The effects of antidepressants on cardiometabolic and other physiological parameters: a systematic review and network meta-analysis

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Summary

Background Antidepressants induce physiological alterations; however, the degree to which these occur in treatment with various antidepressants is unclear. We aimed to compare and rank antidepressants based on physiological side-effects by synthesising data from randomised controlled trials (RCTs).

Methods We searched MEDLINE, EMBASE, PsycINFO, ClinicalTrials.gov, and the US Food and Drug Administration (FDA) website from database inception to April 21, 2025. We included single-blinded and double-blinded RCTs comparing antidepressants and placebo in acute monotherapy of any psychiatric disorder. We did frequentist random-effects network meta-analyses to investigate treatment-induced changes in weight; total cholesterol; glucose; heart rate; systolic and diastolic blood pressure; corrected QT interval (QTc); sodium; potassium; aspartate transferase (AST); alanine transaminase (ALT); alkaline phosphatase (ALP); bilirubin; urea; and creatinine. We did meta-regressions to examine study-level associations between physiological change and age, sex, and baseline weight. We estimated the correlation between depressive symptom severity change and metabolic parameter change.

Findings Of 26 252 citations, 151 studies and 17 FDA reports met inclusion criteria. The overall sample included 58 534 participants, comparing 30 antidepressants with placebo. Median treatment duration was 8 weeks (IQR 6·0–8·5). We observed clinically significant differences between antidepressants in terms of metabolic and haemodynamic effects, including an approximate 4 kg difference in weight-change between agomelatine and maprotiline, over 21 beats-per-minute difference in heart rate change between fluvoxamine and nortriptyline, and over 11 mmHg difference in systolic blood pressure between nortriptyline and doxepin. Paroxetine, duloxetine, desvenlafaxine, and venlafaxine were associated with increases in total cholesterol and, for duloxetine, glucose concentrations, despite all drugs reducing bodyweight. There was strong evidence of duloxetine, desvenlafaxine, and levomilnacipran increasing AST, ALT, and ALP concentrations, although the magnitudes of these alterations were not considered clinically significant. We did not find strong evidence of any antidepressant affecting QTc, or concentrations of sodium, potassium, urea, and creatinine to a clinically significant extent. Higher baseline bodyweight was associated with larger antidepressant-induced increases in systolic blood pressure, ALT, and AST, and higher baseline age was associated with larger antidepressant-induced increases in glucose. We did not observe an association between changes in depressive symptoms and metabolic disturbance.

Interpretation We found strong evidence that antidepressants differ markedly in their physiological effects, particularly for cardiometabolic parameters. Treatment guidelines should be updated to reflect differences in physiological risk, but choice of antidepressant should be made on an individual basis, considering clinical presentation and preferences of patients, carers, and clinicians.

Funding National Institute for Health Research, Maudsley Charity, Wellcome Trust, Medical Research Council.

Published Online
October 21, 2025
https://doi.org/10.1016/
S0140-6736(25)01293-0

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Introduction

Up to 17% of the adult population in Europe and North America are prescribed antidepressants.[1–3] Although they are effective treatments,[4] antidepressants can induce various physiological alterations, including weight gain, blood pressure disturbance, hyponatraemia, and QT prolongation.[5–9] These side-effects have wide-reaching consequences, including discontinuation of treatment and thus poorer psychiatric outcomes.[10] Professional bodies recommend that discussions about side-effects are central to antidepressant prescribing decisions.[11] However, evidence syntheses on which to base these discussions are scarce, and the relative degree to which physiological alterations occur during acute treatment with different antidepressants is unclear.[12] It is also unknown which physiological and demographic factors are associated with

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See Online for appendix

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Research in context

Evidence before this study

Antidepressants can affect the normal or proper functioning of the body's organs (ie, physiological disturbance). However, the degree to which physiological alterations occur in patients treated with various antidepressants remains unclear. We searched PubMed for network meta-analyses of randomised blinded trials examining antidepressant monotherapy for any psychiatric disorder, in which outcomes were change in physiological parameters. We searched using the keywords "antidepressant" AND ("weight" OR "blood pressure" OR "heart rate" OR "QTc" OR "metabolic" OR "glucose" OR "cholesterol" OR "lipid" OR "liver" OR "renal" OR "electrolyte" OR "sodium"), from database inception to April 21, 2025, without language restriction, and filtering for meta-analyses. Of the 711 studies retrieved, no network meta-analyses were identified.

Added value of this study

Our findings show frequent and heterogenous physiological side-effects across different antidepressants. The magnitude of some physiological alterations, in particular change in weight, heart rate, and blood pressure is large and clinically relevant.

Implications of all the available evidence

Given the recognised comorbid physical health burden in people with psychiatric conditions, these results can be used by clinicians and patients to guide the choice of antidepressant.

antidepressant-induced physiological dysregulation. Finally, although there is an association between improvements in psychotic symptoms and antipsychotic-induced metabolic disturbance in people with schizophrenia,[13] it is not known if a similar relationship exists between improvements in depressive symptoms and antidepressant-induced metabolic alterations. To address these questions, we performed a network meta-analysis (NMA) of randomised controlled trials (RCTs) comparing antidepressants used as monotherapy across a range of psychiatric disorders—including major depressive disorder (MDD), anxiety disorders, and bipolar affective disorder—to determine the relative effects of different agents on cardiometabolic, hepatic, and renal parameters.

Methods

Search strategy and selection criteria

The protocol was registered on PROSPERO (CRD42019159328) and the study is reported following PRISMA (appendix pp 2–4).[14] AA, GB, RC, VF, and VM searched Embase, Medline, PsycINFO, ClinicalTrials.gov, and the US Food and Drug Administration (FDA) website from database inception to April 21, 2025, without language restrictions (appendix p 5). We included both single-blinded and double-blinded RCTs that compared antidepressants with a placebo or with another antidepressant when used as monotherapy for the acute treatment (8 weeks, as previously defined[4]) of adults (aged 18 years and older) with a psychiatric disorder (appendix p 5). Eligible psychiatric conditions included MDD, anxiety disorders, bipolar disorder, sleep disorders, schizophrenia, and behavioural addictions. We also included trials in fibromyalgia given the frequent use of antidepressants to treat co-occurring affective symptoms in this population. Trials were required to report at least one physiological parameter. If 8-week data were not available, we selected data closest to 8 weeks. When relevant, clinical trials registry data were used to supplement or clarify published findings.

Data extraction

Pairs of investigators (AA, RC, VF, and GB) independently screened references and extracted study-level data, with discrepancies adjudicated by AA and TP. We extracted mean and SD, SE, or 95% CIs for changes from trial initiation to end of treatment or final value scores for drug and placebo groups in the following outcomes: weight (kg); systolic–diastolic blood pressure (mmHg); heart rate (beats per min [bpm]); corrected QT interval (QTc; msec); glucose, total cholesterol, sodium, potassium, and urea (all mmol/L); bilirubin and creatinine (μmol/L); aspartate transferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP; all IU/L). We also extracted publication year; total depressive symptom change (mean and variance, measured using Hamilton or Montgomery–Åsberg Depression Rating Scales); baseline weight; study duration; mean age; sex (% female); and ethnicity (% White). Authors were contacted to request unreported data. We used the Cochrane Risk of Bias 2 tool[15] to classify risk of bias for studies, and the Risk Of Bias due to Missing Evidence in Network meta-analysis tool to evaluate publication bias (appendix pp 5–7).[16]

Data analysis

Analyses were carried out in R (version 4.2.2). For pairwise comparisons informed by ten or more studies we synthesised data in a random-effects meta-analysis with the metafor package (version 3.8–1).[17] The relative treatment effect on each physiological parameter and for each treatment comparison was estimated as mean difference with 95% CIs, apart from QTc, where we calculated standardised mean difference (SMD) owing to different calculations used in its derivation across studies. We investigated heterogeneity by monitoring τ (SD of random effects). We assessed small study effects and publication bias using Egger's regression and we evaluated the possibility of publication bias by inspecting contour-enhanced funnel plots.

Transitivity—the core assumption of NMA—requires that studies grouped by treatment comparisons are

