A meta-analysis of effects of selective serotonin reuptake inhibitors on blood pressure in depression treatment: outcomes from placebo and serotonin and noradrenaline reuptake inhibitor controlled trials

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Background: Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) have been commonly prescribed for depression treatment. However, their effects on blood pressure are unclear.

Materials and methods: Effects on blood pressure of depressive patients in two groups (SSRIs versus placebo and SSRIs versus SNRIs) were evaluated. A search was conducted for double-blind, randomized controlled trials (RCTs) in PubMed, EMBASE, ISI Web of Science, PsycNET, CCRCT, and DARE (up to March 2017). The outcomes were systolic blood pressure (SBP) changes and diastolic blood pressure (DBP) changes from baseline to endpoint or to a certain period of treatment duration. Weighted mean differences (WMDs) and 95% CIs were calculated and pooled using random effects models. The χ2 test and I2 statistics were used to assess heterogeneity. Funnel plots, Begg’s test, and Egger’s test were used to estimate publication bias.

Results: A total of 23 RCTs involving 13,285 participants were included. Patients on SSRIs showed no significant differences in blood pressure changes compared with placebo. In the group of SSRIs versus SNRIs, overall SBP changes and DBP changes revealed statistical significances (WMD 1.5 mmHg, 95% CI −2.15, −0.84, Z=4.46, P<0.00001 and WMD 1.34 mmHg, 95% CI −1.92, −0.75, Z=6.18, P<0.00001). Subgroup analyses on treatment duration and age further evidenced these findings.

Conclusion: It was established that SSRIs did not affect blood pressure, while SNRIs led to a modest increase in SBP and DBP with statistical significance compared with SSRIs.

Keywords: meta-analysis, blood pressure change, depression treatment, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, depression, antidepressant, systolic blood pressure, diastolic blood pressure

Introduction

Major depression manifests kinds of cognitive and biological symptoms, leading to a debilitating condition. Worldwide, 17% of people are likely to experience major depression during their lifetime; it is especially prevalent in patients with cardiovascular disorders.1 It is well established that depressive patients tend to have unhealthy lifestyles including smoking, physical inactivity, and poor medication adherence. This in turn exacerbates cardiovascular conditions including hypertension and left ventricular hypertrophy.2 Depressed individuals, whether with a clinical diagnosis...
of depression, have been reported to have a higher occurrence of morbidity and mortality for cardiovascular events.\(^3\) Some studies indicate that low blood pressure (BP) is associated with increased prevalence of depression, as well as with depressive symptom severity, which is independent of age, sex, or cardiovascular disease,\(^4\) even independent of baseline BP or other risk factors usually associated with hypertension. This association is not explained by the use of antidepressants or antihypertensive medications.\(^5\) The Three City Study confirms that both depressed men and women have lower systolic blood pressure (SBP) and diastolic blood pressure (DBP), which are unrelated to antihypertensive or psychotropic agents.\(^6\) In contrast, a meta-analysis suggests anxiety and hypertension are significantly correlated, drawing the conclusion that anxiety is an independent risk factor for incident hypertension.\(^7\) Anxiety and depression are closely linked.\(^8\) A previous review also showed an increased risk of hypertension in depressed patients and an increased risk of depression in hypertensive patients.\(^9\)

Besides controversies regarding the connection between depression and BP level, the role of antidepressants in mood disorders such as anxiety and depression and BP is equivocal. Tricyclic antidepressants have been reported to result in higher mean SBP and DBP, thus making hypertension stage 1 more likely.\(^10\) Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), the second-generation antidepressants, are prescribed for both anxiety and depression, consisting of a tower of strength in treatment of affective disorders. Escitalopram results in a slight decrease in BP without dose effect, though not clinically meaningful.\(^11\) Furthermore, it has been reported that a modest reduction in SBP and DBP could be observed when statistically comparing fluoxetine with placebo during short-term treatment.\(^12\) Effects of venlafaxine and duloxetine on BP have been depicted in previous studies.\(^13-15\) Nevertheless, whether SSRIs increase or decrease BP during the treatment duration of depression and whether significantly different BP variations exist between SSRIs and SNRIs seem ambiguous. It is reported that SSRIs can affect cardiovascular function.\(^16\) SSRIs are rarely associated with cardiac death but cause side effects such as hypotension and mild bradycardia.\(^17\) SNRIs can cause elevation of BP, particularly of DBP. Does antidepressant use act to confound the relationship between psychopathology and BP?

