Somatic monitoring of patients with mood and anxiety disorders

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7

The relative risk for QT(c)-interval prolongation across different classes of antidepressants: a systematic review and meta-analysis

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ABSTRACT

Objective

To investigate the effects of antidepressant classes and individual agents as compared with placebo, as well as the relative risks across antidepressants, on the (absolute or heartrate-corrected) QT-/QTc-interval via meta-analyses of clinical trials.

Data sources

We searched the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE (January 31, 2017), with additional reports identified by scanning the reference lists of selected studies. Search terms were electrocardiography, electrocardiogram, ECG, QT, and QTc, in combination with antidepressants, the names of classes of antidepressants and individual antidepressants, and in combination with randomized controlled trial and controlled clinical trial. No restriction by language or publication date was applied. The protocol for his meta-analysis has been registered in the PROSPERO International prospective register of systematic reviews from the National Institute for Health Research/University of York Centre for Reviews and Dissemination (PROSPERO 2017: CRD42017056531).

Study selection

Two reviewers independently identified prospective clinical trials that reported on QT(c)-change or QT(c)-interval prior to and following administration of antidepressants commonly used in clinical practice versus placebo or versus another antidepressant.

Data extraction and synthesis

Two reviewers independently extracted study-level data including study design (parallel group or crossover), population characteristics, method of QT(c)-measurement, treatment and outcome data, and information for bias assessment and study quality. Differences between antidepressants and/or placebo were expressed as Hedges' *g* and pooled using random effects models. The impact of heterogeneity between studies was assessed using I^2 and fixed effects models were presented if I^2 was less than 50%. Publication bias was assessed by testing funnel plot asymmetry, reporting the Begg & Mazumdar rank correlation and Egger's regression intercept.

Results

Sixty-one articles involving 20,433 subjects were included. Pooled TCA results were indicative of prolongation of QT(c)-interval versus placebo (SMD=0.47; 95%CI: 0.04 - 0.91), although none of the individual TCAs showed significantly increased QT(c) prolongation. SSRIs showed a small but significant increase in QT(c)-interval relative to placebo (SMD=0.17; 95%CI: 0.08 - 0.27). Of the individual SSRIs, only escitalopram

significantly differed from placebo (SMD=0.21; 95%CI: 0.10 - 0.33). For SNRIs, no significant differences in QT(c)-prolongation were found for either the class (SMD= -0.01; 95%CI: -0.15 - 0.13) or the individual antidepressants. Likewise, no significant differences in QT(c) prolongation were found for either the group of mianserin, reboxetine, trazodone, vilazodone and vortioxetine (SMD=0.00; 95%CI: -0.04 - 0.04) or the individual agents. Monoamine oxidase inhibitors (MAOIs; phenelzine only) resulted in a shorter QT(c) than placebo (SMD=-0.60; 95%CI: -1.12 - -0.09). Direct comparisons between antidepressants were in fewer patients and revealed significant prolongation for primarily TCA versus other agents of the same or different classes.

Conclusions

We conclude that, in therapeutic dose, TCAs have a moderate and SSRIs a small prolonging effect on QT(c)-interval, whereas SNRIs, MAOIs, or other antidepressants do not have a QT-c prolonging effect. Within the SSRI class, escitalopram has a small but significant effect on QT(c); within the TCA-class no specific drug could be identified to account for the significant overall-effect. This information is important for clinicians when considering prescribing antidepressants, especially in subjects already at risk for QT(c)-prolongation.

INTRODUCTION

Delayed cardiac repolarization as measured by an electrocardiogram's prolonged QT interval has been linked to an increased risk of ventricular arrhythmias, and especially Torsades de Pointes (TdP). Because of its inverse relationship to heart rate, the measured QT-interval is routinely corrected to a heart-rate-independent value known as the QTc-interval. QT(c)-prolongation can lead to ventricular fibrillation and sudden cardiac death.[1] The absolute risk of cardiac arrhythmias such as TdP is generally low (14 per 10,000 patients over 1 year; 95% confidence interval (CI) 11-17/10,000) and sudden cardiac death occurs even more rarely.[1] However, apart from demographic characteristics and somatic conditions, medications may augment the risk for these severe outcomes.[2,3]

In patients admitted to psychiatric hospitals, the prevalence of long QT(c)-interval has been estimated to be 1.6%, and that of drug-induced QT(c)-prolongation 0.9%.[4] Although antipsychotics have the largest potential for sudden cardiac death due to ventricular arrhythmias (2.9 incident cases per 1000 patient years)[5], some antidepressants have proven to prolong the QT(c)-interval as well.

However, the current evidence regarding QT(c)-prolongation induced by antidepressants is often conflicting. One previous meta-analysis showed that significant QT(c)-prolongation was induced by tricyclic antidepressants (TCA; i.e. amitriptyline, doxepin, nortriptyline) as compared with selective serotonin reuptake inhibitors (SSRI), and by some individual SSRIs (i.e. citalopram, escitalopram, sertraline) as compared with placebo.[6] A large cross-sectional study additionally found dose-response associations between the use of amitriptyline, citalopram and escitalopram and QT(c)-prolongation.[7] The use of other commonly prescribed antidepressants – including nortriptyline and sertraline – was not associated with QT(c)-prolongation in this study.[7] A recent review of non-SSRIs stated that overdose situations with venlafaxine and bupropion constitute the highest risk for QT(c)-prolongation, and that current literature is insufficient to draw conclusions on many of the other antidepressants.[8] In contrast, a cross-sectional study based on electronic health records showed an inverse dose-response relationship for bupropion and QT(c)-durations.[7] In addition, QT(c)-shortening as compared with placebo has been reported for fluvoxamine and duloxetine.[6,9] Moreover, existing reviews on antidepressant-induced QT(c)-prolongation are limited by focus on a particular class or an individual antidepressant, or contain outdated searches or an insufficient systematic approach.

In the current systematic review, we therefore will meta-analyse all available clinical trial data concerning the QT(c)-effects of all commonly prescribed antidepressants. We aimed to investigate the effects of different antidepressant classes and individual antidepressants on the absolute or heartrate-corrected QT(c)-interval as compared with placebo as well as the relative risks across antidepressants.

METHODS

This meta-analysis has been registered in the PROSPERO International prospective register of systematic reviews from the National Institute for Health Research/University of York Centre for Reviews and Dissemination (PROSPERO 2017: CRD42017056531).[10]

Data sources and searches

The Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE were searched systematically. The exact search strategies are described in the PROSPERO registration.[10] In short, in all searches (performed until January 31st, 2017) we used the following terms: electrocardiography, electrocardiogram, ECG, and QT, in combination with antidepressants, the names of classes of antidepressants and individual antidepressants, combined with terms for (randomized) controlled trial. We also searched reference lists of selected studies for cross-references.

Study selection

Two reviewers (M.S. and A.S.) independently performed the study selection, with discrepancies resolved through discussion or a third opinion (H.G.R.). For eligibility, studies had to be clinical trials (not necessarily randomized), of the parallel or crossover type, blinded or open-label. We identified studies of antidepressant drugs commonly used in clinical psychiatric practice and belonging to the following classes: tricyclic antidepressants (TCAs; amitriptyline, clomipramine, desipramine, dothiepin/dosulepin, doxepin, imipramine, lofepramine, maprotiline, nortriptyline, trimipramine), selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), selective noradrenalin reuptake inhibitors (SNRIs; desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine), mono-amine oxidase inhibitors (MAOIs; moclobemide, phenelzine, selegiline, tranylcypromine), and other antidepressants (agomelatine, bupropion, hyperforin, hypericum/st John's wort, mianserin, mirtazapine, nefazodone, reboxetine tianeptine, trazodone, vilazodone, vortioxetine). Grey literature, e.g. conference abstracts, was eligible for inclusion as well. We applied no restrictions by language or publication date. Eligible studies were included if change in QT(c)-interval following administration of an antidepressant versus placebo or versus another antidepressant was investigated. For inclusion in the meta-analyses, studies should report the prospective QT(c)-change in a way that these could be pooled in the meta-analysis, e.g. show appropriate statistical information, and/or provide these outcomes on request. QT data could be either uncorrected or heart rate-corrected. Populations could be either healthy volunteers or patients with a physical and/or mental condition for which antidepressants are indicated. We excluded overdose or intoxication studies, and (to avoid interaction effects) studies that investigated antidepressants as add-on treatments, e.g. with antipsychotics.

Data extraction

For the articles that met the inclusion criteria, the following data were extracted: study design (parallel group/crossover), setting, study population, method of ECG monitoring, QT-correction formula (preferably Fridericia, then Bazett, then another formula[11]), details of the intervention and control conditions, type of outcomes, times of measurement, information for quality assessment and risk of bias (see below). For quantitative data-synthesis, for each intervention arm, we extracted the number of subjects, the pre- and post QT(c) measurements and their standard deviation (SD) or standard error (SE). If available, we also extracted the difference in QT(c) - change±SD between intervention arms. Data extraction was performed by two independent reviewers (M.S. and A.S.) and discrepancies were resolved by consensus or a third opinion (H.G.R.). If specific data were not available, study authors were contacted and reminded once.

Bias assessment

The methodological quality of the included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias.[12] The assessment covered random sequence generation, allocation concealment, blinding participants/personnel, blinding of outcome assessment, completeness of outcome data and selective reporting. Each of these was explicitly rated and graded as being of low, high or uncertain risk of bias. Assessment of risk of bias was performed by two independent reviewers (M.S. and A.S.), who resolved discrepancies by consensus or a third opinion (P.R.B/H.G.R.).

Statistical analyses

All analyses were carried out in R (version 3.5.0) using the 'metafor' package.[13] We calculated Hedges' *g* and its SE (representing a standardized mean difference (SMD) of QT(c)-change between interventions), based on mean differences for QT(c) change per intervention arm[14], and calculated 95% confidence intervals (CIs) and two-sided *p* values. Positive values indicate that QT(c) increased in the antidepressant group versus the control group, whereas negative values indicate that QT(c) decreased in the antidepressant versus control group. Effect sizes of 0.2 to 0.5 can be interpreted as small, 0.5 to 0.8 as moderate, and greater than 0.8 as large effects. If the SMD between interventions and/or per intervention arm were not given, we calculated the pre-post changes and SE of the effect size estimates in each intervention arm under the assumption of a pre-test post-test correlation: r=0.5.

For crossover designs, we captured the paired nature of these observations with an adapted formula for Hedges' *g*.[14] Although crossover designs methodologically might better be pooled separately, given their limited number and the adaptation of the calculation of Hedges' *g*, we chose to pool the crossover studies together with the majority of parallel group designed studies and secondarily perform a sensitivity-analysis.

We estimated the pooled effect sizes based on a random effects model, using restricted maximum-likelihood (REML) estimation to estimate the amount of heterogeneity in the effect sizes.[15] We investigated evidence for heterogeneity between studies using the chi-squared test and quantified the impact of any heterogeneity using I^2.[14] If I^2 was <50% we also report the fixed effects pooled estimate. We further explored heterogeneity using meta-regression to evaluate the effects of antidepressant heartrate correction formulae (Fridericia/Bazett/other/no correction) and age. Publication bias was assessed by testing funnel plot asymmetry, reporting the Begg & Mazumdar rank correlation and Egger's regression intercept. For meta-analyses with 10 or fewer studies, we did not make funnel plots because the power would be too low to distinguish chance from real asymmetry.[16]

We performed sensitivity analyses to assess the influence of our assumptions of r=0.5 between pre- and post-measurements, inclusion of crossover design and risk of bias. If the SMD between interventions, and/or per intervention arm were not given, we calculated the pre-post changes and SE of the effect size estimates in each intervention arm under the assumption of a pre-test post-test correlation of 0.5. Studies with complete data showed a pre-test post-test correlation range of 0.4 to 1.0. We therefore repeated our analyses with an assumed correlation of 0.4 and 0.8. In addition, we performed sensitivity analyses without studies with a crossover design, or studies with considerable (upper 25%) risk of bias.

