

RESEARCH

Antidepressant use and risk of adverse outcomes in older people: population based cohort study

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Abstract

Objectives To investigate the association between antidepressant treatment and risk of several potential adverse outcomes in older people with depression and to examine risks by class of antidepressant, duration of use, and dose.

Design Cohort study of people aged 65 and over diagnosed as having depression.

Setting 570 general practices in the United Kingdom supplying data to the QResearch primary care database.

Participants 60 746 patients diagnosed as having a new episode of depression between the ages of 65 and 100 years from 1 January 1996 to 31 December 2007 and followed up until 31 December 2008.

Main outcome measures Hazard ratios associated with antidepressant use for all cause mortality, attempted suicide/self harm, myocardial infarction, stroke/transient ischaemic attack, falls, fractures, upper gastrointestinal bleeding, epilepsy/seizures, road traffic accidents, adverse drug reactions, and hyponatraemia, adjusted for a range of potential confounding variables. Hazard ratios were calculated for antidepressant class (tricyclic and related antidepressants, selective serotonin reuptake inhibitors, other antidepressants), dose, and duration of use and for commonly prescribed individual drugs.

Results 54 038 (89.0%) patients received at least one prescription for an antidepressant during follow-up. A total of 1 398 359 antidepressant prescriptions were issued: 764 659 (54.7%) for selective serotonin reuptake inhibitors, 442 192 (31.6%) for tricyclic antidepressants, 2203 (0.2%) for monoamine oxidase inhibitors, and 189 305 (13.5%) for the group of other antidepressants. The associations with the adverse outcomes differed significantly between the antidepressant classes for seven outcomes. Selective serotonin reuptake inhibitors were associated with the highest adjusted hazard ratios for falls (1.66, 95% confidence interval 1.58 to 1.73) and hyponatraemia (1.52, 1.33 to 1.75) compared with when antidepressants were not being used. The group of other

antidepressants was associated with the highest adjusted hazard ratios for all cause mortality (1.66, 1.56 to 1.77), attempted suicide/self harm (5.16, 3.90 to 6.83), stroke/transient ischaemic attack (1.37, 1.22 to 1.55), fracture (1.64, 1.46 to 1.84), and epilepsy/seizures (2.24, 1.60 to 3.15), compared with when antidepressants were not being used. Tricyclic antidepressants did not have the highest hazard ratio for any of the outcomes. Significantly different associations also existed between the individual drugs for the same seven outcomes; trazodone (tricyclic antidepressant), mirtazapine, and venlafaxine (both in the group of other antidepressants) were associated with the highest rates for some of these outcomes. Absolute risks over 1 year for all cause mortality were 7.04% for patients while not taking antidepressants, 8.12% for those taking tricyclic antidepressants, 10.61% for selective serotonin reuptake inhibitors, and 11.43% for other antidepressants.

Conclusions Selective serotonin reuptake inhibitors and drugs in the group of other antidepressants were associated with an increased risk of several adverse outcomes compared with tricyclic antidepressants. Among individual drugs, trazodone, mirtazapine, and venlafaxine were associated with the highest risks for some outcomes. As this is an observational study, it is susceptible to confounding by indication, channelling bias, and residual confounding, so differences in characteristics between patients prescribed different antidepressant drugs that could account for some of the associations between the drugs and the adverse outcomes may remain. Further research is needed to confirm these findings, but the risks and benefits of different antidepressants should be carefully evaluated when these drugs are prescribed to older people.

Introduction

Depression is a common condition in older people, affecting around 10-15% of those living in the community.^{1 2} In the United Kingdom, depression is largely treated in primary care with antidepressant drugs. Antidepressants are one of the most

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commonly prescribed drug groups in primary care. Around 39 million prescriptions for antidepressants were issued in the community in England in 2009 across all ages, an increase of 35% over five years.³ Prescriptions increased most for the class of selective serotonin reuptake inhibitor antidepressants—a 47% increase over five years, compared with an 18% increase for the class of tricyclic and related antidepressants and a 37% increase for other antidepressants.^{4 5} A systematic review in older people found that tricyclic antidepressants and selective serotonin reuptake inhibitors were equivalent in terms of efficacy but that classic tricyclic antidepressants were associated with a higher discontinuation rate owing to side effects.⁶ The National Institute for Health and Clinical Excellence recommends that the choice of an antidepressant should be guided by consideration of side effects and the patient's preferences but that normally a selective serotonin reuptake inhibitor in generic form should be chosen.⁷

Little is known about more serious adverse effects of antidepressants, particularly in older people, in whom adverse drug events may be more common in the treatment of depression compared with younger groups because of higher levels of comorbidity, age related physiological changes, and polypharmacy.⁸ The under-representation of older people in clinical trials of antidepressants and the fact that most such trials are short term make deriving reliable or precise estimates of the incidence of adverse events in this group difficult.^{9 10} This problem is further compounded when criteria for trials exclude older people with comorbid conditions.¹¹ Although several observational studies have examined different adverse outcomes associated with use of antidepressants,¹² few have been specific to an older population.

We therefore did a large cohort study of antidepressant use in older people to investigate the association between antidepressant treatment and risk of several potential adverse outcomes. We directly compared antidepressant class effects and examined dose and associations with use of commonly prescribed individual drugs. We aimed to derive a comprehensive and integrated picture of the relative safety and balance of risks for antidepressant drugs in older people diagnosed as having depression.

Methods

Full details of the study methods are published in a *Health Technology Assessment* monograph.¹³ We report the key findings of the study here, and further results are presented in the full report.

Setting

In summary, we used the QResearch primary care research database (version 22) to do a cohort study in a large population of primary care patients. Practices that provide data for QResearch use the Egton Medical Information Systems (EMIS) medical records system. EMIS is the major supplier of primary care computer systems in the UK and is in use in around two thirds of UK general practices. The practices that contribute data to QResearch are spread throughout the UK and comprise around 7% of all UK general practices. A comparison of QResearch practices with all UK practices found that practices contributing to QResearch tended to be marginally larger than UK practices overall but were similar in other respects.¹⁴ The database includes data on patients' demographics, consultations, symptoms, diagnoses (including diagnoses made in secondary care obtained from hospital discharge letters), referrals, results of investigations, and prescribed drugs.