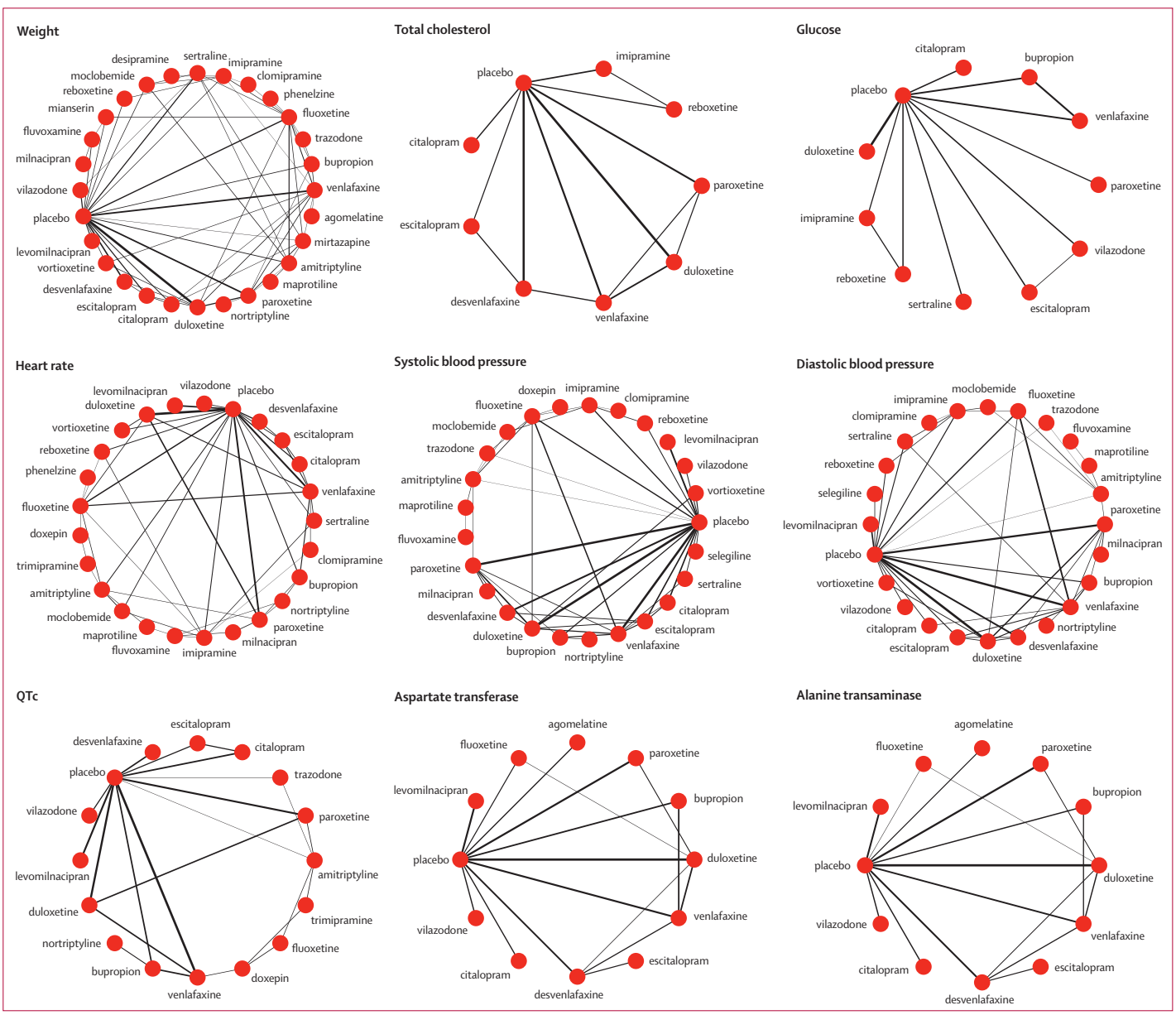
sufficiently similar in the distribution of key effect modifiers, to allow valid indirect comparisons.[18] We assessed this transitivity by examining the distribution of age and sex across treatment comparisons.

We fitted random-effects frequentist NMAs, assuming a common random-effects standard deviation (τ) for all network comparisons. We fitted models in R using the netmeta package (version 2.8–2).[19,20] We generated a Kilim plot summarising the results across all outcomes and antidepressants.[21]

Heterogeneity refers to variation in relative effects across studies comparing the same treatments; we assessed this using τ and visualised it with prediction intervals. Consistency refers to the agreement between direct and indirect evidence in the network; we evaluated this using a global (design-by-treatment inconsistency model) and a local method (SIDE method).[22,23]

We incorporated results into the Confidence in Network Meta-Analysis[24] tool to evaluate credibility of findings, which grades confidence in results of each treatment comparison as high, moderate, low, or very low (appendix pp 6–7).

We hypothesised that inclusion of various study populations might contribute to heterogeneity and inconsistency. Thus, we assessed the sensitivity of findings by repeating each NMA with studies only



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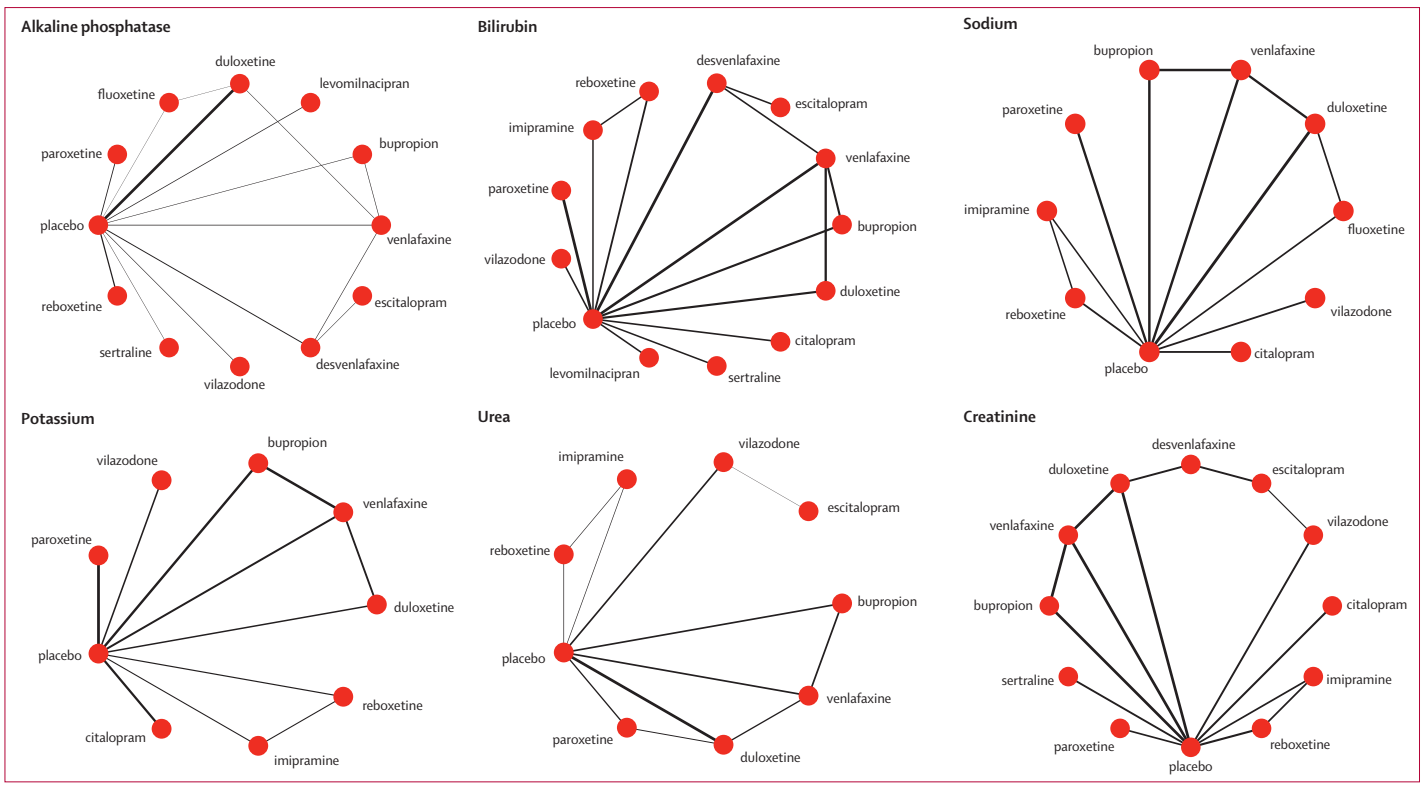


Figure 1: **Network graphs of effects of antidepressant drugs on physiological parameters**
Treatments with direct comparisons are linked with a line; the thickness of connecting lines corresponds to the number of trials evaluating the comparison. QTc=heart-rate corrected QT interval.

examining patients with MDD—ie, excluding studies examining other psychiatric conditions, or studies of MDD with other comorbid psychiatric disorders.

We estimated the proportion of individuals who had clinically relevant change in weight from individual antidepressants. These estimates were derived from NMA results using a model proposed by Furukawa and colleagues.[25] Clinically relevant weight change was defined as gaining or losing 2 kg, consistent with previous reports.[26]

Age, sex, and weight might influence the parameters we were assessing;[27] therefore, as an exploratory analysis, we investigated if these covariates were related to antidepressant-induced physiological changes. Using the metafor package (version 3.8–1),[17] we performed meta-regressions using placebo-controlled data (grouping antidepressants together) aiming to examine the relationship between antidepressant-induced physiological change and mean baseline weight, age, and sex at the study level. We also estimated p values corrected for false discovery rate (p_{FDR}).

In people with schizophrenia, correlations between improvements in psychotic symptom severity and antipsychotic-induced metabolic disturbance are observed.[13] To examine if a similar relationship exists between improvements in depressive symptoms and antidepressant-induced metabolic disturbance, we performed bivariate meta-analyses using placebo-controlled data in studies of MDD alone—ie, excluding studies examining other psychiatric conditions, or studies of MDD with other comorbid psychiatric disorders. We meta-analysed the mean difference for change in weight, total cholesterol, and glucose, and the SMD for change in total depressive symptoms. Given that within-study correlations between the outcomes were not reported, we used a model proposed by Riley and colleagues that overcomes this problem, using the metamisc package (version 0.2.0).[28] We used this model to estimate the correlation at the study level between three physiological parameters (weight, total cholesterol, and glucose) and treatment effects in depressive symptoms, and calculated p values for the null hypothesis of zero correlation. We also estimated p_{FDR}.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Of 26 252 citations retrieved, 151 studies and 17 FDA study reports met inclusion criteria (search process provided in appendix p 8). These trials examined agomelatine (n=2), amitriptyline (n=20), bupropion

(n=3), citalopram (n=5), clomipramine (n=3), desipramine (n=1), desvenlafaxine (n=11), doxepin (n=3), duloxetine (n=27), escitalopram (n=9), fluoxetine (n=32), fluvoxamine (n=7), imipramine (n=15), levomilnacipran (n=6), maprotiline (n=3), mianserin (n=2), milnacipran (n=3), mirtazapine (n=10), moclobemide (n=4), nortriptyline (n=4), paroxetine (n=27), phenelzine (n=1), reboxetine (n=5), selegiline (n=1), sertraline (n=14), trazodone (n=4), trimipramine (n=3), venlafaxine (n=31), vilazodone (n=6), and vortioxetine (n=2) monotherapy for MDD, psychotic depression, atypical depression, MDD with generalised anxiety disorder, MDD with multi-somatoform disorder, MDD with pain, dysthymia, obsessive compulsive disorder, generalised anxiety disorder, social anxiety disorder, panic disorder, post-traumatic stress disorder, fibromyalgia, and bipolar

