

A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database

CAC Coupland, P Dhiman, G Barton, R Morriss,
A Arthur, T Sach and J Hippisley-Cox



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Abstract

A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database

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Objectives: The aim of this study was to establish the relative safety and balance of risks for antidepressant treatment in older people. The study objectives were to (1) determine relative and absolute risks of predefined adverse events in older people with depression, comparing classes of antidepressant drugs [tricyclic and related antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and other antidepressants] and commonly prescribed individual drugs with non-use of antidepressant drugs; (2) directly compare the risk of adverse events for SSRIs with TCAs; (3) determine associations with dose and duration of antidepressant medication; (4) describe patterns of antidepressant use in older people with depression; and (5) estimate costs of antidepressant medication and primary care visits.

Design: A cohort study of patients aged 65 years and over diagnosed with depression.

Setting: The study was based in 570 general practices in the UK supplying data to the QResearch database.

Participants: Patients diagnosed with a new episode of depression between the ages of 65 and 100 years, from 1 January 1996 to 31 December 2007. Participants were followed up until 31 December 2008.

Interventions: The exposure of interest was treatment with antidepressant medication. Antidepressant drugs were grouped into the major classes and commonly prescribed individual drugs were identified.

Main outcome measures: There were 13 predefined outcome measures: all-cause mortality, sudden cardiac death, suicide, attempted suicide/self-harm, myocardial infarction, stroke/transient ischaemic attack (TIA), falls, fractures, upper gastrointestinal bleeding, epilepsy/seizures, road traffic accidents, adverse drug reactions and hyponatraemia.

Results: In total, 60,746 patients were included in the study cohort. Of these, 54,038 (89.0%) received at least one prescription for an antidepressant during follow-up. The associations with the adverse outcomes were significantly different between the classes of antidepressant drugs for seven outcomes. SSRIs were associated with the highest adjusted hazard ratios (HRs) for falls [1.66, 95% confidence interval (CI) 1.58 to 1.73] and hyponatraemia (1.52, 95% CI 1.33 to 1.75), and the group of other antidepressants was

associated with the highest HRs for all-cause mortality (1.66, 95% CI 1.56 to 1.77), attempted suicide/self-harm (5.16, 95% CI 3.90 to 6.83), stroke/TIA (1.37, 95% CI 1.22 to 1.55), fracture (1.63, 95% CI 1.45 to 1.83) and epilepsy/seizures (2.24, 95% CI 1.60 to 3.15) compared with when antidepressants were not being used. TCAs did not have the highest HR for any of the outcomes. There were also significantly different associations between the individual drugs for seven outcomes, with trazodone, mirtazapine and venlafaxine associated with the highest rates for several of these outcomes. The mean incremental cost (for all antidepressant prescriptions) ranged between £51.58 (amitriptyline) and £641.18 (venlafaxine) over the 5-year post-diagnosis period.

Conclusions: This study found associations between use of antidepressant drugs and a number of adverse events in older people. There was no evidence that 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. Among individual drugs trazodone, mirtazapine and venlafaxine were associated with the highest rates for some outcomes. Indication bias and residual confounding may explain some of the study findings. The risks of prescribing antidepressants need to be weighed against the potential benefits of these drugs.

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Contents

List of abbreviations	vii
Executive summary	ix
1. Introduction	1
Antidepressant medication	1
Suicide, overdose and poisoning	2
Ischaemic heart disease	2
Fracture	2
Road traffic accidents	2
Other outcomes	2
Cost-effectiveness	2
Need for the current study	3
2. Methods	5
Aims and objectives	5
Study design summary	5
Setting	6
Cohort study design	6
Inclusion and exclusion criteria	6
Outcomes	7
Exposures	8
Confounding variables	9
Sample size	10
Statistical analysis	10
Self-controlled case-series study	12
Cost-effectiveness analysis	13
Protocol changes	17
Ethical arrangements	18
3. Results	19
Results of descriptive analyses	19
Results of time-varying analyses for the study outcomes	34
Overall summary of results across all outcomes	91
Results of health economic analyses	93
4. Discussion	117
Summary of the main findings	117
Strengths of the study	119
Limitations of the study	120
Interpretation of the study findings in light of previous research	122
5. Conclusions	135
Implications for health care	135
Implications for further research	135
Conclusions	136

Acknowledgements	137
References	139
Appendix 1 Read codes used for depression and severity	151
Appendix 2 Cost-effectiveness analysis – sensitivity analysis	155
Appendix 3 Final protocol	165
Appendix 4 Original protocol	181
Health Technology Assessment programme	197

List of abbreviations

ADR	adverse drug reaction
BMI	body mass index
BNF	<i>British National Formulary</i>
CHD	coronary heart disease
CI	confidence interval
DDD	defined daily dose
EMIS	Egton Medical Information Systems
GI	gastrointestinal
GP	general practitioner
GPRD	General Practice Research Database
HR	hazard ratio
HRQoL	health-related quality of life
ICD-9	<i>International Classification of Diseases</i> , Ninth Revision
ICD-10	<i>International Classification of Disease</i> , Tenth Revision
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
MAOI	monoamine oxidase inhibitor
MI	myocardial infarction
NICE	National Institute for Health and Clinical Excellence
NSAID	non-steroidal anti-inflammatory drug
QALY	quality-adjusted life-year
RTA	road traffic accident
SD	standard deviation
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic and related antidepressant
TIA	transient ischaemic attack

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Depression is a common and debilitating condition in older people. People diagnosed with depression are generally prescribed antidepressant drugs, which they might receive for a long period of time. Adverse drug events may be more common in the treatment of depression in older people than in younger age groups owing to higher levels of comorbidity, physiological changes and polypharmacy, but few studies have been carried out in this group.

The aim of this study was to establish the relative safety and balance of risks for antidepressant treatment in older people.

Objectives

The project had five key objectives:

1. to determine the relative and absolute risks of predefined adverse events in older people diagnosed with depression, comparing classes of antidepressant drugs [tricyclic and related antidepressants (TCAs) selective serotonin reuptake inhibitors (SSRIs); monoamine oxidase inhibitors (MAOIs); other antidepressants] as well as commonly prescribed individual drugs with non-use of antidepressant drugs.
2. to directly compare the risk of adverse events for SSRIs with TCAs
3. to determine how dose and duration of antidepressant medication are associated with the risk of adverse events
4. to describe patterns of antidepressant use in older people diagnosed with depression, in particular the types and doses prescribed, the durations and the proportions of people switching between different antidepressant classes
5. to estimate costs of antidepressant medication and primary care visits in older people diagnosed with depression, comparing patients by class of antidepressant drug.

Methods

Design

The study was a retrospective cohort study of patients aged 65 years and over diagnosed with depression and identified using the QResearch primary care database. A self-controlled case-series analysis was nested within the cohort study; this is an analysis 'within' patients, which removes the effects of indication bias and unmeasured confounding for variables that do not vary over time.

Setting

The study was based in 570 general practices in the UK supplying data to the QResearch (version 22) database.

Participants

The cohort study comprised patients diagnosed with a new episode of depression. Patients were eligible if they had a recorded diagnosis of depression between the ages of 65 and 100 years

which was recorded between 1 January 1996 and 31 December 2007 and occurred at least 12 months after registration with a study practice. Patients were excluded if they were temporary residents or had a recorded diagnosis of depression or prescriptions for antidepressants in the previous 12 months or if they had a diagnosis of schizophrenia, bipolar disorder or other types of psychoses. The cohort was followed up until 31 December 2008.

Patients in the cohort who had each of the outcomes of interest constituted the samples for the self-controlled case-series analysis.

Exposures

Details were extracted for all antidepressant medications prescribed during the follow-up period, including information on the prescription date, type of drug, dose and duration. The antidepressant drugs were grouped for analysis according to the major classes (TCAs, SSRIs, MAOIs, other antidepressant drugs) and commonly prescribed individual drugs were identified (TCAs – amitriptyline, dosulepin, lofepramine, trazodone; SSRIs – citalopram, escitalopram, fluoxetine, paroxetine, sertraline; and others – mirtazapine, venlafaxine). Combined treatment with different drugs was also assessed. Duration and dose of the drugs were examined where numbers were sufficient.

Outcome measures

Outcomes were extracted from the primary-care computer records and linked death certificates of patients in the cohort if they occurred after the index date and up until 31 December 2008. There were 13 predefined outcome measures: all-cause mortality, sudden cardiac death, suicide, attempted suicide/self-harm, myocardial infarction, stroke/transient ischaemic attack (TIA), falls, fractures, upper gastrointestinal bleeding, epilepsy/seizures, road traffic accidents, adverse drug reactions (ADRs) and hyponatraemia.