RESULTS

Study identification and selection

Our systematic searches identified 1479 records. In total we selected 61 studies involving in total 20.433 subjects.[17-76] A list of excluded studies is available on request. Figure 1 illustrates the study retrieval and selection strategy.

Study characteristics

Table 1 shows the characteristics of the selected studies. Sample sizes ranged from n=8[30] to n=6886.[75] Fifty-seven studies were double-blind[17-31,33-35,37-39,41-46,48-76], one was single-blind[32], two were open-label[36,40], and one had a blinded electrocardiogram reading.[47] Seven studies had a crossover design, and the remaining fifty-four studies had a parallel design (including 50 placebo-controlled and 39 antidepressant-controlled comparisons). The duration of the studies ranged from 7 days to 27 weeks, with a median duration of 6 weeks.

With respect to the included populations, all but three[33,34,51] of the studies were based on both male and female participants. Fifty-five studies were done in adult populations[23-76] and six in children or adolescents.[17-22] Five studies included healthy subjects, whereas in other studies antidepressants were used in depressive disorder (72%), general or social anxiety disorder (7%), fibromyalgia (5%), obsessive-compulsive disorder (3%), panic

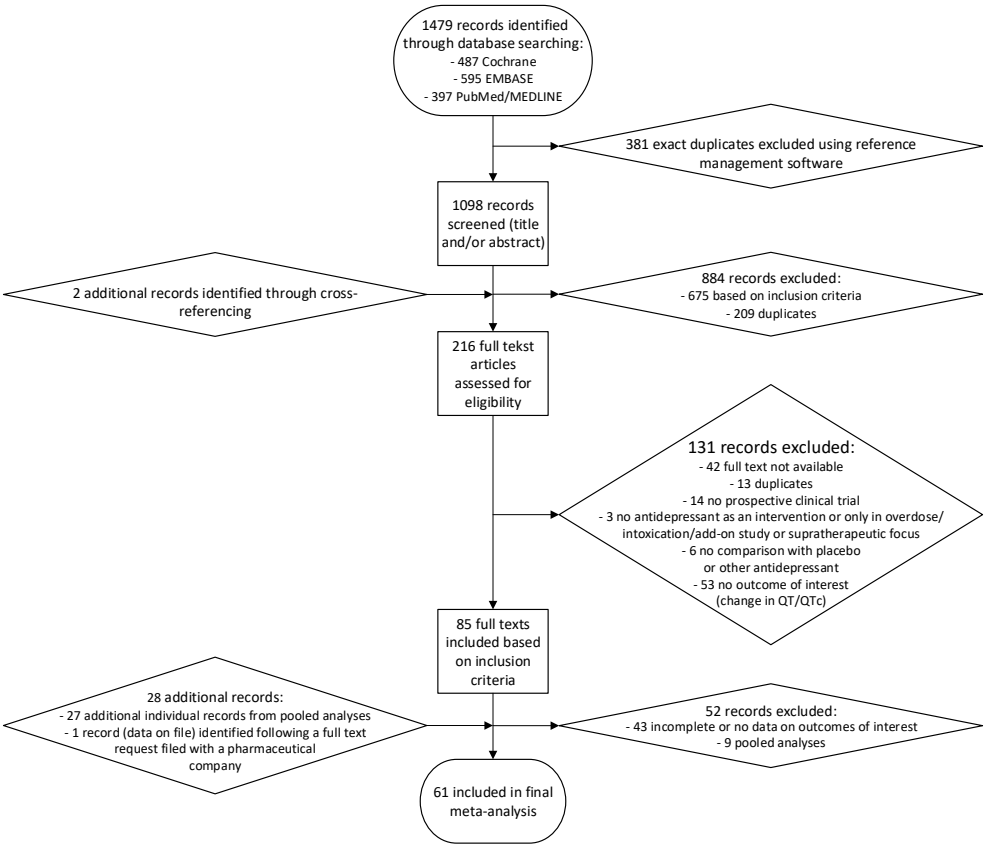


Figure 1. Flow chart of study inclusion for the meta-analysis

disorder (2%), seasonal affective disorder (2%), agitation in possible Alzheimer's disease (2%), or functional gastrointestinal disorders (2%).

QT(c)-effects in antidepressants versus placebo

Figure 2 illustrates the pooled results of comparisons of the pre-post differences in QT(c) change scores between antidepressants and placebo, involving in total 18.533 subjects (for details see Supplemental table 1).

Pooled TCA results (Figure 2A) were indicative of significantly prolonged QT(c)-intervals versus placebo (SMD=0.47; 95%CI: 0.04 - 0.91; seven studies, total n=195 subjects). Of the individual TCA comparisons, none of the antidepressants showed significantly increased QT(c) prolongation as compared with placebo. No comparisons with placebo were found for clomipramine, desipramine, dothiepin/dosulepin, lofepramine, or trimipramine.

Pooled SSRI results (Figure 2B) showed significantly more QT(c) prolongation for SSRI than for placebo (SMD=0.17; 95%CI: 0.08 - 0.27; sixteen studies, total n=6.631 subjects).

Of the individual SSRI, only escitalopram significantly differed from placebo (SMD=0.21; 95%CI: 0.10 - 0.33).

Pooled SNRI results (Figure 2C) showed no significant differences in QT(c) prolongation for either the class (SMD=-0.01; 95%CI: -0.15 - 0.13; eight studies, total=6.771 subjects) or the individual antidepressants as compared with placebo. None of the included studies showed a placebo-comparison for desvenlafaxine or milnacipran.

Pooled MAOI results are shown in Figure 2D. In two studies (total n=66 subjects) comparing MAOI to placebo, phenelzine resulted in a shorter QT(c) than placebo (SMD=-0.60; 95%CI: -1.12- -0.09). No comparisons with placebo were found for moclobemide, selegiline, or tranylcypromine.

In pooled data from the 'other' antidepressants (Figure 2E), no significant differences in QT(c) prolongation were found for either this remaining group in total (SMD=-0.00; 95%CI: -0.05 - 0.04; six studies, total n=6.905 subjects) or its individual agents versus placebo. None of the included studies showed a placebo-comparison for agomelatine, bupropion, hyperforin, hypericum/st John's wort, mirtazapine, nefazodone or tianeptine.

Heterogeneity

All placebo comparisons except for the two MAOI studies (I^2=6.8%) showed substantial heterogeneity between studies (all I^2>50%), indicating that random effects models were most appropriate. Fixed effects model estimates for MAOI vs. placebo were -0.60 (SMD); 95%CI -1.10 - -0.10).

Heterogeneity based on the use of (different) QT-correction formulae was investigated for all placebo comparisons for antidepressant classes. Meta-regression analyses revealed a significant QT-correction effect in the class of SNRI (p<0.01). The Bazett correction formula used by one study (3 comparisons)[54] resulted in a significantly increased QT(c) prolongation risk as compared to eight other SNRI studies using Fridericia correction. Exclusion of this study substantially changed the Hedge's *g* of SNRI versus placebo from SMD=-0.01 (95%CI: -0.15 - 0.13) to SMD=-0.10 (95%CI: -0.18 - -0.02), indicative of significant more QT(c)-shortening than placebo. None of the other classes revealed a significant effect for the QT-correction formula used.

The potentially different effects of antidepressant classes on QT(c) by age could not be analysed by meta-regression, because the number of studies in children/adolescents or elderly was too small. Visual inspection of the data did not suggest an extra increase in risk of QT(c) prolongation in children/adolescents (amitriptyline, duloxetine, fluoxetine)[17,20-22] or elderly (citalopram, duloxetine).[27,50]

QT(c)-effects compared between antidepressants

Table 2 shows, within and across classes of antidepressants, the direct comparisons between antidepressants with respect to the pre-post change in QT(c) interval, involving in total 8,076 subjects. The following antidepressants showed statistically significant

Table 1. Characteristics of the studies included in the meta-analyses[17-76]

Source	Design	Study type	Blinding	Duration, weeks (unless otherwise specified)	Population/ antidepressant indication	Sex	Presence of cardiac disease	Active medication	Active medication, dose, mg (unless otherwise specified)
Asnis et al. 2013	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No current cardiac disease	levomilnacipran	40/80/120
Atkinson et al. 2014	RCT	Parallel	Double-blind	10	Depressive disorder	Mixed	No current cardiac disease	duloxetine	90.6
Badyal et al. 2006	RCT	Parallel	Open-label	6	Depressive disorder	Mixed	No current cardiac disease	duloxetine	40-120
Baker et al. 1997	RCT	Parallel	Double-blind	6	Depressive disorder	Mixed	No current cardiac disease	fluoxetine	37
Bakish et al. 2014	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No current cardiac disease	levomilnacipran	40/80
Burgess et al. 1979	CT	Cross-over	Double-blind	4-6	Depressive disorder	Mixed	No current cardiac disease	amitriptyline	150
Chogle and Saps 2014	RCT	Parallel	Double-blind	>1 month	Functional abdominal pain/ dyspepsia/ IBS	Mixed	No restrictions for cardiac disease	amitriptyline	10-20
Chappell et al. 2008	RCT	Parallel	Double-blind	27	Fibromyalgia	Mixed	No current cardiac disease	From Choy et al. 2009: duloxetine	From Choy et al. 2009: 20-120
Russell et al. 2008	RCT	Parallel	Double-blind	6 months	Fibromyalgia	Mixed	No restrictions for cardiac disease		
Arnold et al. 2004	RCT	Parallel	Double-blind	12	Fibromyalgia	Mixed	No current cardiac disease		
Cournoyer et al. 1987	RCT	Parallel	Double-blind	3	Depressive disorder	Mixed	No current cardiac disease	trimipramine	200
Czekalla et al. 1997	RCT	Parallel	Double-blind	6	Depressive disorder	Mixed	No restrictions for cardiac disease	hypericum extract	1800

Active medication, n	Control medication	Control medication, dose, mg (unless otherwise specified)	Control medication, n	Age, years (range or mean(±SD) unless otherwise specified)	ECG-method	QTc-correction formula	Funding	Bias rating, no. of low risk: unclear risk: high risk
130/121/117	placebo	N/A	138	41.6±13.1 (levomilnacipran 40 mg), 41.0±12.8 (levomilnacipran 80 mg), 40.3±11,9 (levomilnacipran 120 mg), 41.3±11.3 (placebo)	12-lead ECG	Bazett	Forest Laboratories	3:2:1
93	fluoxetine placebo	33.9 N/A	92 87	Median 13.5	Not reported	Fridericia	Eli Lilly	4:1:1
13	venlafaxine	75-225	13	42	Not reported	Not reported	Torrent Pharmaceuticals	3:2:1
20	doxepine	169	19	40 (doxepine), 45 (fluoxetine	12-lead ECG	Bazett	Eli Lilly	4:2:0:
176/180	placebo	N/A	176	18-75	12-lead ECG	Fridericia	Forest Laboratories	5:1:0
6	mianserin	60	8	24-61	High speed ECG	Bazett	Organon Laboratories	4:1:1
12	placebo	N/A	18	9-17	12-lead ECG	Not reported	None reported	3:3:0
From Choy et al. 2009: 876	From Choy et al. 2009: placebo	From Choy et al. 2009: N/A	From Choy et al. 2009: 535	50.5±10.7	Not reported	No correction (QT)	Eli Lilly and Boehringer Ingelheim	4:1:1
				51	Not reported	Fridericia	Eli Lilly and Boehringer Ingelheim	5:1:0
				49.9±12.3 (duloxetine), 48.3±11.3 (placebo)	Not reported	Fridericia	Eli Lilly	5:1:0
17	amitriptyline	200	16	26-72	Not reported	No correction (QT)	None reported	5:1:0
84	imipramine	150	76	25-70	Not reported	Bazett	None reported	3:3:0