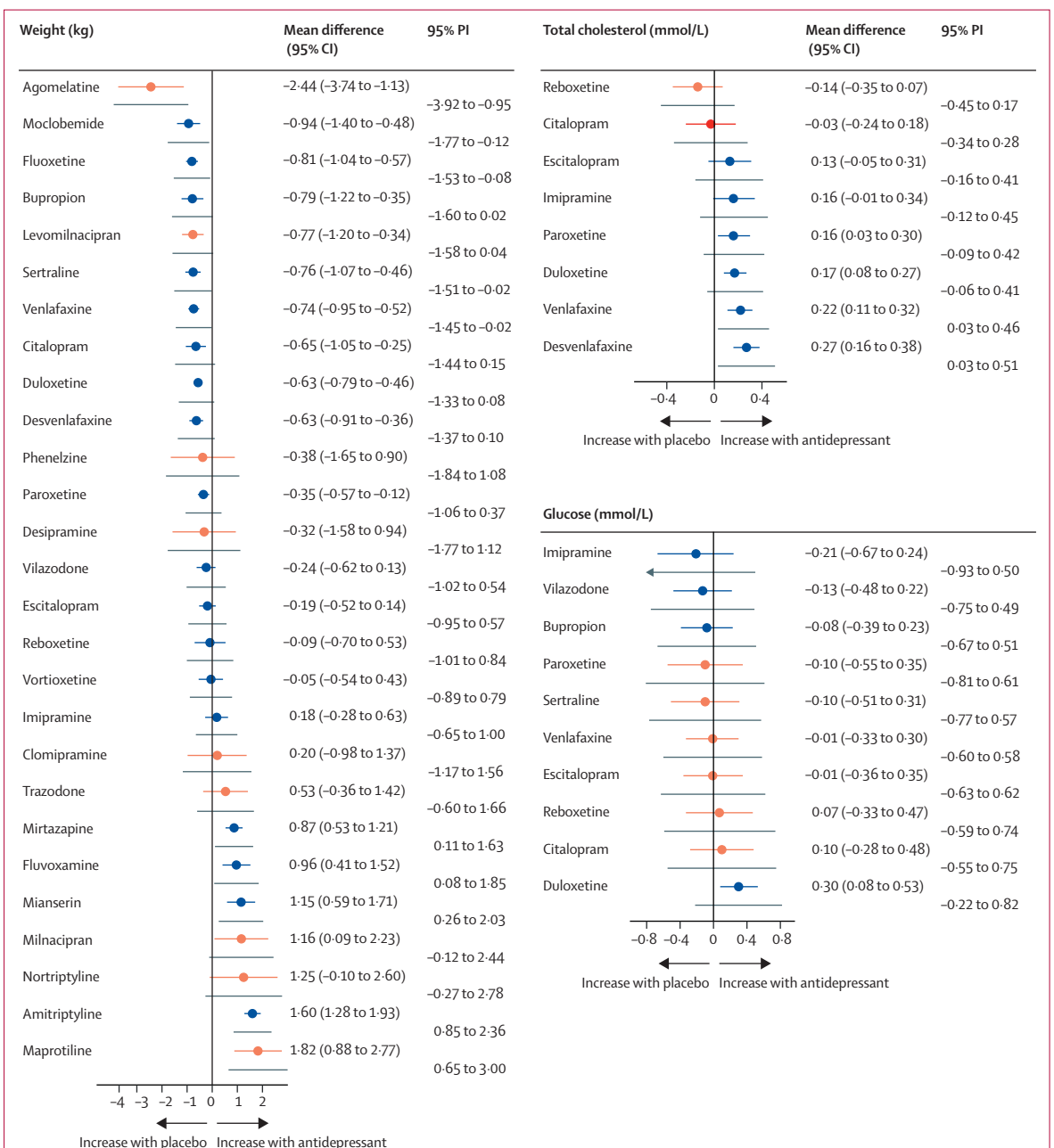
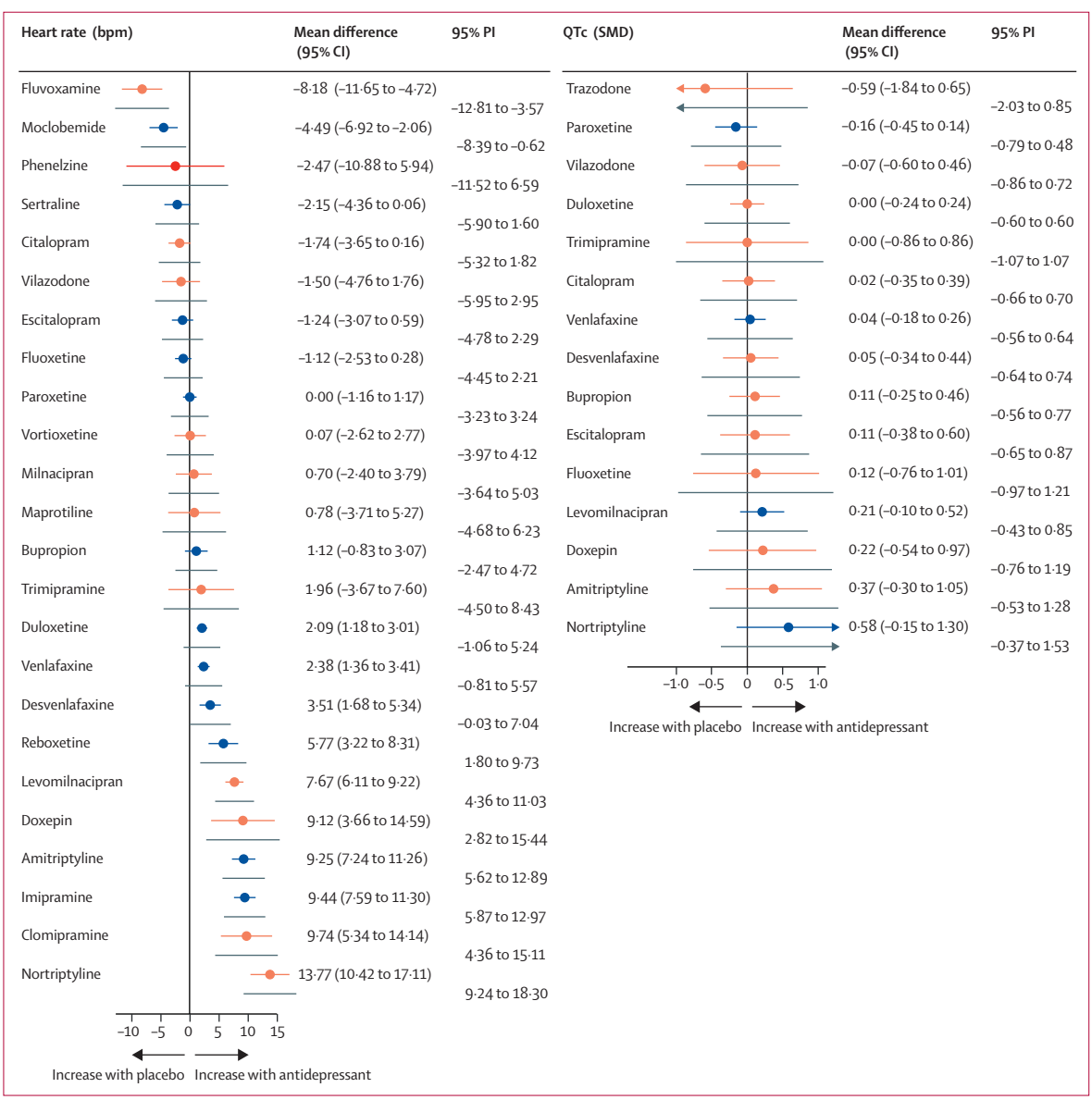


Figure 2: **Network plots for mean differences of antidepressant drugs compared with placebo**
Drugs are ordered from lowest to highest mean difference. Colours indicate the confidence in the evidence for a given comparison: blue is moderate, orange is low, and red is very low. Confidence of outcomes was graded using the Confidence in Network Meta-Analysis application. Grey lines immediately below each coloured line indicate the PI corresponding to that antidepressant–placebo comparison. PI=prediction interval.

affective disorder (appendix pp 9–49). The overall sample included 58 534 participants (41 937 antidepressant-treated, 16 597 placebo-treated). The mean age was 44·7 years (SD 15·8), 62·0% of participants with reported data were female versus 38·0% male, and 74·8% with reported ethnicity were White. Treatment duration was 3–12 weeks (median 8 weeks [IQR 6·0–8·5]). Risk of bias was deemed high for four trials (appendix pp 50–56).