Analysis

In the cohort analysis, Cox proportional hazard models were used to estimate the associations of the outcomes with antidepressant use, treating antidepressant use as time varying and adjusting for potential confounding variables. Conditional Poisson regression was used to estimate relative incidence rates for defined time periods of risk after antidepressant prescriptions in the self-controlled case-series analyses.

Analysis of costs

In the base-case analysis, the cohort study data were used to estimate prescription costs for all antidepressant drugs over 1- and 5-year post-diagnosis periods compared with those prescribed no antidepressants, after controlling for differences between patients prescribed different antidepressants. For each outcome measure the subsequently calculated incremental costs were combined with estimates of the incremental number of averted events, to estimate the incremental cost per adverse event averted.

Results

A total of 60,746 patients were included in the study cohort. Of these patients, 54,038 (89.0%) received at least one prescription for an antidepressant drug during follow-up, and 6708 (11.0%) received no antidepressant prescriptions. A total of 1,398,359 antidepressant prescriptions were received during the follow-up period: 54.7% for SSRIs, 31.6% for TCAs, 0.2% for MAOIs and 13.5% for the group of other antidepressant drugs. The median duration of treatment with antidepressants during follow-up was 364 days. Patients prescribed SSRIs were less likely than patients prescribed TCAs or other antidepressants to either stop after a single prescription or

switch to another drug class in the year following their first prescription (37% for SSRIs, 48% for TCAs, 50% for the group of other antidepressants).

The associations with the adverse outcomes were significantly different between the classes of antidepressant drugs for seven outcomes. For these outcomes use of SSRIs had the highest adjusted hazard ratios (HRs) for falls [1.66, 95% confidence interval (CI) 1.58 to 1.73] and hyponatraemia (1.52, 95% CI 1.33 to 1.75), and the group of other antidepressants had the highest adjusted HRs for overall mortality (1.66, 95% CI 1.56 to 1.77), attempted suicide/self-harm (5.16, 95% CI 3.90 to 6.83), stroke/TIA (1.37, 95% CI 1.22 to 1.55), fracture (1.63, 95% CI 1.45 to 1.83) and epilepsy/seizures (2.24, 95% CI 1.60 to 3.15), all compared with when antidepressants were not being used. TCAs did not have the highest HR for any of the outcomes. Use of a combination of antidepressant drugs had higher HRs than any of the three main classes for eight outcomes.

The associations with the adverse outcomes were also significantly different between the individual drugs for seven outcomes. Trazodone (a tricyclic-related antidepressant) was associated with the highest adjusted HR for all-cause mortality and one of the highest HRs for attempted suicide/self-harm. Mirtazapine (in the group of other antidepressants) was associated with the highest rate of attempted suicide/self-harm and one of the highest rates for all-cause mortality and stroke/TIA. Venlafaxine (also in the group of other antidepressants) was associated with higher rates of stroke/TIA, fracture and epilepsy/seizures than the other drugs and one of the highest rates for all-cause mortality, attempted suicide/self-harm and falls. Citalopram (an SSRI) was associated with the highest rate of falls, but rates were similar for all of the SSRIs. Three SSRIs (citalopram, escitalopram and fluoxetine) were associated with significantly increased risks of hyponatraemia but paroxetine and sertraline were not. There was some evidence of increased rates of ADRs associated with lofepramine and sertraline. The TCAs, amitriptyline and dosulepin, had the lowest rates for many of these outcomes.

For all outcomes, rates tended to be highest in the first 28 days of starting antidepressant drugs, and also within 28 days of stopping medication. The absolute and excess risks were highest for all-cause mortality, falls, fracture, stroke/TIA and attempted suicide, and were low for the other outcomes. The self-controlled case-series results were generally consistent with the results from the cohort study analyses, but differed for attempted suicide/self harm and stroke/TIA.

The mean incremental cost (for all antidepressant prescriptions) ranged between £51.58 (amitriptyline) and £641.18 (venlafaxine) over the 5-year post-diagnosis period. None of the eleven most commonly prescribed antidepressant drugs were estimated to consistently be the most cost-effective across the different adverse outcomes studied.

Conclusions

This study has found significant associations between use of antidepressant drugs and a number of adverse events in people aged 65 years and older with depression. There was no evidence that the use of SSRIs or drugs in the group of other antidepressants was associated with a reduced risk of any of the adverse outcomes compared with TCAs; however, these drugs may be associated with an increased risk for certain outcomes. Examination of individual drugs has found that trazodone, mirtazapine and venlafaxine were associated with the highest rates for several outcomes.

Limitations of this study include possible indication and channelling bias, and residual confounding. The presence and severity of depression change over time and this is likely to

affect comparisons between treated and untreated periods of time. Differences in characteristics between patients prescribed different antidepressant drugs may account for some of the differences in associations between the drugs and the adverse outcomes, although the analyses adjusted for many potential confounding variables.

The risks of prescribing an antidepressant drug need to be weighed against the potential benefits of these drugs.

Implications for health care

In this study, SSRIs and drugs in the group of other antidepressants were not associated with a reduced risk of any of the adverse outcomes compared with TCAs, and they may even be associated with an increased risk for certain outcomes. This implies a careful evaluation of benefits and adverse outcomes is needed when prescribing antidepressants to older people, which should include consideration of TCAs and tailoring of drugs to individual patients.

In this study, mirtazapine, venlafaxine and trazodone were associated with higher rates than the other antidepressants for a number of outcomes including all-cause mortality and attempted suicide/self-harm. These potential risks should be considered when prescribing these drugs.

Use of a combination of antidepressants was associated with an increased risk for many of the adverse events studied; although this may reflect increased severity of depression and lack of response to monotherapy, it is a matter of concern and use of a higher dose of a single antidepressant should be considered as an alternative to combined treatment where appropriate.

This study found that rates of most outcomes were highest in the first 28 days after starting an antidepressant, which would support careful monitoring during the first weeks after prescribing antidepressants in older people.

Recommendations for research (in priority order)

1. A long-term community-based randomised clinical trial is needed to compare benefits and common adverse effects between a low-dose TCA and an SSRI for older people with depression.
2. Meta-analyses of randomised controlled trials of antidepressants in relation to adverse events in older people should be carried out to confirm these findings.
3. These findings should be confirmed using other data sources of older people in a community setting.
4. Further studies are needed to develop algorithms to individualise the risks associated with antidepressant use, so that patients at highest risk of these adverse events can be monitored closely.
5. Further research could be conducted to estimate the loss in utility associated with different types of adverse events. This would enable the health economic analysis to be based on quality-adjusted life-years and so allow estimation of the relative cost-effectiveness of different antidepressants.

Funding

The National Institute for Health Research Technology programme.

Chapter 1

Introduction

Depression is a common and debilitating condition in older people, affecting around 14% of older people living in the community.¹ Depression is largely treated in primary care in the UK, and usually with antidepressant medication, which is one of the most commonly prescribed drug groups in primary care. There were 36 million prescriptions issued in the community for antidepressants in England in 2008, an increase of 6.3% compared with the previous year.² For people aged 60 years and over an estimated 14 million antidepressant prescriptions were issued in 2007, an increase of 10.1% compared with the previous year and 79.0% compared with 2000 (figures from data provided by the NHS Information Centre).

Antidepressant medication

The first antidepressant drugs were developed in the 1950s, these were from the drug classes known as monoamine oxidase inhibitors (MAOIs) and tricyclic and related antidepressants (TCAs). Drugs known as selective serotonin reuptake inhibitors (SSRIs) were introduced in the 1980s and other new antidepressant drugs have been introduced since then. Reviews and meta-analyses of trials of these drugs have shown that all classes of antidepressant drug are more effective than placebo in terms of reducing symptoms of depression, particularly for more severe depression, but that the different antidepressant classes have largely similar efficacy.^{3–7} A systematic review in older people found that TCAs and SSRIs were equivalent in terms of efficacy but that classical TCAs were associated with a higher discontinuation rate due to side effects.⁵ The National Institute for Health and Clinical Excellence (NICE) recommended in 2009 that the choice of an antidepressant should be guided by consideration of side effects and patient preferences, but that normally an SSRI in generic form should be chosen.³

Although the benefits of antidepressants have been studied in many randomised controlled trials, most such trials are short term, in selected populations and comparatively little is known about their relative safety. Adverse drug events may be more common in the treatment of depression in older people compared with younger groups owing to higher levels of comorbidity, age-related physiological changes and polypharmacy.⁸ The under-representation of older people in clinical trials of antidepressants makes it difficult to derive reliable or precise estimates of the incidence of adverse events in this group.^{9,10} This problem is further compounded when trial exclusion criteria exclude older people with comorbid conditions.¹¹

Although some observational studies have examined the effects of antidepressant drugs on single adverse outcomes, few, if any, studies have directly compared adverse event rates across a range of important clinical outcomes. Studies of single outcomes have identified a number of adverse outcomes that may be associated with antidepressants, but an intrinsic problem with these study designs is the difficulty of distinguishing between any effects of antidepressant medication and the effect of depression itself.