Table 1. (continued)

Source	Design	Study type	Blinding	Duration, weeks (unless otherwise specified)	Population/ antidepressant indication	Sex	Presence of cardiac disease	Active medication	Active medication, dose, mg (unless otherwise specified)
Drye et al. 2014	RCT	Parallel	Double-blind	3	Probable Alzheimer's disease and clinically significant agitation	Mixed	No restrictions for cardiac disease	citalopram	30
Edwards and Goldie 1983	RCT	Parallel	Double-blind	4	Depressive disorder	Mixed	No current cardiac disease	mianserin	90
Edwards et al. 1989	RCT	Parallel	Double-blind	4	Depressive disorder	Mixed	No current cardiac disease	paroxetine	30
Emslie et al. 2014	RCT	Parallel	Double-blind	10	Depressive disorder	Mixed	No current cardiac disease	duloxetine	30/60
Evans and Cox 1981	RCT	Parallel	Double-blind	4	Depressive disorder	Mixed	No restrictions for cardiac disease	dothiepin	150
FDA citalopram, 2011	RCT	Cross-over	Double-blind	9 days (20 mg), 22 days (60 mg)	Healthy subjects	Unknown	No current cardiac disease	citalopram	20/60
FDA escitalopram, 2011	RCT	Cross-over	Double-blind	9 days (10 mg), 22 days (30 mg)	Healthy subjects	Unknown	No current cardiac disease	escitalopram	10/30
Fleishaker et al. 2001	RCT	Cross-over	Open-label	1	Healthy subjects	Mixed	No restrictions for cardiac disease	reboxetine	4/8/12
Georgotas et al. 1987	RCT	Parallel	Double-blind	7	Depressive disorder	Mixed	No restrictions for cardiac disease	nortriptyline	83-96 ng/ml plasma level
Glassman et al. 2002	RCT	Parallel	Double-blind	24	Depressive disorder	Mixed	Current cardiac disease	sertraline	50-200

Active medication, n	Control medication	Control medication, dose, mg (unless otherwise specified)	Control medication, n	Age, years (range or mean(±SD) unless otherwise specified)	ECG-method	QTc-correction formula	Funding	Bias rating, no. of low risk: unclear risk: high risk
22	placebo	N/A	22	75±9	Not reported	Not reported	National Institute on Aging and National Institute of Mental Health	5:1:0
11	maprotiline placebo	150-225 N/A	10 13	43 (mianserin), 35 (maprotiline), 42 (placebo)	High speed ECG	Bazett	None reported	5:1:0
11	placebo	N/A	9	22-62	High speed ECG	Bazett	Beecham Pharmaceuticals	5:1:0
85/78	fluoxetine placebo	20 N/A	79 88	Median 13.2	Not reported	Fridericia	Eli Lilly	4:1:1
14	doxepine	150	14	16-75	Not reported	Not reported	Boots	3:3:0
119/119	placebo	N/A	119	31.5	12-lead ECG	Individual correction	Forest Pharmaceuticals	2:4:0
120/120	placebo	N/A	120	27.3	12-lead ECG	Individual correction	Forest Pharmaceuticals	2:4:0
20/20/20	placebo	N/A	20	24-54	12-lead ECG	Fridericia	None reported	4:1:1
16	phenelzine placebo	74-81% MAO inhibition N/A	14 14	55-82	Not reported	Not reported	National Institute of Mental Health	4:2:0
159	placebo	N/A	157	57	12-lead ECG	Not reported	Pfizer, Suzanne C. Murphy Foundation, Thomas and Caroline Royster Research Fund, Perry and Martin Granoff Family Foundation	3:3:0

Table 1. (continued)

Source	Design	Study type	Blinding	Duration, weeks (unless otherwise specified)	Population/ antidepressant indication	Sex	Presence of cardiac disease	Active medication	Active medication, dose, mg (unless otherwise specified)
Hanash et al. 2012	RCT	Parallel	Double-blind	52	Prophylaxis for depression	Mixed	Current cardiac disease	escitalopram	10
Hewer et al. 1995	CT	Parallel	Double-blind	3	Depressive disorder	Mixed	No current cardiac disease	fluvoxamine	200
Kim et al. 2015	RCT	Parallel	Double-blind	24	Depressive disorder	Mixed	Current cardiac disease	escitalopram	5-20
Kuhs and Rudolf 1990	RCT	Parallel	Double-blind	6	Depressive disorder	Mixed	No current cardiac disease	paroxetine	30
Lader et al. 2004	RCT	Parallel	Double-blind	24	SAD	Mixed	No restrictions for cardiac disease	escitalopram	5-20
Laird et al. 1993	RCT	Parallel	Double-blind	6	Depressive disorder	Mixed	No restrictions for cardiac disease	imipramine	180
Flament et al. 1985	RCT	Cross-over	Double-blind	5	OCD	Mixed	No restrictions for cardiac disease	From Leonard et al. 1995: desipramine	From Leonard et al. 1995: 75-250

Active medication, n	Control medication	Control medication, dose, mg (unless otherwise specified)	Control medication, n	Age, years (range or mean(±SD) unless otherwise specified)	ECG-method	QTc-correction formula	Funding	Bias rating, no. of low risk: unclear risk: high risk
80	placebo	N/A	78	65.3±12.1 (escitalopram), 64.2±12.2 (placebo)	12-lead ECG	Bazett	Danish Heart Foundation, Danish Medical Research Council and Lundbeck	5:1:0
18	maprotiline	200	15	20-65	12-lead ECG	Bazett	None reported	3:2:1
91	placebo	N/A	86	59.3±10.8	Not reported	Not reported	Lundbeck, Korea Health 21 R&D, Ministry of Health and Welfare Republic of Korea and Basic Science Research Program through the National Research Foundation of Korea (KRF) funded by the Ministry of Science, ICT and Future Planning	6:0:0
14	amitriptyline	150	17	41±12	Not reported	Bazett	None reported	4:1:1
499	placebo	N/A	163	18-65	Not reported	Fridericia	Lundbeck	2:3:1
14	fluvoxamine placebo	240 N/A	17 15	23-81	12-lead ECG	Not reported	Kali-Duphar Laboratories	4:2:0
From Leonard et al. 1995: 39	From Leonard et al. 1995: clomipramine	From Leonard et al. 1995: 68-250	From Leonard et al. 1995: 47	10-18	Not reported	Bazett	National Institute of Mental Health	3:3:0

Table 1. (continued)

Source	Design	Study type	Blinding	Duration, weeks (unless otherwise specified)	Population/ antidepressant indication	Sex	Presence of cardiac disease	Active medication	Active medication, dose, mg (unless otherwise specified)
Leonard et al. 1989	RCT	Cross-over	Double-blind	5	OCD	Mixed	No restrictions for cardiac disease		
Lundbeck Takeda pooled data (unpublished)	RCT	Parallel	Unknown	8	Depressive disorder or GAD (not both)	Mixed	No current cardiac disease	vortioxetine	1-20
Rickels et al. 2009	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No current cardiac disease	From Liebowitz et al. 2011: vilazodone	From Liebowitz et al. 2011: 40
Khan et al. 2011	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No current cardiac disease		
McGrath et al. 1987	CT	Parallel	Blinded-ECG	6	Depressive disorder	Mixed	No current cardiac disease	phenelzine amitriptyline	75 220
Van de Merwe et al. 1984	RCT	Parallel	Double-blind	4	Depressive disorder	Mixed	No current cardiac disease	trazodone	223
Montgomery et al. 2013	RCT	Parallel	Double-blind	10	Depressive disorder	Mixed	No current cardiac disease	levomilnacipran	75-100
Nair et al. 1993	RCT	Parallel	Double-blind	5	Depressive disorder	Mixed	No current cardiac disease	trimipramine	139-144
Nelson et al. 2006	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No current cardiac disease	duloxetine	40-120
Nilsson et al. 2004	RCT	Parallel	Double-blind	19	Depressive disorder	Mixed	No current cardiac disease	fluoxetine	20-60
O'Brien et al. 1991	RCT	Parallel	Single-blind	6	Depressive disorder	Mixed	No restrictions for cardiac disease	tranylcypromine	22

Active medication, n	Control medication	Control medication, dose, mg (unless otherwise specified)	Control medication, n	Age, years (range or mean(±SD) unless otherwise specified)	ECG-method	QTc-correction formula	Funding	Bias rating, no. of low risk: unclear risk: high risk
				7-19	Not reported	Bazett	National Institute of Mental Health	4:2:0
3863	venlafaxine duloxetine placebo	unknown unknown N/A	109 831 2083	45.9±13.7 (overall)	12-lead ECG	Fridericia	Lundbeck/ Takeda	0:6:0
From Liebowitz et al. 2011: 436	From Liebowitz et al. 2011: placebo	From Liebowitz et al. 2011: N/A	From Liebowitz et al. 2011: 433	18-63	12-lead ECG	Fridericia	Clinical Data, PGxHealth Division	4:2:0
				18-70	12-lead ECG	Fridericia	Clinical Data, PGxHealth Division	4:2:0
22 11	imipramine mianserin placebo	248 143 N/A	23 21 16	41±11	Limb lead electrocardiograms	Not reported	None reported	3:1:2
6	amitriptyline placebo	95 N/A	5 3	20-61	High speed ECG	Bazett	None reported	3:3:0
278	placebo	N/A	279	44 (levomilnacipran), 45 (placebo)	Not reported	Fridericia	Forest Research Institute, a subsidiary of Forest Laboratories and Pierre Fabre Médicament	5:1:0
18	doxepine	125-138	17	68.6±5.1 (trimipramine), 71.1±4.1 (doxepine)	12-lead ECG	Not reported	Rhone-Poulenc Rorer Canada	3:3:0
736	paroxetine	20	359	43.2±12.2	Not reported	Not reported	Eli Lilly	3:2:1
88	placebo	N/A	73	9-17	12-lead ECG	Fridericia	Eli Lilly	3:3:0
18	amitriptyline	136	18	18-64	12-lead ECG	Linear regression equation	Aware	4:2:0

Table 1. (continued)

Source	Design	Study type	Blinding	Duration, weeks (unless otherwise specified)	Population/ antidepressant indication	Sex	Presence of cardiac disease	Active medication	Active medication, dose, mg (unless otherwise specified)
Pohl et al. 2003	RCT	Parallel	Double-blind	8	Healthy subjects	Mixed	No current cardiac disease	fluoxetine	20
Raskin et al. 2008	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No current cardiac disease	duloxetine	60
Feighner and Overø 1999	RCT	Parallel	Double-blind	6	Depressive disorder	Mixed	No current cardiac disease	From Rasmussen et al. 1999: citalopram	From Rasmussen et al. 1999: 10/20/40/60
Bougerol et al. 1997	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No current cardiac disease		
Robinson and Doogan 1982	RCT	Cross-over	Double-blind	9 days	Healthy subjects	Male	No current cardiac disease	fluvoxamine	50
Robinson et al. 1982	CT	Parallel	Double-blind	6	Depressive disorder	Mixed	No current cardiac disease	phenelzine	60
Roose et al. 1998	RCT	Parallel	Double-blind	6	Depressive disorder	Mixed	Current cardiac disease	paroxetine	22
Burke et al. 2002	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No restrictions for cardiac disease	From Thase et al. 2013: escitalopram	From Thase et al. 2013: 10-20
Rapaport et al. 2004	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No restrictions for cardiac disease		
Wade et al. 2002	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No current cardiac disease		
Lepola et al. 2003	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No restrictions for cardiac disease		
Bose et al. 2008	RCT	Parallel	Double-blind	8	GAD	Mixed	No current cardiac disease		