Study cohort

The target population for the cohort study was all patients in the QResearch database with a recorded diagnosis of depression made when they were aged 65 and over and between 1 January 1996 and 31 December 2007. We used the first such diagnosis as the index diagnosis. We used computer recorded Read codes to identify a diagnosis of depression, using case definitions similar to those that have been used in previous studies.^{15 16} Patients with a previous recorded diagnosis of depression before the age of 65 were eligible for inclusion in the study to increase the representativeness of the study cohort. We excluded patients if any of the following applied: they were aged 100 years or more at diagnosis; the diagnosis occurred less than 12 months after registration with a study practice or after the installation date of the practice's EMIS computer system; they were temporary residents; they had a diagnosis of depression in the 12 months before their index recorded diagnosis of depression; they had been prescribed antidepressants in the 12 months before their recorded diagnosis of depression; or they had a diagnosis of schizophrenia, bipolar disorder, or other types of psychoses. We defined the date of entry in the study for each patient as the date of the first recorded diagnosis of depression after age 65 within the study period or the date of the first prescription for an antidepressant after age 65 if that occurred before the recorded date of depression.

Outcome data

We followed the cohort until 31 December 2008. We extracted information on adverse outcomes during follow-up from the primary care computer records on the basis of computer recorded Read codes (which include diagnoses made in primary and secondary care) and also from the linked death certificates by using ICD-9 (international classification of diseases, 9th revision) and ICD-10 codes if patients had died during the follow-up period. We included outcomes only if they occurred after the study entry date and up to 31 December 2008. The pre-specified outcomes were all cause mortality, attempted suicide/self harm, myocardial infarction, stroke/transient ischaemic attack, falls, fractures (upper limb, lower limb, ribs, skull, vertebrae, pelvis), upper gastrointestinal bleeding, epilepsy/seizures, road traffic accidents, adverse drug reactions (including bullous eruption), and hyponatraemia.

Three other pre-specified outcomes were sudden cardiac death, suicide (including open verdicts), and overdose/poisoning from antidepressants, but the numbers of patients identified with these outcomes were small, which limited the analyses that could be done. We did an additional analysis using stroke as an outcome, excluding transient ischaemic attacks.

Exposure data

The primary exposure of interest was treatment with antidepressant drugs. We extracted information on all individual prescriptions for antidepressants during follow-up, including detailed information on the drug name and formulation, dosage instructions, and numbers of tablets issued for each prescription. We grouped antidepressant drugs for analysis according to the major classes of antidepressants as described in the *British National Formulary*¹⁷: tricyclic and related antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and other antidepressants.

Some patients received prescriptions for different drugs within a class or drugs from different classes on the same date. We classified these prescriptions as combined prescriptions for some analyses (results not presented but available from the authors).

We determined the duration of each prescription in days by dividing the number of tablets prescribed by the dosing directions (for example, number of tablets to be taken each day). To calculate the daily dose of each prescription, we multiplied the specified dose of each tablet prescribed by the number of tablets to be taken each day, where this could be evaluated. To enable comparison of doses between the antidepressant classes, we converted daily dose to a defined daily dose, by using values assigned by the World Health Organization's Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atc_ddd_index).

Confounding variables

The potential confounding variables included in the analysis were age at study entry date; sex (male, female); year of diagnosis of depression; previous recorded diagnosis of depression before age 65; severity of index diagnosis of depression (categorised as mild, moderate, or severe on the basis of the Read code for the index diagnosis, using codes for each category published by Martinez and colleagues,¹⁶ and some classification by a member of the study team (RM) for Read codes for depression not included in the published list; the Read codes and their severity categorisation are given in the web appendix); deprivation, based on Townsend deprivation score for the patient's postcode,¹⁸ categorised into fifths according to the overall QResearch population; smoking status (non-smoker, ex-smoker, current smoker); comorbidities at baseline (coronary heart disease, diabetes, hypertension, stroke/transient ischaemic attack, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, identified by using appropriate computer recorded Read codes in the patients' records); use of other drugs at baseline (statins, non-steroidal anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics); and previous falls before baseline (for the analysis of fracture).

Statistical analysis

We used Cox's proportion hazards models to do separate analyses for each outcome. We used time to the first recorded diagnosis of each outcome in the analyses and excluded patients who already had the outcome recorded at baseline. We censored patients who did not have the outcome of interest during follow-up at the earliest of date of death, date of leaving the practice, date of the latest download of data, or the study end date (31 December 2008). We treated antidepressant use as a time varying exposure to account for patients stopping treatment and changing between treatments during follow-up. For the main analyses, we considered patients to be exposed to treatment if no gaps of more than 90 days existed between the end of one prescription and the start of the next.

The analysis calculated hazard ratios and 95% confidence intervals for antidepressant treatment, both unadjusted and adjusted for the potential confounding variables described above, excluding patients with missing values for smoking status or deprivation. The main analyses examined use of each class of antidepressants (selective serotonin reuptake inhibitors, tricyclic antidepressants, and other antidepressants) compared with no current treatment and also directly compared selective serotonin reuptake inhibitors and the group of other antidepressants with tricyclic antidepressants. We did analyses for antidepressant dose, categorising dose for each antidepressant class into three categories (≤ 0.5 defined daily doses, > 0.5 and ≤ 1.0 defined daily doses, and > 1.0 defined daily doses). We did tests of trend using continuous dose in defined daily doses for each class. We examined duration of treatment as a time varying exposure based

on time since starting antidepressant treatment and time since stopping treatment categorised for each antidepressant class as no use, 1-28 days' use, 29-84 days' use, and 85 or more days' use and periods of 1-28 days, 29-84 days, and 85-182 days after stopping treatment. We compared use of individual antidepressant drugs with no current treatment when numbers were sufficient. We excluded patients who had taken monoamine oxidase inhibitors at any time during follow-up from these analyses, as numbers were too small to allow precise estimates to be made.

We used a P value of < 0.01 (two tailed) to assess statistical significance. We did Wald's significance tests to determine whether the categorical variable for antidepressant class was significant overall and to test for equality of effects of the different classes, excluding the category of no current treatment, to determine whether significant differences existed between the classes. We also did this for the analyses of individual drugs. We assessed whether the assumption of proportional hazards was valid graphically. We used Stata (v10.1) for all analyses.

We estimated absolute risks for each outcome at one year from the index date, firstly in patients while they were not taking antidepressant treatment and then combining this with the adjusted hazard ratios for antidepressant class and individual drugs to calculate adjusted absolute risks in the treated groups by using a published formula.¹⁹ We included all eligible patients in the database in our analyses to maximise power.

Results

A total of 88 701 patients in the QResearch database had a recorded diagnosis of depression made at the age of 65 and over between 1 January 1996 and 31 December 2007. After we consecutively excluded 22 patients aged 100 and over at diagnosis, 3178 patients with schizophrenia, bipolar disorder, or other psychoses, 15 690 who had joined the practice in the previous year, and 9065 with a diagnosis of depression or a prescription for an antidepressant in the previous year, 60 746 eligible patients remained. These patients were from 570 QResearch practices, including 543 in England, 14 in Wales, four in Scotland, and nine in Northern Ireland.

