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QTc changes and early major adverse cardiovascular events associated with antidepressant treatment for major depressive disorder in adults: individual participant data network meta-regression of double blind randomised trials

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ABSTRACT

OBJECTIVE

To compare the effect of specific antidepressants with placebo on heart rate corrected QT interval (QTc) during the first eight weeks of treatment for major depressive disorder in adults, and to investigate whether antidepressant use is associated with early major cardiovascular adverse events (MACE).

DESIGN

Individual participant data (IPD) network meta-regression and aggregate pairwise meta-analysis.

DATA SOURCES

Individual and aggregate level data from randomised controlled trials identified through Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS, Medline, Medline In-Process, PsycINFO, the websites of regulatory agencies, and international registers.

METHODS

IPD were harmonised to enhance comparability and analysed using network meta-regressions to explore the interplay with baseline QTc, age, sex assigned at birth, body mass index, serum potassium level, and estimated glomerular filtration rate. The primary outcome was changes in QTc Fridericia (QTcF) associated with specific antidepressants and placebo after taking into account modifiable and non-modifiable risk factors. Aggregate data on early MACE were analysed using pairwise meta-analysis comparing antidepressants with placebo.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Double blind randomised trials of adults (≥18 years) with major depressive disorder diagnosed according to standardised, operationalised criteria.

RESULTS

Of 130 unique randomised controlled trials identified, 35 (27%) included individual level data (8679 participants) on QTc with placebo and 10 antidepressants (amitriptyline, bupropion, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, trazodone, venlafaxine, vortioxetine). Compared with placebo, escitalopram and amitriptyline were associated with increased QTc intervals (8.7 milliseconds (ms), 95% credibility interval (CrI) 1.6 to 15.8, and 5.3 ms, 0.8 to 9.8, respectively). When risk factors were considered, amitriptyline and escitalopram were also associated with the highest QTc prolongations (58.8% and 21.3%, respectively), whereas venlafaxine and vortioxetine were often associated with the lowest QTc intervals (24.1% and 9.7%, respectively). Important variability of effects was observed, especially for escitalopram, fluoxetine, and mirtazapine. An aggregate analysis of 139 trials (52 398 participants) did not identify an association between antidepressant use and increased rates of early MACE and non-suicidal death compared with placebo (risk difference 0.01%, 95% CrI -0.01% to 0.02%).

CONCLUSIONS

The effect of specific antidepressants on QTc interval differed between adults with depression. No evidence associated antidepressant use with early MACE and non-suicidal sudden death. To support shared decision making and taking into account the trade-off between benefits and harms, individual modifiable and non-modifiable risk factors should be considered when choosing antidepressants.

SYSTEMATIC REVIEW REGISTRATION

Open Science Framework https://osf.io/c8k65/.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Antidepressants are widely prescribed but the choice of treatment often results from a trial-and-error approach

Some antidepressants have been linked with an increased risk of QTc prolongation and subsequent early major adverse cardiovascular events (MACE)

Specific warnings have been issued for some antidepressants, such as amitriptyline, citalopram, and escitalopram

WHAT THIS STUDY ADDS

The effect of specific antidepressants on the QTc interval varies considerably, with treatment specific effects accounting for small changes to QTc intervals

Approaches such as labelling antidepressants as proarrhythmic or not oversimplify the complex interplay resulting in QTc changes and early MACE

Patients and clinicians should be equipped with tools allowing individual prognostication of cardiovascular treatment effects, considering modifiable and non-modifiable risk and treatment effects

Introduction

Antidepressants are the preferred treatment for moderate to severe depression and are also widely prescribed for other mental health conditions.[1] A total of 8.89 million people received an antidepressant in England between 2024 and 2025,[2] in line with an overall increasing trend in daily consumption worldwide.[3]

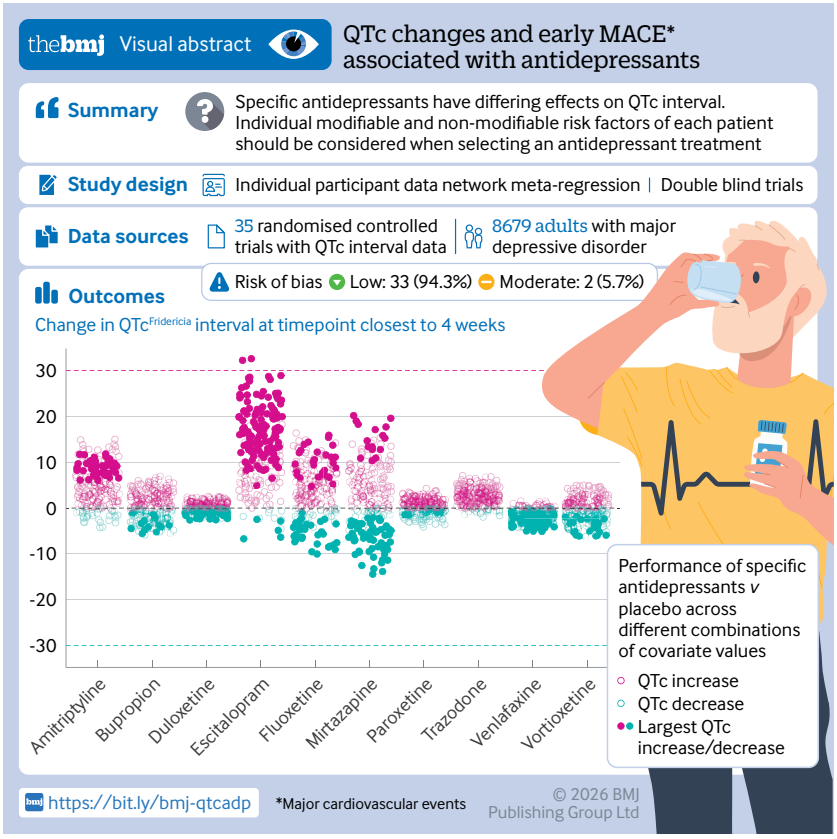
In terms of tolerability, antidepressants have been associated with a risk of prolongation of heart rate

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corrected QT interval (QTc) due to the blockage of several ion channels in the heart. Although QTc prolongation does not necessarily lead to major cardiovascular events, such as torsade de pointes and sudden death, it represents an index of delayed ventricular repolarisation that is widely used because it is readily measurable and can provide early warnings for proarrhythmic states (box 1).[4] The effect on cardiac electrical activity prompted concerns about the use of antidepressants for acquired QTc prolongation or worsening of pre-existing conditions, such as congenital long QT syndrome.[4 5] Specific warnings were issued about the interaction between antidepressants and other drugs known to increase QTc (eg, several antibiotics, like macrolides and fluoroquinolones), but also about specific antidepressants as monotherapy (namely, citalopram and escitalopram) with a dose dependent effect.[5 6] As a consequence, the maximum dosage of citalopram and escitalopram in the UK was limited to 40 mg and 20 mg, respectively, for adults older than 65 years.[6] Concerns about similar effects on QTc exist for other selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, mirtazapine, and tricyclic antidepressants.[5] Preliminary evidence identified a dose effect only for citalopram, escitalopram, and amitriptyline,[7] although several confounding factors and the unclear magnitude of such changes casts uncertainty over the cardiovascular implications of using antidepressants in real world practice.[8 9] The association between antidepressants and sudden cardiac death is usually limited to pharmacovigilance reports, where causal relations are difficult to assess given the absence of a control group and the interplay between many potential risk factors (eg, potassium level, age, body mass index (BMI), baseline QTc, and pre-existing cardiovascular conditions).