Age and sex were similarly distributed across treatment comparisons (appendix pp 57–58). There were ten pairwise comparisons with ten or more studies (appendix pp 59–68). We found some evidence of small study effects and publication bias for the comparisons of duloxetine, paroxetine, and venlafaxine with placebo for change in systolic blood pressure, and for the comparison of paroxetine with placebo for change in diastolic blood pressure. Network graphs are shown (figure 1). Estimated effects for mean change and standardised mean change in physiological parameter for antidepressants with placebo as the reference treatment are shown (figures 2–4), along with a Kilim plot summarising results across all outcomes and antidepressants (figure 5). League tables comparing antidepressants for each parameter are provided in the appendix (pp 69–83). Local assessments of inconsistency and Confidence in Network Meta-Analysis confidence ratings are shown in the appendix (pp 84–168). Following methodological recommendations, we avoided the notion of statistical significance in characterising our results.[29]

For change in weight, 116 studies compared 27 different antidepressants (32 249 participants) with placebo



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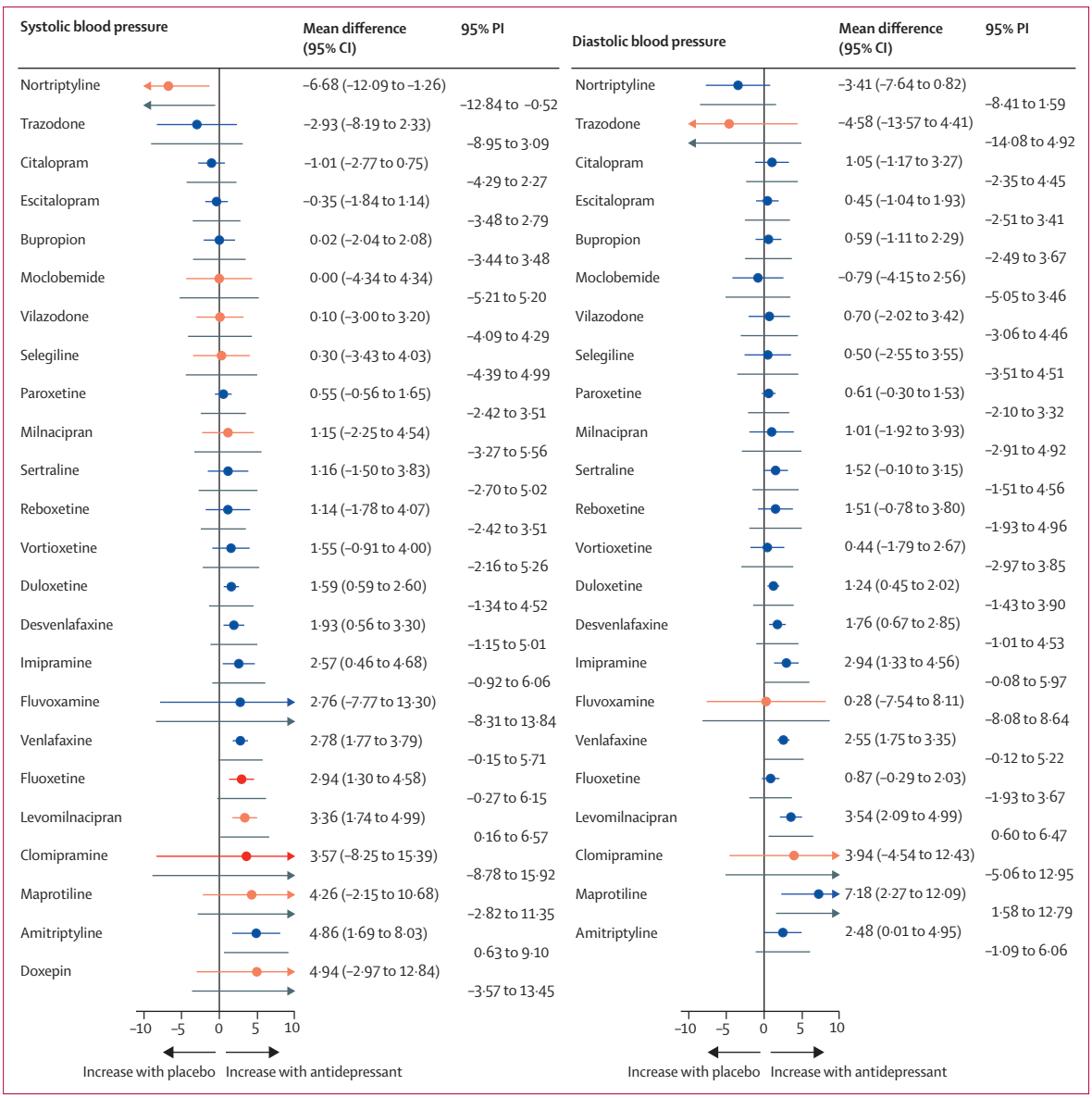

Figure 3: **Network plots for mean differences of antidepressant drugs compared with placebo**
Drugs are ordered from lowest to highest mean difference. Colours indicate the confidence in the evidence for a given comparison: blue is moderate, orange is low, and red is very low. Confidence of outcomes was graded using the Confidence in Network Meta-Analysis application. Grey lines immediately below each coloured line indicate the PI corresponding to that antidepressant–placebo comparison. bpm=beats per minute. PI=prediction interval. QTc=heart-rate corrected QT interval. SMD=standardised mean difference.

(12 614 participants). When compared with placebo, we found strong evidence of weight loss (mean difference relative to placebo/kg) with agomelatine (–2·44 [95% CI –3·74 to –1·13]), moclobemide (–0·94 [–1·40 to –0·48]), fluoxetine (–0·81 [–1·04 to –0·57]), bupropion (–0·79 [–1·22 to –0·35]), levomilnacipran (–0·77 [–1·20 to –0·34]), sertraline (–0·76 [–1·07 to –0·46]), venlafaxine (–0·74 [–0·95 to –0·52]), duloxetine (–0·63 [–0·79 to –0·46]), citalopram (–0·65 [–1·05 to –0·25]), desvenlafaxine (–0·63 [–0·91 to –0·36]), and paroxetine (–0·35 [–0·57 to –0·12]; figure 2). By contrast, we found strong evidence of weight gain with maprotiline (1·82 [0·88 to 2·77]), amitriptyline (1·60 [1·28 to 1·93]), milnacipran (1·16 [0·09 to 2·23]), mianserin (1·15 [0·59 to 1·71]), fluvoxamine (0·96 [0·41 to 1·52]), and mirtazapine (0·87 [0·53 to 1·21]). We found weaker evidence of weight gain with nortriptyline and trazodone. We found little evidence of change in weight with phenelzine, desipramine, vilazodone, escitalopram, vortioxetine, reboxetine, imipramine, and clomipramine. τ was 0·31 kg, considered small in the context of the observed changes. Inspection of prediction intervals

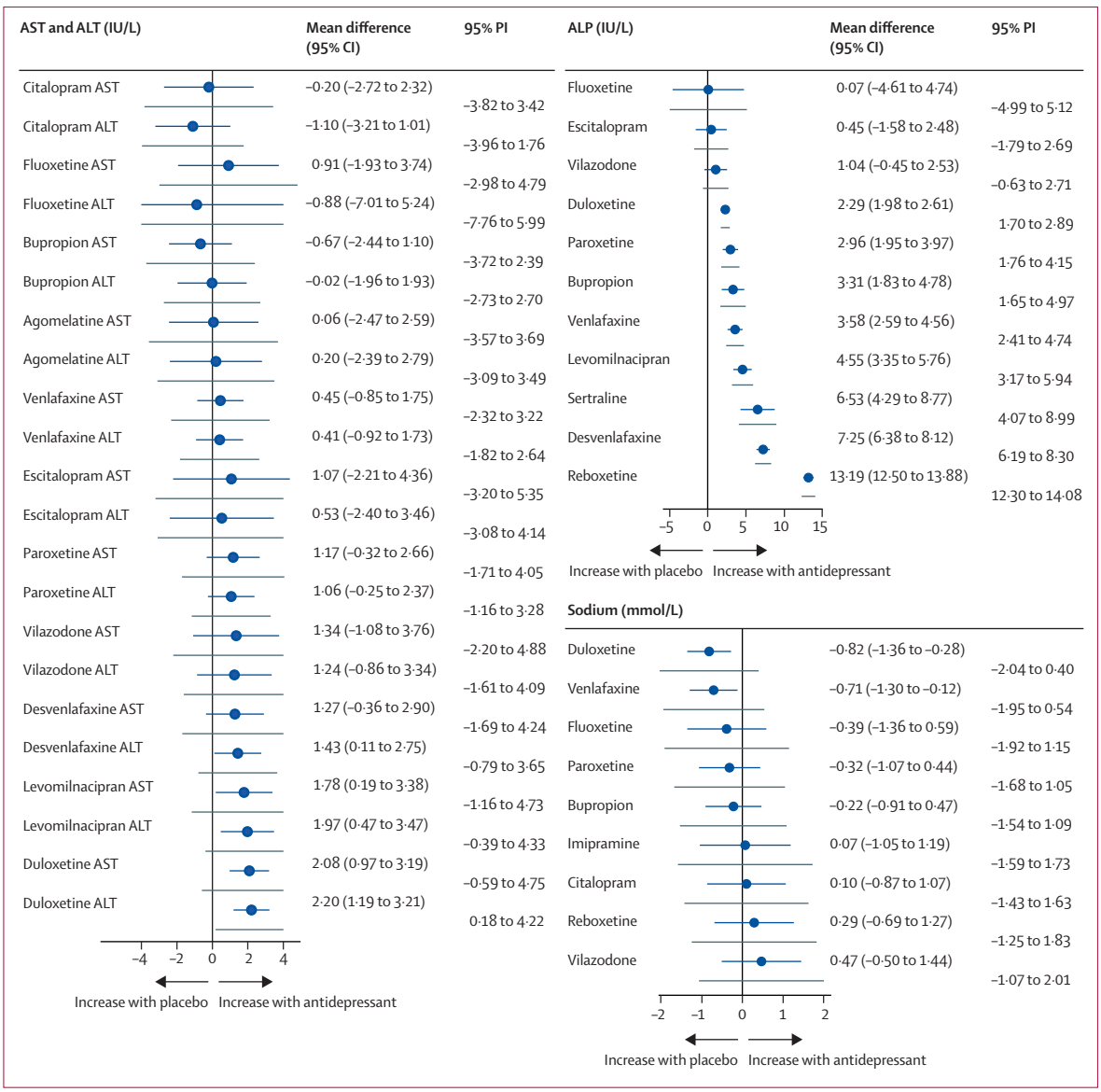

Figure 4: **Network plots for mean differences of antidepressant drugs compared with placebo**
Drugs are ordered from lowest to highest mean difference. Colours indicate the confidence in the evidence for a given comparison: blue is moderate, orange is low, and red is very low. Confidence of outcomes was graded using the Confidence in Network Meta-Analysis application. Grey lines immediately below each coloured line indicate the PI corresponding to that antidepressant–placebo comparison. ALP=alkaline phosphatase. ALT=alanine transaminase. AST=aspartate transferase. PI=prediction interval.

confirmed that heterogeneity was low, because for most treatment comparisons prediction intervals and CIs led to similar conclusions. The global Q score for inconsistency was 194·66 (p<0·0001), and 15 of 378 treatment comparisons were inconsistent (p<0·05), including some disagreements between direct and indirect evidence. Certainty of evidence was very low in two of 378 comparisons. We estimated that some antidepressants (eg, maprotiline and amitriptyline) cause clinically relevant weight gain in up to 48% of patients (table). By contrast, agomelatine causes clinically important weight loss in an estimated 55% of patients.