Table 1 shows baseline characteristics of the study cohort. The mean age of the study cohort was 75.0 years, and the cohort contained 20 230 (33.3%) men and 40 516 (66.7%) women. The total number of person years of follow-up was 305 188, with a mean of 5.0 (SD 3.3) years per patient.

Patterns of antidepressant treatment

During follow-up, 54 038 (89.0%) patients received at least one prescription for an antidepressant drug, and a total of 1 398 359 prescriptions for antidepressants were issued. A total of 6484 (10.7% of 60 746) patients had only a single prescription for an antidepressant, and 6624 (10.9%) received 60 prescriptions or more during follow-up. The median duration of treatment with antidepressants during follow-up was 364 (interquartile range 91-1029) days.

Selective serotonin reuptake inhibitors were the most commonly prescribed drug class, comprising 54.7% (764 659) of the total antidepressant prescriptions. Patients received 442 192 (31.6% of all antidepressant prescriptions) prescriptions for tricyclic antidepressants and 189 305 (13.5%) for the group of other antidepressants. Monoamine oxidase inhibitor drugs were the least commonly prescribed class, comprising only 0.2% (2203 prescriptions) of the total prescriptions issued. Because of the small number of prescriptions for monoamine oxidase inhibitors,

we excluded patients prescribed these drugs from further analysis. Table 2 shows the prescribed doses by antidepressant class for the prescriptions where this could be evaluated. Doses tended to be lowest for tricyclic antidepressants—70.0% of prescriptions were for ≤ 0.5 defined daily doses, compared with 13.8% for selective serotonin reuptake inhibitors and 19.2% for the group of other antidepressants.

The 10 most commonly prescribed antidepressant drugs (citalopram hydrobromide (selective serotonin reuptake inhibitor), fluoxetine hydrochloride (selective serotonin reuptake inhibitor), amitriptyline hydrochloride (tricyclic antidepressant), dosulepin hydrochloride (tricyclic antidepressant), paroxetine hydrochloride (selective serotonin reuptake inhibitor), venlafaxine hydrochloride (other), sertraline hydrochloride (selective serotonin reuptake inhibitor), mirtazapine (other), lofepramine (tricyclic antidepressant), and escitalopram (selective serotonin reuptake inhibitor)) comprised 93.6% (n=1 309 056) of all antidepressant prescriptions. As only slightly fewer prescriptions for trazodone hydrochloride (tricyclic antidepressant) were issued, we considered the 11 most commonly prescribed drugs, comprising 96.0% (n=1 342 731) of all prescriptions, separately in some analyses (fig 1).

Results of analyses by antidepressant class

Tables 3 and 4 show the results of the analysis by antidepressant class. All classes of antidepressant drug were associated with significantly increased risks of all cause mortality, attempted suicide/self harm, falls, fractures, and upper gastrointestinal bleeding compared with when these drugs were not being used. Selective serotonin reuptake inhibitors and the group of other antidepressant drugs were associated with increased risks of stroke/transient ischaemic attack and epilepsy/seizures; selective serotonin reuptake inhibitors were also associated with increased risks of myocardial infarction and hyponatraemia.

The associations with the adverse outcomes differed significantly between the classes of antidepressant drugs for seven outcomes: all cause mortality, attempted suicide/self harm, stroke/transient ischaemic attack, falls, fracture, epilepsy/seizures, and hyponatraemia. For these outcomes, when compared directly with tricyclic antidepressants, selective serotonin reuptake inhibitors were associated with significantly higher rates of all cause mortality (adjusted hazard ratio 1.32, 95% confidence interval 1.26 to 1.39), stroke/transient ischaemic attack (1.15, 1.05 to 1.26), falls (1.27, 1.20 to 1.35), fracture (1.26, 1.15 to 1.37), epilepsy/seizures (1.80, 1.32 to 2.43), and hyponatraemia (1.44, 1.19 to 1.75). We found no significant difference for attempted suicide/self harm (1.27, 0.97 to 1.66).

The group of other antidepressants had significantly higher rates compared with tricyclic antidepressants for all cause mortality (adjusted hazard ratio 1.43, 1.33 to 1.54), attempted suicide/self harm (3.04, 2.21 to 4.17), stroke/transient ischaemic attack (1.35, 1.18 to 1.54), fracture (1.31, 1.15 to 1.50), and epilepsy/seizures (2.20, 1.46 to 3.30). We found no significant difference for falls (1.07, 0.97 to 1.17) or hyponatraemia (1.21, 0.90 to 1.64). Tricyclic antidepressants were not associated with significantly higher rates of any of the outcomes when compared with selective serotonin reuptake inhibitors or the group of other antidepressants.

We found similar results in an additional analysis that included only strokes as an outcome rather than strokes and transient ischaemic attacks. For example, the adjusted hazard ratio was 1.05 (0.95 to 1.17) for tricyclic antidepressants, 1.21 (1.11 to 1.32) for selective serotonin reuptake inhibitors, and 1.44 (1.24

to 1.67) for other antidepressants, all compared with when antidepressants were not being used.

The proportional hazards assumption of the Cox proportional hazards model was reasonable for most outcomes, although we found some indication of convergence for stroke/transient ischaemic attack, upper gastrointestinal bleeding, and hyponatraemia towards the end of the follow-up period.

Results of analyses for individual antidepressant drugs

Figure 2 shows adjusted hazard ratios associated with the 11 most commonly prescribed individual drugs. We found significant differences between the associations with these drugs ($P < 0.01$) for all cause mortality, attempted suicide/self harm, stroke/transient ischaemic attack, falls, fracture, epilepsy/seizures, and hyponatraemia.

Trazodone (a tricyclic antidepressant) was associated with the highest adjusted hazard ratio for all cause mortality and one of the highest hazard ratios for attempted suicide/self harm. Mirtazapine (in the group of other antidepressants) was associated with the highest adjusted hazard ratio for attempted suicide/self harm and one of the highest for all cause mortality and stroke/transient ischaemic attack. Venlafaxine (in the group of other antidepressants) was associated with higher adjusted hazard ratios for stroke/transient ischaemic attack, fracture, and epilepsy/seizures than the other drugs and with one of the highest for all cause mortality and attempted suicide/self harm. Citalopram (a selective serotonin reuptake inhibitor) was associated with the highest adjusted hazard ratio for falls, but risks were similar for all of the selective serotonin reuptake inhibitors.

Three selective serotonin reuptake inhibitors (citalopram, escitalopram, and fluoxetine) were associated with significantly increased risks of hyponatraemia, but paroxetine and sertraline were not. We found some evidence of increased rates of adverse drug reactions associated with lofepramine and sertraline. Amitriptyline and dosulepin (both tricyclic antidepressants) had the lowest risks for many of these outcomes.