Currently, evidence linking individual predisposing risk factors of QTc prolongation with individual antidepressants is limited. While high QTc values are associated with increased risk for ventricular arrhythmias, many individuals willing to start an antidepressant are likely to have clinically negligible QTc values. The real impact of individual characteristics on QTc for asymptomatic people with a "borderline" QTc is unclear but often translates to delays in accessing care or limitations in available choices.[10] Caution is advised when other risk factors exist, but available guidance does not detail the cardiovascular risk for individualised changes to QTc interval. The antidepressant selection process remains a trial-and-error approach skewed towards potential benefits. Clinicians are left to decide whether they should proceed to further assessments, such as baseline electrocardiology (ECG), before antidepressants are started, with implications on treatment delays and costs. A recent meta-analysis of randomised controlled trials on depression in adults did not find evidence of differences in QTc between specific antidepressants and placebo.[11] However, aggregated data meta-analyses have the important weaknesses of data availability and heterogeneous reporting of safety outcomes, greatly limiting clinical interpretability of findings.[12] Moreover, to explore the interplay between risk factors and QTc changes at an individual level, individual patient data (IPD) are required.

We investigated the impact of specific antidepressants on QTc interval in adults who started treatment for major depressive disorder, taking into account modifiable and non-modifiable risk factors and whether antidepressant use for acute depression is associated with early major adverse cardiovascular events (MACE), including non-suicidal sudden death.



Methods

We registered the study protocol with Open Science Framework (https://osf.io/c8k65/). Supplementary appendix 3.1 lists the changes from the original plan.

Search strategy

To identify randomised controlled trials on antidepressants for major depressive disorder in adults (≥18 years), we replicated the search strategy of a previously published systematic review,[13] updated to 18 March 2026 (see supplementary appendix 4).

Eligibility criteria

We mirrored the original eligibility criteria used in a previous study, focusing on published and unpublished double blind randomised controlled trials comparing antidepressants as monotherapy with each other or with placebo in the acute treatment of major depressive disorder in adults (see supplementary appendix 5).[13]

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Box 1: QT prolongation and correction methods used in clinical practice

QT prolongation indicates an abnormally long QT interval on an electrocardiogram. It reflects delayed ventricular repolarisation and represents an increased risk of torsades de pointes and other potentially fatal arrhythmias. Because the non-corrected QT interval shortens as heart rate increases, QT is commonly corrected by heart rate to estimate the QT at heart rate levels within the expected range; Bazett's formula (QT divided by the square root of the RR interval) and Fridericia's formula (QT divided by the cube root of the RR interval) formulas are widely used for this purpose. However, Bazett's formula tends to overcorrect at high heart rates and undercorrect at low heart rates, which can lead to spurious classification of QT prolongation and inappropriate clinical decisions.[41]

For ongoing treatments with drugs suspected to increase QT, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) recommended "careful consideration of potential benefits and harms, dose reduction or gradual withdrawal" for patients with a QTc Fridericia interval between 480 milliseconds (ms) and 500 ms and "gradual withdrawal" for intervals higher than 500 ms.[6]

Selection process

At least two trained researchers independently screened the titles or abstracts of all records and then the full text to identify new potentially eligible studies. Disagreements were discussed with a third senior researcher.

Data collection

Effect of specific antidepressants on QTc interval

As part of the PETRUSHKA (personalising antidepressant treatment for unipolar depression combining individual choices, risks, and big data) project,[14] we contacted all data owners of the identified and eligible double blind randomised controlled trials.[13] We obtained IPD from 130 trials (40 013 participants), accessed across local and online secure research environments.[14 15] We inspected IPD and associated trial specific documents (ie, protocol, study procedures, and case report forms) to extract data on QTc and the a priori selected covariates of interest. Having access to both data and relevant documentation minimised the risk of selective data sharing bias (ie, data on QTc were collected but not shared).

Association between antidepressant use and early MACE

As MACE are commonly reported in trial reporting procedures, we complemented information from QTc changes and early MACE onset with aggregate data to investigate non-suicidal sudden death. At least two trained researchers independently extracted the relevant data. Comparison of extracted data was automated to highlight potential inconsistencies, addressed through consensus or, when not possible, through involvement of a third senior researcher.

Outcomes

Effect of specific antidepressants on QTc

We explored QTc changes using IPD. The QTc Fridericia (QTcF) formula was selected over the QTc Bazett (QTcB) formula to mirror regulatory agencies and available evidence showing QTcF to be less sensitive to extreme heart rate values than QTcB.[6 8 16] In a sensitivity analysis, we replicated all the analyses with QTcB (see supplementary appendices 1.10, 1.13, and 1.14). To address our first aim, we investigated the following outcomes:

- Change of QTcF at the timepoint closest to four weeks (range 1-8 weeks) (primary outcome). We assessed the risk of bias for our primary outcome across several domains: sequence generation; allocation concealment; masking of participant, therapist, or assessor; unpublished data; selective reporting bias; and attrition bias.
- Proportion of participants with a QTcF >500 milliseconds (ms) at the timepoint closest to four weeks (range 1-8 weeks) (secondary outcome).[8]
- Proportion of participants with an increase in QTcF from baseline of at least 60 ms at the timepoint closest to four weeks (range 1-8 weeks) (secondary outcome).[8]

We prioritised timepoints up to eight weeks because QTc changes occur in days or weeks rather than months, and eight weeks is a commonly used timepoint in randomised controlled trials on antidepressants. Drug induced QTc changes are expected to occur by the time the drug nears steady state (see supplementary appendix 1.2).[17]

Association between antidepressant use and early MACE

We investigated two outcomes. Firstly, the proportion of participants with prolonged QTcF who experienced MACE (ie, ventricular arrhythmias or sudden death, or both) by week 4 (range 1-8 weeks) from available IPD. Specifically, we intended to investigate the occurrence of these events between 450 and 500 ms in men, between 470 and 500 ms in women, and above 500 ms in both men and women (secondary outcome).[18] Secondly, the proportion of non-suicidal sudden deaths from aggregate data comparing antidepressants with placebo. Considering the young age of participants recruited in antidepressant trials, we assumed every non-suicidal sudden death to be a potential sudden cardiac death, unless further details were provided in published and unpublished records.

Predisposing risk factors

For our analyses on IPD, we a priori defined several covariates (see supplementary appendix 1.3): sex assigned at birth, age, QTc interval before randomisation, serum potassium level, BMI, and estimated glomerular filtration rate (eGFR). Dose was not included as a covariate because not enough studies explored fixed dose effects, and current methodological frameworks are limited to inclusion of pre-randomisation variables (see supplementary appendix 3.1).

Missing data

For our analyses on IPD, where required and possible, we recalculated QTcF and QTcB from QTc and heart rate from the closest timepoint within the eligible timeframe (ie, 1-8 weeks). For missing potential

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covariates (ie, measured before the randomisation), we performed multiple imputations accounting for study effects.