For change in total cholesterol, 21 studies compared eight different antidepressants (6033 participants) with a placebo (2799 participants). There was strong evidence of an increase in total cholesterol (mean difference relative to placebo/mmol/L) with desvenlafaxine (0·27 [95% CI 0·16 to 0·38]), venlafaxine (0·22 [0·11 to 0·32]), duloxetine (0·17 [0·08 to 0·27]), and paroxetine (0·16 [0·03 to 0·30]; figure 2). There was weaker evidence of an increase in total cholesterol with imipramine and escitalopram. We found little evidence of change in total cholesterol with citalopram and reboxetine. τ was 0·10, considered medium-large in the context of observed

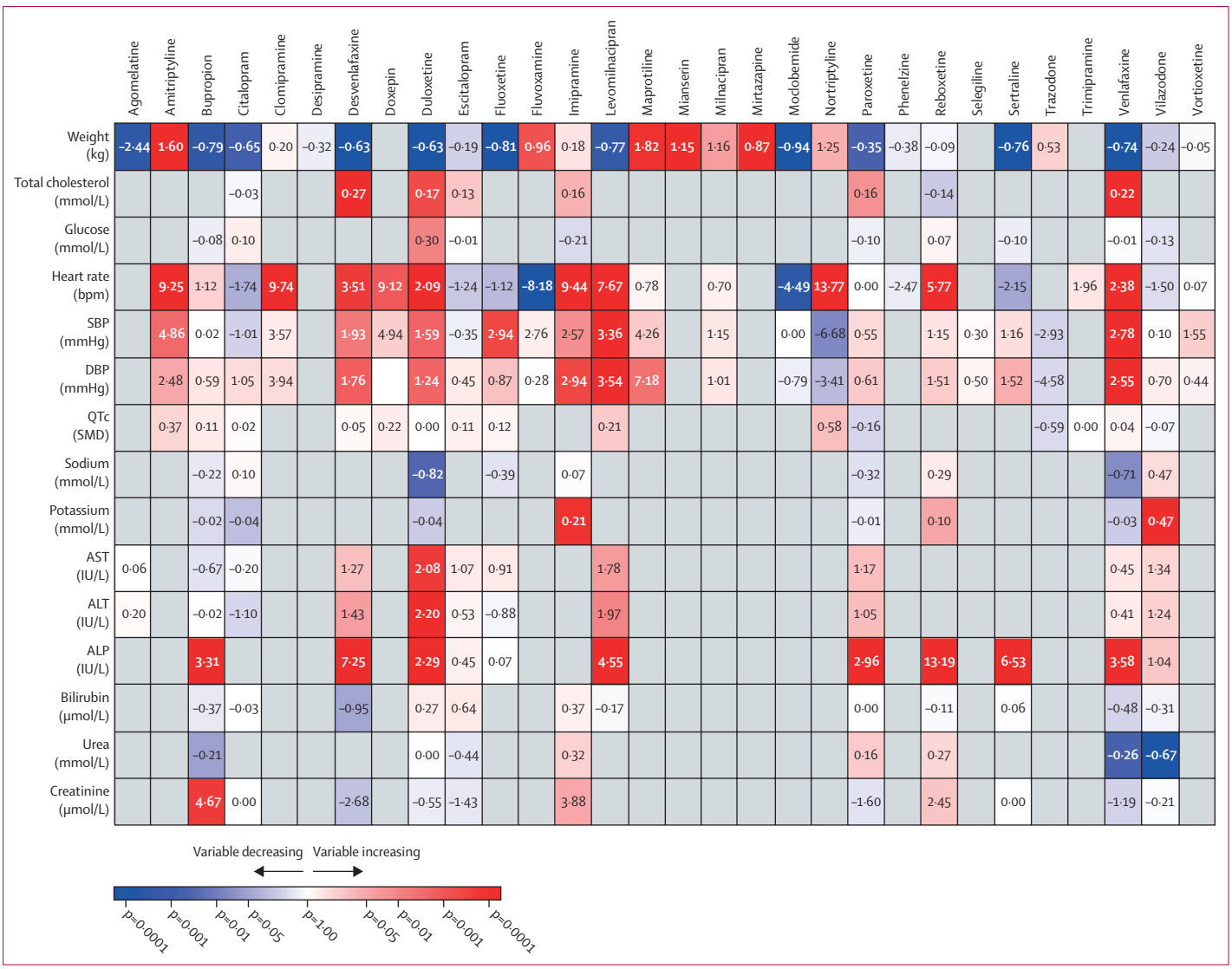

***Figure 5*: Kilim plot comparing antidepressants for 15 physiological parameters**

The colours correspond to the strength of the statistical evidence regarding the relative effects *vs* placebo. A cell with a deep blue colour indicates that the corresponding drug is associated with a significant decrease in that parameter compared to placebo. Conversely, a deep red cell indicates strong evidence that the drug is associated with a significant increase in that parameter. Colours closer to white indicate lack of evidence on whether the drug performs better or worse than placebo. Grey squares indicate that data were not available. Numbers reflect the mean change (standardised mean change for QTc interval) for each parameter and treatment versus placebo. ALP=alkaline phosphatase. ALT=alanine transaminase. AST=aspartate transferase. DBP=diastolic blood pressure. QTc=heart-rate corrected QT interval. SBP=systolic blood pressure.

changes. The global Q score for inconsistency was 43·49 (p=0·0004), and two of 36 treatment comparisons were shown to be inconsistent. Certainty of evidence was very low in four of 36 comparisons.

For change in glucose, 14 studies compared ten different antidepressants (3729 participants) with placebo (2240 participants). There was strong evidence of an increase in glucose (mean difference relative to placebo/mmol/L) with duloxetine (0·30 [95% CI 0·08 to 0·53]; figure 2). However, we did not find evidence of change in glucose with imipramine, vilazodone, bupropion, paroxetine, sertraline, venlafaxine, escitalopram, reboxetine, or citalopram. τ was 0·18, considered large in the context of the observed changes. The global Q score for inconsistency was 17·9 (p=0·012); no hotspots of inconsistency were identified. There were no comparisons with very low certainty of evidence.

For change in heart rate, 80 studies compared 24 different antidepressants (24132 participants) with placebo (8435 participants). There was strong evidence of an increase in heart rate (mean difference relative to placebo/bpm) with nortriptyline (13·77 [95% CI 10·42 to 17·11]), clomipramine (9·74 [5·36 to 14·14]), imipramine (9·44 [7·59 to 11·30]), amitriptyline (9·25 [7·24 to 11·26]), doxepin (9·12 [3·66 to 14·59]), levomilnacipran (7·67 [6·11 to 9·22]), reboxetine

	≥2 kg weight gain	≥2 kg weight loss
Maprotiline	48·1% (38·3–58·0)	15·7% (10·5–22·4)
Amitriptyline	46·3% (43·4–49·3)	20·3% (18·3–22·5)
Vortioxetine	45·7% (44·7–46·7)	45·9% (44·9–46·9)
Milnacipran	43·8% (36·1–51·7)	27·8% (21·6–34·9)
Fluvoxamine	42·8% (39·1–46·6)	30·3% (27·0–33·8)
Nortriptyline	41·8% (28·2–56·5)	18·6% (10·3–30·1)
Mirtazapine	41·8% (39·4–44·2)	29·9% (27·8–32·1)
Escitalopram	37·9% (36·1–39·6)	39·9% (38·1–41·7)
Citalopram	37·2% (35·3–39·1)	43·4% (41·4–45·3)
Vilazodone	37·4% (35·3–39·4)	40·0% (37·9–42·1)
Levomilnacipran	35·4% (33·2–37·6)	43·4% (41·1–45·7)
Imipramine	34·9% (31·4–38·6)	32·2% (28·8–35·7)
Desvenlafaxine	34·2% (32·6–35·7)	41·6% (39·9–43·3)
Paroxetine	34·4% (33·0–35·8)	38·9% (37·4–40·4)
Trazodone	34·3% (25·8–43·7)	24·3% (17·3–32·6)
Duloxetine	33·8% (32·9–34·8)	41·4% (40·4–42·4)
Venlafaxine	33·3% (32·1–34·5)	42·1% (40·8–43·5)
Mianserin	31·9% (21·8–43·6)	4·1% (2·0–7·6)
Sertraline	30·9% (28·9–32·8)	41·1% (39·0–43·3)
Reboxetine	30·2% (25·1–35·7)	31·8% (26·6–37·4)
Clomipramine	30·1% (19·4–42·8)	26·1% (16·4–38·3)
Bupropion	29·8% (27·0–32·7)	40·9% (37·7–44·1)
Fluoxetine	28·7% (27·1–30·3)	40·6% (38·8–42·4)
Desipramine	27·1% (17·3–39·0)	32·9% (22·0–45·6)
Moclobemide	21·8% (18·4–25·5)	38·9% (34·3–43·7)
Phenelzine	21·2% (11·0–35·5)	29·3% (16·6–45·4)
Placebo	19·4% (19·0–19·9)	19·4% (19·0–19·9)
Agomelatine	11·2% (5·8–19·5)	54·8% (40·6–68·4)

Data shown are % (95% CI). Treatments are ranked in descending order based on the estimated proportion of individuals gaining ≥2 kg.