We found similar results in an additional analysis that only included strokes as an outcome rather than strokes and transient ischaemic attack, except for a higher hazard ratio associated with trazodone (adjusted hazard ratio 1.48, 1.08 to 2.04) compared with when antidepressants were not being used.

Analyses by dose and duration

We found significant trends (at $P < 0.01$) with dose of tricyclic antidepressants and selective serotonin reuptake inhibitors for all cause mortality, falls, and epilepsy/seizures. We also found a significant dose-response relation between dose of tricyclic antidepressants and fracture (see web extra table A). For most outcomes, risks were highest in the first 28 days of use and also in the first 28 days after stopping antidepressant treatment (see web extra table B).

Absolute risks

Table 5 shows absolute risks at one year by antidepressant class and individual drug for each of the adverse outcomes. The absolute risks were highest for all cause mortality, stroke/transient ischaemic attack, falls, and fracture. Absolute risks for all cause mortality over one year were 7.04% for patients while not taking antidepressants, 8.12% for those taking tricyclic antidepressants, 10.61% for selective serotonin reuptake inhibitors, and 11.43% for other antidepressants.

Discussion

This observational study found significant associations between use of antidepressant drugs and several severe adverse outcomes in people aged 65 and older with depression. We found no evidence that use of selective serotonin reuptake inhibitors or drugs in the group of other antidepressants were associated with a reduced risk of any of the adverse outcomes compared with tricyclic antidepressants. However, compared with tricyclic antidepressants, selective serotonin reuptake inhibitors may be associated with an increased risk of certain outcomes, including all cause mortality, stroke/transient ischaemic attack, falls, fracture, epilepsy/seizures, and hyponatraemia, and the group of other antidepressants may be associated with an increased risk of all cause mortality, attempted suicide/self harm, stroke/transient ischaemic attack, fracture, and epilepsy/seizures. Examination of individual drugs found that trazodone, mirtazapine, and venlafaxine were associated with the highest rates for some outcomes. To our knowledge, this is the first published systematic assessment of the safety of commonly used antidepressants in older patients across a range of serious adverse outcomes.

Possible explanations for findings

Tricyclic antidepressants were prescribed at lower doses than were selective serotonin reuptake inhibitors and other antidepressant drugs, which could in part explain our findings. However, within separate categories of dose, tricyclic antidepressants still tended to be associated with lower adjusted hazard ratios for all cause mortality, attempted suicide/self harm, stroke/transient ischaemic attack and epilepsy/seizures within each dose category. Also, this reflects prescribing patterns in primary care, and some evidence shows that low dose tricyclic antidepressants are similar to higher dose tricyclics in terms of reducing symptoms of depression.^{7 20}

Rates of most outcomes were highest in the first 28 days after starting an antidepressant, and also in the first 28 days after stopping. For all cause mortality, myocardial infarction, stroke/transient ischaemic attack, adverse drug reactions, and hyponatraemia, we found some evidence that rates were reduced after 85 days of use. Changes in the severity of depression, particularly after starting antidepressant treatment, could explain why increases in rates of adverse events were generally most marked in the first 28 days after a prescription, when the depression is likely to be more severe, and could also explain the reductions in rates for some outcomes after 85 days of use when the depression may be resolving. This will have less effect on direct comparisons between antidepressant classes or individual drugs than on comparisons with non-use of antidepressants. The increased rates after stopping treatment may reflect patients stopping the drugs because of an onset of illness or after being admitted to hospital or a residential home, and increased rates of adverse events may be associated with these factors rather than being a direct effect of withdrawal.

Strengths and limitations

This was a large population based study with broad inclusion criteria, so the findings are generalisable to the population of older people diagnosed as having depression in primary care. This is in contrast with clinical trials, which generally have strict inclusion and exclusion criteria, tending to lead to the exclusion of many older people who have comorbidities or are taking drugs for other conditions. In addition, we included all eligible patients, which reduced selection bias. The study size enabled us to detect associations with relatively rare adverse events.

The data were recorded prospectively, so all information on prescriptions for antidepressants and potential confounding variables was recorded before the occurrence of an adverse outcome, meaning that recall bias will not have occurred. We adjusted our analyses for several potential confounding variables, including comorbidities and use of other drugs.

We had detailed information on prescriptions for antidepressants issued in primary care throughout the follow-up period, so we could do comprehensive analyses investigating effects of individual drugs, dose, and duration. This contrasts with many cohort or case-control studies in which information on antidepressant use is self reported or collected only at the start of the study.

The main concern with observational studies such as this one is indication bias. Indication bias occurs when patients are prescribed drugs for a condition that is itself associated with the outcome of interest. This means that apparent associations with a drug may be due to the condition for which it was prescribed rather than to the drug itself. To reduce this bias, we restricted our study cohort to include only patients with a recorded diagnosis of depression, so that all patients, whether treated or not, had the same indication for treatment. This is important, as depression itself is associated with many adverse outcomes.²¹⁻²³ Some systematic differences are still likely between patients who are treated and those who are not. Those who are not treated are likely to have less severe depression and may have poorer physical health, such that they are considered too frail for antidepressant treatment. We adjusted for many factors that could differ between groups, including age, sex, severity of depression, several comorbidities, and use of other drugs. Generally, the adjustment did not have a large effect on the results. However, although we adjusted for severity of the initial diagnosis of depression, we could use only a crude measure as we did not have a validated depression severity score. We cannot therefore exclude the possible effect of residual confounding on our results.

Direct comparisons between treated groups are less susceptible to confounding by indication, or confounding due to factors influencing prescribing of treatment, but are still subject to channelling bias, whereby different antidepressant drugs with similar indications might be prescribed according to varying characteristics of patients. An example of this would be the preferential prescribing of selective serotonin reuptake inhibitors rather than tricyclic antidepressants to frail patients at greater risk of falling.²⁴ Again, adjusting for a range of potential confounding factors would be expected to reduce the effect of this bias; for example, in the analysis of fracture we adjusted for falls at baseline as well as for many other confounders. This bias would also be less likely to apply to comparisons between individual drugs within a class than to comparisons between classes.

Residual confounding may remain in the findings, as certain potential confounding variables may not be recorded on the database or may not be recorded in sufficient detail to completely remove their confounding effect. As a supplementary analysis, we did a self controlled case series analysis. This is a within patients comparison, which implicitly removes the effects of all characteristics that vary between patients, irrespective of whether or in how much detail they have been recorded on the database, assuming that they do not vary over time within the observation period.²⁵ The results from the case series analyses were generally consistent with the cohort analyses, although the risks for attempted suicide/self harm for the group of other antidepressants were lower.¹³ These analyses, however, are also susceptible to confounding from time varying factors. We

cannot, therefore, exclude the possible effect of residual confounding for these results.