Statistical analyses

QTc changes with specific antidepressants

We performed a series of network meta-regressions. As the IPD were accessible across different online secure platforms, we performed a two stage IPD network meta-regression. In the first stage, we explored the relative treatment effects and the treatment-covariate interactions for each included study. In the second stage, we combined the derived parameters within a multivariate mixed effects bayesian meta-analytical model (see supplementary appendix 1.8). Continuous outcomes were analysed using mean differences and for binary outcomes we used odds ratios. While we emphasise the role of individualising the antidepressant specific risk based on an individual's own predisposing risk factors, we recognise that in some settings the availability of modifiable and non-modifiable risk factors before drug treatment may be challenging. To address this issue, we further explored the clinical impact of our findings (primary outcome, predicted QTcF interval) across 216 possible combinations of set values for each of our covariates (see supplementary appendix 1.15). We repeated all analyses using QTcB as sensitivity analyses for our primary outcome.

Association between antidepressant use and early MACE

To analyse the association between antidepressants and non-suicidal sudden death, we performed an aggregate meta-analysis of published and unpublished double blind randomised controlled trials comparing antidepressants with placebo,[13] further detailing intervention subgroups based on common antidepressant classes.[19] As we expected several studies with no events in all arms, we calculated the pooled effect size as risk difference alongside 95% credibility intervals (CrIs) and 95% prediction intervals (PIs). To confirm the robustness of our findings, we replicated the analyses under different model assumptions to handle studies with zero events, either by including them (inverse variance), accounting for zero events and low proportions (arcus sinus difference), or by excluding arms with zero events (Mantel-Haenszel) (see supplementary appendix 2.2).

Patient and public involvement

We consulted three patients and members of the public, identified from a larger group of people with lived experience of depression established for a parallel project involving key outcomes that could be addressed with IPD.[14] They joined a multidisciplinary panel together with experts in methodology, cardiology, and psychiatry. We discussed known outcomes based on what we anticipated to be available, asking for feedback on their importance and prioritisation and whether further outcomes should be considered (eg, non-suicidal sudden death). Two moderators (EGO, AC) supported the discussion and recorded final decisions about outcomes.

Results

Out of the 524 randomised controlled trials (116 791 participants) identified as eligible, we obtained IPD for 130 (about 40 000 participants), corresponding to 25% of known randomised controlled trials (and 34% of adult participants ever involved in double blind randomised controlled trials on antidepressants for the acute treatment of depression). Out of the studies that provided IPD, 35 (26.9%) included individual level data on QTc and contributed to our primary analysis (see supplementary appendix 1). Supplementary appendix 1.3 provides a list of the included studies. We did not identify important issues in terms of IPD integrity (see supplementary appendix 1). For 19 trials (14.6%) on mirtazapine and six (4.6%) on trazodone, we could not access full trial related supporting documentation to check selective data sharing bias—11 (8.5%) and two (1.5%), respectively, provided data on QTc (see supplementary appendix 1). Out of the 35 trials with available IPD, 33 (94.3%) were rated as overall low risk of bias and two (5.7%) as overall moderate risk of bias (see supplementary appendix 6). The included studies comprised a total of 8679 participants, including 5468 (63.0%) female participants, and mean age 47 years (standard deviation (SD) 15.2 years). Our analyses included placebo (2329 participants, 26.8%) and 10 antidepressants (amitriptyline, bupropion, duloxetine, escitalopram, fluoxetine, mirtazapine, paroxetine, trazodone, venlafaxine, vortioxetine), totalling 6350 participants (73.2%). Duloxetine was the most investigated active intervention (1258 participants, 14.5%) and escitalopram was the least represented intervention in our network (186 participants, 2.1%). Mean baseline values for other variables were: QTcF 403 ms (SD 32.0 ms), BMI 26 (SD 6.4), potassium 4.3 mmol/L (SD 0.4 mmol/L), and eGFR 96 mL/min/1.73m^2 (SD 33.7 mL/min/1.73m^2). Overall, 330 participants (3.8%) had at least one concomitant drug associated with a risk of QTc prolongation, 156 participants (1.8%) had at least one drug associated with a possible risk of QTc prolongation, and 851 participants (9.8%) had at least one drug associated with a conditional risk of QTc prolongation. For cardiovascular baseline comorbidities, 152 participants (1.8%) had a history of chronic non-infarction ischaemic heart disease (see supplementary appendix 1.7).

QTc changes with specific antidepressants

When we analysed treatment specific effects independently from all other covariates, mirtazapine was associated with a significant shortening of QTcF (-27.68 ms, 95% CrI -55.01 to -34.45) compared with placebo. Fluoxetine was associated with the longest QTcF prolongation albeit not statistically significant (21.84 ms, -7.70 to 51.38). We observed a specific treatment-covariate interaction between mirtazapine and baseline QTcF values (0.09 ms per additional

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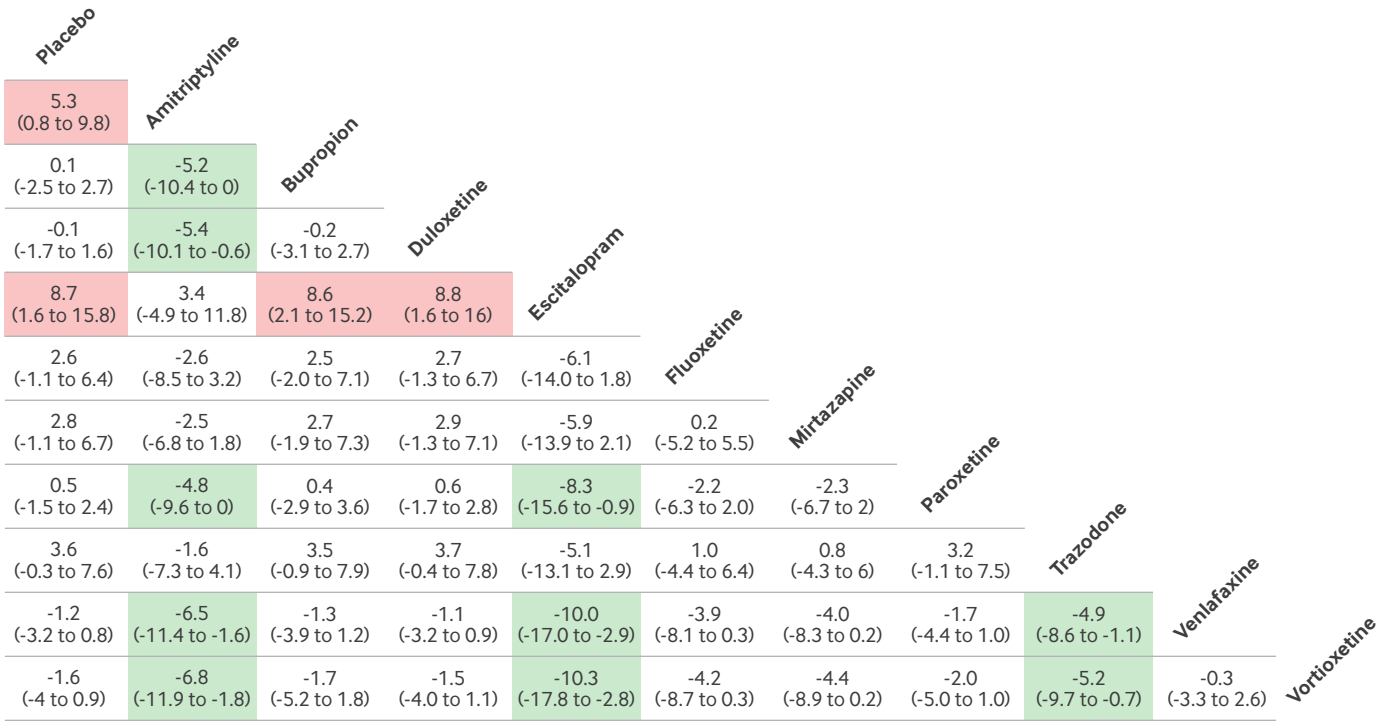