Currently, reports of effects on BP exerted by SSRIs are rather scarce, and there is a lack of detailed analysis investigating effects on BP. Considering that the magnitude of BP changes has not been described elaborately enough with SSRI and SNRI administration, we conducted this meta-analysis in terms of BP change, providing directly perceived clinical evidence. In this context, we reported BP changes during SSRI treatment for depression compared with placebo and SNRIs, respectively.

### Materials and methods

#### Data search

All randomized, double-blind clinical trials which compared SSRIs with SNRIs or placebo in treatment of depression were searched and assessed for inclusion. A computerized search was performed in PubMed, EMBASE, ISI Web of Science, PsycNET, CCRCT, and DARE (up to March 2017) for original research articles. Reference lists of relevant studies and reviews were further examined to reveal additional studies. Search terms included “fluoxetine”, “citalopram”, “escitalopram”, “fluvoxamine”, “sertraline”, “paroxetine”, “placebo”, “venlafaxine”, “duloxetine”, “milnacipran”, “major depressive disorder” (MDD), “depression”, and “randomized controlled trial” (RCT). The comparison interventions were placebo treatments or SNRIs. Detailed data including changes of SBP and DBP were carefully examined. We excluded open-label trials and studies with insufficient information about BP.

#### Patients

The inclusion criteria for patients were: a) outpatients or inpatients meeting the diagnostic standard of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or text revision (DSM-IV TR) diagnosis of MDD, and b) single episode or recurrent MDD. There was no age restriction. Exclusion criteria were: a) past or current presence of seizure disorder; b) depression with psychotic feature, diagnosis of schizophrenia, schizoaffective disorder, and bipolar disorder; c) posttraumatic stress disorder; d) uncontrolled hypertension; e) female patients who were pregnant or lactating; and f) a history of alcohol or substance dependence or abuse.

#### Data extraction and quality assessment

For each trial, we extracted data recorded in a standardized Excel file, including the first author, year of publication, sample size, population age, treatment duration, medication doses, and checked by a third investigator. Two investigators extracted the data and trial quality information from the studies selected for inclusion in the meta-analysis independently to evaluate eligibility. If the studies were approved to meet inclusion criteria by both reviewers, the trials were included in the analysis. Any inconsistencies were reviewed
and resolved by discussion and consensus. Outcome variables were the effects of individual BP changes.

For each eligible trial, risks of bias were assessed in detail, according to the bias assessment of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.10). Treatment agents, blinding, and randomization were demonstrated in detail according to the primary trials.

Statistical analysis
We calculated continuous outcomes using weighted mean differences (WMDs) with 95% CIs, since each study used the same outcome for the studied adverse effects, and this preserves the original BP change, which is intuitively interpreted (eg, a WMD of 5 means a 5 mmHg difference in BP between the two groups). The inverse variance statistical method and random effects model were applied to calculate pooled data. When SDs were not reported, they were derived from other available data or we contacted authors to supply the statistics.

In the absence of data from authors, we used the average SDs of other studies with the same medication.18

We evaluated study heterogeneity by χ² test and I² statistics, with statistical significance set at χ² P<0.1 and I²>50% indicating heterogeneity. We conducted sensitivity analyses by reestimating pooled WMD by omitting one study at a time to evaluate the influence of each individual study on the overall meta-analysis. Furthermore, for comparing SSRIs with SNRIs, we conducted subgroup analyses based on treatment durations (long-term and short-term) and different ages (≥18 years and <18 years) to clarify potential sources of heterogeneity.

Publication bias was assessed by conducting Begg’s test and Egger’s test. If Pr or P-value was <0.05, publication bias of the meta-analysis was considered representative of statistical significance. Data were processed by using the computer program Review Manager (version 5.3, the Nordic Cochrane Centre, Copenhagen, Denmark; The Cochrane Collaboration, 2014) chiefly, and STATA (version 12.0; StataCorp LP, College Station, TX, USA) was used in the quantitative assessment of publication bias and sensitivity analyses as supplement.