Active medication, n	Control medication	Control medication, dose, mg (unless otherwise specified)	Control medication, n	Age, years (range or mean(±SD) unless otherwise specified)	ECG-method	QTc-correction formula	Funding	Bias rating, no. of low risk: unclear risk: high risk
6	placebo	N/A	7	32.6±9,8 (fluoxetine), 28.2±5.0 (placebo)	24-hour holter ECG	No correction (QT)	None reported	4:2:0
207	placebo	N/A	104	65-90	Not reported	Fridericia	Eli Lilly and Boehringer Ingelheim	3:3:0
From Rasmussen et al. 1999: 144/149/ 254 /113	From Rasmussen et al. 1999: fluoxetine Placebo	From Rasmussen et al. 1999: 20 N/A	From Rasmussen et al. 1999: 100 146	18-65	Not reported	Bazett	Lundbeck	3:2:1
				19-73	Not reported	Bazett	Lundbeck	5:1:0
25	placebo	N/A	25	40-60	24-hour holter ECG	Bazett	Duphas	5:1:0
45	amitriptyline	150	39	19-67	12-lead ECG	Not reported	National Institute of Mental Health	3:2:1
37	nortriptyline	40-220 ng/ml plasma level	26	58±11 (paroxetine), 58±13 (nortriptyline)	12-lead ECG	Not reported	Smith-Kline Beecham Pharmaceuticals	4:1:1
From Thase et al. 2013: 1839	From Thase et al. 2013: placebo	From Thase et al. 2013: N/A	From Thase et al. 2013: 1707	40.7±12.3 (escitalopram 10 mg), 39.6±12.0 (escitalopram 20 mg), 41.1±10.6 (placebo)	Not reported	Fridericia	Forest Pharmaceuticals	4:2:0
				18-81	Not reported	Fridericia	Forest Laboratories	3:3:0
				18-65	Not reported	Fridericia	Lundbeck	4:2:0
				43±11 (escitalopram), 43±12 (placebo)	Not reported	Fridericia	Lundbeck	4:2:0
				37.6±11.5	Not reported	Fridericia	None reported	4:2:0

Table 1. (continued)

Source	Design	Study type	Blinding	Duration, weeks (unless otherwise specified)	Population/ antidepressant indication	Sex	Presence of cardiac disease	Active medication	Active medication, dose, mg (unless otherwise specified)
Kasper et al. 2005a	RCT	Parallel	Double-blind	8	Depressive disorder	Mixed	No restrictions for cardiac disease		
Goodman et al. 2005	RCT	Parallel	Double-blind	8	GAD	Mixed	No restrictions for cardiac disease		
Stahl et al. 2004	RCT	Parallel	Double-blind	10	Panic disorder (with or without agoraphobia)	Mixed	No current cardiac disease		
Kasper et al. 2005b	RCT	Parallel	Double-blind	12	GSAD	Mixed	No current cardiac disease		
Upward et al. 1988	RCT	Parallel	Double-blind	4	Depressive disorder	Mixed	No current cardiac disease	fluoxetine	60-80
Veith et al. 1982a	RCT	Parallel	Double-blind	3	Depressive disorder	Mixed	No current cardiac disease	desipramine	200
Veith et al. 1982b	RCT	Parallel	Double-blind	4	Depressive disorder	Male	Current cardiac disease	imipramine	129
Wenger et al. 1983	CT	Parallel	Double-blind	6	Depressive disorder	Male	No restrictions for cardiac disease	bupropion	552
White et al. 1983	RCT	Parallel	Double-blind	4	Depressive disorder	Mixed	No current cardiac disease	tranylcypromine	36

RCT randomized clinical trial; CT clinical trial (non-randomized); IBS irritable bowel syndrome; GAD generalized anxiety disorder; SAD social anxiety disorder; GSAD generalized social anxiety disorder; OCD obsessive compulsive disorder; SD standard deviation; ECG electrocardiogram; QTc heart rate-corrected QT-interval.

Active medication, n	Control medication	Control medication, dose, mg (unless otherwise specified)	Control medication, n	Age, years (range or mean(±SD) unless otherwise specified)	ECG-method	QTc-correction formula	Funding	Bias rating, no. of low risk: unclear risk: high risk
				65-93	12-lead ECG	Fridericia	None reported	4:1:1
				18-80	12-lead ECG	Fridericia	Forest Laboratories	3:2:1
				18-80	Not reported	Fridericia	Forest Laboratories	3:2:1
				38±11	Not reported	Fridericia	Lundbeck	3:1:2
11	amitriptyline	150-200	12	24-63	High speed ECG	Bazett	Lilly Industries	3:2:1
26	amitriptyline	200	20	19-58	12-lead ECG	Not reported	None reported	4:2:0
8	doxepine placebo	153 N/A	9 8	39-74	12-lead ECG	Not reported	None reported	5:1:0
23	amitriptyline	151	23	50 (bupropion), 39 (amitriptyline)	ECG on rhythm strips	Not reported	None reported	4:1:1
10	amitriptyline	250	12	22-57	Not reported	Not reported	National Institute of Mental Health	4:2:0

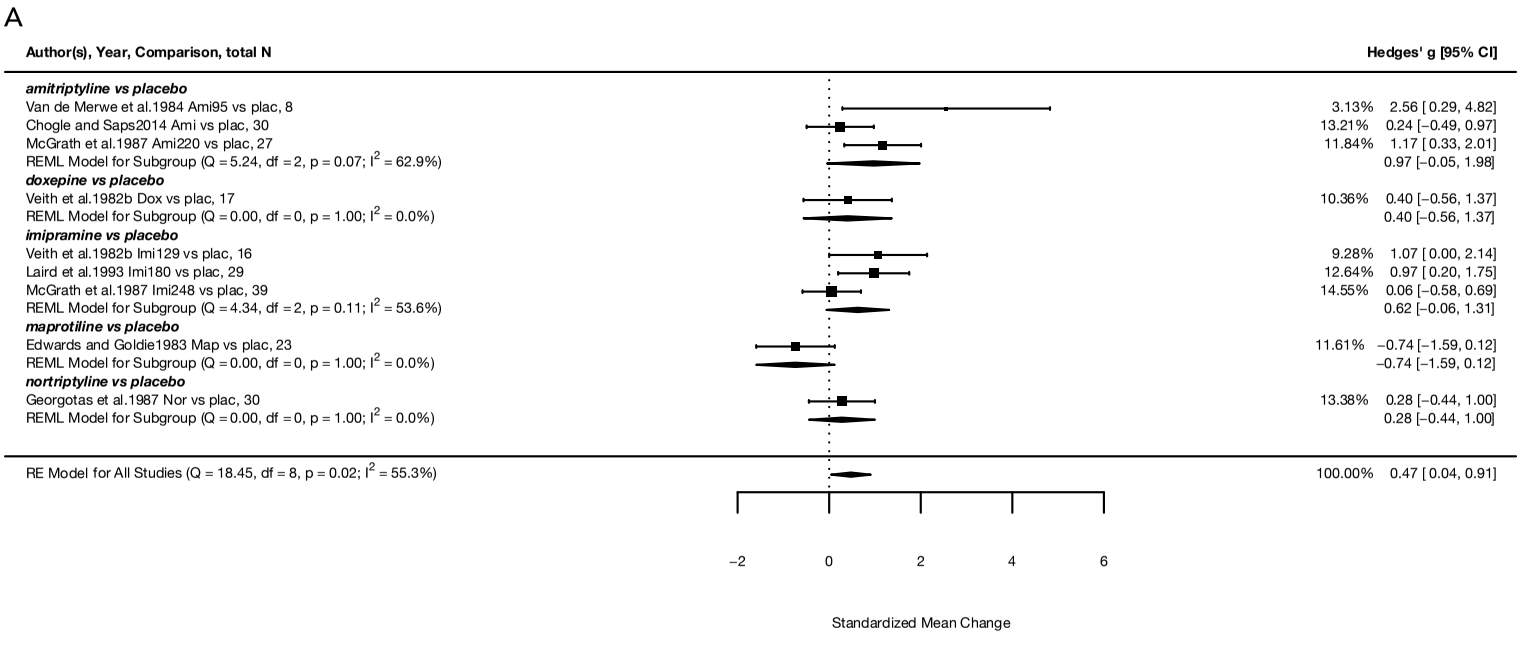
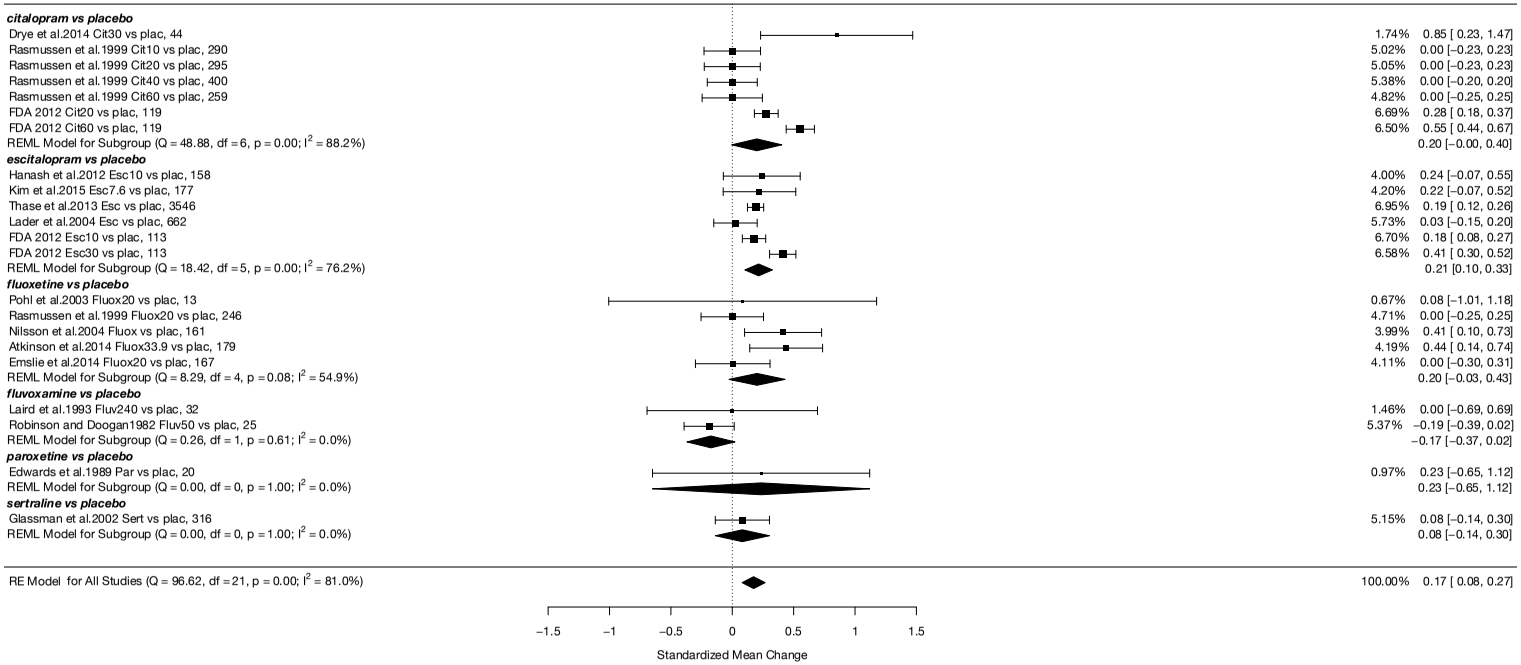
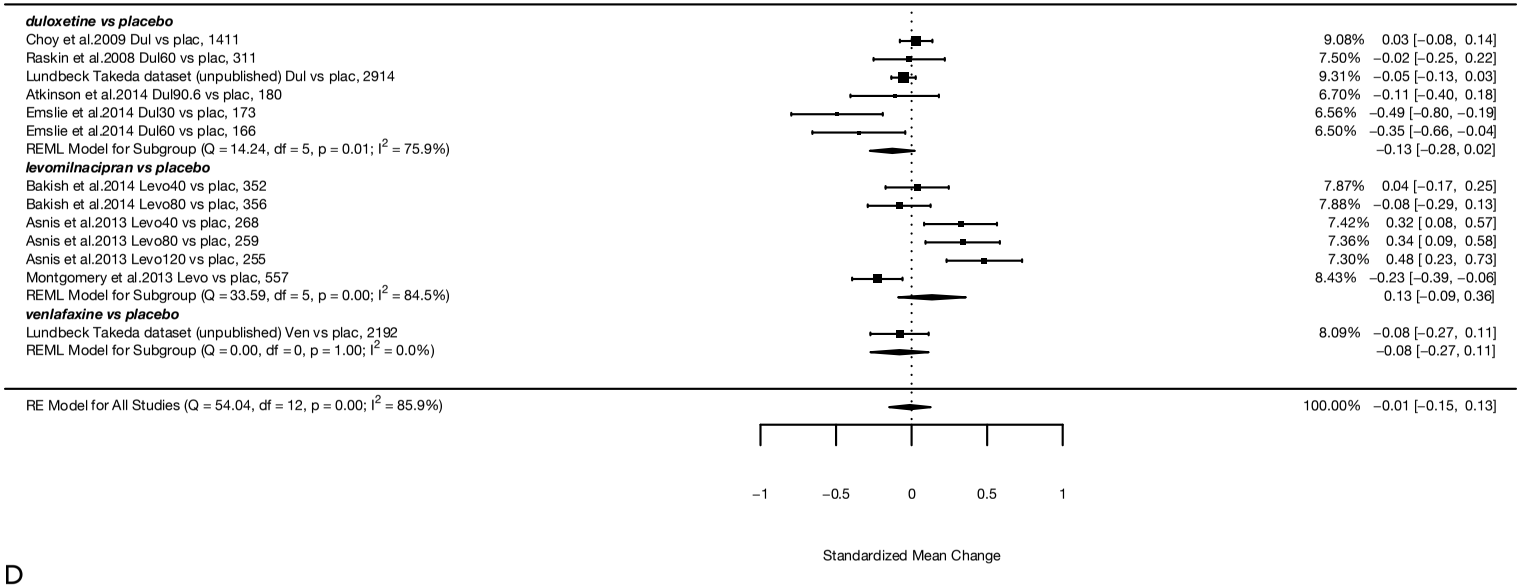