Suicide, overdose and poisoning

Antidepressants, particularly TCAs, are an important cause of deaths by overdose and poisoning.¹² Observational studies across all age groups have found associations between antidepressant use and suicide, but have been unable to rule out confounding by indication.¹³ There is little evidence to support any difference in terms of class of antidepressant and risk of suicide,¹⁴ but studies have tended to look at risks across all ages or among adolescents and young adults.¹⁵

Ischaemic heart disease

An increased risk of ischaemic heart disease was found in one study to be associated with use of the TCA dosulepin (formerly known as dothiepin), but not other TCAs or SSRIs;¹⁶ however, other studies have found no evidence of an increased risk of myocardial infarction (MI) among users of antidepressants¹⁷ or have suggested that an increased risk of MI may be explained by confounding factors relating to depression itself rather than specific adverse drug effects.¹⁸

Fracture

Findings from case-control¹⁹ and case-series studies²⁰ indicate that the risk of hip fracture is elevated with use of TCAs and SSRIs among older people, although the magnitude of the increased risk did not differ between these two classes of antidepressant.¹⁹

Road traffic accidents

Studies that have formally tested the effects of antidepressants on driving performance have found that sedating antidepressants have a similar effect to alcohol,²¹ but there is little evidence in relation to road traffic accident (RTA) risk.

Other outcomes

Hyponatraemia associated with antidepressant use is rare, but is an adverse event that disproportionately affects older people.^{22,23} Gastrointestinal (GI) bleeding has been found to be more common among those taking SSRIs who are aged 80 years or over,²⁴ although there is a lack of consensus as to whether or not the risk of GI bleeding associated with SSRI use is further increased with concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs).^{25–27}

Other outcomes for which there is some evidence of an association with antidepressant use include all-cause mortality,^{28,29} sudden cardiac death,³⁰ stroke,^{31,32} seizures³³ and adverse drug reactions (ADRs),³⁴ but results are not consistent and there is a lack of evidence in older people.

Cost-effectiveness

In England, the annual cost of depression to the NHS and Personal Social Services has been estimated to be £1.7B compared with £5.8B in terms of lost employment and absenteeism.³⁵ More than 4% of hospital admissions have been estimated to be owing to ADRs^{36,37} and preventable

harm from medicines has been estimated to cost the NHS more than £750M per annum.³⁸ This, coupled with the fact that health-care resources are scarce,³⁹ means that it is important to compare the relative costs associated with different antidepressants and their relative (dis)benefits in terms of adverse events averted.

Need for the current study

The gaps in the research into adverse effects of antidepressant drugs specifically in older people, and the lack of consistent findings, pose problems for policy-makers and clinicians who are prescribing these drugs and making choices as to the most appropriate drug for individual older patients. Primary care databases with their large volumes of high-quality data on representative populations over many years are well suited to the study of unintended effects of medication. In this study we use a large primary care database containing information on prescriptions for antidepressants and a range of potential adverse effects to derive a more integrated picture of the balance of risks for antidepressant drugs in older people who are diagnosed with depression.

Chapter 2

Methods

Aims and objectives

The overall aim of the study was to establish the relative safety and balance of risks for antidepressant drugs in older people, in order to provide a robust evidence base to support decision making for policy-makers and clinicians prescribing these medications to individual patients.

The project had five key objectives:

1. to determine the relative and absolute risks of predefined adverse events in older people diagnosed with depression, comparing classes of antidepressant drugs (TCAs, SSRIs, MAOIs and other antidepressants) and commonly prescribed individual antidepressant drugs with non-use of antidepressant drugs
2. to directly compare the risk of adverse events in patients prescribed SSRIs against TCAs
3. to determine how dose and duration of prescribed antidepressant medication are associated with the risk of an adverse event
4. to describe patterns of antidepressant use in older people diagnosed with depression, in particular the types and doses prescribed, the durations and the proportions switching between different antidepressants (TCAs, SSRIs and other antidepressant drugs)
5. to estimate the costs of antidepressant medication and primary-care visits in older people who are diagnosed with depression, comparing patients by class of antidepressant drug (TCAs, SSRIs and other antidepressants).

Study design summary

The study used a large primary care database (QResearch) to investigate the relative safety and costs of antidepressant drugs in older people.

Two main approaches were used to achieve the study objectives:

1. cohort study analysis
2. nested self-controlled case-series analysis.

The cohort study analysis was used to estimate relative and absolute rates associated with exposures for a number of adverse outcomes, adjusting for potential confounding variables. The self-controlled case-series method^{40,41} was used to estimate the relative incidence of the adverse outcomes in different risk periods of antidepressant use compared with periods of non-use, using data from only cases with the outcomes. This method is useful for investigating the short-term effects of drug exposures on the risk of acute outcomes, as it eliminates problems of confounding from unmeasured variables, providing that they remain constant throughout the observation period.⁴¹

Setting

The study was undertaken using data from the QResearch primary-care research database (www.qresearch.org). This is a large general practice research database containing the anonymised electronic health-care records of over 12 million patients ever registered with more than 600 general practices throughout England, Wales, Scotland and Northern Ireland. 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 within two-thirds of all UK general practices. The practices that contribute data to QResearch form a representative sample of around 7% of all UK general practices, and there are practices in every strategic health authority and each health board in England, Wales and Scotland. Version 22 of the QResearch database was used for the present study.

The information recorded on the database includes patient demographic data (year of birth, gender, socioeconomic data derived from the UK 2001 census), characteristics (height, weight, smoking status), symptoms, clinical diagnoses, consultations, referrals, prescribed medications and results of investigations.

Detailed analyses have compared QResearch practices with all UK practices and found that practices contributing to QResearch are somewhat larger than UK practices overall but are very similar in other respects.⁴² The age–gender structure of the population has been compared with that reported in the 2001 census. There was good correspondence for all of these measures, although the QResearch population is slightly older and has marginally higher prevalence figures for some diagnoses than less recent data.⁴³

The QResearch database has previously been used to examine the risks and benefits associated with a number of commonly prescribed drugs including statins^{44,45} and NSAIDs.^{46,47}

Cohort study design

The target population for the cohort study was all patients in the QResearch database with a recorded diagnosis of depression made between 1 January 1996 and 31 December 2007 and when the patients were aged 65 years and over. We used computer-recorded Read codes to identify a major depressive disorder or unipolar depression, using case definitions similar to those that have been used in previous studies.^{15,16} The codes used are listed in *Appendix 1*.

The cohort was followed up until 31 December 2008. Information was extracted on potential confounding variables at baseline and on all prescriptions for antidepressants during follow-up, along with information on adverse outcomes during follow-up.

Inclusion and exclusion criteria

Patients were eligible for inclusion in the cohort study if:

- they had a recorded diagnosis of depression in their medical record
- the diagnosis was made at the age of 65 years or over
- the diagnosis was recorded between 1 January 1996 to 31 December 2007
- they were aged no more than 100 years at diagnosis

- the diagnosis occurred at least 12 months after registration with a study practice and after the installation date of the practice EMIS computer system.

Patients were excluded from the cohort study if any of the following were true:

- they were temporary residents
- they had a previous diagnosis of depression in the 12-month period prior to their index-recorded diagnosis of depression
- they had been prescribed antidepressants in the 12-month period prior to their recorded diagnosis of depression
- they had a diagnosis of schizophrenia, bipolar disorder or other types of psychoses.

Using these criteria, patients were eligible for inclusion in the study cohort if they did not receive any antidepressant treatment following a diagnosis of depression. They were also eligible for inclusion if they had a previous diagnosis of depression, made before the age of 65 years, as long as it was not in the 12 months before the index diagnosis.

Patients who received prescriptions for antidepressants but did not have a recorded diagnosis of depression were not eligible for inclusion; this was because the prescriptions may have been for indications other than depression (such as insomnia or trigeminal neuralgia), and we wanted to ensure that the cohort was restricted to patients with depression to reduce potential indication bias.

The index date which marked the date of entry into the study cohort was defined as the date of the first recorded diagnosis of depression after the age of 65 years, or the date of the first prescription for an antidepressant after age 65 years in patients if that occurred before the recorded date of depression.