Results
The initial search yielded 1,824 abstracts, of which 628 full texts were inspected, as outlined in Figure 1. There were 23 non-duplicated trials19-41 comparing SSRI intervention with placebo or SNRIs included for this meta-analysis, after excluding other interventions and those with lack of analyzable data about BP or length of intervention shorter than 4 weeks. Except for four studies based on children and teenagers,26,29,30,40 all other trials included adults. There were 15 trials available for analysis of comparing SSRIs with placebo. One study included patients with MDD combined with a history of acute myocardial infarction or unstable angina.20 Two trials were about MDD combined with coronary artery disease23 or depressive disorders combined with acute coronary syndrome,33 respectively. Considering the fact that comorbid cardiovascular diseases were in a steady state, antihypertensive and other cardiovascular medications were prescribed on stable doses for study duration, the previously mentioned three trials were included in the analysis. A total of 18 trials comparing SSRIs with two SNRIs were included. No qualified studies on fluvoxamine and milnacipran were identified. There were six trials including different medication doses or durations; thus, those data of identically designed studies were all included in the analysis. In all, the group of SSRIs versus placebo included 4,662 patients and 8,623 patients in the SSRIs versus SNRIs group.

Table 1 outlines the main characteristics of the 23 RCTs. Figure 2 presents the summary of the risk of bias of each individual study.

BP changes in SSRI groups versus placebo
Differences between individual SSRIs and placebo regarding SBP and DBP changes are summarized in Figures 3 and 4. Overall, SSR1 interventions were associated with a pooled SBP change of −0.04 mmHg (95% CI −0.68, 0.59) versus placebo (Figure 3), indicating no significant difference with Z=0.14, P=0.89. Subgroup difference test revealed no significant difference: χ²=3.46, df=4, P=0.48, I²=0%.