Fig 1 | Mean differences in QTc (change in milliseconds with 95% credibility interval) associated with antidepressant treatment using the QTc Fridericia formula. Differences are located at the intersection between column defining and row defining treatments (in alphabetical order after placebo). Values >0 (red) favour the column-defining treatment, whereas values <0 (green) favour the row-defining treatment

baseline ms, 95% CrI 0.00 to 0.17 ms) and between vortioxetine and potassium serum level (-3.55 ms per additional mmol/L, 95% CrI -6.96 to -0.14 ms).

When taking into account mean values for all covariates (age, sex, baseline QTcF, BMI, serum potassium, and eGFR; see supplementary appendix 1.9), amitriptyline (5.3 ms, 95% CrI 0.8 to 9.8) and escitalopram (8.7 ms, 1.6 to 15.8) were associated with a significant but small average increase in QTcF compared with placebo. In head to head comparisons, bupropion, duloxetine, paroxetine, venlafaxine, and vortioxetine accounted for lower QTcF changes compared with amitriptyline and escitalopram (range 4.8-10.3 ms; fig 1); venlafaxine and vortioxetine accounted also for lower QTcFchanges compared with trazodone (4.9 ms and 5.2 ms, respectively; fig 1). Similar findings were observed for QTcB, with overall greater mean differences (see supplementary appendix 1.10).

We then explored the effects of individual characteristics on QTcF interval. We observed important differences for age: compared with placebo, mirtazapine (7.60 ms, 95% CrI 1.60 to 13.52) and amitriptyline (9.47 ms, 1.67 to 17.28) significantly increased QTcF in young adults, whereas in older adults a significant QTcF prolongation was observed with fluoxetine (8.41 ms, 1.32 to 15.56) and escitalopram (19.39 ms, 4.35 to 34.27). Figure 2 shows the overall effects at ages 30, 45, 60, and 75 with mean values for all the other covariates. All potential combinations of the considered risk factors can be explored through a dedicated Shiny app (https://egostinelli.shinyapps.io/QTcF).

Figure 3 shows the performance of antidepressants in terms of QTcF interval across different sets of values for the considered risk factors. Across these combinations, escitalopram (94.0%), trazodone (91.7%), and amitriptyline (85.7%) often resulted in an increase in QTcF interval, with escitalopram (58.8%), amitriptyline (21.3%), and fluoxetine (12.5%) often associated with the highest QTcF prolongations. Across the considered combinations, out of the antidepressants that were never associated with the highest QTcF increase, venlafaxine (24.1%), duloxetine (13.4%), and vortioxetine (9.7%) more often resulted in a decrease in QTcF interval (table 1).

Owing to the lack of IPD, we could not run the pre-planned inferential analyses on QTc above 500 ms (seven out of 8679 participants, 0.08%) or changes from baseline above 60 ms (56 out of 8679 participants, 0.65%) (see supplementary appendices 1.13 and 1.14).

Association between antidepressant use and early MACE

Out of the 8679 participants included in our IPD sample, none experienced episodes of torsade de pointes or sudden non-suicidal death throughout their trial participation. Ten participants (0.12%) experienced syncope (paroxetine=4, mirtazapine=2, trazodone=2, amitriptyline=1, duloxetine=1). We also analysed the aggregate level data from the

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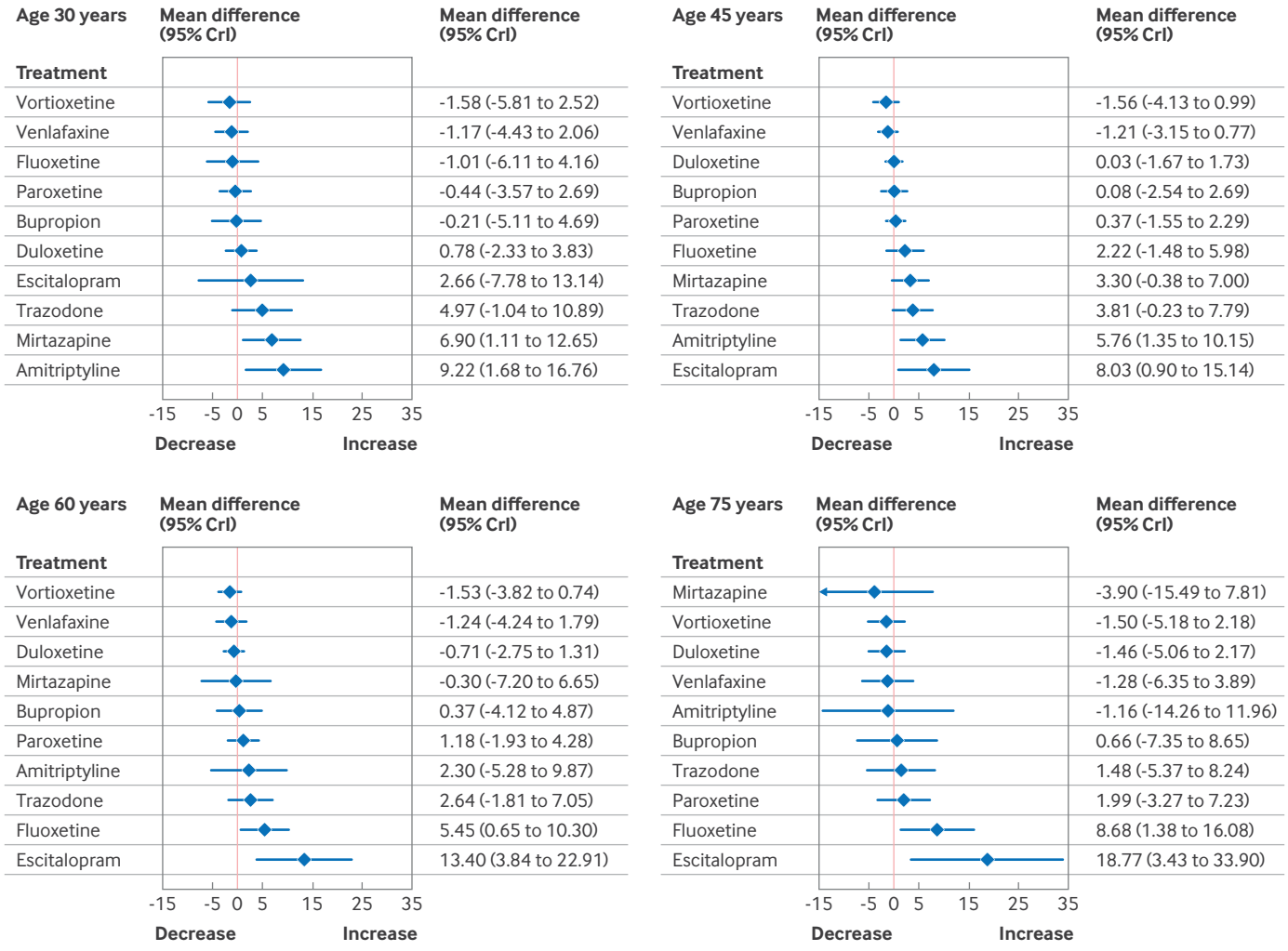