We did not specifically validate our outcomes as part of this study. However, reviews of validation studies in other UK primary care databases have shown overall high levels of validity, and we would expect similar levels of validity in QResearch.^{26 27} For example, Khan reported that particularly high (>90%) proportions of cases recorded in the general practice record were confirmed when further information was obtained for several outcomes including cerebrovascular disease, hip fracture, and upper gastrointestinal bleeding.²⁷ We included information from death certificates to identify additional patients with the outcomes, which will have reduced misclassification.

We have assessed only potential adverse effects of antidepressants in this study and not potential benefits, as very limited data are available for evaluating effectiveness of the different antidepressants in the QResearch database.

Comparison with other studies

Several observational studies have examined the effects of antidepressant drugs on single adverse outcomes, although few have been done specifically in older people or have examined them as a subgroup and few, if any, studies have directly compared adverse event rates across a range of important clinical outcomes. These studies have identified several adverse outcomes that may be associated with antidepressants, but an intrinsic problem with observational studies of antidepressants is the difficulty of distinguishing between the effects of antidepressant drugs and depression itself.

Attempted suicide/self harm

Relatively few studies have looked at antidepressants and attempted suicide/self harm in older people. A meta-analysis of randomised controlled trials registered with the US Food and Drug Administration found a reduced risk of suicidal behaviour and ideation associated with antidepressants in the group aged 65 years and over.²⁸ It found no evidence of a difference between drug classes across people of all ages. A systematic review of observational studies also found a reduction in risk of suicide or attempted suicide associated with use of selective serotonin reuptake inhibitors in the subgroup aged 65 years and older.²⁹ Little evidence supports or refutes our findings of increased rates associated with mirtazapine, venlafaxine, and trazodone compared with other antidepressants, and these warrant further investigation.

Myocardial infarction and stroke

The literature contains no clear findings for risk of myocardial infarction and antidepressant use in older people. Some studies have found an increased risk of myocardial infarction associated with antidepressant use,³⁰⁻³³ some have found a protective effect,³⁴⁻³⁶ and others have found no association.³⁷ An increased risk has been observed as being restricted to tricyclic antidepressants or selective serotonin reuptake inhibitors,^{32 33} applying across classes,^{30 31} or restricted to particular drugs.¹⁵ Evidence of a protective effect is largely limited to selective serotonin reuptake inhibitors.^{34 35}

Findings from previous studies of antidepressants and risk of stroke are inconsistent, but some studies have found (as we did) a possible increase in risk among users of selective serotonin reuptake inhibitors and the group of other antidepressants.^{37 38} If selective serotonin reuptake inhibitors have an effect on occurrence of stroke, this may result from an increased risk of bleeding complications, as these drugs limit uptake of blood

serotonin by platelets, which leads to inhibition of platelet aggregation, thereby preventing haemostasis by platelets.^{39 40} This mechanism could explain an association specifically with haemorrhagic stroke, but we were not able to distinguish between ischaemic and haemorrhagic stroke in this study.

Falls and fracture

A review of 78 studies found that the effects of tricyclic antidepressants and selective serotonin reuptake inhibitors on the risk of falls were generally similar across studies; few data were available for other antidepressants.⁴¹ Two studies specifically in older patients found that selective serotonin reuptake inhibitors in particular were strongly associated with the risk of falls.^{42 43} A cohort study of patients aged 60 and over found that selective serotonin reuptake inhibitors were associated with a more than twofold increase in the risk of falls but found no significant increase for other antidepressants.⁴⁴ Findings from the literature suggest that selective serotonin reuptake inhibitors and tricyclic antidepressants are associated with increased fracture rates,^{24 45-47} with possibly somewhat higher rates for selective serotonin reuptake inhibitors than for tricyclic antidepressants.⁴⁵⁻⁴⁷ Little evidence exists for other antidepressants. Our findings of a more marked and prolonged increase in risk for selective serotonin reuptake inhibitors compared with tricyclic antidepressants are in general agreement with this. The increased risk of fracture associated with antidepressant use may be due to an increased risk of falls, but some evidence also shows reduced bone mineral density in users of selective serotonin reuptake inhibitors.^{48 49}

Gastrointestinal bleeding

Gastrointestinal bleeding has been found in some studies to be more common among patients taking selective serotonin reuptake inhibitors,^{50 51} including those aged 65 years and over.⁵² A proposed mechanism for this finding is that these drugs block serotonin reuptake by platelets, leading to impairment of the platelet haemostatic response.⁵³ A study that adjusted for a wide range of potential confounding factors found a small increased risk of gastrointestinal bleeding among users of selective serotonin reuptake inhibitors, which is comparable in magnitude to ours, with no association for tricyclic antidepressants.⁵⁴ We found some evidence that venlafaxine is associated with a particularly increased risk of gastrointestinal bleeding, which has also been found in other studies.^{51 54}

Hyponatraemia

Hyponatraemia associated with antidepressant use is an adverse event that disproportionately affects older people.^{55 56} Studies have shown that hyponatraemia is associated most strongly with use of selective serotonin reuptake inhibitors,⁵⁶⁻⁵⁸ and our findings are in accordance with that. In these studies, hyponatraemia developed within the first few weeks of treatment and resolved within a few weeks after treatment was discontinued. These cases are thought to be almost entirely due to the development of the syndrome of inappropriate secretion of antidiuretic hormone, preventing the reabsorption of water and sodium ions in the distal tubule of the kidney precipitated by selective serotonin reuptake inhibitors.^{58 59}

Other outcomes

Other outcomes for which some evidence of an association with antidepressant use exists include all cause mortality,^{60 61} seizures,⁶² road traffic accidents,^{63 64} and adverse drug reactions,⁶⁵

but results are not consistent and evidence in older people with which to compare our findings is lacking.

Clinical implications and future research

Some of our findings are unexpected—in particular, that contrary to expectations tricyclic antidepressants seem to be the safest class of antidepressant in older people for the adverse outcomes considered in this study. Tricyclic antidepressants were prescribed at lower doses than the other drugs, but some evidence shows that low dose tricyclic antidepressants are similar to higher dose tricyclics in reducing symptoms of depression.^{7,20} Little evidence exists as to whether low dose tricyclic antidepressants are as efficacious as selective serotonin reuptake inhibitors at higher doses in the treatment of depression; in addition, tricyclic antidepressants may be associated with higher discontinuation rates owing to side effects such as sedation and dry mouth.⁶ The potential risks and benefits of different antidepressants therefore need careful consideration when these drugs are prescribed to older people.