![Figure 1 Flow chart of study selection. Abbreviation: RCT, randomized controlled trial.](https://www.dovepress.com/.../A-meta-analysis-of-effects-of-antidepressants-on-blood-pressure)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Main inclusion criteria</th>
<th>Mean age (SD), years</th>
<th>Duration (weeks)</th>
<th>Intervention, number, and doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenox-Smith and Jiang 2008</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Citalopram 43 (11.2)</td>
<td>12</td>
<td>Citalopram (20–60 mg/d), N=205</td>
</tr>
<tr>
<td>Glassman et al 2002</td>
<td>RCT, double-blind</td>
<td>MDD and AMI or UA</td>
<td>Sertraline 56.8 (11.1)</td>
<td>16</td>
<td>Sertraline (50–200 mg/d), N=186</td>
</tr>
<tr>
<td>Nierenberg et al 2007</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Placebo 57.6 (10.4)</td>
<td>8</td>
<td>Escitalopram (10 mg/d), N=274</td>
</tr>
<tr>
<td>Coleman et al 2001</td>
<td>RCT, double-blind</td>
<td>Major depression</td>
<td>Placebo 36.7 (19–62)</td>
<td>6</td>
<td>Fluoxetine (20–60 mg/d), N=101</td>
</tr>
<tr>
<td>Nemeroff et al 2007</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Placebo 40.4 (11.7)</td>
<td>12</td>
<td>Different SSRIs 16.0 (1.6)</td>
</tr>
<tr>
<td>Oslin et al 2003</td>
<td>RCT, double-blind</td>
<td>Depressive disorder</td>
<td>Placebo 36.7 (19–62)</td>
<td>6</td>
<td>Fluoxetine (20–60 mg/d), N=101</td>
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<td>RCT, double-blind</td>
<td>MDD</td>
<td>Placebo 40.4 (11.7)</td>
<td>12</td>
<td>Venlafaxine 15.8 (1.5)</td>
</tr>
<tr>
<td>Brent et al 2008</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Citalopram 43 (11.2)</td>
<td>12</td>
<td>Citalopram (20–60 mg/d), N=205</td>
</tr>
<tr>
<td>Sheehan et al 2009</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Citalopram 43 (11.2)</td>
<td>12</td>
<td>Citalopram (20–60 mg/d), N=205</td>
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<tr>
<td>Lesperance et al 2007</td>
<td>RCT, double-blind</td>
<td>MDD and CAD</td>
<td>Sertraline 56.8 (11.1)</td>
<td>16</td>
<td>Sertraline (50–200 mg/d), N=186</td>
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<td>Emleslie et al 2014</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Placebo 57.6 (10.4)</td>
<td>8</td>
<td>Duloxetine (40 mg/d) 48 (56)</td>
</tr>
<tr>
<td>Brent et al 2008</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Fluoxetine 37.9 (11.5)</td>
<td>6</td>
<td>Fluoxetine (20–60 mg/d), N=101</td>
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<tr>
<td>Sheehan et al 2009</td>
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<td>Placebo 39.9 (13.0)</td>
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<td>Duloxetine (80 mg/d) 56 (62)</td>
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<tr>
<td>Lesperance et al 2007</td>
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<td>MDD and CAD</td>
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<td>12</td>
<td>Duloxetine (60 mg/d), N=112</td>
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<td>Emleslie et al 2014</td>
<td>RCT, double-blind</td>
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<td>Placebo 58.4 (9.16)</td>
<td>12</td>
<td>Duloxetine (60 mg/d), N=112</td>
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<tr>
<td>Emleslie et al 2015</td>
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<td>MDD</td>
<td>Placebo 39.9 (13.0)</td>
<td>12</td>
<td>Duloxetine (60 mg/d), N=112</td>
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<td>Croft et al 1999</td>
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<td>MDD</td>
<td>Paroxetine 42.9 (12.5)</td>
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<td>Duloxetine (60 mg/d), N=112</td>
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<td>MDD</td>
<td>Paroxetine 42.9 (12.5)</td>
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<td>Duloxetine (60 mg/d), N=112</td>
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<tr>
<td>Kim et al 2015</td>
<td>RCT, double-blind</td>
<td>Depressive disorders and ACS</td>
<td>Duloxetine 43.4 (12.2)</td>
<td>12</td>
<td>Duloxetine (60 mg/d), N=112</td>
</tr>
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<td>Keller et al 2007</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Fluoxetine 40.0 (11.6)</td>
<td>10</td>
<td>Fluoxetine (20–40 mg/d), N=126</td>
</tr>
<tr>
<td>Detke et al 2004</td>
<td>RCT, double-blind</td>
<td>MDD</td>
<td>Paroxetine 42.0 (10.6)</td>
<td>8</td>
<td>Paroxetine (20–40 mg/d), N=126</td>
</tr>
<tr>
<td>Allard et al 2004</td>
<td>RCT, double-blind</td>
<td>Major depression</td>
<td>Placebo 43.7 (12.2)</td>
<td>24</td>
<td>Placebo, N=274, placebo, N=137</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluoxetine 37.5 (5.7)</td>
<td>8</td>
<td>Citalopram (10–20 mg/d), N=75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Venlafaxine 72.5 (5.7)</td>
<td>8</td>
<td>Venlafaxine (75–150 mg/d), N=73</td>
</tr>
</tbody>
</table>

(Continued)
A pooled DBP change in SSRIs versus placebo group was 0.08 mmHg (95% CI -0.43, 0.60), with no statistical significance, $Z=0.32, P=0.75$ (Figure 4). There was no significant difference in DBP changes among subgroups: $\chi^2=1.01, df=4, P=0.91, I^2=0\%$.

### BP changes in SSRIs versus SNRIs groups

Twenty-eight studies reported BP changes in SSRIs versus SNRIs. In the pooled analysis, overall SBP changes and DBP changes revealed statistically significant differences ($WMD=-1.5\text{ mmHg}, 95\% \text{ CI} -2.15, -0.84, Z=4.46, P<0.00001$, Figure 5, and $WMD=-1.34\text{ mmHg}, 95\% \text{ CI} -1.92, -0.75, Z=6.18, P<0.00001$, Figure 6). There was a low level of heterogeneity across all studies in BP changes ($I^2=39\%, P=0.02$, Figure 5), while a medium level of heterogeneity was detected in DBP changes ($I^2=54\%, P=0.0004$, Figure 6).