Table: **Estimated proportion of individuals with clinically relevant weight changes with each antidepressant included in the network meta-analysis of weight change**

(5·77 [3·22 to 8·31]), desvenlafaxine (3·51 [1·68 to 5·34]), venlafaxine (2·38 [1·36 to 3·41]), and duloxetine (2·09 [1·18 to 3·01]; figure 3). By contrast, there was strong evidence of a reduction in heart rate with fluvoxamine (–8·18 [–11·65 to –4·72]) and moclobemide (–4·49 [–6·92 to –2·06]). There was weak evidence of a reduction in heart rate with fluoxetine, escitalopram, citalopram, and sertraline. We found little evidence of change in heart rate with phenelzine, vilazodone, paroxetine, vortioxetine, milnacipran, maprotiline, bupropion, and trimipramine. τ was 1·53 bpm, considered small in the context of the observed changes, and conclusions drawn from prediction intervals and CIs were similar. The global Q score for inconsistency was 213·64 (p<0·0001), and hotspots of inconsistency were identified in six of 231 comparisons. Certainty of evidence was very low in 30 of 300 comparisons.

For change in systolic blood pressure, 73 studies compared 24 different antidepressants (23 593 participants) with placebo (8350 participants). There was strong evidence of an increase in systolic blood pressure (mean difference relative to placebo/mmHg) with amitriptyline (4·86 [95% CI 1·69 to 8·03]), levomilnacipran (3·36 [1·74 to 4·99]), fluoxetine (2·94 [1·30 to 4·58]), venlafaxine (2·78 [1·77 to 3·79]), imipramine (2·57 [0·46 to 4·68]), desvenlafaxine (1·93 [0·56 to 3·30]), and duloxetine (1·59 [0·59 to 2·60]; figure 3). By contrast, there was strong evidence of a reduction in systolic blood pressure with nortriptyline (–6·68 [–12·09 to –1·26]). We found little evidence of change in systolic blood pressure with trazodone, citalopram, escitalopram, bupropion, moclobemide, vilazodone, selegiline, paroxetine, milnacipran, sertraline, reboxetine, vortioxetine, fluvoxamine, clomipramine, maprotiline, and doxepin. τ was 1·38 mmHg, considered large in the context of the observed changes. However, the prediction intervals did not change our conclusions when compared with CIs. The global Q score for inconsistency was 136·39 (p<0·0001), and hotspots of inconsistency were identified in three of 300 treatment comparisons. Certainty of evidence was very low in 46 of 300 comparisons.

For change in diastolic blood pressure, 75 studies compared 23 different antidepressants (23 917 participants) with placebo (8230 participants). There was strong evidence of an increase in diastolic blood pressure (mean difference relative to placebo/mmHg) with amitriptyline (2·48 [95% CI 0·01 to 4·95]), maprotiline (7·18 [2·27 to 12·09]), levomilnacipran (3·54 [2·09 to 4·99]), venlafaxine (2·55 [1·75 to 3·35]), imipramine (2·94 [1·33 to 4·56]), desvenlafaxine (1·76 [0·67 to 2·85]), and duloxetine (1·24 [0·45 to 2·02]; figure 3). There was weak evidence of an increase in diastolic blood pressure with fluoxetine, sertraline, and reboxetine. We found little evidence of change in diastolic blood pressure with clomipramine, fluvoxamine, vortioxetine, milnacipran, paroxetine, selegiline, vilazodone, moclobemide, bupropion, escitalopram, citalopram, trazodone, and nortriptyline. τ was 1·27 mmHg, considered large in the context of the observed changes. However, conclusions drawn from prediction intervals and CIs were similar. The global Q score for inconsistency was 226·70 (p<0·0001), and three of 276 treatment comparisons were found to be inconsistent. There were no comparisons with very low certainty of evidence.

For change in QTc, 29 studies compared 15 antidepressants (7392 participants) with placebo (3559 participants). There was weak evidence of an increase in QTc (SMD relative to placebo) with nortriptyline (0·58 [95% CI –0·15 to 1·30]) and amitriptyline (0·37 [–0·30 to 1·05]; figure 3). We found little evidence of change in QTc with doxepin, levomilnacipran, fluoxetine, escitalopram, bupropion, desvenlafaxine, venlafaxine, citalopram, trimipramine, duloxetine, vilazodone, paroxetine, and trazodone. τ was 0·26, considered large in the context of observed

changes. The global Q score for inconsistency was 119·97 (p<0·0001) and one of 120 treatment comparisons was inconsistent. Certainty of evidence was very low in one of 120 comparisons.

For change in AST and ALT, 23 (AST) and 22 (ALT) studies compared the same 11 antidepressants with placebo (AST: 8926 antidepressant-treated, 4325 placebo-treated; ALT: 9028 antidepressant-treated, 4166 placebo-treated). There was strong evidence of an increase in both AST and ALT (mean difference relative to placebo/IU/L) with duloxetine (AST 2·08 [95% CI 0·97 to 3·19]; ALT 2·20 [1·19 to 3·21]) and levomilnacipran (AST 1·78 [0·19 to 3·38]; ALT 1·97 [0·47 to 3·47]; figure 4). There was strong evidence of an increase in ALT and weaker evidence of an increase in AST with desvenlafaxine (ALT 1·43 [0·11 to 2·75]; AST 1·27 [–0·36 to 2·90]). There was also weak evidence of an increase in both AST and ALT with paroxetine and vilazodone. We found little evidence of change in AST and ALT with citalopram, fluoxetine, agomelatine, venlafaxine, and escitalopram. τ was 1·13 IU/L for AST and 0·80 IU/L for ALT, both considered large in the context of observed changes. Global Q scores for inconsistency were 46·78 (p=0·0001) for AST and 25·22 (p=0·066) for ALT. Neither NMAs showed evidence of local inconsistency. There were no comparisons with very low certainty of evidence.

For ALP, 25 studies compared 11 antidepressants (7928 participants) with placebo (4265 participants). There was strong evidence of an increase in ALP (mean difference relative to placebo/IU/L) with reboxetine (13·19 [95% CI 12·50 to 13·88]), desvenlafaxine (7·25 [6·38 to 8·12]), sertraline (6·53 [4·29 to 8·77]), levomilnacipran (4·55 [3·35 to 5·76]), venlafaxine (3·58 [2·59 to 4·56]), bupropion (3·31 [1·83 to 4·78]), paroxetine (2·96 [1·95 to 3·97]), and duloxetine (2·29 [1·98 to 2·61]; figure 4). There was weak evidence of an increase in ALP with vilazodone (1·04 [–0·45 to 2·53]). We found little evidence of a change in ALP with fluoxetine and escitalopram. τ was 0·23 IU/L, considered small in the context of observed changes, and the prediction intervals did not change our conclusions when compared with CIs. The global Q score for inconsistency was 30·63 (p=0·032) and one of 45 treatment comparisons was inconsistent. There were no comparisons with very low certainty of evidence.

For bilirubin, 20 studies compared 12 antidepressants (7656 participants) with placebo (3590 participants). We did not find evidence of change in bilirubin with bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, imipramine, levomilnacipran, paroxetine, reboxetine, sertraline, venlafaxine, or vilazodone. τ was 0·84 µmol/L, considered large in the context of observed changes. The global Q score for inconsistency was 121·81 (p<0·0001) but no hotspots of inconsistency were identified. There were no comparisons with very low certainty of evidence.

For change in sodium, 14 studies compared 9 antidepressants (4281 participants) with placebo (1948 participants). There was strong evidence of a reduction in sodium concentrations (mean difference relative to placebo/mmol/L) with duloxetine (–0·82 [95% CI –1·36 to –0·28]) and venlafaxine (–0·71 [–1·30 to –0·12]; figure 4). We found little evidence of change in sodium with fluoxetine, paroxetine, bupropion, imipramine, citalopram, reboxetine, and vilazodone. τ was 0·46 mmol/L, considered large in the context of the observed changes. The global Q score for inconsistency was 28·08 (p=0·0018), but no hotspots of inconsistency were identified. There were no comparisons with very low certainty of evidence.

We did not find strong evidence of any antidepressant affecting levels of potassium, urea, and creatinine to a clinically significant extent. Full results are presented in the appendix (p 169).

Sensitivity analyses focusing only on studies of MDD gave broadly similar estimated effects, and heterogeneity and inconsistency assessments did not materially change (appendix pp 170–175).

At the study level, there was strong evidence that higher mean baseline bodyweight was associated with larger antidepressant-induced increases in systolic blood pressure (n=38, estimate=0·23 mmHg per 1 kg increase in weight [95% CI 0·08–0·37]; p=0·0018; p_{FDR}=0·0081), ALT (n=13, estimate=0·18 IU/L per 1 kg increase in weight [0·11–0·26], p<0·0001, p_{FDR}<0·0001), and AST (n=13, estimate=0·17 IU/L per 1 kg increase in weight [0·04–0·29], p=0·0078, p_{FDR}=0·023; appendix p 176). There was also evidence that higher baseline mean age was associated with larger antidepressant-induced increases in glucose (n=11, estimate=0·01 mmol/L per 1 year increase in age [0·01–0·02], p<0·0001, p_{FDR}<0·0001). We did not find evidence of sex influencing antidepressant-induced physiological alterations.