Outcomes

The selected study outcomes were ones for which previous research had indicated some possible associations with use of antidepressants. Information on these outcomes was extracted from the primary-care computer records of patients in the cohort and also the linked death certificates for patients who had died during the study period. Outcomes were included only if they occurred after the date of entry into the study cohort and up to 31 December 2008. Computer-recorded Read codes and ICD-9/ICD-10 codes (*International Classification of Diseases*, Ninth Revision⁴⁸/Tenth Revision⁴⁹), where appropriate, were used to identify patients with each of the outcomes. We used lists of Read codes and ICD-9/ICD-10 codes that had been used in other studies where available, and also searched through lists of Read codes and ICD-9/ICD-10 codes to identify any additional appropriate codes or to define new lists if necessary. Final lists of codes were developed after discussion and agreement between the research team members.

The 13 outcomes that were assessed were:

- all-cause mortality
- sudden cardiac death
- suicide (including open verdicts)
- attempted suicide/self-harm
- myocardial infarction
- stroke/transient ischaemic attack (TIA)

- falls
- fractures (upper limb, lower limb, ribs, skull, vertebrae, pelvis)
- upper GI bleeding
- epilepsy/seizures
- RTAs
- adverse drug reactions (including bullous eruption)
- hyponatraemia.

An additional prespecified outcome was overdose/poisoning from antidepressants, but the number of patients identified with this outcome was too small for analysis.

We identified suicides as patients either with a code for suicide or an open verdict on their death certificate or patients with a Read code for attempted suicide who died within 30 days. The Read codes used for attempted suicide were based on those used in other studies.^{15,50} For RTAs we restricted the Read codes to those that indicated a motor vehicle crash, as in the study by Gibson and colleagues,⁵¹ and excluded codes that specified that the patient was a passenger. The date of occurrence of the outcome used in analysis was the first recorded date of the outcome during follow-up.

Exposures

The primary exposure of interest was treatment with antidepressant medication. The QResearch database contains detailed information on prescriptions issued to patients, including the name and formulation, dosage instructions and numbers of tablets issued for each prescription. We extracted details of all prescriptions for antidepressants in patients in our cohort, following their index date (earliest of date of first diagnosis of depression or date of first prescription for an antidepressant after the age of 65 years) and up to 31 December 2008 (or date of death or leaving the practice if this was earlier).

Antidepressant drugs were grouped for analysis according to the major classes of antidepressants as described in section 4.3 (Antidepressant drugs) of the *British National Formulary* (BNF),⁵² namely:

- tricyclic and related antidepressants (TCAs – subsection 4.3.1)
- monoamine oxidase inhibitors (MAOIs – subsection 4.3.2)
- selective serotonin reuptake inhibitors (SSRIs – subsection 4.3.3)
- other antidepressants (subsection 4.3.4).

The drugs in each category were:

- TCAs – amitriptyline hydrochloride, amoxapine, clomipramine hydrochloride, desipramine, dosulepin hydrochloride, doxepin, imipramine, imipramine hydrochloride, lofepramine, maprotiline hydrochloride, mianserin hydrochloride, nortriptyline, protriptyline hydrochloride, trazodone hydrochloride, trimipramine, viloxazine hydrochloride
- MAOIs – isocarboxazid, moclobemide, phenelzine, tranylcypromine
- SSRIs – citalopram hydrobromide, citalopram hydrochloride, escitalopram, fluoxetine hydrochloride, fluvoxamine maleate, paroxetine hydrochloride, sertraline hydrochloride
- Other antidepressants – duloxetine, flupentixol, L-tryptophan, mirtazapine, nefazodone hydrochloride, reboxetine, tryptophan, venlafaxine hydrochloride.

Some of these drugs have now been withdrawn but were in use at some time during the study period. Some patients received prescriptions for different drugs within a class or drugs from different classes on the same date. These prescriptions were classified as combined prescriptions for some analyses.

We determined the duration of each prescription in days by dividing the number of tablets prescribed by the dosing directions (e.g. number of tablets to be taken per day). In some cases in which the number of tablets prescribed was recorded, but the dosing directions were missing or not sufficiently detailed for this calculation to be made, we used an assumed duration based on the median duration of prescriptions for those prescriptions for which dosing directions were available, taking account of the number of tablets prescribed. On this basis we assumed a duration of 7 days if between 7 and 27 tablets were prescribed, a duration of 28 days if the number of tablets prescribed was between 28 and 99, and a duration of 56 days if the number of tablets prescribed was more than 100. If fewer than seven tablets were prescribed we assumed that the prescription duration in days was equal to the number of tablets prescribed. If the quantity of tablets prescribed was missing we assumed a duration of 28 days.

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. To enable comparison of doses between the antidepressant classes, we converted the dose per day for each prescribed drug to a defined daily dose (DDD), defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. We used the DDD values assigned by the World Health Organization's Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atc_ddd_index). If patients had two or more prescriptions for the same drug on the same day, we added the doses from these prescriptions.

Confounding variables

We identified potential confounding variables to be included in the cohort study analysis. These were:

- age at index date (baseline)
- gender (male, female)
- year of diagnosis of depression (index date)
- previous recorded diagnosis of depression before the age of 65 years
- severity of index diagnosis of depression [categorised as mild, moderate or severe, based on the Read code for the index diagnosis, using codes published by Martinez and colleagues¹⁵ and some additional classification by a member of the study team (RM)]
- deprivation, based on Townsend deprivation score for the patient's postcode⁵³
- smoking status (non-smoker, ex-smoker, current smoker)
- comorbidities at baseline [coronary heart disease (CHD), diabetes, hypertension, stroke/TIA, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder], identified using appropriate Read codes in the patient's records
- use of other drugs at baseline (statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, hypnotic/anxiolytic drugs).

In addition, for the analysis of suicide as an outcome, previous attempted suicide at baseline was considered as a confounding variable, and for the analysis of fracture previous falls at baseline was considered as a confounding variable.

Sample size

All eligible patients aged 65 years and over diagnosed with incident depression between 1 January 1996 and 31 December 2007 in the QResearch database were included in the cohort study. A feasibility study showed there are approximately 5.0 million person-years of observation and 18,000 incident cases of depression arising from patients aged 65 years and older between 1996 and 2005 on the database.

Assuming 88% of patients aged 65 years and over diagnosed with depression are prescribed an antidepressant drug as we found in our feasibility study, and for a rare outcome with an incidence of 5 per 1000 per year (e.g. upper GI event⁴⁷ or lower limb fracture⁵⁴), and an average follow-up of 5 years, we anticipated that the study would be able to detect a relative risk of 1.5 with 88% power and a 5% significance level comparing those on antidepressants with those not on antidepressants. For all-cause mortality with a mortality rate of 53 per 1000 per year (Office for National Statistics, 2001 figures for England and Wales; www.statistics.gov.uk) the study would be able to detect a relative risk of 1.15 with 95% power. In direct comparisons between TCAs and SSRIs, assuming that 39% of patients on antidepressants take TCAs and 50% take SSRIs, the study would be able to detect a relative risk of 1.4 with 86% power for rare outcomes and 1.12 with 92% power for all-cause mortality.

Statistical analysis

All analyses were carried out using STATA (version 10.1; StataCorp LP, College Station, TX, USA). We calculated incidence rates of diagnosed depression in people aged 65 years and over, using all eligible cases of depression in the study cohort as the numerator and person-years for people aged 65 years and over in the QResearch database as the denominator.

We described baseline characteristics of patients in the study cohort using summary statistics. We described patterns of antidepressant use according to class of antidepressant prescribed, duration of use and dose, and examined which individual drugs were prescribed most frequently. We compared the patients' baseline characteristics according to the class of antidepressant prescribed. We calculated the proportions of patients who switched between different antidepressant classes at any time within the study period and within the first year of being prescribed an antidepressant.

We calculated the number of treatment episodes for depression during follow-up, where a treatment episode was defined as a period of antidepressant treatment without gaps of more than 90 days between the end of a prescription and the start of the next prescription. A prescription after more than 90 days was counted as the start of a new treatment episode.

We examined variation between practices in patterns of antidepressant prescribing by dividing the total number of prescriptions for each class of antidepressant by the total number of all antidepressant prescriptions in each practice and summarised the variation in these proportions across the practices.