### Short-/long-term duration

SBP changes between SSRIs and SNRIs in short-term duration ($\leq 8$ weeks) and long-term duration ($>8$ weeks) differed statistically ($WMD=-1.51\text{ mmHg}, 95\% \text{ CI} -2.44, -0.58, Z=3.18, P=0.001$ and $WMD=-1.46\text{ mmHg}, 95\% \text{ CI} -2.42, -0.49, Z=2.95, P=0.003$) (Figure 5). Significant differences were observed in DBP changes in short-/long-term duration ($WMD=-1.10\text{ mmHg}, 95\% \text{ CI} -1.82, -0.39, Z=3.04, P=0.002$ and $WMD=-1.49\text{ mmHg}, 95\% \text{ CI} -2.37, -0.61, Z=3.31, P=0.0009$) (Figure 6). Tests for subgroup differences of SBP and DBP changes revealed no significant difference: $\chi^2=0.09, df=1, P=0.76, I^2=0\%$ and $\chi^2=0.37, df=1, P=0.54, I^2=0\%$.

### Different ages

A significant difference in SBP changes resulting from age ($<18$ or $\geq 18$ years) was observed when comparing SSRIs with SNRIs ($WMD=-1.31\text{ mmHg}, 95\% \text{ CI} -2.31, -0.31, Z=2.56, P=0.01$ and $WMD=-1.51\text{ mmHg}, 95\% \text{ CI} -2.31, -0.70, Z=3.68, P=0.0002$) (Figure 7). DBP changes resulting from age between SSRIs and SNRIs showed a statistical difference ($WMD=-1.84\text{ mmHg}, 95\% \text{ CI} -3.66, -0.01, Z=1.97, P=0.05$ and $WMD=-1.24\text{ mmHg}, 95\% \text{ CI} -1.85, -0.63, Z=3.96, P<0.0001$) (Figure 8). Tests for subgroup differences of SBP and DBP changes revealed no significant difference: $\chi^2=0.09, df=1, P=0.76, I^2=0\%$ and $\chi^2=0.37, df=1, P=0.54, I^2=0\%$.

### Publication bias and sensitivity analysis

We assessed the possibility of publication bias in the articles, which compared the effects on BP in groups of SSRIs versus placebo and SSRIs versus SNRIs. The funnel plot of Begg illustrated a symmetrical distribution of the points, suggesting a lack of publication bias. No obvious publication bias was found by Begg’s test and Egger’s test (Figure 9). Sensitivity analyses by reestimating pooled WMD when excluding one study at a time showed similar results (Figures 10 and 11).
Discussion

The main purpose of this meta-analysis was to critically evaluate the effects of SSRIs and SNRIs on BP in quantification. As illustrated in our randomized, double-blind meta-analysis, WMDs varied little among five kinds of SSRIs when compared with placebo. A test on the subgroups revealed no statistical difference, indicating little difference in BP among the five kinds of SSRIs. SSRIs might not cause more apparent fluctuation of BP than placebo. In terms of definite BP changes, each SSRI may be associated with <3 mmHg variation during the period of trials, which showed no close connection with management of BP, at the same time suggesting that SSRIs might be safe in regard to BP. Furthermore, it is reported that depressive disorder is associated with average lower levels of SBP and DBP and less hypertension.

With regard to changes in BP caused by SSRIs versus SNRIs, WMDs were significantly different, though the exact numerical values were small with variations of <3 mmHg. A conclusion that fluctuations in BP were not significantly different in groups of SSRIs compared with placebo may be drawn from our meta-analysis, it may be inferred that SNRIs could lead to higher BP than SSRIs. Both in short-term and long-term duration, SNRIs were associated with escalation of SBP and DBP to some extent. These findings are consistent with conclusions drawn in the previous reports focusing on venlafaxine. Mean BP and supine DBP increase with incremental doses of venlafaxine. Incidence of clinically significant increases in BP can be lower at doses below 200 mg daily, and only doses above 300 mg/day lead to statistical and clinical significance of the incidence of elevated supine DBP. A previous study reported that duloxetine at supratherapeutic doses increases supine SBP and DBP by maxima of ~12 mmHg and 7 mmHg above baseline, respectively. Doses of venlafaxine and duloxetine in the included trials of our analysis varied between 75–375 mg/d and 40–120 mg/d, respectively. Because of the paucity of eligible studies and dose modulations, analysis for different doses of medications was not conducted. Nevertheless, it is reliable to highlight that greater BP changes are associated with SNRIs compared to SSRIs; thus, clinicians should monitor BP periodically throughout treatment with venlafaxine and duloxetine.

Depression is associated with reductions in heart rate variability and might be related to low cardiac vagal control, as well as central autonomic dysfunction, a shift of autonomic balance toward sympathetic predominance, leading to cardiovascular somatic symptoms of depression such as higher heart rate and BP lability.