Fig 2 | Mean difference in QTc (change in milliseconds with 95% CrI) associated with antidepressant treatment using the QTc Fridericia formula compared with placebo at different ages. CrI=credibility interval

studies included in a previously published network meta-analysis on antidepressants in adults with major depression.[13] We did not find evidence of an increased risk of sudden death events associated with antidepressants compared with placebo across 139 trials (52 398 participants): in total, only 12 events were reported (antidepressants: nine events out of 34 575 participants, 0.03%; placebo: three events out of 17 823 participants, 0.02%; risk difference 0.01%, 95% CrI -0.01% to 0.02%, 95% PI -0.09% to 0.11%). No effect was observed for any of the considered drug classes. Comparable findings were observed when applying the alternative model assumptions (inverse variance, arcus sinus difference, Mantel-Haenszel) (see supplementary appendices 2.2 and 2.3).

Discussion

This study analysed IPD from 35 double blind randomised controlled trials (8679 patients) to assess the effect of specific antidepressants on the QTc interval in adults with depression while accounting for several clinically important modifiable and non-modifiable risk factors. We corroborated our findings with available evidence on non-suicidal sudden death (suspected MACE) from a larger sample of published and unpublished randomised controlled trials.[13] Overall, we identified different effects across antidepressants, with amitriptyline and escitalopram often associated with small increases in QTc intervals and venlafaxine and vortioxetine with decreased QTc intervals. For individual characteristics (ie, sex, age, QTc interval before starting an antidepressant, potassium level, BMI, and eGFR), we observed important variability of effects, especially for escitalopram, fluoxetine, and mirtazapine. We did not find evidence associating antidepressants with increased rates of early MACE and non-suicidal death compared with placebo.

Clinical and policy implications

The present findings call for mental health guidelines to take into consideration the differences across antidepressants in terms of QTc prolongation.[20] Our results are in line with MHRA's caution when prescribing escitalopram,[6] considering how drug

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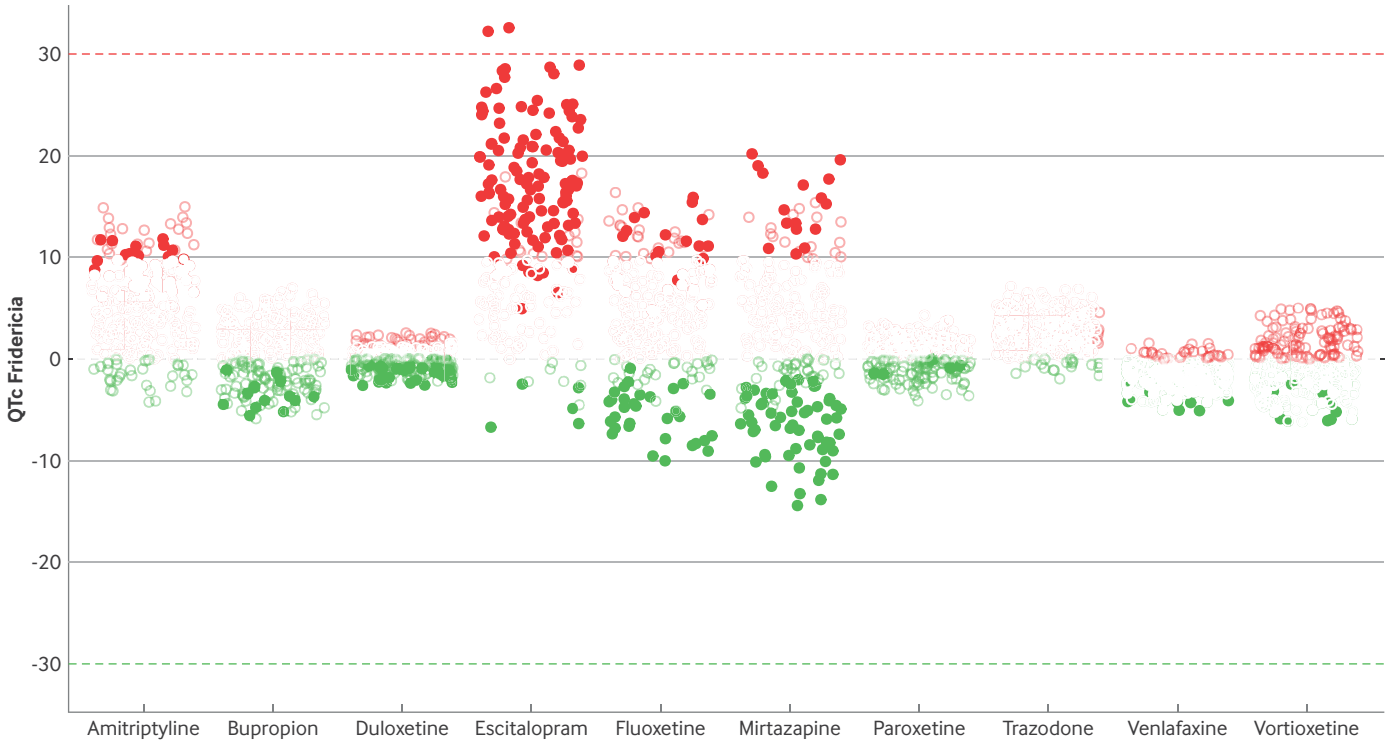


Fig 3 | Performance of specific antidepressants versus placebo across different combinations of sex and baseline values of age (30, 50, and 70 years), QTc Fridericia formula (350, 400, and 450 ms), body mass index (18, 22, 27, and 35), serum potassium level (3.5, 4, and 4.5 mmol/L), and a fixed value for estimated glomerular filtration rate (96 mL/min/1.73m^2). Green circles indicate a QTc decrease and red circles indicate a QTc increase. Green and red points indicate that for that specific set of covariate values, the considered antidepressant was the one providing the largest QTc decrease or QTc increase, respectively, across all the considered antidepressants

performance varied based on the risk factors of sex, age, QTc interval before starting an antidepressant, potassium level, BMI, and eGFR, instead of relying on average effects. Drug induced torsade de pointes is considered a rare event, estimated between 0.8 and 1.2 patients per million person years across European countries.[21] As such, it is not surprising that none of the 8679 participants included in our analyses experienced these events, as our sample size was likely underpowered. We further expanded our original analyses to aggregate data from 52 398 participants and found rates of sudden non-suicidal death comparable to estimates in the general population across European countries (36.8 to 39.7 people per 100 000 person years),[22] which did not suggest a causal link between antidepressant use and sudden non-suicidal deaths.