Figure 2. Pooled results of comparisons of the pre-post differences in QT(c)-change scores between antidepressant classes and placebo (total n=18,533 subjects) using restricted maximum-likelihood (REML) estimation under the assumption of a pre-test post-test correlation of r=0.5. Antidepressant classes vs. placebo: tricyclic antidepressants (TCAs; panel A), selective serotonin reuptake inhibitors (SSRIs; panel B), selective noradrenaline reuptake inhibitors (SNRIs; panel C), monoamine oxidase inhibitors (MAOIs; panel D) and other antidepressants (panel E). Ami amitriptyline; plac placebo; Dox doxepine; Imi imipramine; Map maprotiline; Nor notriptyline; Cit citalopram; Esc escitalopram; Fluox fluoxetine; Fluv fluvoxamine; Par paroxetine; Sert sertraline; Dul duloxetine; Levo levomilnacipran; Ven venlafaxine; Phen phenelzine; Mian mianserine; Rebox reboxetine; Traz trazodone; Vilaz vilazodone; Vor vortioxetine.

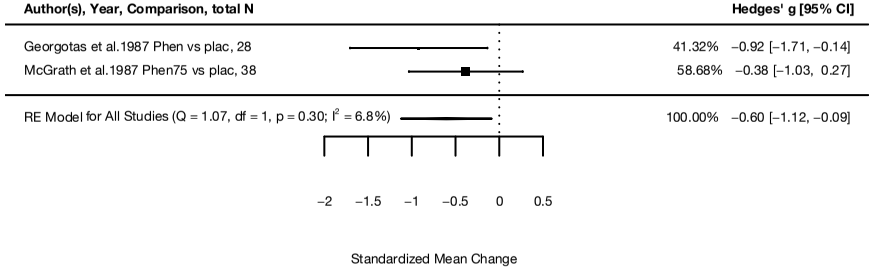
B


Author(s), Year, Comparison, total N
Hedges' g [95% CI]
citalopram vs placebo
Drye et al.2014 Cit30 vs plac, 44
1.74% 0.85 [0.23, 1.47]
Rasmussen et al.1999 Cit10 vs plac, 290
5.02% 0.00 [−0.23, 0.23]
Rasmussen et al.1999 Cit20 vs plac, 295
5.05% 0.00 [−0.23, 0.23]
Rasmussen et al.1999 Cit40 vs plac, 400
5.38% 0.00 [−0.20, 0.20]
Rasmussen et al.1999 Cit60 vs plac, 259
4.82% 0.00 [−0.25, 0.25]
FDA 2012 Cit20 vs plac, 119
6.69% 0.28 [0.18, 0.37]
FDA 2012 Cit60 vs plac, 119
6.50% 0.55 [0.44, 0.67]
REML Model for Subgroup (Q = 48.88, df = 6, p = 0.00; I² = 88.2%)
0.20 [−0.00, 0.40]
escitalopram vs placebo
Hanash et al.2012 Esc10 vs plac, 158
4.00% 0.24 [−0.07, 0.55]
Kim et al.2015 Esc7.6 vs plac, 177
4.20% 0.22 [−0.07, 0.52]
Thase et al.2013 Esc vs plac, 3546
6.95% 0.19 [0.12, 0.26]
Lader et al.2004 Esc vs plac, 662
5.73% 0.03 [−0.15, 0.20]
FDA 2012 Esc10 vs plac, 113
6.70% 0.18 [0.08, 0.27]
FDA 2012 Esc30 vs plac, 113
6.58% 0.41 [0.30, 0.52]
REML Model for Subgroup (Q = 18.42, df = 5, p = 0.00; I² = 76.2%)
0.21 [0.10, 0.33]
fluoxetine vs placebo
Pohl et al.2003 Fluox20 vs plac, 13
0.67% 0.08 [−1.01, 1.18]
Rasmussen et al.1999 Fluox20 vs plac, 246
4.71% 0.00 [−0.25, 0.25]
Nilsson et al.2004 Fluox vs plac, 161
3.99% 0.41 [0.10, 0.73]
Atkinson et al.2014 Fluox33.9 vs plac, 179
4.19% 0.44 [0.14, 0.74]
Emslie et al.2014 Fluox20 vs plac, 167
4.11% 0.00 [−0.30, 0.31]
REML Model for Subgroup (Q = 8.29, df = 4, p = 0.08; I² = 54.9%)
0.20 [−0.03, 0.43]
fluvoxamine vs placebo
Laird et al.1993 Fluv240 vs plac, 32
1.46% 0.00 [−0.69, 0.69]
Robinson and Doogan1982 Fluv50 vs plac, 25
5.37% −0.19 [−0.39, 0.02]
REML Model for Subgroup (Q = 0.26, df = 1, p = 0.61; I² = 0.0%)
−0.17 [−0.37, 0.02]
paroxetine vs placebo
Edwards et al.1989 Par vs plac, 20
0.97% 0.23 [−0.65, 1.12]
REML Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%)
0.23 [−0.65, 1.12]
sertraline vs placebo
Glassman et al.2002 Sert vs plac, 316
5.15% 0.08 [−0.14, 0.30]
REML Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%)
0.08 [−0.14, 0.30]
RE Model for All Studies (Q = 96.62, df = 21, p = 0.00; I² = 81.0%)
100.00% 0.17 [0.08, 0.27]
−1.5
−1
−0.5
0
0.5
1
1.5
Standardized Mean Change