Some studies support the hypothesis that depression is associated with lower BP. However, how BP changes when depressive symptoms are ameliorated still remains obscure. Antidepressant agents, such as SSRIs and SNRIs,
Table 3  A forest plot of RCTs comparing SSRI group with placebo group for change in systolic blood pressure.

Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor.

Table 4  (Continued)
Sertraline
Glassman et al 2002\(^{22}\)  2  10.95  186  3  11.53  183  5.0  –1.00 (–3.29, 1.29)
Coff et al 1999\(^{21}\)  1  9.82  119  –0.1  8.87  121  4.8  –1.10 (–1.25, 3.45)
Subtotal (95% CI)  305  304  9.8  0.04 (–2.02, 2.09)
Heterogeneity: $I^2=80.8; \chi^2=1.57, df=1 (P=0.21); I^2=36\%$
Test for overall effect: $Z=0.03 (P=0.97)$

Escitalopram
Nierenberg et al 2007\(^{19}\)  –0.9  8.76  274  0.3  9.23  137  7.6  –1.20 (–3.06, 0.66)
Kim et al 2015\(^{23}\)  0.7  12.11  108  –0.9  12.31  109  2.5  1.60 (–1.65, 4.85)
Subtotal (95% CI)  382  246  10.1  –0.13 (–2.80, 2.54)
Heterogeneity: $I^2=69.9; \chi^2=2.15, df=1 (P=0.14); I^2=53\%$
Test for overall effect: $Z=0.10 (P=0.92)$

Citalopram
Lesperance et al 2007\(^{20}\)  0.3  11.15  142  –1.1  10.99  142  4.0  1.40 (–1.18, 3.98)
Subtotal (95% CI)  142  142  4.0  1.40 (–1.18, 3.98)
Heterogeneity: not applicable
Test for overall effect: $Z=1.07 (P=0.29)$

Total (95% CI)  2,402  2,260  100  0.08 (–0.43, 0.60)
Heterogeneity: $I^2=0.01; \chi^2=16.09, df=16 (P=0.45); I^2=1\%$
Test for overall effect: $Z=0.32 (P=0.75)$
Test for subgroup differences: $\chi^2=1.01, df=4 (P=0.91); I^2=0\%$

Figure 4 A forest plot of RCTs comparing SSRI group with placebo group for change in diastolic blood pressure. Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor.

Study or subgroup  | SSRI  Mean (SD)  | Placebo  Mean (SD)  | Weight (%)  | Mean difference IV, random, 95% CI  | Mean difference IV, random, 95% CI  |
---|---|---|---|---|---|
Sertraline  | 10.95 (186)  | 11.53 (183)  | 5.0  | –1.00 (–3.29, 1.29)  |  |
Citalopram  | 8.76 (274)  | 9.23 (137)  | 7.6  | –1.20 (–3.06, 0.66)  |  |
Citalopram  | 12.11 (108)  | 12.31 (109)  | 2.5  | 1.60 (–1.65, 4.85)  |  |
Citalopram  | 11.15 (142)  | 10.99 (142)  | 4.0  | 1.40 (–1.18, 3.98)  |  |

Figure 5 A forest plot of RCTs comparing SSRI group with SNRI group for change in systolic blood pressure change of short-/long-term duration. Abbreviations: RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