The primary statistical analysis comprised a series of survival analyses to assess the relationship between exposure to antidepressant drugs and the adverse outcomes. We used Cox's proportion hazards models, with antidepressant exposure treated as a time-varying exposure. The entry date into the analysis was the index date (earliest of first diagnosis of depression or first antidepressant prescription from the age of 65 years or over) and the outcome date was the earliest of either

the date of diagnosis of the outcome of interest or the date of death if the outcome was recorded on their death certificate. We used only the first recorded diagnosis of the outcome of interest rather than recurrent events. Patients who did not have the outcome of interest were censored at the earliest of date of death, date of leaving the practice, date of the latest download of data or the study end date. For the analysis of each outcome we excluded patients who had already had the outcome at baseline. The time-varying analysis accounts for patients changing between treatments during follow-up and changing from treatment to no treatment, and the hazard ratio (HR) estimated from this analysis is interpreted as the ratio of the instantaneous rate (i.e. the hazard rate) of the outcome of interest in those on treatment compared with the rate in patients not on treatment at each time point throughout the follow-up period, for those still at risk at each particular time. The model assumes that this ratio has a constant value throughout the follow-up period. For the main analyses, patients were considered to be exposed to a drug if there were no gaps of more than 90 days between the end of one prescription and the start of the next prescription to allow for not having a precise date when the patient finished the prescription. If there were gaps of more than 90 days between the end of one prescription and the start of the next prescription then patients counted as exposed to antidepressant medication for the first 90 days and then unexposed for the remaining period.

The analysis calculated HRs and 95% confidence intervals (CIs) for:

- current use of each separate class of antidepressants (SSRIs, TCAs and other antidepressants) compared with no current treatment
- selective serotonin reuptake inhibitors and other antidepressants compared with TCAs
- antidepressant dose according to antidepressant class, using a time-varying approach based on dose of current prescription. We categorised dose for each class into three groups – (1) ≤ 0.5 DDDs, (2) > 0.5 and ≤ 1.0 DDDs and (3) > 1.0 DDDs – and included dummy variables for these categories in the statistical models. We also carried out tests of trend for each antidepressant class, by fitting a separate model that contained the dose in DDDs for each class as continuous variables
- duration of use, again using a time-varying approach; this analysis also considered the effects of time since last prescription for an antidepressant drug. We categorised duration of use according to antidepressant class as no use, 1–28 days' use, 29–84 days' use, 85+ days' use, and washout periods of 1–28 days, 29–84 days and 85–182 days since stopping antidepressant medication
- individual drugs compared with no treatment where numbers were sufficient.

We carried out unadjusted analyses and adjusted for the potential confounding variables described above. For two outcomes, sudden cardiac death and suicide, we used a restricted set of confounding variables as numbers of events were small, namely age, gender, CHD, diabetes, hypertension, and use of statins, aspirin and antihypertensive drugs for sudden cardiac death, and age, gender, severity of depression, previous attempted suicide and use of lithium for suicide, as these were considered likely to be the main confounders for those outcomes. We used a p -value of < 0.01 (two-tailed) to assess statistical significance, but reported 95% CIs for estimation purposes.

In the analyses of antidepressant class we carried out Wald's significance tests to determine whether there were significant differences between the classes overall, excluding the group with no current treatment. We also did this for the analyses of individual drugs. We performed analyses of interaction between antidepressant class and patient's characteristics (age, gender), use of other medications and comorbidities using likelihood ratio tests. We carried out an additional complete case analysis where we also adjusted for body mass index (BMI). We checked the assumptions of the Cox proportional hazards model graphically with log minus log plots.

We estimated absolute risks of the adverse events at 1, 2 and 5 years from the baseline date. For each outcome we calculated the absolute risk in patients while they were not taking antidepressant treatment and used this with the adjusted HRs for antidepressant class and individual drugs to calculate adjusted absolute risks in the treated groups using a published formula.⁵⁵ From these we determined the number of additional events per 10,000 treated patients compared with those receiving no treatment by subtracting the absolute risk in the group while not on treatment from the adjusted absolute risks in the treated groups, assuming associations to be causal.

Self-controlled case-series study

A limitation of the cohort design approach is that it can be vulnerable to indication bias and residual confounding, whereby relevant confounding variables may be imprecisely recorded or not recorded at all in primary-care records (e.g. diet, physical activity). The self-controlled case-series method has been proposed as a means of addressing this problem.^{56,57} It is an internally controlled method whereby analyses are carried out only in patients with the outcome of interest, thereby eliminating the effect of indication bias and unmeasured confounding for variables that do not vary over time. It is of most relevance for acute events occurring within a short period after exposure. The method has previously been used to examine the relationship between antidepressant use and hip fracture²⁰ and MI.¹⁸

Self-controlled case-series study design

The self-controlled case-series analyses included only patients who had the outcomes of interest. Cases with each type of adverse event were identified; these were cases with a diagnosis of the adverse event between 1 January 1996 and 31 December 2008. We used only the first recorded diagnosis of the outcome of interest rather than recurrent events. Patients for whom the outcome was recorded as occurring on the same day as their first antidepressant prescription were distinguished in the analysis. Cases without any antidepressant prescriptions were included in the analyses to improve adjustment for age.⁵⁷

We used the extracted information on antidepressant prescriptions during the study period for cases with each outcome to identify periods of exposure to antidepressants and a baseline period. We accounted for multiple periods of exposure in the analysis, defining a period of antidepressant treatment as one without gaps of more than 90 days between the end of a prescription and the start of the next prescription. A prescription after more than 90 days counted as a new treatment episode. We categorised the time periods of exposure as 0 days (day of first prescription in each treatment episode); 1–28 days after the first prescription; 29–84 days and 85+ days (remaining treatment period); and periods after stopping treatment (1–28 days, 29–84 days and 85–182 days after stopping). The day of stopping treatment was taken as the date of the last prescription in the treatment episode plus the duration of the prescription. The 28 days before the first prescription in each treatment episode was considered as a separate category, as occurrence of the outcome of interest in this period could affect the probability of receiving an antidepressant prescription. All time periods outside these specified risk periods contributed to the baseline unexposed time periods. These risk periods were selected as they enable examination of short-term and longer-term effects of antidepressants on the risks of adverse events and are similar to those used in other studies of antidepressants.^{18,20} *Figure 1* illustrates the time periods used.

We used conditional Poisson regression to estimate the relative incidence of each of the outcomes of interest for the defined time periods of risk compared with the baseline period. We adjusted for age in the analyses (65–69, 70–74, 75–79, 80–84, 85+ years). We used a *p*-value of <0.01 (two-tailed) to assess statistical significance. Where the outcome was a fatal one we used only

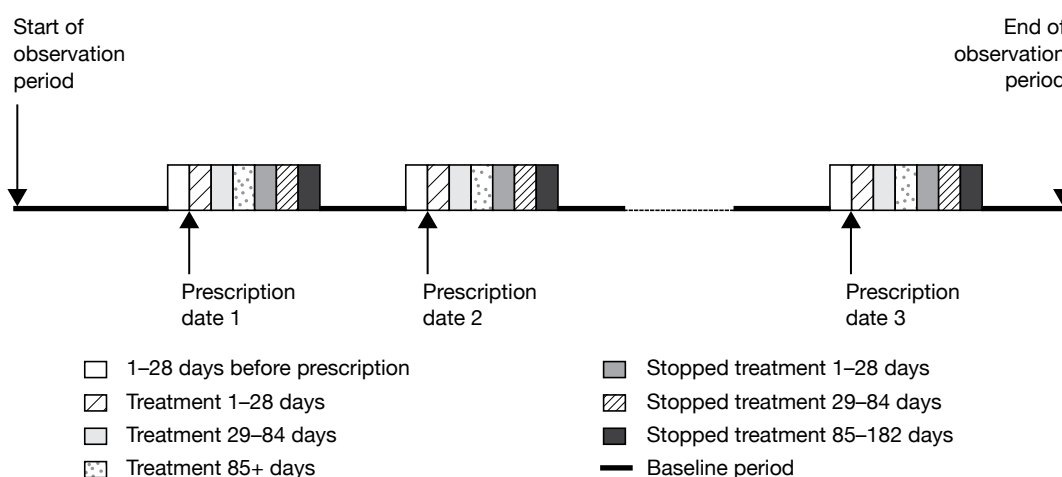


FIGURE 1 Risk periods in the self-controlled case-series design.

time from the first prescription in the observation period for analysis, as otherwise the method is invalid.

Sample size for self-controlled case-series study

To detect a rate ratio of 2.0 in a risk period of 1–28 days after the first prescription for an antidepressant with 80% power and 5% significance, with a proportion of 0.015 (28/1825) in the risk period of 28 days compared with an average observation period of 5 years, 1002 exposed cases would be required for each outcome.⁵⁸ We anticipated having at least this number for all-cause mortality and falls. To detect a rate ratio of 3.0 in a risk period of 1–28 days then 231 exposed cases would be required. We anticipated having around this number for rarer outcomes such as GI events (incidence rate 5/1000/year).

Cost-effectiveness analysis

Objective

We sought to estimate the costs of health-care resource use in older people who had been diagnosed with depression and compare these for patients who had been prescribed different antidepressant drugs and classes of antidepressant drugs, while controlling for patient characteristics and other factors. Adverse event rates were also estimated enabling us to estimate and compare the cost per adverse event averted for different antidepressants.