Further research is needed to confirm our findings. Few randomised trials of antidepressants have been done in older people, in a primary care setting, with sufficient size and length of follow-up to assess adverse outcomes as well as benefits, so a long term randomised trial of antidepressants in older people with depression in primary care is needed to compare benefits and risks of more common adverse events between a selective serotonin reuptake inhibitor and a low dose tricyclic antidepressant. Research is also needed to confirm our findings with other data sources of older people in a community setting and to assess any risks associated with switching between antidepressant drugs. If our findings are confirmed in other studies, this would have implications for the selection of antidepressant treatment in older people, who are already at higher risk of many of these adverse outcomes.

Conclusions

This study has found that selective serotonin reuptake inhibitors and drugs in the group of other antidepressants were associated with an increased risk of several adverse outcomes compared with tricyclic antidepressants. Among the most commonly prescribed individual drugs, trazodone, mirtazapine, and venlafaxine were associated with the highest rates for some outcomes. As this is an observational study, it is susceptible to confounding by indication, channelling bias, and residual confounding. Other differences in characteristics may exist between patients prescribed different antidepressant drugs, which we have not adjusted for and which may account for some of the associations between the drugs and the adverse outcomes. Further research is needed to confirm these findings.

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Contributors: CC was involved in the conception and design of the study, analysing and interpreting data, and reviewing the literature; she wrote the draft manuscript. PD was involved in the design of the study, statistical analysis, interpreting data, and reviewing the literature. RM and AA were involved in the conception and design of the study, interpretation of data, and reviewing the literature. GB was involved in interpretation of data and reviewing the literature. JH-C was involved in the conception and design of the study, extracted the data, and was

involved in interpretation of data and reviewing the literature. All authors critically reviewed the paper. CC is the guarantor.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: all authors had financial support from the NIHR Health Technology Assessment Programme (project number 06/42/01) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; JH-C is director of QResearch, which is a not for profit venture between the University of Nottingham and EMIS (commercial supplier of general practice clinical computer systems), and director of ClinRisk Ltd (medical software company); RM has received financial support for speaking at meetings sponsored by several pharmaceutical companies about the non-drug treatment of depression and bipolar disorder; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The project was independently peer reviewed by the QResearch Scientific Board and has been reported to Trent Research Ethics Committee in accordance with the agreed procedure.

Data sharing: The patient level data from the QResearch databases are specifically licensed according to the governance framework. See www.qresearch.org for further details.

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What is already known on this topic

Depression is common in older people, and antidepressants including selective serotonin reuptake inhibitors (SSRIs), tricyclic and related antidepressants (TCAs), and other antidepressants are extensively used in its treatment

SSRIs are the most widely used antidepressants, and their use is increasing

Comparatively little is known about safety of these drugs in older people

What this study adds

Significant differences exist between different antidepressant drugs and their associations with several adverse events in people aged 65 and older with depression

No evidence was found that use of SSRIs or drugs in the group of other antidepressants were associated with a reduced risk of any of the adverse outcomes compared with TCAs

However, they may be associated with an increased risk for certain outcomes

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Tables

Table 1 | Characteristics of study cohort at baseline. Values are numbers (percentages) unless stated otherwise

Characteristic	Study cohort (n=60 746)
Female sex	40 516 (66.7)
Age group (years):	
65-74	31 341 (51.6)
75-84	21 497 (35.4)
≥85	7908 (13.0)
Mean (SD) age (years)	75.0 (7.6)
Severity of depression (index diagnosis):	
Mild	42 281 (69.6)
Moderate	15 639 (25.7)
Severe	2826 (4.7)
Recorded history of depression before age 65	8943 (14.7)
Smoking status:	
Non-smoker	33 656 (55.4)
Ex-smoker	13 005 (21.4)
Smoker	10 989 (18.1)
Not recorded	3096 (5.1)
Townsend deprivation score:	(n=59 003)
Lowest fifth	12 840 (21.8)
Second fifth	11 681 (19.8)
Third fifth	12 264 (20.8)
Fourth fifth	12 315 (20.9)
Highest fifth	9903 (16.8)
Comorbidities	
Coronary heart disease	11 981 (19.7)
Diabetes	6169 (10.2)
Hypertension	23 654 (38.9)
Stroke/transient ischaemic attack	6448 (10.6)
Any cancer	5032 (8.3)
Dementia	1091 (1.8)
Epilepsy/seizures	953 (1.6)
Parkinson's disease	869 (1.4)
Hypothyroidism	3956 (6.5)
Obsessive-compulsive disorder	119 (0.2)
Previous falls	4979 (8.2)
Drugs at baseline	
Anticonvulsants	1671 (2.8)
Antihypertensive drugs	30 363 (50.0)
Antipsychotics	5332 (8.8)
Aspirin	17 863 (29.4)
Hypnotics/anxiolytics	14 391 (23.7)
Lithium	148 (0.2)
Non-steroidal anti-inflammatory drugs	34 618 (57.0)
Statins	10 283 (16.9)

Table 2| Doses prescribed by antidepressant class in defined daily doses*. Values are numbers of prescriptions (column percentages)

Defined daily dose (DDD) prescribed	Antidepressant class		
	Tricyclic antidepressants	Selective serotonin reuptake inhibitors	Other
≤0.5 DDD	250 208 (70.0)	96 870 (13.8)	27 912 (19.2)
>0.5/≤1 DDD	75 922 (21.2)	505 093 (72.0)	77 286 (53.2)
>1/≤1.5 DDD	26 139 (7.3)	25 037 (3.6)	33 511 (23.1)
>1.5 DDD	5308 (1.5)	75 021 (10.7)	6664 (4.6)
Total	357 577	702 021	145 373

*Dose prescribed could not be calculated for all prescriptions issued during study period either because dosing directions were not recorded or insufficient detail was recorded or, for certain drugs, DDD value was not available; doses were combined when patients received more than one prescription with different doses for same drug on same day.