Study or subgroup  | SNRIs  Mean (SD)  | Placebo  Mean (SD)  | Weight (%)  | Mean difference IV, random, 95% CI  | Mean difference IV, random, 95% CI  |
---|---|---|---|---|---|
Short-term treatment  | 12.23 (274)  | 10.65 (273)  | 5.5  | –2.10 (–4.02, –0.18)  |  |
Lenox-Smith and Jiang 2008\(^{19}\)  | 12.56 (205)  | 13.64 (199)  | 4.0  | –0.10 (–2.66, 2.46)  |  |
Oslin et al 2003\(^{23}\)  | 18.74 (17.2)  | 27.28 (27)  | 0.3  | 3.00 (–9.64, 15.64)  |  |
Brent et al 2008\(^{24}\)  | 14.46 (16.8)  | 15.12 (16.6)  | 3.0  | –2.80 (–5.97, 0.37)  |  |
Emilie et al 2014\(^{24}\)  | 9.52 (112)  | 9.22 (105)  | 4.2  | –0.90 (–3.19, 1.39)  |  |
Emilie et al 2014\(^{24}\)  | 9.52 (112)  | 9.61 (114)  | 4.2  | 0.20 (–2.29, 2.69)  |  |
Emilie et al 2015\(^{25}\)  | 8.72 (226)  | 8.93 (332)  | 6.8  | –1.20 (–2.69, 0.29)  |  |
Keller et al 2007\(^{24}\)  | 9.79 (266)  | 11.18 (781)  | 7.0  | –1.50 (–2.91, –0.09)  |  |
Keller et al 2007\(^{24}\)  | 9.52 (185)  | 9.21 (530)  | 6.5  | –3.00 (–4.58, –1.42)  |  |
Detke et al 2004\(^{26}\)  | 12.2 (70)  | 13.6 (70)  | 1.9  | 0.70 (–3.58, 4.98)  |  |
Detke et al 2004\(^{26}\)  | 12.2 (70)  | 12.7 (74)  | 2.1  | –2.10 (–6.17, 1.97)  |  |
Allard et al 2004\(^{26}\)  | 11.2 (75)  | 15.26 (73)  | 1.9  | 2.48 (–1.84, 6.80)  |  |
Perahia et al 2006\(^{27}\)  | 15.15 (24.2)  | 12.6 (70)  | 1.7  | –0.50 (–5.09, 4.09)  |  |
Perahia et al 2006\(^{27}\)  | 15.15 (24.2)  | 13.6 (80)  | 0.1  | 1.80 (–2.81, 6.41)  |  |
Atkinson et al 2014\(^{28}\)  | 10.67 (114)  | 10.63 (113)  | 3.7  | –2.90 (–5.67, –0.13)  |  |
Wade et al 2007\(^{28}\)  | 11.32 (112)  | 10.56 (114)  | 3.5  | –6.20 (–9.06, –3.34)  |  |
Subtotal (95% CI)  | 12.88  | 12.45  | 0.46  | –1.46 (–2.42, –0.49)  |  |
Heterogeneity: $I^2=1.42; \chi^2=25.71, df=14 (P=0.03); I^2=46\%$
Test for overall effect: $Z=2.95 (P=0.003)$

Total (95% CI)  | 3.661  | 5.014  | 100  | –1.50 (–2.15, –0.84)  |  |
Heterogeneity: $I^2=1.08; \chi^2=44.20, df=27 (P=0.02); I^2=39\%$
Test for overall effect: $Z=4.46 (P<0.00001)$
Test for subgroup differences: $\chi^2=0.01, df=1 (P=0.94); I^2=0\%$
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**Table 6.** A forest plot of RCTs comparing SSRi group with SNRi group for change in diastolic blood pressure change of short-/long-term duration.

**Figure 6.** A forest plot of RCTs comparing SSRi group with SNRi group for change in diastolic blood pressure change of short-/long-term duration.

**Abbreviations:** RCTs, randomized controlled trials; SSRi, selective serotonin reuptake inhibitor; SNRi, serotonin and noradrenaline reuptake inhibitor.

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of premature deaths and disabling strokes. Depression and coronary heart disease (CHD) are well known to be associated, and in that case patients may suffer from both diseases and be at higher risk for myocardial infarction. With the existence of the hypothesis that BP can partly explain the association between cardiovascular disease and psychopathology, SSRIs may be more suitable than SNRIs because of improvement in CHD prognosis for depressive patients with CHD.

The included trials recorded office BP, which showed the incapability to reveal the circadian BP rhythm. There is research indicating that even a mildly depressive mood is associated with larger among-day BP variability (BPV). Moreover, BPV is more sensitive in reflecting depression-associated changes of autonomic function as compared to heart rate variability. Prior studies have shown that a higher morning BP surge is positively correlated with depressive symptoms and is associated with stroke risk independently in older hypertensive patients. Low-frequency component of systolic BPV, a surrogate of sympathetic vasomotor tone, can show blunted response with depressive scores, even in the absence of clinically significant alterations in BP, thus acting as a strong predictor of depressive symptoms. In addition, some studies suggest low-frequency component of systolic BPV may be a potential biomarker of neurovascular functioning, contributing to a better understanding of the interaction between MDD and cardiovascular disease. It has been reported that fluvoxamine has a potency to diminish autonomic cardiac activity, and its effect might be partially mediated by changes in BPV.