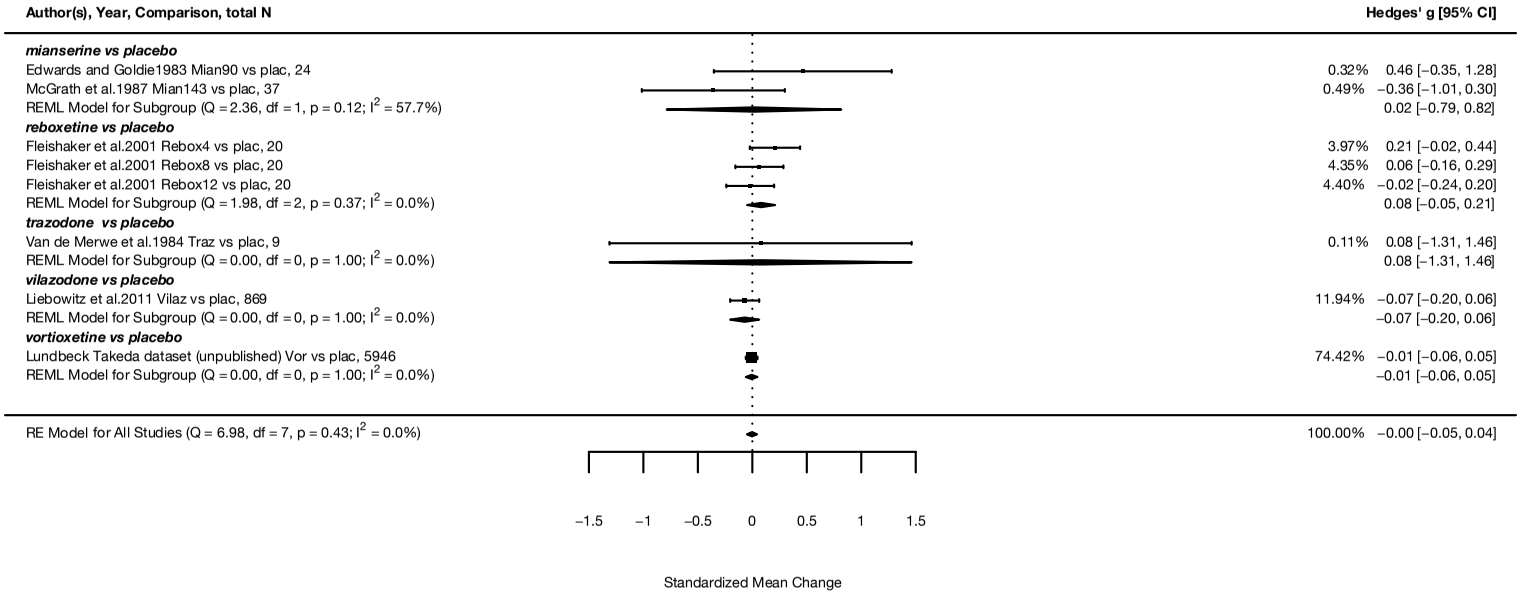
C


Author(s), Year, Comparison, total N
Hedges' g [95% CI]
duloxetine vs placebo
Choy et al.2009 Dul vs plac, 1411 9.08% 0.03 [−0.08, 0.14]
Raskin et al.2008 Dul60 vs plac, 311 7.50% −0.02 [−0.25, 0.22]
Lundbeck Takeda dataset (unpublished) Dul vs plac, 2914 9.31% −0.05 [−0.13, 0.03]
Atkinson et al.2014 Dul90.6 vs plac, 180 6.70% −0.11 [−0.40, 0.18]
Emslie et al.2014 Dul30 vs plac, 173 6.56% −0.49 [−0.80, −0.19]
Emslie et al.2014 Dul60 vs plac, 166 6.50% −0.35 [−0.66, −0.04]
REML Model for Subgroup (Q = 14.24, df = 5, p = 0.01; I² = 75.9%) −0.13 [−0.28, 0.02]
levomilnacipran vs placebo
Bakish et al.2014 Levo40 vs plac, 352 7.87% 0.04 [−0.17, 0.25]
Bakish et al.2014 Levo80 vs plac, 356 7.88% −0.08 [−0.29, 0.13]
Asnis et al.2013 Levo40 vs plac, 268 7.42% 0.32 [0.08, 0.57]
Asnis et al.2013 Levo80 vs plac, 259 7.36% 0.34 [0.09, 0.58]
Asnis et al.2013 Levo120 vs plac, 255 7.30% 0.48 [0.23, 0.73]
Montgomery et al.2013 Levo vs plac, 557 8.43% −0.23 [−0.39, −0.06]
REML Model for Subgroup (Q = 33.59, df = 5, p = 0.00; I² = 84.5%) 0.13 [−0.09, 0.36]
venlafaxine vs placebo
Lundbeck Takeda dataset (unpublished) Ven vs plac, 2192 8.09% −0.08 [−0.27, 0.11]
REML Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%) −0.08 [−0.27, 0.11]
RE Model for All Studies (Q = 54.04, df = 12, p = 0.00; I² = 85.9%) 100.00% −0.01 [−0.15, 0.13]
−1
−0.5
0
0.5
1
Standardized Mean Change

D


Author(s), Year, Comparison, total N
Hedges' g [95% CI]
Georgotas et al.1987 Phen vs plac, 28 41.32% −0.92 [−1.71, −0.14]
McGrath et al.1987 Phen75 vs plac, 38 58.68% −0.38 [−1.03, 0.27]
RE Model for All Studies (Q = 1.07, df = 1, p = 0.30; I² = 6.8%) 100.00% −0.60 [−1.12, −0.09]
−2
−1.5
−1
−0.5
0
0.5
Standardized Mean Change

E


Author(s), Year, Comparison, total N
Hedges' g [95% CI]
mianserine vs placebo
Edwards and Goldie1983 Mian90 vs plac, 24
0.32% 0.46 [−0.35, 1.28]
McGrath et al.1987 Mian143 vs plac, 37
0.49% −0.36 [−1.01, 0.30]
REML Model for Subgroup (Q = 2.36, df = 1, p = 0.12; I² = 57.7%)
0.02 [−0.79, 0.82]
reboxetine vs placebo
Fleishaker et al.2001 Rebox4 vs plac, 20
3.97% 0.21 [−0.02, 0.44]
Fleishaker et al.2001 Rebox8 vs plac, 20
4.35% 0.06 [−0.16, 0.29]
Fleishaker et al.2001 Rebox12 vs plac, 20
4.40% −0.02 [−0.24, 0.20]
REML Model for Subgroup (Q = 1.98, df = 2, p = 0.37; I² = 0.0%)
0.08 [−0.05, 0.21]
trazodone vs placebo
Van de Merwe et al.1984 Traz vs plac, 9
0.11% 0.08 [−1.31, 1.46]
REML Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%)
0.08 [−1.31, 1.46]
vilazodone vs placebo
Liebowitz et al.2011 Vilaz vs plac, 869
11.94% −0.07 [−0.20, 0.06]
REML Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%)
−0.07 [−0.20, 0.06]
vortioxetine vs placebo
Lundbeck Takeda dataset (unpublished) Vor vs plac, 5946
74.42% −0.01 [−0.06, 0.05]
REML Model for Subgroup (Q = 0.00, df = 0, p = 1.00; I² = 0.0%)
−0.01 [−0.06, 0.05]
RE Model for All Studies (Q = 6.98, df = 7, p = 0.43; I² = 0.0%)
100.00% −0.00 [−0.05, 0.04]
−1.5
−1
−0.5
0
0.5
1
1.5
Standardized Mean Change

differences in change scores. Clomipramine was associated with more QT(c)-prolongation than desipramine.[77] Amitriptyline resulted in more QT(c)-prolongation than mianserin,[24,47] phenelzine,[47,55] paroxetine,[45] and trazodone.[30] Imipramine resulted in more QT(c) prolongation than fluvoxamine[46], hypericum[26], and phenelzine.[47] Nortriptyline resulted in more QT(c) prolongation than phenelzine.[41] Mianserin resulted in more QT(c) prolongation than maprotiline[38] and phenelzine.[47]

Risk of bias

Bias assessment

Risk of bias judgements are presented in Figure 3 (for details see Supplemental table 2). Bias risk (low=1, unclear=2, high=3) had a sum score range of 6 to 11, with mean 7.3 and median 9. Most studies included presented a low risk of selection bias by randomly generating the sequence of allocation (90.2%) and precluding performance bias (91.8%). Prevention of selection bias by allocation concealment was not described in most studies (73.3%), leading to an unclear risk. The risk of reporting bias appeared low in most studies (83.6%).

Publication bias

Inspection of the funnel plot of SSRI as compared with placebo showed no indication for publication-bias (Begg & Mazumbar p=0.22; Egger p=0.98). For the remaining classes (TCA, SNRI, MAOI and other), publication bias could not be reliably evaluated by funnel plots or the Begg & Mazumbar approach, since their placebo-comparisons all included less than 10 studies.

Sensitivity analyses

The assumption of pre-test post-test correlation r=0.5 was assessed by rerunning the class comparisons with placebo with assumed correlations of r=0.4 and r=0.8 (see Supplemental table 3). Relative to the initial results, considerable influence (>10% change) was found when we assumed r=0.8 for TCAs (SMD increased from 0.45 (95%CI 0.04 - 0.91) to 0.75 (95%CI 0.13 – 1.37) and MAOIs (i.e. phenelzine; SMD increased from -0.60 (95%CI -1.10 - -0.10) to -0.71 (95%CI -1.21 - -0.20).

Exclusion of crossover design studies from pooled analyses did not change the results. SSRIs still showed more QT(c) prolongation than placebo (SMD=0.12; 0.05 – 0.19), the group of other antidepressants had similar QT(c) prolongation as placebo (SMD=-0.01; -0.05 – 0.04) and amitriptyline showed higher QT(c) prolongation than mianserin (SMD=1.58; 0.74 – 2.42).

Exclusion of the studies with the highest 255 risk of bias (i.e. sum score 10 or 11; Supplemental table 2) from the pooled placebo comparisons with antidepressant classes did slightly change some of the effects, see Supplemental table 4. The SNRIs then showed a borderline significant shortening effect on QT(c) interval with SMD=-0.12 (-0.25 to -0.00).

DISCUSSION

Based on available prospective clinical studies, the current overview pooled data concerning the QT(c)-prolonging effects of commonly prescribed antidepressants. TCAs and to a lesser extent SSRIs are associated with increased QT(c)-prolongation as compared with placebo. In contrast, MAOIs (only phenelzine data available), SNRIs, and other antidepressants do not increase the risk of QT(c)-prolongation. In addition, the TCA amitriptyline appeared to be less safe with respect to QT(c)-prolongation risk than various other individual antidepressants from the same or other classes. Within the class of TCAs, clomipramine – which was not directly compared to amitriptyline – also appears to have a more prolonging effect on QTc-interval than desipramine.

Effects across classes and between antidepressants

TCAs have an increased risk of QT(c)-prolongation. Supportive (non-placebo-controlled) evidence comes from a systematic review evaluating cardiovascular effects of TCAs in children and adolescents.[78] In this study in 636 children, the QTc interval increased 4% to 10% for desipramine, clomipramine, nortriptyline, amitriptyline and imipramine, which was interpreted by the authors as 'uncertain but probably minor clinical significance'. A previous meta-analysis additionally showed that TCAs prolong QT(c) more than SSRIs (+7 milliseconds (msec) on average).[6] Based on pooled data from seven studies (n=195), the current review compared TCAs with placebo and confirmed the moderate QT(c) prolonging risk of TCAs (Hedges' g=0.47).

This placebo-controlled class effect of TCAs was based on a pooling with moderate heterogeneity (I^2=55.3%). Except for maprotiline, consistent QT(c) prolongation effects were observed for all TCAs. Post-hoc exclusion of the maprotiline study[38] indeed resulted in a substantial decrease of heterogeneity (I^2=27.9%) and an increase of the QT(c) prolonging TCA class effect (Hedges' g=0.59). The distinct position of maprotiline with respect to cardiovascular safety among the TCAs is not evident, as a pharmacovigilance database report contrarily showed maprotiline to be associated with a significantly higher risk for adverse (particularly arrhythmic) cardiovascular reactions compared to the risk of all antidepressants.[79] In our analyses, none of the individual TCAs showed a statistically significant QT(c)-prolongation as compared with placebo, which might be explained by the small sample sizes (n<40) of individual studies and the fact that only amitriptyline and imipramine data were based on more than one trial. The largest effect size for individual TCAs was found for amitriptyline (Hedges' g=0.97). The original studies showed crude placebo-controlled QT(c)-prolongations of on weighted average +16 msec, and studies with higher dosages of amitriptyline reported more prolongation than for low-doses.[17,30,47] Although amitriptyline in a recent large network meta-analysis has been shown to be one of the most effective antidepressants[80], its QT(c)-prolonging ability as a side effect should be considered when choosing this antidepressant for treatment.

In patients using an SSRI, a smaller increased risk of QT(c) prolongation is observed. Previously, Beach et al. also concluded that SSRI as a class show significant, but small

Table 2 Comparisons of QT(c) effects between antidepressants in n=8,076 subjects

Intervention vs comparison	SMD [95% CI]$_{REML\ r=0.5}$	Change difference$_{msec}$ (SE/SD), p-value	Studies	Unique subjects intervention group (n unique studies)	Unique subjects comparison group (n unique studies)
TCA vs TCA				107 (7)	125 (7)
amitriptyline vs desipramine		7.00 (SD 8.86), n.s.	Veith et al. 1982a	20 (1)	26 (1)
amitriptyline vs imipramine		21.90 (SD 7.62), n.s.	McGrath et al. 1987	11 (1)	23 (1)
amitriptyline vs trimipramine		-2.00 (SE 14.14), n.s.	Cournoyer et al. 1987	16 (1)	17 (1)
clomipramine vs desipramine		7.24 (SD 3.87), p=0.0001	Leonard et al. 1995	20 (1)	19 (1)
dothiepin vs doxepin		-0.59 (SD 7.58), n.s.	Evans and Cox 1981	14 (1)	14 (1)
doxepin vs imipramine		-20.00 (SE 22.52), n.s.	Veith et al. 1982b	9 (1)	8 (1)
doxepin vs trimipramine		13.00 (SE 15.36), n.s.	Nair et al. 1993	17 (1)	18 (1)
TCA vs SSRI				103 (6)	117 (6)
amitriptyline vs fluoxetine		-4.00 (SE 9.70), n.s.	Upward et al. 1988	12 (1)	11 (1)
amitriptyline vs paroxetine		19.00 (SD 9.91), p<0.05	Kuhs and Rudolf 1990	17 (1)	14 (1)
doxepin vs fluoxetine		8.00 (SE 9.37), n.s.	Baker et al. 1997	19 (1)	20 (1)
imipramine vs fluvoxamine		20.00 (SE 8.35), p<0.05	Laird et al. 1993	14 (1)	17 (1)
maprotiline vs fluvoxamine		8.00 (SE 6.69), n.s.	Hewer et al. 1995	15 (1)	18 (1)
nortriptyline vs paroxetine		-10.00 (SE 5.15), n.s.	Roose et al. 1998	26 (1)	37 (1)
TCA vs Other				154 (6)	153 (6)
amitriptyline vs bupropion		-4.80 (SD 4.81), n.s.	Wenger et al. 1983	23 (1)	23 (1)
amitriptyline vs mianserin	1.15 [0.39 - 1.91]		Burgess et al. 1979[a], McGrath et al. 1987	17 (2)	29 (2)
amitriptyline vs trazodone		28.60 (SD 7.79), p<0.001	Van de Merwe et al. 1984	5 (1)	6 (1)
imipramine vs hypericum		9.00 (SD 3.32), p<0.01	Czekalla et al. 1997	76 (1)	84 (1)
imipramine vs mianserin		8.30 (SD 6.58), n.s.	McGrath et al. 1987	23 (1)	21 (1)
maprotiline vs mianserin		-12.00 (SE 3.61), p<0.01	Edwards and Goldie 1983	10 (1)	11 (1)