The role of individual risk factors should be emphasised and carefully considered when prescribing antidepressants. The effects on QTc are likely to be incremental, with a cumulative effect when combined with other risk factors (eg, prescription of other drugs with a potential to increase QTc, serum potassium level outside of the expected range). Our findings highlight how choosing among specific antidepressants exclusively based on average performances and not considering potential risk factors may fail to capture the complex interplay with individual characteristics. More precise estimation using IPD, harmonisation of data and correction formulas, and inclusion of modifiable and non-modifiable risk factors at an individual level are crucial steps forward from the previously available evidence.[11] In that analysis, all antidepressants showed particularly wide 95% PIs for average effects crossing the line of no effect, with the narrowest one being 1.2 standardised mean difference (duloxetine, venlafaxine), highlighting increased variance. Individual variability in terms of modifiable and non-modifiable risk factors beyond what the population represented by randomised controlled trial data (eg, values closer to the tails of a distribution for a specific risk factor, co-occurring treatments known to impact the QTc interval) should be taken into account when considering the magnitude of the observed QTc changes. Such changes are more likely to be predisposing factors contributing incremental effects in producing proarrhythmic states, such as abnormally short or long QT intervals, rather than the direct cause of lethal arrhythmias unless coupled with a broader cluster of individual risk factors. Overall, our findings highlight the complexity and limitations in labelling a specific antidepressant in practice as safe or harmful from a cardiovascular perspective. We

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Table 1 | Frequency of QTc increases and decreases and largest QTc changes across 216 combinations of covariate values for antidepressants compared with placebo. Values in brackets are percentages out of the 216 combinations

Antidepressant	QTc increases		QTc decreases	
	Largest	Any	Any	Largest
Amitriptyline	46 (21.3)	185 (85.7)	31 (14.4)	0 (0)
Bupropion	0 (0)	118 (54.6)	98 (45.4)	13 (6.0)
Duloxetine	0 (0)	109 (50.5)	107 (49.5)	29 (13.4)
Escitalopram	127 (58.8)	203 (94.0)	13 (6.0)	5 (2.3)
Fluoxetine	27 (12.5)	160 (74.1)	56 (25.9)	32 (14.8)
Mirtazapine	16 (7.4)	128 (59.3)	88 (40.7)	59 (27.3)
Paroxetine	0 (0)	125 (57.9)	91 (42.1)	5 (2.3)
Trazodone	0 (0)	198 (91.7)	18 (8.3)	0 (0)
Venlafaxine	0 (0)	26 (12.0)	190 (88.0)	52 (24.1)
Vortioxetine	0 (0)	98 (45.4)	118 (54.6)	21 (9.7)

Increases and decreases in QTc are defined independently from the magnitude of a QTc change.

developed a Shiny App (https://egostinelli.shinyapps.io/QTcF) to help patients and clinicians identify the specific risk of QTc prolongation for each individual, depending on clinical and personal characteristics. We believe this app is an important step in allowing patients and clinicians to consider the trade-off with potential benefits and harms in a shared decision making process, as recommended by the UK National Institute for Health and Care Excellence.[23]

We did not find evidence from double blind randomised controlled trials linking early MACE and antidepressants, in contrast with early pharmacovigilance reports that supported the existing warnings for citalopram and escitalopram in the UK alongside tricyclic antidepressants as "drugs known to prolong QT interval."[6] Recent pharmacovigilance data (yellow card) show a decrease in reports for citalopram related fatal cardiac adverse reactions: from 18 patients during 2004-14 to 10 during 2015-25.[24] In the year after the MHRA warning (2015), four cardiac adverse reactions were reported—the highest number of events per year since yellow card data became available in 1995.[24] No fatal cardiac adverse reactions have been recorded with escitalopram since 2008, replicating findings from registry studies of no risk of sudden unexpected or cardiac death associated with citalopram or escitalopram compared with other selective serotonin reuptake inhibitors.[25] These data should be contextualised with the number of patients receiving these drugs, with the evidence on prescription patterns of citalopram and escitalopram being available only from 2019 showing a constant pattern for citalopram (14 322 200 items prescribed in 2015, 13 398 318 in 2024) and an increasing trend for escitalopram (919 450 items prescribed in 2015, 1 936 885 in 2024).[26 27] A possible explanation of the peak in reported fatal cardiac adverse reactions associated with citalopram could be notoriety bias, defined as "a selection bias in which a case has a greater chance of being reported if the subject is exposed to the studied factor known to cause, thought to cause, or likely to cause the event of interest."[28] The impact of notoriety bias on pharmacovigilance data has been investigated and a disproportionally increased reporting of prolonged QTc was associated with trazodone (the only investigated antidepressant) after the US Food and Drug Administration issued a safety alert.[29 30] Another explanation could be that the effect of warnings from regulatory bodies on clinicians' practice are short lived, with common pitfalls being failure either to routinely monitor the effects of antidepressants after being prescribed or to report these events to designated pharmacovigilance agencies.

Future directions

We identified considerable variation in QTc changes between use of specific antidepressants for individual patients, and for some beyond the 30 ms the European Medicines Agency suggests as a threshold of potential clinical interest.[8] Reflecting recent calls to consider the physical health side effects associated with psychotropics,[31] implementation of routine monitoring of physical health data is gaining interest. However, obtaining a baseline electrocardiogram from every patient requiring an antidepressant is beyond the capacity of many healthcare systems, thus limiting the inclusion of QTc in clinical decision aids and routine care. Technological advancements enable the collection of complex data, facilitating the implementation of relevant biological health data in real world care. The use of wearables has been shown to reliably measure the QTc interval, saving considerable time and allowing the inclusion of QTc and other physical variables in precision medicine.[32] Models based on randomised controlled trial and electronic healthcare record data for licenced drugs could be further expanded with information from concentration-QTc modelling from phase 1 studies for new molecules,[33] allowing early comparative safety data. Implementing interactive warnings in electronic health record systems without causing alert fatigue is likely to be another key upcoming challenge to support clinicians with the best available evidence base. Follow-up care should be individualised, with more frequent monitoring of patients more likely to develop increases in QTc, resulting in an overall optimisation of available healthcare resources.