Data extraction

The analysis used data from the cohort of patients described above. In addition to data on antidepressant prescriptions, adverse outcomes and patient characteristics, some additional health economic data were extracted. These were the number of practice nurse, community nurse and general practitioner (GP) visits for each patient during the follow-up period from diagnosis with depression up to the earliest of the study end date (31 December 2008), the date of death (if applicable), the date the patient left the study practice (if applicable) or the date of the latest download of data. The use of secondary care is not routinely recorded within the QResearch database, so we were unable to include this information in the analyses.

Analyses

Where technologies have an impact on costs and outcomes over a patient's lifetime, conducting analysis over a lifetime horizon is appropriate.⁵⁹ Within this study, data were available, however,

for only up to 13 years, therefore we sought to estimate the costs of antidepressant prescriptions and practice nurse, community nurse and GP visits that would be expected to fall upon the health service within the first 5 years post diagnosis for depression in patients aged ≥ 65 years, and compare these with patients prescribed different antidepressant drugs. In line with the statistical analysis, a 5-year perspective was chosen in the base-case analysis, as the mean length of follow-up was 5.02 years for patients in this study; a large proportion of patients would, thereby, have complete data over this period. We first identified patients for whom at least 5 years of data were available (we therefore excluded those who were diagnosed after 1 January 2004 as the study end date was 31 December 2008). Patients who died before the 5-year follow-up was complete were included in the analysis, but those who moved practices within 5 years (i.e. had incomplete data) were not. Patients who died were included, as resource-use data were available up to the date of death and this constituted the burden upon the NHS over the 5-year period. Patients who moved practices before the 5-year follow-up was complete were not included, as to include only the data up to the point at which they left the GP practice could result in an underestimation of the health-care resources that would be used by such patients over a 5-year period. However, with a view to assess whether those who switched practices had different costs from those who remained with the same practice for the whole 5-year period we compared the 1-year costs (for those patients for whom this was available) for those who were diagnosed on or before 1 January 2004, but switched practices within the 5-year period with the costs for those who were diagnosed within the same period and remained with the same practice for a 5-year period. Costs were estimated in pounds sterling (£) at 2007–8 cost-year levels.

Prescription costs

Unit costs for each drug were estimated using data from the Prescription Cost Analysis database (for the financial year 2007–8),⁶⁰ which is based on the September 2007 version of the BNF.⁵² Within the database, unit costs are estimated at the level of the individual chemical after calculating the weighted average (mean) cost, based on the unit cost and number of prescriptions prescribed for each individual preparation. In order to check that the mean prescription cost for each individual chemical, as calculated within the Prescription Cost Analysis database,⁶⁰ was applicable to those aged ≥ 65 years, we compared the average dose for each prescription (at the level of the chemical) for patients in our study with that for all prescriptions in the Prescription Cost Analysis database. To do this we extracted the dose for each prescription (including tablets and solutions) for each patient. By taking account of the number of prescriptions at each dose, the weighted average dose was estimated for each type of chemical. The same method was used to estimate the weighted average dose for the Prescription Cost Analysis data. These values were then compared.

To estimate the expected mean cost over a 5-year period post diagnosis for each patient, we assigned the unit cost for each chemical to each prescription, where the unit cost was assumed to be equivalent to the weighted average from the Prescription Cost Analysis database,⁶⁰ assuming that the mean prescription dosage for each individual chemical, as calculated within the Prescription Cost Analysis database, was applicable to those aged ≥ 65 years, where costs in future years (≥ 1 year post diagnosis) were discounted at 3.5% per annum.⁶¹ Furthermore, to compare costs for patients who were prescribed different antidepressant drugs, we identified patients who were first prescribed each type of antidepressant drug within the first 12 months of diagnosis of depression (of those prescribed an antidepressant within 12 months of diagnosis, 88.3% had a prescription on the date of diagnosis and 93.5% had a prescription within 30 days). Subsequently, for each of the 11 most commonly prescribed antidepressant drugs within our data set, we estimated the mean total prescription cost over the 5-year period post diagnosis. Patients were categorised according to the drug they received first (those initially prescribed more than one antidepressant were excluded from the analyses).

Mean costs were also estimated for the antidepressant classes (TCAs, SSRIs and other antidepressants), based on the weighted average prescription costs for all of the TCA, SSRI and other antidepressant prescriptions. We also identified patients who were not prescribed any antidepressant drugs within the 5-year period. In addition to estimating the mean total prescription cost for each antidepressant drug in question, we estimated the mean total prescription cost for all antidepressant drugs prescribed to each patient in the time period. Again these values were compared for patients who were prescribed the 11 most commonly prescribed antidepressant drugs within our data set and for all TCAs, SSRIs and other antidepressants. Finally, the mean prescription costs (for both the antidepressant drug in question and all antidepressant drugs) associated with each of the 11 antidepressant drugs were ranked from lowest to highest cost.

Costs associated with practice nurse, community nurse and general practitioner visits

We estimated the costs associated with practice nurse, community nurse and GP visits using unit costs extracted from Curtis,⁶² where all contacts with a practice nurse and GP were assumed to take place at the practice, and all contacts with a community nurse were assumed to be home visits. These visit costs were estimated over the same 5-year period as above, where future costs were discounted and the mean visit cost for each type of health professional was estimated for the 11 most commonly prescribed antidepressant drugs and the antidepressant classes (TCAs, SSRIs, and other antidepressants), as well as for those who received no antidepressant prescriptions within the 5-year period. Additionally, we compared the summation of the total visit cost and the total prescription cost for all antidepressant drugs (referred hereafter as the overall visit plus prescription cost) for the same groups of individuals. The mean overall visit plus prescription costs were ranked from lowest to highest.

Adverse events and their associated costs

Data were extracted on the 13 specific adverse events as detailed above. We used the absolute risks for each of these adverse events for each of the different antidepressant drugs as described previously, along with those for periods of non-use of antidepressants, to estimate the number of additional adverse events per 10,000 patients treated that one would expect to occur in a 5-year period, for each of the different antidepressant drugs compared with no treatment. We used these figures to estimate the mean number of first events that one would estimate each patient to have while receiving a prescription for each of the antidepressants in question. First, we needed to align the time period for the number of events with that for the cost data. This was a period of 5 years, except when a patient died before the end of the time period. Thus, the mean period over which costs were estimated was less than 5 years, if any of the patients prescribed a particular prescription died within the 5-year period. Second, after estimating the mean follow-up time for patients prescribed each type of prescription, we estimated what proportion of the 5-year period this constituted and accordingly estimated the mean expected number of events (per patient) that would be estimated to occur in that period (events in future years were discounted at a rate of 3.5% per annum). These same calculations were performed in order to estimate the number of adverse events (per patient) that would be expected for those prescribed the 11 most commonly prescribed antidepressant drugs, and for the antidepressant classes in the first 5 years post diagnosis. Subsequently, the incremental number of adverse events was estimated by taking the difference between the estimated number of adverse events for patients prescribed each of these antidepressants and the estimated number for patients prescribed no antidepressants. These analyses were performed for each of the 13 adverse events.

After calculating the mean expected number of events (per person) it was necessary to consider the issue of assigning costs to each of the different types of adverse events. Though we knew

whether an event had occurred, the QResearch database does not routinely contain non-primary care resource-use data and, thus, it was difficult to estimate the actual resource use associated with each event. We considered whether we could make an assumption about the mean cost associated with each adverse event, informed by wider literature (where applicable). Though we might, for example, be able to assume the secondary-care costs associated with each fall admission to be equivalent to that for the weighted average of the three fall descriptions contained within the National Schedule of Reference Costs,⁶³ not all falls reported in primary care result in an admission. Alternatively, it could be that secondary-care costs represent an underestimate, as this would exclude additional rehabilitation and community follow-up costs that might occur. Thus, we considered assigning a cost to each of these types of adverse events to be highly speculative. Moreover, to use precise figures might portray an element of robustness that was not appropriate. As a consequence we did not include adverse event costs within our analyses.

Base-case analysis

Of the aforementioned analyses, which included different elements of NHS costs, the mean total prescription cost for all antidepressant drugs was considered to constitute the base case. Visit costs were not included within the base-case analysis as visits would have been made for a number of reasons, many of which might have been unrelated to the particular antidepressant(s) prescribed, the patients' depression and/or associated comorbidities. That said, within such a large sample it could be argued that non-depression-related costs would be approximately equivalent across different types of antidepressants and that by calculating the incremental cost, between different antidepressants, non-depression-related costs would be excluded.