Table 2. (continued)

Intervention vs comparison	SMD [95% CI]$_{REML\ r=0.5}$	Change difference$_{msec}$ (SE/SD), p-value	Studies	Unique subjects intervention group (n unique studies)	Unique subjects comparison group (n unique studies)
TCA vs MAOI				119 (5)	109 (5)
amitriptyline vs phenelzine	1.21 [0.81 - 1.61]		McGrath et al. 1987, Robinson et al. 1982	50 (2)	67 (2)
amitriptyline vs tranylcypromine	0.30 [-0.22 - 0.82]		O'Brien et al. 1991, White et al. 1983	30 (2)	28 (2)
imipramine vs phenelzine		10.8 (SD 7.76), p=0.0006	McGrath et al. 1987	23 (1)	22 (1)
nortriptyline vs phenelzine		40.0 (SE 9.21), p<0.001	Georgotas et al. 1987	16 (1)	14 (1)
SSRI vs SSRI				660 (1)	100 (1)
citalopram vs fluoxetine	0.00 [-0.13 - 0.13]		Rasmussen et al. 1999	660 (1)	100 (1)
SSRI vs SNRI				530 (3)	992 (3)
fluoxetine vs duloxetine	0.45 [-0.28 - 0.63]		Atkinson et al. 2014, Emslie et al. 2014	171 (2)	256 (2)
paroxetine vs duloxetine		0.50 (SD 1.69), p=0.77	Nelson et al. 2006	359 (1)	736 (1)
SNRI vs SNRI				**844 (2)**	**122 (2)**
duloxetine vs venlafaxine	-0.24 [-0.92 - 0.45]		Badyal et al. 2006, Lundbeck Takeda pooled data (unpublished)	844 (2)	122 (2)
SNRI vs Other				109 (1)	3863 (1)
venlafaxine vs vortioxetine		-1.10 (SD 1.93), n.s.	Lundbeck Takeda pooled data (unpublished)	109 (1)	3863 (1)
MAOI vs Other				22 (1)	21 (1)
phenelzine vs mianserin		-2.5 (SD 7.07), p=0.03	McGrath et al. 1987	22 (1)	21 (1)

[a] crossover design, appropriate Hedges' *g* formula applied (see methods)
msec milliseconds; n.s. not significant (p>0.05).

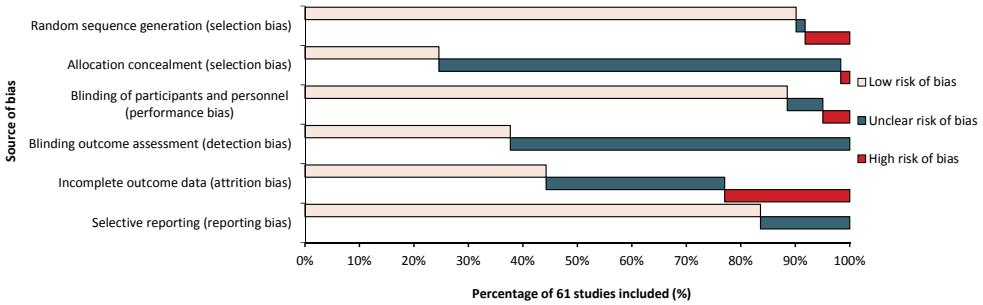


Figure 3. Risk of bias judgements using the Cochrane Collaboration's tool for assessing risk of bias

prolongation of the QTc interval of on average (+6 millisec) as compared with placebo.[6] We have replicated this small effect (Hedges' *g*=0.17), while doubling the unique number of subjects (n=6663) and examining standardized instead of crude mean differences. The overall heterogeneity of QT(c) effects across SSRIs was large (I^2=81.0%). The QT(c)-prolonging effect was observed for all SSRIs except fluvoxamine, which is in line with the previous meta-analysis.[6] Post hoc exclusion of the fluvoxamine studies[46,51] did not decrease heterogeneity (I^2=79.0%).

With respect to the QT(c)-prolonging effects of individual SSRIs as compared with placebo, effect sizes were comparable for most agents, although we only found a significant QT(c)-prolongation for escitalopram (n=3994). This corroborates findings of two previous meta-analyses, either based on twelve RCTs (n=3536[81]), or on a cross-over study (n=113[82]) in healthy subjects.[6] We could not replicate the previous findings of a statistically significant QT(c)-prolongation for citalopram and paroxetine[6]. This might be explained by our more conservative approach to include data, which precluded inclusion of the artificially calculated 40 mg data of the influential FDA citalopram data.[76] Additionally, we could not use data of some studies on citalopram[83,84] and paroxetine[59], included in previous meta-analyses, since essential statistical information was not provided on repeated request.

The comparison of MAOI versus placebo provided no evidence for QT(c)-prolongation by phenelzine. The pooled available data of two small prospective trials on phenelzine (n=66) even showed a decreased risk of QT(c) prolongation.[41,47] In addition, phenelzine consistently showed a lower risk of QT(c)-prolongation than TCA (i.e. amitriptyline, imipramine and nortriptyline), or mianserin.[47] To the best of our knowledge, QT(c) data from prospective controlled trials on MAOI have not been reviewed before. Some support for the relative safety of MAOI with respect to proarrythmia comes from a pharmacovigilance surveillance report.[79] Based on data of 169,278 psychiatric inpatients treated with antidepressants between 1993 and 2010, the report describes that monotherapy of 3,756 subjects with tranylcypromine or moclobemide was not significantly associated with increased risk for arrhythmia (defined as QT(c) post-value >500msec or pre-post change >60msec).

We found no evidence that SNRI or other antidepressants increase the risk of QT(c) prolongation. One systematic review has previously described the risk of QT/QTc prolongation among the newer, non-SSRI antidepressants bupropion, desvenlafaxine, duloxetine, levomilnacipran, mirtazapine, venlafaxine, and vilazodone.[85] This overview was based on studies with various designs, including some controlled trials, but mostly manufacturer communications, retrospective studies and case reports. Corroborative with our conclusion, the authors state that the risk of QT(c) prolongation is low with most of the newer antidepressants at therapeutic doses, although mixed results are presented for bupropion and desvenlafaxine (particularly in overdose-situations). Of the individual antidepressants, Wernicke at al. pooled the placebo-controlled safety data from available duloxetine trials.[9] Based on ECGs from 4704 subjects, duloxetine was associated with a non-significant shortening of QT(c)-interval as compared with placebo. Although the authors mentioned that this might reflect increases in heartrate, we have corroborated this small but statistically non-significant effect for duloxetine in a larger population of 5067 subjects.

In summary, we found a significant moderate effect for TCA and a small but significant effect for SSRI. Within these two classes, the smallest effects on QTc-prolongation were found for nortriptyline and maprotiline, and for fluvoxamine and sertraline, respectively. We expect that the small effect in SSRIs, despite the more robust evidence base, is clinically less relevant relatively to the moderate effects found in TCAs, which are based on a smaller overall pooled population. Within class differences between drugs might especially be important for patients who already have a risk factor for QTc prolongation and/or cardiac arrhythmias.[86]

Strengths and limitations

This review has some important strengths: its systematic search, inclusion of all different classes of antidepressants, use of data from large numbers of patients, and analysis of these data by both pooling and meta-regression. Despite these strengths, some limitations should be mentioned. First, the evidence base for the QT(c)-risk of many antidepressants, including TCAs, is still weak with lacking information for eighteen antidepressants in our meta-analyses and few head-to-head comparisons. Of twenty comparisons between individual antidepressants and placebo, ten are based on only one trial (with sample sizes between n=9 (trazodone) to n=5,946 (vortioxetine)). Eleven out of twenty head-to-head comparisons are based on <100 patients. Therefore, moderate effects might have been missed.

Second, many small differences between the studies existed, e.g. differences in design, method of ECG recording, whether and how QT intervals were corrected for heart-rate and time points for QT(c) change measurement. These differences between the studies undoubtedly introduced heterogeneity between the studies, which urged us to use a more conservative statistical approach with random effects models, that might have underestimated QT(c)-prolonging effects of antidepressants. A meta-regression based on

variation in QT correction showed a significant effect of Bazett (overestimation) versus Fridericia in SNRI, but not in other classes.

Third, for studies in which the SMD between interventions and/or per intervention arm were not given, we calculated the pre-post changes and standard error of the effect size estimates in each arm under the assumption of a pre-test post-test correlation r=0.5. However, sensitivity analyses showed that this assumption was not irrelevant. As all TCA studies with complete data showed a pre-post correlation higher than 0.5 (range 0.7-1.0), effect sizes may have been underestimated. Therefore, TCA might increase the QT(c) interval as compared with placebo even to a moderate-to-large effect of SMD=0.75.

Fourth, we pooled data from antidepressants with various dosages within the clinical range, excluding studies with supra-therapeutic dosages or over-dose situations. In addition to the RCT-evidence, a dose-response-relationship is one of the characteristics which supports causality of associations. However, we did not yet thoroughly investigate a dose-response relationship. Instead of a linearly increasing risk, there might be a threshold dosage, above which an otherwise safe antidepressant could become QT(c) prolonging. Therefore, from both a scientific and a clinical perspective, a more detailed study of the influence of antidepressant dosage is important.

Fifth, we found few studies that were carried out in populations vulnerable for QT(c)-prolongation. We had expected to examine and determine the effects of higher age, as these groups might be more vulnerable to QT(c) prolongation. However, this data was not available. Nevertheless, a sensitivity analysis by inspection of the sparse data in children/adolescents or elderly did suggest an effect of age. Importantly, although the effects of antidepressants on QT(c) interval may be small, they can add up and become relevant for patients having other risk factors for QT(c) prolongation. A systematic review of case-reports reported on the prevalence of risk factors for arrhythmia in 249 cases of TdP induced by non-cardiac drugs, including antipsychotic and antidepressant medication.[2] Apart from the use of medication, TdP cases on average had 2.2 other risk factors, such as female sex, use of other QT(c) prolonging drugs (interaction), cardiac disease, vulnerability to QT(c) prolongation, or hypokalaemia. A Swedish pharmacovigilance study additionally showed that older age might be a risk factor for TdP, as 72% of the cases were 65 years or older (range 15-90 years).[3] Studies investigating the effects of antidepressants on QT(c) in such vulnerable populations could yield more fine-grained evidence, as in these populations the effects of antidepressants on QTc might be most important to know.