We did not find evidence of a correlation between change in depressive symptom severity and change in weight, glucose concentrations, or total cholesterol concentrations (appendix p 177).

Discussion

Our main findings are that antidepressants can induce cardiometabolic and other physiological alterations and that these vary between antidepressants. Marked differences were particularly evident for change in weight, heart rate, and blood pressure, with clinically significant differences in effects between drugs, including an approximate 4 kg difference in weight change between agomelatine and maprotiline, over 21 bpm difference in heart rate change between fluvoxamine and nortriptyline, and over 11 mmHg difference in systolic blood pressure between nortriptyline and doxepin. We estimate that some antidepressants (eg, maprotiline and amitriptyline) cause clinically important weight gain in almost half of individuals prescribed them. To the best of our knowledge, this meta-analysis is the first to examine

study-level associations between baseline parameters and antidepressant-induced physiological changes after a short course of treatment. We found that at the study level, bodyweight is associated with antidepressant-induced changes in haemodynamic and hepatic parameters, and age with antidepressant-induced metabolic changes. In contrast to studies in people with schizophrenia, in which improvements in psychotic symptom severity were correlated with antipsychotic-induced metabolic disturbance,[13] we did not observe a correlation between change in depressive symptoms and metabolic alterations in individuals with MDD.

We acknowledge some limitations to our study. Although we used strict inclusion criteria to obtain a homogenous sample, there was evidence of inconsistency for NMAs of all parameters except for AST, potassium, and urea. Inconsistency might have been secondary to imbalances in the distribution of some effect-modifiers observed across comparisons and small-study effects and publication bias noted in pairwise meta-analysis. Although we hypothesised that the inclusion of various study populations might contribute to inconsistency, sensitivity analyses focusing only on studies of MDD did not materially change inconsistency assessments or measures of effect, supporting the inclusion of these data in primary analyses. Furthermore, only 3% of studies were deemed to be at high risk of bias, and confidence in the evidence of the comparisons across all parameters was very low for only 4% of treatment comparisons. Despite the scope of our review, the number of RCTs reporting several important parameters—most notably for metabolic outcomes—was scarce, reflecting broader gaps in the evidence base, and highlighting the need for those outcomes to be routinely measured in future trials. Despite attempts to contact authors, we were unable to obtain data for several trials. Some unexpected or isolated findings might reflect true pharmacological differences between drugs but could also represent statistical artefacts arising from outlying data; future studies using larger individual participant datasets or mechanistically focused designs are needed to clarify these observations. Moreover, meta-regression analyses were based on study-level data and are therefore vulnerable to ecological fallacy;[30] these require replication with individual patient data. In particular, the absence of sex-stratified results in most trials limited our ability to assess sex-specific effects, highlighting the need for future studies to report outcomes separately for men and women. Finally, although categorical thresholds (eg, QTc >500 ms or development of torsade de pointes [TdP]) might better characterise some adverse outcomes, such data are inconsistently reported in RCTs. Continuous outcomes offer a practical proxy, enabling estimates of how many individuals might cross clinically relevant thresholds based on shifts in both mean and distribution. Importantly, risk does not rise abruptly at fixed cut-offs, such as 500 ms for QTc, but increases incrementally. Modelling outcomes as continuous variables more accurately reflects underlying biological risk.

In the general population it is estimated that for every kg increase in bodyweight, cardiovascular disease risk increases by approximately 3%.[31] Furthermore, increased heart rate is associated with greater lifetime risk of death.[32] For example, in men older than 50 years, every beat increase in heart rate is associated with a 3% higher risk for all-cause death.[33] Moreover, in patients with hypertension, risk of stroke death increases by 1% for every 1 mmHg increase in untreated systolic blood pressure.[34] Taking amitriptyline as an illustration, these data suggest that 8 weeks of treatment with amitriptyline, which increases weight by approximately 1·5 kg, heart rate by 9 bpm, and systolic blood pressure by 5 mmHg, could lead to important increases in cardiovascular disease risk and mortality. It should be noted that our data reflect mean effects and, although illustrative of the potential implications, the effect on a given individual's risk for disease will vary depending on the pre-existing risk profile. Nevertheless, given the widespread use of antidepressants, even relatively small differences in cardiometabolic parameters could have a major effect at the population level. Weight gain was most evident with antidepressants that antagonise histamine H1 and serotonin 5-HT2C receptors, such as mirtazapine and several tricyclic antidepressants. This finding is consistent with their pharmacology, as H1 and 5-HT2C antagonism is associated with weight gain.[35] However, most antidepressants we examined were associated with reductions in bodyweight. This finding contrasts with results of longer-term population-based cohort studies that have observed weight gain associated with antidepressant prescription.[6] The absence of an adequate control group and confounding by indication in the observational studies[36] could explain the discrepancy in findings from our results, which are based on RCTs. Of note, despite paroxetine, duloxetine, desvenlafaxine, and venlafaxine reducing bodyweight, they were associated with increases in total cholesterol or glucose concentrations. Previous cross-sectional studies have observed an association between antidepressant prescription and metabolic dysregulation, although usually in the context of weight gain.[37] Further work is required to clarify the long-term relationship between antidepressants and change in weight and broader metabolic disturbance. We found strong evidence of clinically relevant increases in blood pressure with the serotonin–noradrenaline reuptake inhibitors (SNRIs) duloxetine, desvenlafaxine, venlafaxine, and levomilnacipran, and the tricyclic antidepressants imipramine, maprotiline, and amitriptyline. These results align with their shared noradrenergic activity and are consistent with previous reports linking these antidepressant classes with risk of hypertension.[5] We did not find strong evidence of any antidepressant affecting potassium, urea, or creatinine concentrations to a

clinically significant extent. Although we did not observe strong evidence of QTc prolongation or clinically relevant sodium reduction with any antidepressant in our NMA, large register-based studies report otherwise. For example, Farmand and colleagues[7] and Leth-Møller and colleagues[8] identified citalopram as having the highest risk of hyponatraemia, with duloxetine and venlafaxine showing lower risk—patterns not reflected in our RCT-based findings. Similarly, Danielsson and colleagues[9] found citalopram most frequently associated with TdP, in contrast to the minimal QTc effects seen in our analysis. These discrepancies probably reflect methodological differences. RCTs typically enrol younger, healthier individuals (mean age in our NMA was 44·7 years), use monotherapy, and report mean physiological changes rather than categorical events, which might lead to underestimation of real-world risks. In contrast, observational studies include broader, older populations, but are more susceptible to confounding. For instance, citalopram's perceived tolerability might lead to its preferential use in older individuals or those with medically complex conditions, inflating risk signals. Notably, the mean age of participants in the study by Farmand and colleagues was 74·0 years,[7] whereas in the study performed by Danielsson and colleagues,[9] the mean age of patients who developed TdP was 71·5 years in men and 74·0 years in women. Danielsson and colleagues also reported that most TdP cases occurred in patients aged 65 years and older with comorbidities and receiving polypharmacy. We interpret our findings as complementary to observational real-world data and emphasise the importance of integrating both evidence sources in clinical decision making. Specifically, our results suggest limited short-term changes in sodium concentrations and QTc duration in patients who were middle-aged, relatively healthy, and monotherapy-treated, but observational data highlight potential long-term risks, especially in older adults with comorbidities who receive polypharmacy. Of 11 antidepressants examined, eight were strongly associated with increased ALP concentrations, of which the SNRIs desvenlafaxine, levomilnacipran, and duloxetine were also associated with increased AST and ALT concentrations. Although the magnitude of these alterations is not clinically significant, this transaminase–ALP pattern is consistent with reports of some of these antidepressants causing cholestasis.[38]

Given the recognised co-morbid physical health burden in people with depression and resultant effects on morbidity and mortality,[39] our findings can be used by clinicians and patients to guide choice of antidepressant. Furthermore, these results can be incorporated into digital tools to facilitate shared decision making and provide patients with personalised treatment options.[12] However, other side-effects not covered in this NMA, such as sexual dysfunction, emotional blunting, and gastrointestinal disturbance, as well as differences in efficacy amongst antidepressants, should also be considered.[4] Furthermore, it is not known if antidepressant-induced physiological effects persist over time (eg, whether increases in heart rate observed with nortriptyline and related agents are sustained or transient); this could be examined by a future meta-analysis of maintenance-phase RCTs. Importantly, our findings should be put in the context of population-based studies showing that patients with depression who receive antidepressant treatment have lowered risk of suicide and all-cause mortality.[40]

In conclusion, we found strong evidence that antidepressants differ markedly in their physiological effects, particularly for cardiometabolic parameters. Treatment guidelines should be updated to reflect differences in physiological risk, but choice of antidepressant should be made on an individual basis, considering clinical presentation and preferences of patients, carers, and clinicians.