Before comparing costs for different antidepressant drugs it was necessary to adjust for any patient characteristics and clinical factors that might differ between patients prescribed different antidepressant drugs. Consequently, we used linear regression analyses to estimate the difference between the mean total prescription cost (for all antidepressant drugs) for patients prescribed each of the 11 most commonly prescribed antidepressant drugs, compared with patients not prescribed antidepressant drugs, controlling for the following variables: gender, age at diagnosis, calendar year at diagnosis, depression severity, depression before age 65 years, smoking status, Townsend score, baseline comorbidities (CHD, stroke, diabetes, hypertension, cancer, dementia, epilepsy/seizures, falls, attempted suicide, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder) and previous use of certain drugs at baseline (statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsant drugs, hypnotic/anxiolytic drugs).

Levels of cost-effectiveness

After adjusting for the aforementioned factors it was possible to estimate the mean incremental total prescription cost (for all antidepressant drugs) for each of the 11 most commonly prescribed antidepressant drugs compared with patients who received no prescriptions. We have described above the calculation of the estimated incremental number of adverse events for each of the 11 most commonly prescribed antidepressant drugs. These cost and event data were used to calculate the incremental cost (mean incremental prescription cost for all antidepressant drugs) per adverse event averted, for different antidepressant drugs, via the efficiency frontier^{64,65} [the efficiency frontier connects the potentially cost-effective (i.e. non-dominated) options]. The efficiency frontier can be calculated by first identifying the antidepressant drug with the lowest mean prescription cost (for all antidepressant drugs), hereafter referred to as *lowest cost*. Other antidepressant drugs that are dominated⁶⁶ by another antidepressant drug (i.e. have a higher mean cost and are estimated to be associated with a greater number of adverse events) can then be excluded, as can antidepressant drugs that are subject to extended dominance⁶⁶ (i.e. where combinations of other drugs have equivalent or lower mean cost and fewer adverse

events). Extended dominance would be apparent if an option was less effective and had a higher incremental cost-effectiveness ratio (ICER) in terms of adverse events than an alternative option.⁶⁷ The remaining antidepressant drugs will be located on the efficiency frontier, where one can calculate the incremental cost per averted event (mean incremental cost/expected incremental number of averted events) (ICER) for each antidepressant drug located on the efficiency frontier. Previous studies^{65,67} provide further details of how ICERs are calculated when evaluating multiple options. These methods were used to calculate the mean incremental cost per averted event (and associated efficiency frontier) for each of the 13 adverse events, comparing the 11 most commonly prescribed antidepressant drugs to each other and the different antidepressant classes (TCAs, SSRIs and other antidepressants).

There is no previously defined threshold (in terms of willingness to pay) against which to compare levels of incremental cost per case averted (in order to assess whether the expected costs would be considered to be worthwhile, i.e. constitute value for money). However, given that the study group patients are aged ≥ 65 years it is unlikely that averting a particular adverse event would, on average, result in a gain of 20 quality-adjusted life-years (QALYs) (after discounting). For example, were one to extend life by 20 years and increase health-related quality of life (HRQoL) by 0.5 years (e.g. assuming HRQoL was initially 0.5, giving a resulting HRQoL of 1.0), then this would equate to a QALY gain of < 20 (after discounting) and it seems unlikely that avoiding an adverse event would (on average) be associated with such a large QALY gain. On that basis, given that NICE has stated that interventions that cost $> £30,000$ per QALY are unlikely to be deemed cost-effective,⁵⁹ if the incremental cost per adverse event averted were $> £600,000$, for a particular option, then, assuming it would not result in a QALY gain of > 20 , it would be unlikely to be deemed cost-effective. In the light of this, we assumed that all options which had a cost per adverse event averted of $> £600,000$ would not form part of the efficiency frontier.

Sensitivity analysis

Sensitivity analysis⁶⁶ was undertaken in order to estimate the robustness of our results, where the incremental cost of different antidepressant drugs and the incremental cost per adverse event avoided were recalculated using different assumptions. Results were first recalculated using the summation of the total visit cost and the total prescription cost for all antidepressant drugs. One might expect people who have been prescribed different antidepressant drugs to have different consultation rates in primary care, for example consultation rates might be higher for patients prescribed certain antidepressant drugs, as some are more prone to dose changes (this may be more applicable to TCAs than SSRIs) or consultation rates may be higher due to side effects. These results are presented in *Appendix 2* and summarised in the main text.

A further sensitivity analysis was to estimate costs and adverse events rates over a 1-year period, enabling data to be used from a greater number of patients, as estimation of 5-year costs resulted in the exclusion of those who were diagnosed post 1 January 2004. Thus, all previously defined costs and adverse events were recalculated for all patients in the study database for a 1-year period (this resulted in the inclusion of all patients, except those who left their practice within 1 year of diagnosis or were initially prescribed more than one antidepressant). The same methods as described previously were used, in which costs and benefits were not discounted as they occurred in the first year of care.

Protocol changes

We specified in the protocol that we would adjust for government office region, BMI and alcohol in addition to other confounders. We did not, however, adjust for these three variables owing to missing data and to avoid having unstable models. We did additionally adjust for study year and

adjusted the suicide outcome for attempted suicide at baseline and the fracture outcome for falls at baseline.

We specified in the protocol that in the self-controlled case-series analysis we would use the risk periods 0 days, 1–14 days, 15–28 days and 29–84 days, remaining treatment period and the washout period (a period of 182 days after stopping treatment), and that the 14 days before the first prescription would be considered as a separate category. These categories were changed slightly to those detailed previously after discussion within the study team and prior to statistical analysis to allow more detailed analysis of effects of stopping and increased numbers in some periods.

We specified in the protocol that the cost of adverse events would be estimated using patient-specific resource-use data (identified using the QResearch database). As discussed previously, this was not undertaken, as examination of secondary care resource-use data within the QResearch database revealed that this was not routinely recorded by all GP practices within the database.

We specified in the protocol that a literature search would be performed with a view to identify the quality of life of older people with depression. One of the proposed uses of these data was to aid the comparison of quality of life between patients with depression who had been prescribed different types of antidepressants and those not prescribed antidepressants. Our literature search did not identify any such studies for older people and, hence, this analysis was not undertaken (this issue of disutility associated with different adverse events is discussed further in *Chapter 4*). In the absence of quality of life data, as outlined in the protocol, we used the ‘incremental cost per adverse event averted’ technique to compare different antidepressants.

Ethical arrangements

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 with the Committee.

Chapter 3

Results

Results of descriptive analyses

Selection of study cohort

A total of 88,701 patients in the QResearch database were diagnosed with depression at age 65 years or over between 1 January 1996 and 31 December 2007. After consecutively excluding 22 patients aged 100 years 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, there were 60,746 eligible patients remaining who formed the study cohort. *Figure 2* shows the selection of patients for the study cohort.

The 60,746 patients included in the study were from 570 QResearch practices in the UK. These practices included 543 in England, 14 in Wales, 4 in Scotland and 9 in Northern Ireland. The practices in England were spread throughout the regions, with 32 in the North-East, 61 in the North-West, 59 in Yorkshire and the Humber, 85 in the East Midlands, 45 in the West Midlands, 43 in the East of England, 70 in London, 81 in the South-East and 67 in the South-West. The total number of patients registered with eligible practices during the study period was 9,583,082.

Incidence of diagnosed depression

Table 1 shows the incidence rates of diagnosed depression in people aged 65 year and over, by gender and age group. Rates were higher in women than in men, although the difference was less marked with increasing age.

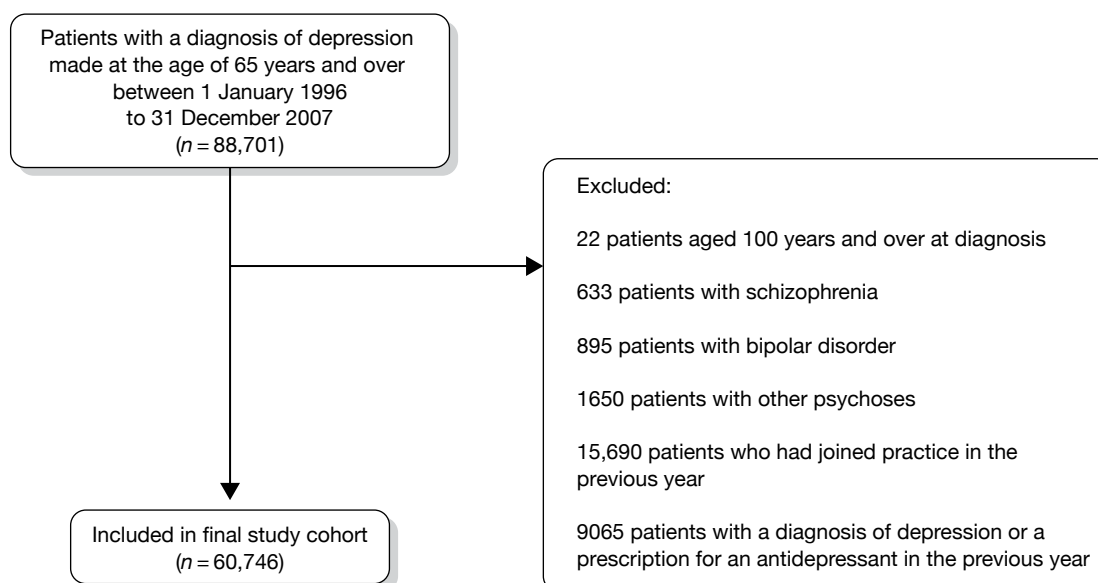


FIGURE 2 Selection of patients for the study cohort.