Table 3| Hazard ratios for six adverse outcomes (all cause mortality, attempted suicide/self harm, myocardial infarction, stroke/transient ischaemic attack, falls, and fractures) by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	No of events*	Hazard ratio (95% CI)	
		Unadjusted	Adjusted†
All cause mortality			
Not taking antidepressants	8210	1.00	1.00
Tricyclic antidepressants	2337	0.99 (0.95 to 1.04)	1.16 (1.10 to 1.22)
Selective serotonin reuptake inhibitors	5782	1.61 (1.55 to 1.66)	1.54 (1.48 to 1.59)
Other antidepressants	1268	1.77 (1.66 to 1.87)	1.66 (1.56 to 1.77)
Total events/total patients	17 597/60 640		
Attempted suicide/self harm			
Not taking antidepressants	150	1.00	1.00
Tricyclic antidepressants	89	1.67 (1.27 to 2.18)	1.70 (1.28 to 2.25)
Selective serotonin reuptake inhibitors	178	2.22 (1.77 to 2.78)	2.16 (1.71 to 2.71)
Other antidepressants	79	5.80 (4.41 to 7.63)	5.16 (3.90 to 6.83)
Total events/total patients	496/59 536		
Myocardial infarction			
Not taking antidepressants	1264	1.00	1.00
Tricyclic antidepressants	362	1.02 (0.91 to 1.15)	1.09 (0.96 to 1.23)
Selective serotonin reuptake inhibitors	614	1.16 (1.05 to 1.27)	1.15 (1.04 to 1.27)
Other antidepressants	110	1.01 (0.83 to 1.23)	1.04 (0.85 to 1.27)
Total events/total patients	2350/56 428		
Stroke/transient ischaemic attack			
Not taking antidepressants	2811	1.00	1.00
Tricyclic antidepressants	791	1.01 (0.93 to 1.10)	1.02 (0.93 to 1.11)
Selective serotonin reuptake inhibitors	1384	1.19 (1.12 to 1.27)	1.17 (1.10 to 1.26)
Other antidepressants	317	1.35 (1.21 to 1.52)	1.37 (1.22 to 1.55)
Total events/total patients	5303/54 198		
Falls			
Not taking antidepressants	5208	1.00	1.00
Tricyclic antidepressants	1704	1.20 (1.14 to 1.27)	1.30 (1.23 to 1.38)
Selective serotonin reuptake inhibitors	3575	1.71 (1.64 to 1.79)	1.66 (1.58 to 1.73)
Other antidepressants	631	1.45 (1.34 to 1.58)	1.39 (1.28 to 1.52)
Total events/total patients	11 118/55 669		
Fracture			
Not taking antidepressants	2507	1.00	1.00
Tricyclic antidepressants	809	1.23 (1.13 to 1.33)	1.26 (1.16 to 1.37)
Selective serotonin reuptake inhibitors	1597	1.61 (1.51 to 1.72)	1.58 (1.48 to 1.68)
Other antidepressants	341	1.64 (1.46 to 1.84)	1.64 (1.46 to 1.84)
Total events/total patients	5254/52 814		

*Based on numbers included in unadjusted analyses.

†Adjusted for sex, age (five year bands), year, severity of depression, depression before age 65, smoking status, Townsend deprivation score, coronary heart disease, diabetes, hypertension, cancer, dementia, Parkinson’s disease, hypothyroidism, obsessive-compulsive disorder, epilepsy/seizures, statins, non-steroidal anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, and hypnotics/anxiolytics; all outcomes except stroke/transient ischaemic attack also adjusted for stroke/transient ischaemic attack at baseline; fracture outcome also adjusted for falls at baseline.

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Table 4| Hazard ratios for five adverse outcomes (upper gastrointestinal bleeding, epilepsy/seizures, road traffic accidents, adverse drug reactions, and hyponatraemia) by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	No of events*	Hazard ratio (95% CI)	
		Unadjusted	Adjusted†
Upper gastrointestinal bleeding			
Not taking antidepressants	671	1.00	1.00
Tricyclic antidepressants	229	1.21 (1.04 to 1.41)	1.29 (1.10 to 1.51)
Selective serotonin reuptake inhibitors	365	1.27 (1.11 to 1.44)	1.22 (1.07 to 1.40)
Other antidepressants	79	1.36 (1.08 to 1.72)	1.37 (1.08 to 1.74)
Total events/total patients	1344/59 389		
Epilepsy/seizures			
Not taking antidepressants	223	1.00	1.00
Tricyclic antidepressants	58	0.99 (0.74 to 1.32)	1.02 (0.76 to 1.38)
Selective serotonin reuptake inhibitors	177	1.98 (1.62 to 2.43)	1.83 (1.49 to 2.26)
Other antidepressants	39	2.32 (1.67 to 3.24)	2.24 (1.60 to 3.15)
Total events/total patients in analysis	497/59 691		
Road traffic accidents			
Not taking antidepressants	252	1.00	1.00
Tricyclic antidepressants	56	0.83 (0.62 to 1.11)	0.86 (0.64 to 1.15)
Selective serotonin reuptake inhibitors	96	0.92 (0.72 to 1.16)	0.89 (0.70 to 1.13)
Other antidepressants	15	0.71 (0.42 to 1.19)	0.67 (0.39 to 1.14)
Total events/total patients	419/59 678		
Adverse drug reactions			
Not taking antidepressants	417	1.00	1.00
Tricyclic antidepressants	139	1.09 (0.89 to 1.32)	1.06 (0.86 to 1.29)
Selective serotonin reuptake inhibitors	231	1.20 (1.02 to 1.42)	1.16 (0.98 to 1.37)
Other antidepressants	37	1.00 (0.71 to 1.40)	0.95 (0.68 to 1.34)
Total events/total patients	824/60 170		
Hyponatraemia			
Not taking antidepressants	503	1.00	1.00
Tricyclic antidepressants	155	0.99 (0.82 to 1.18)	1.05 (0.87 to 1.27)
Selective serotonin reuptake inhibitors	383	1.62 (1.42 to 1.86)	1.52 (1.33 to 1.75)
Other antidepressants	62	1.38 (1.06 to 1.80)	1.28 (0.98 to 1.67)
Total events/total patients	1103/60 300		

*Based on numbers included in unadjusted analyses.

†Adjusted for sex, age (five year bands), year, severity of depression, depression before age 65, smoking status, Townsend deprivation score, coronary heart disease, stroke/transient ischaemic attack, diabetes, hypertension, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, non-steroidal anti-inflammatory drugs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, hypnotics/anxiolytics; all outcomes except epilepsy/seizures also adjusted for epilepsy/seizures at baseline.

Table 5| Absolute risks of adverse outcomes over one year by antidepressant class and top 11 most commonly prescribed antidepressant drugs