Conclusions and implications

With this meta-analysis of more than twenty thousand patients, being the largest evidence base on QTc prolonging effects of antidepressants to date, we conclude that therapeutic doses of TCAs have a moderate and SSRIs a small prolonging effect on QT(c) duration. SNRIs, MAOIs and other antidepressants do not increase the QT(c) interval.

Given the aforementioned limitations, future placebo-controlled data on QT(c) prolongation of antidepressants and especially head-to-head comparisons are still needed.

Besides, even when the risk of QT(c)-prolongation and dose-response relationships will become clearer, choosing an appropriate antidepressant for individual patients requires a weighing between efficacy, safety and individual patient characteristics. Particularly in patients who *a priori* are at risk of QT(c)-prolongation[86], this choice can be a downright challenge. Therefore, it would be most insightful for clinical practice if future QT(c)-studies would also be performed in groups vulnerable for QT(c)-prolongation or cardiac arrhythmias, e.g. in elderly patients.

The aggregated data of reviews like the current meta-analysis can be used by organizations responsible for medication policy, e.g. CredibleMeds, the FDA or the EMA, but also for guideline committees. This review will therefore serve as an evidence base for decisions on whether ECG monitoring should be advised for certain antidepressants or patient-groups when treated with specific antidepressants, or whether patients should be excluded from using antidepressants with increased risk of QT(c)-prolongation. Ideally, such recommendations should be accompanied by a suggestion of alternatives, preferably within the class of antidepressants. This will help to specifically reduce the risk of the rare but potentially lethal proarrhythmic complications and restrict the indication of time-consuming ECG monitoring to vulnerable patients.

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SUPPLEMENTAL MATERIALS

Supplemental table 1. QT(c) effects in antidepressants versus placebo (also shown in Figure 2)

	Standardized mean difference (SMD) [95% CI]$_{\text{REML or FE, r=0.5}}$ [a]	N unique subjects active medication (n unique studies)	N unique subjects placebo (n unique studies)
TCA versus placebo	**0.47 [0.04 - 0.91]$_{\text{REML}}$** [b]	**108 (7)**	**87 (7)**
amitriptyline	0.97 [-0.05 - 1.98]$_{\text{REML}}$	28 (3)	37 (3)
clomipramine	x	x	x
desipramine	x	x	x
dothiepin/dosulepin	x	x	x
doxepin	0.40 [-0.56 - 1.37]$_{\text{REML}}$ [b]	9 (1)	8 (1)
imipramine	0.62 [-0.06 - 1.31]$_{\text{REML}}$	45 (3)	39 (3)
lofepramine	x	x	x
maprotiline	-0.74 [-1.59 - 0.12]$_{\text{REML}}$	10 (1)	13 (1)
nortriptyline	0.28 [-0.44 - 1.00]$_{\text{REML}}$	16 (1)	14 (1)
trimipramine	x	x	x
SSRI versus placebo	**0.17 [0.08 - 0.27]$_{\text{REML}}$** [b]	**4000 (16)** [cd]	**2895 (16)** [cd]
citalopram	0.20 [-0.00 - 0.40]$_{\text{REML}}$	801 (3) [c]	287 (3) [c]
escitalopram	0.21 [0.10 - 0.33]$_{\text{REML}}$	2612 (5) [c]	2147 (5) [c]
fluoxetine	0.20 [-0.03 - 0.43]$_{\text{REML}}$	365 (5)	401 (5)
fluvoxamine	-0.17 [-0.37 - 0.02]$_{\text{REML}}$ -0.17 [-0.37 - 0.02]$_{\text{FE}}$	42 (2) [d]	40 (2) [d]
paroxetine	0.23 [-0.65 - 1.12]$_{\text{REML}}$	11 (1)	9 (1)
sertraline	0.08 [-0.14 - 0.30]$_{\text{REML}}$	159 (1)	157 (1)
SNRI versus placebo	**-0.01 [-0.15 - 0.13]$_{\text{REML}}$**	**3289 (8)**	**3490 (8)**
desvenlafaxine	x	x	x
duloxetine	-0.13 [-0.28 - 0.02]$_{\text{REML}}$	2170 (5)	2897 (5)
levomilnacipran	0.13 [-0.09 - 0.36]$_{\text{REML}}$	1002 (3)	593 (3)
milnacipran	x	x	X
venlafaxine	0.08 [-0.27 - 0.11]$_{\text{REML}}$	109 (1)	2083 (1)
MAOI versus placebo	**-0.60 [-1.12 - -0.09]$_{\text{REML}}$** [b]	**36 (2)**	**30 (2)**
phenelzine	-0.60 [-1.12 - -0.09]$_{\text{REML}}$ [b]	36 (2)	30 (2)
moclobemide	x	x	x
selegiline	x	x	x
tranylcypromine	x	x	x
Other AD versus placebo	**-0.00 [-0.05 - 0.04]$_{\text{REML}}$**	**4337 (6)** [e]	**2568 (6)** [e]
agomelatine	x	x	x
bupropion	x	x	x
hyperforin	x	x	x
hypericum/st John's wort	x	X	x
mianserin	0.02 [-0.79 - 0.82]$_{\text{REML}}$	32 (2)	29 (2)
mirtazapine	x	x	X
nefazodone	x	x	x
reboxetine	0.08 [-0.5 - 0.21]$_{\text{REML}}$	20 (1) [e]	20 (1) [e]

Supplemental table 1. (continued)

	Standardized mean difference (SMD) [95% CI]$_{\text{REML or FE, r=0.5}}$[a]	N unique subjects active medication (n unique studies)	N unique subjects placebo (n unique studies)
tianeptine	x	x	x
trazodone	**0.08 [-1.31 - 1.46]$_{\text{REML}}$**	**6 (1)**	**3 (1)**
vilazodone	-0.07 [-0.20 - 0.06]$_{\text{REML}}$	436 (1)	433 (1)
vortioxetine	-0.01 [-0.06 - 0.05]$_{\text{REML}}$	3863 (1)	2083 (1)

[a] Effects are standardized mean differences (pooled Hedges' *g*); if >0 the drug increases QTc time relative to placebo.
[b] Significant, p<0.05.
[c] Including FDA 2012 subsets, cross-over; n=119 received citalopram and placebo; n=120 received escitalopram and placebo; appropriate Hedges' *g* formula applied (see methods).
[d] Including Robinson& Doogan1982, cross-over, n=25 received fluvoxamine and placebo; appropriate Hedges' *g* formula applied (see methods).
[e] Fleishaker2001, cross-over trial in which n=20 received three doses of reboxetine and placebo; appropriate Hedges' *g* formula applied (see methods).
SMD Standardized Mean Difference; REML Random Effects Model; FE Fixed Effects Model.

Supplemental table 2. Total scores for risk of bias assessment criteria from the Cochrane Collaboration's tool for assessing risk of bias, number of studies (%)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Low risk of bias	55 (90.2%)	15 (24.6%)	56 (91.8%)	23 (37.7%)	27 (44.3%)	51 (83.6%)
Unclear risk of bias	1 (1.6%)	45 (73.8%)	2 (3.3%)	38 (63.3%)	20 (32.8%)	10 (16.4%)
High risk of bias	5 (8.2%)	1 (1.6%)	3 (4.9%)	0 (0.0%)	14 (23.0%)	0 (0.0%)

The sum score range of bias risk was 6 to 11 (with low=1, unclear=2, high=3). The 21.3% highest bias risk scores were given to the following studies: Hewer1995; Badyal2006; Upward1988; Asnis2013; Robinson1982; Nelson2006; Goodman2005; Stahl2004; Feighner1997; McGrath1987; Lader2004; Kasper2005b; LundbeckTakeda data short-term MDD+GAD.

Supplemental table 3. QT(c) effects in antidepressant classes versus placebo by assumed pre-post-value correlations of r=0.4, r=0.5 and r=0.8.

	Standardized mean difference (SMD) [95% CI], r=0.4	Standardized mean difference (SMD) [95% CI], r=0.5	Standardized mean difference (SMD) [95% CI], r=0.8	N subjects antidepressant (n unique studies)	N subjects placebo (n unique studies)
TCA versus placebo	0.43 [0.02 - 0.83] $_{REML}$[b]	0.47 [0.04 - 0.91] $_{REML}$[b]	0.75 [0.13 - 1.37] $_{REML}$[b]	108 (7)	87 (7)
SSRI versus placebo	0.17 [0.08 - 0.27] $_{REML}$[b]	0.17 [0.08 - 0.27] $_{REML}$[b]	0.18 [0.09 - 0.28] $_{REML}$[b]	4000 (16)[cd]	2895 (16)[cd]
SNRI versus placebo	-0.01 [-0.15 - 0.13] $_{REML}$	-0.01 [-0.15 - 0.13] $_{REML}$	-0.01 [-0.15 - 0.13] $_{REML}$	3289 (8)	3490 (8)
MAOI versus placebo	-0.58 [-1.08 - -0.08] $_{FE}$[b]	-0.60 [-1.10 - -0.10] $_{FE}$[b]	-0.71 [-1.21 - -0.20] $_{FE}$[b]	36 (2)	30 (2)
Other AD versus placebo	0.02 [-0.09 - 0.13] $_{REML}$	-0.00 [-0.05 - 0.04] $_{REML}$	0.02 [-0.08 - 0.13] $_{REML}$	4337 (6)[e]	2568 (6)[e]

[a] Effects are standardized mean differences (pooled Hedges' *g*); if >0 the drug increases QTc time relative to placebo.
[b] significant, p<0.05.
[c] Including FDA 2012 subsets, cross-over; n=119 received citalopram and placebo; n=120 received escitalopram and placebo; appropriate Hedges' *g* formula applied (see methods).
[d] Including Robinson& Doogan1982, cross-over, n=25 received fluvoxamine and placebo; appropriate Hedges' *g* formula applied (see methods).
[e] Fleishaker2001, cross-over trial in which n=20 received three doses of reboxetine and placebo; appropriate Hedges' *g* formula applied (see methods).
SMD Standardized Mean Difference; REML Random Effects Model; FE Fixed Effects model.

Supplemental table 4. QT(c) effects in antidepressant classes versus placebo after exclusion of studies with highest bias risk

	Standardized mean difference (SMD) [95% CI], r=0.5[a]	N subjects antidepressant (n unique studies)	N subjects placebo (n unique studies)
TCA versus placebo	0.45 [-0.07 - 0.98] $_{REML}$	74 (6)	71 (6)
SSRI versus placebo[cd]	0.18 [0.08 - 0.28] $_{REML}$ [b]	3501 (15)	2732 (15)
SNRI versus placebo	-0.12 [-0.25 - -0.00] $_{REML}$	1973 (6)	1269 (6)
MAOI versus placebo	N/A, one study left	N/A	N/A
Other AD versus placebo[e]	-0.03 [-0.09 - 0.16] $_{REML}$	473 (4)	469 (4)

[a] Effects are standardized mean differences (pooled Hedges' *g*); if >0 the drug increases QTc time relative to placebo.
[b] significant, $p < 0.05$.
[c] Including FDA 2012 subsets, cross-over; n=119 received citalopram and placebo; n=120 received escitalopram and placebo; appropriate Hedges' *g* formula applied (see methods).
[d] Including Robinson& Doogan1982, cross-over, n=25 received fluvoxamine and placebo; appropriate Hedges' *g* formula applied (see methods).
[e] Including Fleishaker2001, cross-over trial in which n=20 received three doses of reboxetine and placebo; appropriate Hedges' *g* formula applied (see methods).
SMD Standardized Mean Difference; REML Random Effects Model; FE Fixed Effects Model.