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### Table 1

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>SSRIs</th>
<th>SNRIs</th>
<th>Weight (%)</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Mean difference IV, random, 95% CI</th>
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<tr>
<td><strong>Age &lt;18 years</strong></td>
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<td>2.8</td>
<td>8.2</td>
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<tr>
<td>Emslie et al 2014</td>
<td>1.7</td>
<td>8.47</td>
<td>112</td>
<td>0.6</td>
<td>8.54</td>
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<tr>
<td>Emslie et al 2015</td>
<td>0.2</td>
<td>7.82</td>
<td>226</td>
<td>1.5</td>
<td>8.02</td>
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<tr>
<td>Atkinson et al 2014</td>
<td>-1.4</td>
<td>8.54</td>
<td>114</td>
<td>1.7</td>
<td>9.57</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>732</td>
<td>683</td>
<td>19.6</td>
<td>-1.84 (-3.86, -0.01)</td>
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Heterogeneity: $t^2=3.23; \chi^2=16.55, df=4 (P=0.002); I^2=76%.

Test for overall effect: $Z=1.97 (P=0.05)$

### Figure 8

A forest plot of RCTs comparing SSRI group with SNRI group for change in diastolic blood pressure change of different ages.

**Abbreviations:** RCTs, randomized controlled trials; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

### Figure 9 (Continued)

A. Begg's funnel plot with pseudo 95% confidence limits

B. Egger's publication bias plot

**Figure 9** (Continued)
on BPV remain scarce, the effect of antidepressants on autonomic nervous system activity is not clear, and relevant study is warranted.

This meta-analysis, however, had some potential limitations. First, the designs of many RCTs met the inclusion criteria, except when the results did not include details about BP; thus, the exclusion of these RCTs and unpublished data may have resulted in bias. Moreover, six included RCTs reported BP changes for different medication doses or durations, and results were all analyzed as an individual trial according to different doses or durations; therefore, overestimation of the treatment effects on BP might happen. Finally, the trials included adults and children or teenagers, and antihypertensive medications were allowed during treatment, which might lead to bias to some extent, although the doses of cardiovascular medication were fixed.

Figure 9 Begg’s test and Egger’s test identified no publication bias. In the group of SSRI versus placebo: Begg’s test: \( Z = 0.33, P = 0.742 \) (A); Egger’s test: \( t = 0.36, P = 0.724 \) (B). In the group of SSRI versus SNRI: Begg’s test: \( Z = 1.19, P = 0.236 \) (C); Egger’s test: \( t = 0.85, P = 0.405 \) (D).

Abbreviations: WMD, weighted mean difference; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor.

A

Meta-analysis estimates, given named study is omitted

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<th>Study</th>
<th>Lower CI limit</th>
<th>Estimate</th>
<th>Upper CI limit</th>
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<td>Glassman et al 2002</td>
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<td>Lesperance et al 2007</td>
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Figure 10 (Continued)
A meta-analysis of effects of antidepressants on blood pressure

**Figure 10** The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of SSRI versus placebo. The pooled WMDs (95% CI) ranged from $-0.19 \ (-0.89, 0.50)$ to $0.10 \ (-0.55, 0.76)$ in systolic blood pressure change (A), and from $-0.01 \ (-0.53, 0.52)$ to $0.19 \ (-0.34, 0.72)$ in diastolic blood pressure change (B), with all showing no statistical significance.

**Notes:** (A) The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of selective serotonin reuptake inhibitor versus placebo in systolic blood pressure change. (B) The sensitivity analysis showed the influence of omitting each study in turn in the meta-analysis of selective serotonin reuptake inhibitor versus placebo in diastolic blood pressure change.

**Abbreviations:** SSRI, selective serotonin reuptake inhibitor; WMDs, weighted mean differences.

**Figure 11** (Continued)
In summary, SSRIs were not established to affect BP fluctuation in depressive patients as a result of their pharmacological characteristics or ameliorating depressive symptoms. SNRIs could result in higher SBP and DBP than SSRIs, although none of them caused sudden substantial BP elevation. While office BP is incapable of reflecting the circadian BP rhythm, future research should be focused on antidepressant medication and BPV.

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Disclosure

The authors report no conflicts of interest in this work.

References


