	0.432	0.517	12	0.142	0.132	12	80.0%	0.29 [-0.01, 0.59]	1993
Total (95% CI)			**36**			**32**	**100.0%**	**0.33 [0.06, 0.60]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%

Test for overall effect: Z = 2.39 (P = 0.02)

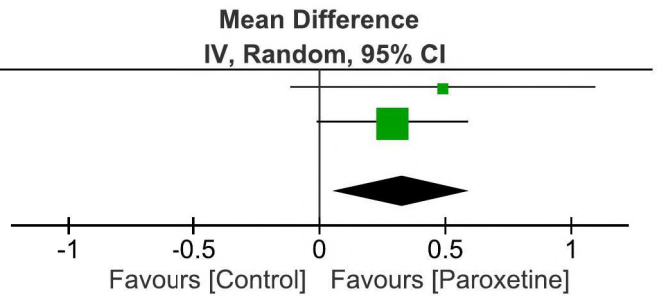

Figure 5