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Another key step would be to leverage genetic data to generate a biological phenotyping of people with depression.[34] Genetic data, increasingly available in clinical care, could provide insight on the background congenital risk (independent from a treatment) as well as individual drug-gene susceptibilities, which other modifiable and non-modifiable risk factors would layer onto (eg, data on comorbidities, concurrent treatments, age).[35 36] One study recently assessed the current status of pharmacogenomic markers associated with drug induced QT prolongation. Although pharmacogenomic markers were found to be inconsistent across the available evidence, they identified promising signals on key gene-drug interactions.[37]

Limitations of this study

This paper has some limitations. Randomised controlled trials are the ideal method for estimating treatment effects. Owing to strict eligibility criteria, however, participants from randomised controlled trials are typically a selected sample. External validity of randomised controlled trial findings could potentially be limited if the distribution of potential effect modifiers in the included sample and in the population of interest diverge. In our analyses we leveraged IPD from 35 double blind randomised controlled trials, considering available modifiable and non-modifiable risk factors. In future, our findings could be complemented with routinely collected QTc data from electronic health record sources, employing appropriate techniques to limit confounding factors such as emulation of target trials. Such a combined approach would allow further investigation of the dynamic interplay between antidepressants and modifiable and non-modifiable risk factors that might be less prominent (eg, clinically abnormal eGFR values) or less common (eg, co-occurring comorbidities and associated concomitant drugs), usually under-represented in randomised controlled trial populations owing to eligibility criteria compared with real world settings.[38] In the real world population, the interaction of these effects may be non-additive (ie, their combined proarrhythmic effect may be greater than the sum of the individual contributions), resulting in greater QTc changes. Employing electronic health record data would also allow the limitation of data availability to be tackled. Despite our efforts to collect IPD from as many trials as possible and the inclusion of 10 antidepressants across different drug classes, not all licensed antidepressants were represented in our analyses. For instance, we could not retrieve QTc data related to citalopram, an antidepressant subject to extensive warnings, together with escitalopram and tricyclic antidepressants.[6 39] The available evidence on the effects of citalopram on QTc frequently aligned with escitalopram, its (S)-enantiomer.[6] Our findings on escitalopram could potentially be used to make inferences about citalopram, a racemic mixture of S-citalopram and R-citalopram, with R-citalopram being largely inactive as a selective serotonin reuptake inhibitor. However, this assumption should be confirmed once QTc data on citalopram become available. Some antidepressants in the network were less represented than others. For instance, only 186 participants in our network were allocated to escitalopram. More data, either from randomised controlled trials or electronic health records, would enable more precision when estimating both the treatment effects and the interplay with the considered risk factors. Although our average estimates of escitalopram performance did not contradict existing international warnings and analyses from aggregate data (less precise but less prone to IPD availability bias),[11] more data are needed to confirm the interplay between treatment effect and modifiable and non-modifiable risk factors on overall QTc changes. Although we accessed data from a quarter of available randomised controlled trials on antidepressants for major depressive disorder in adults, we cannot exclude that further trials collected ECG meta-data in a usable format (eg, recording the QTc in milliseconds either on the study specific case report form or downloaded from dedicated devices into tabular formats, rather than limiting reports to the absence of abnormalities). For 19 (14.6%) trials on mirtazapine and six (4.6%) on trazodone, we could not access full trial related supporting documentation to check selective data sharing bias—11 (8.5%) and two (1.5%), respectively, provided QTc data.

Furthermore, we did not have access to raw recording data from ECG machines. This is likely due to study protocols explicitly defining a set of cardiovascular variables (eg, QTc, QT, and R-R) as source data of interest. In future, electronic health record data inclusive of automatically recorded ECG data and meta-data would allow employment of more sophisticated correction methods (eg, Bogossian correction or JT intervals to account for the impact of wide QRS complexes).

We originally planned also to investigate the effect of antidepressant dose, but methodological limitations prevented the inclusion of this variable in our models (see supplementary appendix 3.1). Currently available models to analyse randomised controlled trial data allow adjustments only for pre-randomisation variables. For this reason, our analyses would have been limited to fixed dose studies; in flexible dose studies, dose is adjusted based on clinical response and tolerability—events happening after randomisation.[40] Unfortunately, our sample lacked enough fixed dose studies for appropriate evaluation in dose-outcome models.

Finally, our analyses were likely underpowered to provide definitive answers on rare events such as early MACE. While the timeframe of eight weeks is adequate for capturing acute drug induced changes in the QTc interval at steady state, QTc prolongation is a proxy outcome that does not invariably translate into MACE. Future consideration of data from electronic health record and post-marketing surveillance over longer timeframes are likely to provide a better framework to detect MACE and investigate potential

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associations with specific antidepressants. Although our aggregate level safety analysis encompassed more than 52 000 patients, the short duration of the randomised controlled trials means that late occurring or low frequency MACE could be underestimated, necessitating caution when extrapolating these findings to long term maintenance treatment.

Conclusions

Although antidepressants are on average safe in terms of QTc prolongation, we observed differences across antidepressants and risk factors at an individual level. Matching individual characteristics with potential benefits and harms associated with a treatment are essential components of personalised approaches and shared decision making. Approaches similar to our Shiny app (https://egostinelli.shinyapps.io/QTcF) could be employed in future to estimate a stratified risk, taking into account co-occurring risk factors. While routine ECG monitoring may have a role in patients with increased baseline risk, our findings suggest that the likelihood of QTc prolongation induced tachyarrhythmias, including torsade de pointes, may increase when antidepressant use overlaps with additional modifiable and non-modifiable risk factors. Additional data, particularly from sources that better reflect real world clinical diversity, are needed to clarify the magnitude of this risk and the circumstances in which such risk may become clinically relevant.

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Contributors: EGO and AC conceptualised the study. EGO, ZL, and AC provided input to the methodology. EGO, SC, GM, AP, FLR, and AC provided input to the data interpretation. EGO, ZL, SC, and CF verified the underlying data. EGO and ZL performed the data analysis. EGO and AC drafted the original manuscript. All authors critically revised the manuscript and approved the final version for publication. EGO is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: EGO has received research and consultancy fees from Angelini Pharma and received funding from the National Institute for Health and Care Research and Wellcome; AP reports participation in regulator mandated phase 4 studies funded by AbbVie, Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, LEO Pharma, Novo Nordisk, Pfizer, and Servier, and on sponsor initiated research projects with Novo Nordisk, all with funds paid to the institution where he is employed (no personal fees); AC has received research and consultancy fees from INCiPiT, Fondazione Cariplo, Lundbeck, Teva, and Angelini Pharma, and received funding from NIHR and Wellcome; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: Data sharing: As data sharing is regulated by agreements with pharmaceutical companies and/or Vivli, individual participant data cannot be openly shared. Where possible, the supplementary file contains aggregate data and summary statistics. The supplementary file also includes the code used to analyse the data in the paper.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We intend to disseminate the results to relevant patient communities via the media relations department of our institutions. We also plan to use social media and the websites of our organisations.