Contributors

TP conceptualised the study, performed the statistical analysis, and wrote the manuscript. AA performed the systematic review and contributed to the writing of the manuscript. TP and AA verified the underlying data reported in the manuscript. RAM, TAF, SG, AH, SJ, ZM, CM, GS, DMT, AT, AHY, OE, ODH, and AC contributed to data interpretation. RC, VF, VM, and GB performed the systematic review and contributed to the writing of the manuscript. ED'A and MB assessed risk of bias, performed Confidence in Network Meta-Analysis assessments, and contributed to the writing of the manuscript. RAM, CM, ZM, AH, SJ, SG, DMT, AY, GS, TAF, AHY, OE, ODH, and AC contributed to the writing of the manuscript. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Declaration of interests

TP has received speaker or consultancy fees from Boehringer Ingelheim, Recordati, Lundbeck, Otsuka, Janssen, CNX Therapeutics, Sunovion, ROVI Biotech, Schwabe Pharma, and Lecturing Minds Stockholm AB; he receives book royalties from Wiley Blackwell; and he co-directs a company that designs digital resources to support treatment of mental illness. RAM has participated in advisory and speaker meetings organised by Otsuka, Karuna, Boehringer Ingelheim, and Janssen. GB has participated in speaker meetings organised by Pfizer. SJ has participated in educational speaker meetings organised by Lundbeck, Otsuka, Sunovion, Janssen, and Boehringer Ingelheim. ODH has received investigator-initiated research funding from or participated in advisory and speaker meetings organised by Angelini, Autifony, Biogen, Boehringer Ingelheim, Eli Lilly, Heptares, Global Medical Education, Invicro, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Rand, Recordati, Roche, and Viatris–Mylan. AHY has delivered paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: AstraZenaca, Boehringer Ingelheim, Eli Lilly, LivaNova, Lundbeck, Sunovion, Servier, Janssen, Allergan, Bionomics, Sumitomo Dainippon Pharma, COMPASS, Sage, Novartis, and Neurocentrx. AC has received research, educational, and consultancy fees from the Italian Network for Paediatric Trials, CARIPLO Foundation, Lundbeck, and Angelini Pharma outside the submitted work. TAF reports personal fees from Boehringer Ingelheim, Daiichi Sankyo, DT Axis, Micron, Shionogi, SONY, and UpToDate, and a grant from DT Axis and Shionogi, outside the submitted work. TAF has a patent (7448125) and a pending patent (2022–082495), and has licensed intellectual properties for Kokoro-app to DT Axis. ED'A received lecture fees from Lundbeck. DMT has received investigator-initiated research grants and spoken at events for AstraZeneca, Eli Lilly, Janssen, Lundbeck, Otsuka, Viatris, and Recordati, and has shares in Myogenes, Saladax, and 428-Pharma. AT has received research, educational, and consultancy fees from Angelini Pharma and lecture fees from Takeda outside the submitted work. CM has participated in educational speaker

meetings organized by AbbVie, Dr Falk, Ferring, Lilly, and Takeda. All other authors declare no competing interests.

Data sharing

The summary data used in analyses (change in physiological parameter expressed as mean [SD]) can be obtained from the corresponding author on request and without restriction. These data will be available from date of publication.

Acknowledgments

TP is supported by the UK National Institute for Health and Care Research (NIHR), Maudsley Charity, the Brain and Behaviour Research Foundation, the UK Academy of Medical Sciences, and the UK Research and Innovation Hub for Metabolic Psychiatry (grant reference MR/Z503563/1, platform grant code MR/Z000548/1). RAM is supported by a Wellcome Trust Clinical Research Career Development Fellowship (224625/Z/21/Z). ODH is supported by the UK Medical Research Council (grant number MC_A656_5QD30_2135), Maudsley Charity (grant number 666), Wellcome Trust (grant number 094849/Z/10/Z) and the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. SJ is funded by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. AHY is supported by the NIHR Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. AC is supported by the NIHR Oxford Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant RP-2017–08-ST2–006), by the NIHR Oxford and Thames Valley Applied Research Collaboration, by the NIHR Oxford Health Biomedical Research Centre (grant NIHR203316) and by Wellcome Trust (GALENOS project). VM is supported by the Swiss National Science Foundation (P500PM_217669). ED'A is supported by NextGenerationEU, the Italian Ministry of University and Research, National Recovery and Resilience Plan, project MNESYS (PE0000006; 1553 11.10.2022), and the ERC Seeds UniBa grant (2023-UNBACLE-0245973), funded by the University of Bari Aldo Moro, Italy. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care.

References

1 Centers for Disease Control and Prevention. Antidepressant use among adults: United States, 2015–2018. https://www.cdc.gov/nchs/products/databriefs/db377.htm (accessed April 21, 2025).
2 Lewer D, O'Reilly C, Mojtabai R, Evans-Lacko S. Antidepressant use in 27 European countries: associations with sociodemographic, cultural and economic factors. *Br J Psychiatry* 2015; **207:** 221–26.
3 Public Health England. Dependence and withdrawal associated with some prescribed medicines, an evidence review. 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940255/PHE_PMR_report_Dec2020.pdf (accessed April 21, 2025).
4 Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; **391:** 1357–66.
5 Calvi A, Fischetti I, Verzicco I, et al. Antidepressant drugs effects on blood pressure. *Front Cardiovasc Med* 2021; **8:** 704281.
6 Gafoor R, Booth HP, Gulliford MC. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: population based cohort study. *BMJ* 2018; **361:** k1951.
7 Farmand S, Lindh JD, Calissendorff J, et al. Differences in associations of antidepressants and hospitalization due to hyponatremia. *Am J Med* 2018; **131:** 56–63.
8 Leth-Møller KB, Hansen AH, Torstensson M, et al. Antidepressants and the risk of hyponatremia: a Danish register-based population study. *BMJ Open* 2016; **6:** e011200.
9 Danielsson B, Collin J, Nyman A, et al. Drug use and torsades de pointes cardiac arrhythmias in Sweden: a nationwide register-based cohort study. *BMJ Open* 2020; **10:** e034560.
10 Milea D, Guelfucci F, Bent-Ennakhil N, Toumi M, Auray JP. Antidepressant monotherapy: a claims database analysis of treatment changes and treatment duration. *Clin Ther* 2010; **32:** 2057–72.
11 National Institute for Health and Care Excellence. Depression in adults: treatment and management. National Institute for Health and Care Excellence, 2022.
12 Pillinger T, Howes OD, Correll CU, et al. Antidepressant and antipsychotic side-effects and personalised prescribing: a systematic review and digital tool development. *Lancet Psychiatry* 2023; **10:** 860–76.
13 Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry* 2020; **7:** 64–77.
14 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62:** 1006–12.
15 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366:** l4898.
16 Chiocchia V, Nikolakopoulou A, Higgins JPT, et al. ROB-MEN: a tool to assess risk of bias due to missing evidence in network meta-analysis. *BMC Med* 2021; **19:** 304.
17 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; **36:** 1–48.
18 Efthimiou O, Debray TP, van Valkenhoef G, et al. GetReal in network meta-analysis: a review of the methodology. *Res Synth Methods* 2016; **7:** 236–63.
19 Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* 2012; **3:** 312–24.
20 Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. netmeta: network meta-analysis using frequentist methods. https://github.com/guido-s/netmeta. 2019.
21 Seo M, Furukawa TA, Veroniki AA, et al. The Kilim plot: A tool for visualizing network meta-analysis results for multiple outcomes. *Res Synth Methods* 2021; **12:** 86–95.
22 Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012; **3:** 98–110.
23 König J, Krahn U, Binder H. Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Stat Med* 2013; **32:** 5414–29.
24 Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Syst Rev* 2020; **16:** e1080.
25 Furukawa TA, Cipriani A, Barbui C, Brambilla P, Watanabe N. Imputing response rates from means and standard deviations in meta-analyses. *Int Clin Psychopharmacol* 2005; **20:** 49–52.
26 Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight maintenance. *Int J Obes (Lond)* 2006; **30:** 391–99.
27 Rocca WA, Boyd CM, Grossardt BR, et al. Prevalence of multimorbidity in a geographically defined American population: patterns by age, sex, and race/ethnicity. *Mayo Clin Proc* 2014; **89:** 1336–49.
28 Riley RD, Thompson JR, Abrams KR. An alternative model for bivariate random-effects meta-analysis when the within-study correlations are unknown. *Biostatistics* 2008; **9:** 172–86.
29 Efthimiou O, White IR. The dark side of the force: multiplicity issues in network meta-analysis and how to address them. *Res Synth Methods* 2020; **11:** 105–22.
30 Fisher DJ, Carpenter JR, Morris TP, Freeman SC, Tierney JF. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ* 2017; **356:** j573.
31 Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. *JAMA* 1995; **273:** 461–65.
32 Zhang GQ, Zhang W. Heart rate, lifespan, and mortality risk. *Ageing Res Rev* 2009; **8:** 52–60.
33 Chen XJ, Barywani SB, Hansson PO, et al. Impact of changes in heart rate with age on all-cause death and cardiovascular events in 50-year-old men from the general population. *Open Heart* 2019; **6:** e000856.
34 Palmer AJ, Bulpitt CJ, Fletcher AE, et al. Relation between blood pressure and stroke mortality. *Hypertension* 1992; **20:** 601–05.

35 Salvi V, Mencacci C, Barone-Adesi F. H1-histamine receptor affinity predicts weight gain with antidepressants. *Eur Neuropsychopharmacol* 2016; **26:** 1673–77.

36 Strine TW, Mokdad AH, Dube SR, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry* 2008; **30:** 127–37.

37 Gramaglia C, Gambaro E, Bartolomei G, et al. Increased risk of metabolic syndrome in antidepressants users: a mini review. *Front Psychiatry* 2018; **9:** 621.

38 Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. *Am J Psychiatry* 2014; **171:** 404–15.

39 Steffen A, Nübel J, Jacobi F, Bätzing J, Holstiege J. Mental and somatic comorbidity of depression: a comprehensive cross-sectional analysis of 202 diagnosis groups using German nationwide ambulatory claims data. *BMC Psychiatry* 2020; **20:** 142.

40 Haukka J, Arffman M, Partonen T, et al. Antidepressant use and mortality in Finland: a register-linkage study from a nationwide cohort. *Eur J Clin Pharmacol* 2009; **65:** 715–20.