	Absolute risks over 1 year (%)										
	All cause mortality	Attempted suicide/self harm	Myocardial infarction	Stroke/TIA	Falls	Fracture	Upper GI bleed	Epilepsy/seizures	RTA	Adverse drug reaction	Hyponatraemia
Antidepressant class											
Not taking antidepressants	7.04	0.25	1.00	2.23	3.46	1.76	0.42	0.21	0.16	0.26	0.29
Tricyclic antidepressants	8.12	0.43	1.09	2.26	4.49	2.18	0.54	0.21	0.13	0.28	0.30
Selective serotonin reuptake inhibitors	10.61	0.55	1.15	2.61	5.67	2.74	0.51	0.38	0.14	0.30	0.44
Other antidepressants	11.43	1.30	1.04	3.04	4.79	2.85	0.57	0.46	0.10	0.25	0.37
Tricyclic antidepressants											
Amitriptyline hydrochloride	7.72	0.27	1.11	2.24	4.54	2.14	0.58	0.24	0.13	0.25	0.33
Dosulepin hydrochloride	7.26	0.48	1.07	2.12	4.28	2.15	0.51	0.10	0.08	0.23	0.24
Lofepamine	10.43	0.66	1.18	2.79	4.61	2.56	0.51	0.28	0.18	0.55	0.27
Trazodone hydrochloride	12.44	1.20	1.04	2.45	5.32	1.70	0.75	0.30	0.24	0.27	0.43
Selective serotonin reuptake inhibitors											
Citalopram hydrobromide	10.69	0.68	1.11	2.71	6.01	2.83	0.56	0.37	0.16	0.29	0.47
Escitalopram	10.06	0.47	1.32	2.70	5.70	2.26	0.45	0.36	0.15	0.29	0.59
Fluoxetine hydrochloride	11.42	0.53	1.31	2.57	5.60	2.76	0.48	0.31	0.11	0.31	0.49
Paroxetine hydrochloride	8.68	0.29	1.11	2.39	4.97	2.56	0.48	0.42	0.14	0.24	0.30
Sertraline hydrochloride	10.20	0.53	0.89	2.70	5.57	2.80	0.44	0.55	0.14	0.42	0.29
Other antidepressants											
Mirtazapine	12.05	1.56	1.11	3.06	4.11	2.56	0.44	0.33	0.07	0.27	0.31
Venlafaxine hydrochloride	11.40	1.17	1.05	3.34	5.74	3.26	0.72	0.61	0.11	0.23	0.44

GI=gastrointestinal; RTA=road traffic accident; TIA=transient ischaemic attack.

*Absolute risks for antidepressant drugs adjusted for confounders listed in table 3.

Figures

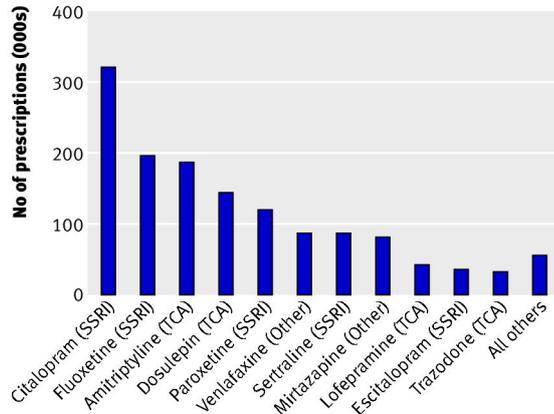


Fig 1 Total number of prescriptions during follow-up for 11 most commonly prescribed antidepressant drugs, in total of 54 038 patients. SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

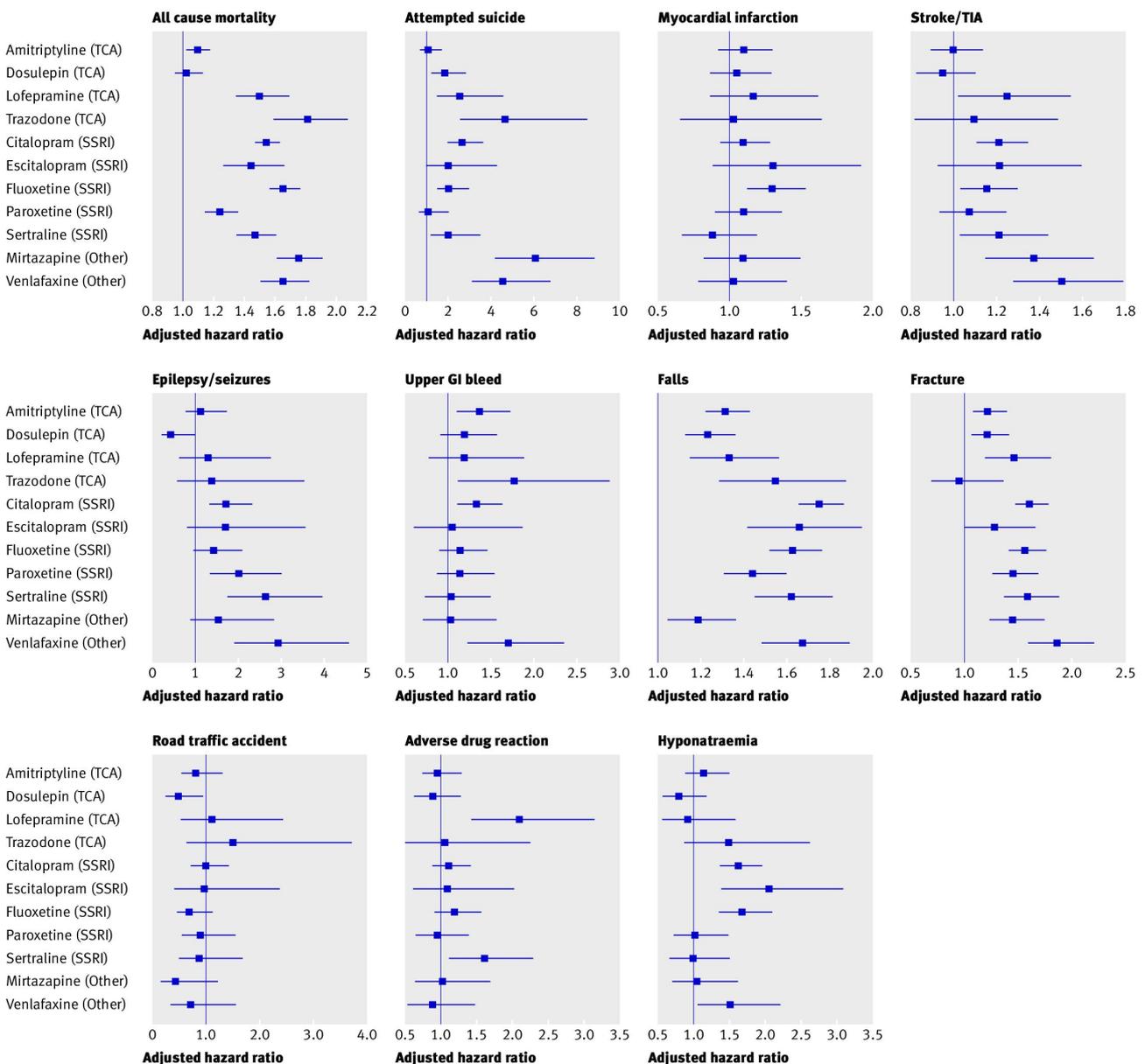


Fig 2 Adjusted (for confounders listed in table 3) hazard ratios (with 95% CI) for outcomes according to 11 most commonly prescribed antidepressant drugs. GI=gastrointestinal; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; TIA=transient ischaemic attack