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1 National Institute for Health and Care Excellence. Depression in adults: treatment and management (NG222). 2022 (accessed 8 Oct 2025). https://www.nice.org.uk/guidance/ng222
2 National Health Service Business Services Authority. 2025 (accessed 7 Sep 2025). https://www.nhsbsa.nhs.uk/statistical-collections/medicines-used-mental-health-england/medicines-used-mental-health-england-201516-202425
3 Organisation for Economic Co-operation and Development. 2025 (accessed 7 Sep 2025). https://data-explorer.oecd.org
4 Davies RA, Ladouceur VB, Green MS, et al. The 2023 Canadian Cardiovascular Society Clinical Practice Update on Management of the Patient With a Prolonged QT Interval. *Can J Cardiol* 2023;39:1285-301. doi:10.1016/j.cjca.2023.06.011
5 Clinical Knowledge Summaries by NICE. 2025 (accessed 7 Sep 2025). https://cks.nice.org.uk/topics/depression/prescribing-information/
6 Medicines and Healthcare products Regulatory Agency. 2014 (accessed 7 Sep 2025). https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-qt-interval-prolongation
7 Castro VM, Clements CC, Murphy SN, et al. QT interval and antidepressant use: a cross sectional study of electronic health records. *BMJ* 2013;346:f288. doi:10.1136/bmj.f288
8 European Medicines Agency. 2005 (accessed 7 Sep 2025). https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-14-clinical-evaluation-qtqts-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-drugs-step-5_en.pdf
9 Nosè M, Barbui C. Do antidepressants prolong the QT interval? *Epidemiol Psychiatr Sci* 2014;23:19-20. doi:10.1017/S204579601300070X
10 Johnson JN, Ackerman MJ. QTc: how long is too long? *Br J Sports Med* 2009;43:657-62. doi:10.1136/bjsm.2008.054734
11 Pillinger T, Arumuham A, McCutcheon RA, et al. The effects of antidepressants on cardiometabolic and other physiological parameters: a systematic review and network meta-analysis. *Lancet* 2025;406:2063-77. doi:10.1016/S0140-6736(25)01293-0
12 Ostinelli EG, Furukawa TA. Data reduction when aggregating information about harms associated with medical interventions. *BMJ Ment Health* 2024;27:e301025. doi:10.1136/bmjment-2024-301025
13 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. doi:10.1016/S0140-6736(17)32802-7
14 Cipriani A, Fernandes KBP, Mulsant BH, et al. A Decision-Support System to Personalize Antidepressant Treatment in Major Depressive Disorder: A Randomized Clinical Trial. *JAMA* 2026;335:1219-31. doi:10.1001/jama.2026.1327
15 Ostinelli EG, Jaquiery M, Liu Q, et al, PETRUSHKA Team. Personnalisation du traitement antidépresseur de la dépression unipolaire associant choix individuels, risques et mégadonnées: l'outil PETRUSHKA. [Personalising Antidepressant Treatment for Unipolar Depression Combining Individual Choices, Risks and big Data: The PETRUSHKA Tool.] *Can J Psychiatry* . 2025:7067437251322399. doi:10.1177/07067437251322399. Epub ahead of print.

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16 Vandenberk B, Vandael E, Robyns T, et al. Which QT Correction Formulae to Use for QT Monitoring? *J Am Heart Assoc* 2016;5:e003264. doi:10.1161/JAHA.116.003264
17 Khatib R, Sabir FRN, Omari C, et al. Managing drug-induced QT prolongation in clinical practice. *Postgrad Med J* 2021;97:452-8. doi:10.1136/postgradmedj-2020-138661
18 Committee for Proprietary Medicinal Products. *The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products* . London. CPMP. 1997
19 Neuroscience based Nomenclature 2R. 2025 (accessed 7 Sep 2025). https://nbn2r.com
20 NHS Dorset. Dorset Medicines Advisory Group (accessed 22 Sep 2025). https://www.nhsdorset.nhs.uk/Downloads/aboutus/medicines-management/Other%20Guidelines/QTc%20prolongation%20-%20guidance%20for%20mental%20health%20prescribers.pdf?UNLID=674279717202582633540
21 Cohagan B, Brandis D. Torsade de Pointes. [Updated 8 Aug 2023]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025 Jan (accessed 5 Nov 2025). https://www.ncbi.nlm.nih.gov/books/NBK459388/
22 Empana JP, Lerner I, Valentin E, et al. Incidence of Sudden Cardiac Death in the European Union. *J Am Coll Cardiol* 2022;79:1818-27. doi:10.1016/j.jacc.2022.02.041
23 National Institute for Health and Care Excellence. *Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes (NG5)* . 2015 (accessed 26 Nov 2025).
24 Yellow Card. 2025 (accessed 7 Sep 2025). https://yellowcard.mhra.gov.uk
25 Ray WA, Chung CP, Murray KT, et al. High-Dose Citalopram and Escitalopram and the Risk of Out-of-Hospital Death. *J Clin Psychiatry* 2017;78:190-5. doi:10.4088/JCP.15m10324
26 Lalji HM, McGrogan A, Bailey SJ. An analysis of antidepressant prescribing trends in England 2015-2019. *J Affect Disord Rep* 2021;6:100205. doi:10.1016/j.jadr.2021.100205
27 OpenPrescribing. Bennett Institute for Applied Data Science, University of Oxford. 2025 (accessed 5 Nov 2025). https://openprescribing.net
28 Bégaud B, Dangoumau J. Pharmaco-épidémiologie: définition, problèmes, méthodologie [Pharmacoepidemiology: definitions, problems, methodology.]. *Therapie* . 2000;55:113-7. French. .
29 Neha R, Subeesh V, Beulah E, et al. Existence of Notoriety Bias in FDA Adverse Event Reporting System Database and Its Impact on Signal Strength. *Hosp Pharm* 2021;56:152-8. doi:10.1177/0018578719882323
30 Food and Drug Administration. 2009 (accessed 7 Sep 2025). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022411s000MedR.pdf
31 Halstead S, Yap CX, Warren N, et al. Holistic prevention and management of physical health side-effects of psychotropic medication: second report of the Lancet Psychiatry Physical Health Commission. *Lancet Psychiatry* 2025;12:673-99. doi:10.1016/S2215-0366(25)00162-2
32 Spaccarotella CAM, Migliarino S, Mongiardo A, et al. Measurement of the QT interval using the Apple Watch. *Sci Rep* 2021;11:10817. doi:10.1038/s41598-021-89199-z
33 Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTc modeling. *J Pharmacokinet Pharmacodyn* 2018;45:383-97. doi:10.1007/s10928-017-9558-5
34 Li D, Lo CWH, Vassos E, et al. T46. UNDERSTANDING ANTIDEPRESSANT CHANGE PATTERNS IN THE UK BIOBANK. *European Neuropsychopharmacology* 2025;99:181. doi:10.1016/j.euroneuro.2025.08.329
35 Noordam R, Sitlani CM, Avery CL, et al. A genome-wide interaction analysis of tricyclic/tetracyclic antidepressants and RR and QT intervals: a pharmacogenomics study from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. *J Med Genet* 2017;54:313-23. doi:10.1136/jmedgenet-2016-104112
36 Young WJ, Lahrouchi N, Isaacs A, et al. Genetic analyses of the electrocardiographic QT interval and its components identify additional loci and pathways. *Nat Commun* 2022;13:5144. doi:10.1038/s41467-022-32821-z
37 Bentestuen MS, Weis CN, Jeppesen CB, et al. Pharmacogenomic markers associated with drug-induced QT prolongation: a systematic review. *Pharmacogenomics* 2025;26:53-72. doi:10.1080/14622416.2025.2481025
38 Choi BJ, Koo Y, Kim TY, et al. Risk of QT prolongation through drug interactions between hydroxychloroquine and concomitant drugs prescribed in real world practice. *Sci Rep* 2021;11:6918. doi:10.1038/s41598-021-86321-z
39 Food and Drug Administration. 2011 (accessed 7 Sep 2025). https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-revised-recommendations-celexa-citalopram-hydrobromide-related
40 Watt JA, Del Giovane C, Jackson D, et al. Incorporating dose effects in network meta-analysis. *BMJ* 2022;376:e067003. doi:10.1136/bmj-2021-067003
41 Richardson DR, Parish PC, Tan X, et al. Association of QTc Formula With the Clinical Management of Patients With Cancer. *JAMA Oncol* 2022;8:1616-23. doi:10.1001/jamaoncol.2022.4194

Supplementary information: Additional material

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