TABLE 1 Incidence rates of diagnosed depression per 10,000 person-years in people aged 65 years and over, by gender and age group, based on the first diagnosis of depression aged 65 years and over

Age band (years)	Cases of depression	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–69	12,532	1,049,470	119.4	117.3 to 121.5
70–74	8278	937,795	88.3	86.4 to 90.2
75–79	8103	828,121	97.8	95.7 to 100.0
80–84	5985	623,191	96.0	93.6 to 98.5
85–89	3808	389,302	97.8	94.8 to 101.0
90+	1810	228,490	79.2	75.6 to 83.0
All ages (65+)	40,516	4,056,369	99.9	98.9 to 100.9
Men				
65–69	6027	1,015,893	59.3	57.8 to 60.8
70–74	4496	840,855	53.5	51.9 to 55.1
75–79	4293	644,640	66.6	64.6 to 68.6
80–84	3121	399,991	78.0	75.3 to 80.8
85–89	1713	193,199	88.7	84.6 to 93.0
90+	580	81,074	71.5	65.9 to 77.6
All ages (65+)	20,230	3,175,651	63.7	62.8 to 64.6

Study cohort

Baseline characteristics of the study cohort are shown in *Table 2*. There were 20,230 (33.3%) men and 40,516 (66.7%) women. There were 31,341 patients who were aged 65–74 years at baseline (51.6%), with 7908 (13.0%) aged 85 years and over. Nearly 20% of patients had a diagnosis of CHD at baseline and 38.9% had hypertension. Substantial proportions were taking prescribed medications at baseline, including antihypertensive drugs (50.0%), aspirin (29.4%), hypnotic/anxiolytic drugs (23.7%) and NSAIDs (57.0%).

Patterns of antidepressant treatment

A total of 1,398,359 prescriptions for antidepressants were received during the study follow-up period. The duration of each prescription could be calculated for 1,244,296 (89.0%) of these, based on the quantity prescribed and dosing directions. The median prescription length was 28 days [interquartile range (IQR) 28 days to 30 days] and more than one-half of these prescriptions were for 28 days' duration (641,811 prescriptions, 51.6%). For 154,063 prescriptions (11.0% of 1,398,359) there was insufficient information on quantity or dosing directions to enable direct calculation of duration, but values were estimated (as described in *Chapter 2*) based on the quantity prescribed, which was available for 147,165 of these prescriptions (95.5%), and where this was missing a value of 28 days was assumed.

Details of the first antidepressant drug prescribed and the total number of prescriptions received during follow-up are shown in *Table 3*. Of the 60,746 patients in the cohort 6708 (11.0%) received no prescriptions for an antidepressant during follow-up and the remaining 54,038 (89.0%) received at least one prescription during follow-up. For nearly half (49.0%) of the patients in the cohort the first antidepressant prescribed was an SSRI, whereas for just over one-third (34.6%) it was a TCA.

The 54,038 patients prescribed antidepressant drugs during follow-up received a median of 12 prescriptions, with a range of 1 to 727. A total of 6484 patients (10.7% of 60,746) had only a

TABLE 2 Characteristics of the study cohort (*n* = 60,746) at baseline

Characteristic	<i>n</i>	%
Gender		
Male	20,230	33.30
Female	40,516	66.70
Age (years)		
65–74	31,341	51.59
75–84	21,497	35.39
85+	7908	13.02
Mean age (SD)		
Overall	74.98 (7.55)	
Male	74.78 (7.22)	
Female	75.09 (7.71)	
Depression severity (index diagnosis)		
Mild	42,281	69.60
Moderate	15,639	25.74
Severe	2826	4.65
Recorded history of depression before age 65 years		
No	51,803	85.28
Yes	8943	14.72
BMI recorded	43,773	72.06
Mean BMI in kg/m ² (SD)	26.55 (4.70)	
Smoking		
Recorded	57,650	94.90
Non smoker	33,656	58.38
Ex smoker	13,005	22.56
Current smoker	10,989	19.06
Comorbidities		
CHD	11,981	19.72
Diabetes	6169	10.16
Hypertension	23,654	38.94
Stroke/TIA	6448	10.61
Any cancer	5032	8.28
Dementia	1091	1.80
Epilepsy/seizures	953	1.57
Parkinson's disease	869	1.43
Hypothyroidism	3956	6.51
Obsessive–compulsive disorder	119	0.20
Medications at baseline		
Anticonvulsants	1671	2.75
Antihypertensives	30,363	49.98
Antipsychotics	5332	8.78
Aspirin	17,863	29.41
Hypnotics/anxiolytics	14,391	23.69
Lithium	148	0.24
NSAIDs	34,618	56.99
Statins	10,283	16.93

SD, standard deviation.

Values are numbers (*n*) and percentages (%), unless stated otherwise.

TABLE 3 Details of the class of antidepressant first prescribed and prescriptions received during follow-up

Antidepressant treatment	No.	% of total
Class of first antidepressant prescribed		
None	6708	11.04
TCA	21,043	34.64
MAOI	31	0.05
SSRI	29,763	49.00
Other	3060	5.04
Combined	141	0.23
Total no. of antidepressant prescriptions per patient in patients with one or more		
Median (IQR)	12 (3 to 34)	
Total antidepressant prescriptions per patient during follow-up		
0	6708	11.04
1	6484	10.67
2–3	7505	12.35
4–6	6340	10.44
7–12	7522	12.38
13–24	8307	13.67
25–36	5233	8.61
37–48	3477	5.72
49–60	2546	4.19
>60	6624	10.90
Total antidepressant prescriptions per patient in first year of follow-up		
0	9086	14.96
1	12,634	20.80
2–3	10,916	17.97
4–6	8962	14.75
7–12	12,853	21.16
13+	6295	10.36
Total duration of prescriptions in follow-up (days)		
Median (IQR)	364 (91 to 1029)	
Total duration of prescriptions in first year of follow-up (days)		
Median (IQR)	140 (56 to 308)	
Total duration of antidepressant prescriptions in follow-up		
1–28 days	4652	8.61
29–84 days	7775	14.39
85–182 days	7219	13.36
182–365 days	7675	14.20
1–2 years	8804	16.29
2–3 years	5255	9.72
3–4 years	3744	6.93
4–5 years	2679	4.96
5+ years	6235	11.54

TABLE 3 Details of the class of antidepressant first prescribed and prescriptions received during follow-up (*continued*)

Antidepressant treatment	No.	% of total
Total episodes of antidepressant treatment during follow-up		
1	25,700	47.56
2	14,354	26.56
3	7016	12.98
4	3470	6.42
5+	3498	6.47
Duration of antidepressant treatment per treatment episode (days)		
Median (IQR)	179 (56 to 528)	
Duration of antidepressant treatment as percentage of follow-up		
Median (IQR)	31.3 (8.4 to 74.2)	

Values are numbers (*n*) and percentages (%), unless stated otherwise.

single prescription and around one-third (20,697, 34.1%) received three prescriptions or fewer during follow-up. The median total duration of treatment with antidepressants during follow-up was 364 days (IQR 91 days to 1029 days), and during the first year of follow-up it was 140 days (IQR 56 days to 308 days).

Table 3 also shows the number of episodes of antidepressant treatment in patients who received at least one prescription for an antidepressant drug during follow-up, where a new treatment episode was defined as one that occurred after a gap of at least 90 days after the end of the previous prescription. Nearly half of the treated patients (47.6%) had only one treatment episode during follow-up, around one-quarter (26.6%) had two treatment episodes and 25.9% had three or more. The median duration of antidepressant treatment per treatment episode was 179 days and the median duration of treatment as a percentage of total follow-up time was 31.3%.

Table 4 shows the total number of prescriptions received during follow-up for each antidepressant class and also for each specific drug, as well as the numbers of patients with one or more prescriptions for each drug. SSRIs were the most commonly prescribed drug class with more than three-quarters of treated patients being prescribed an SSRI during follow-up and 54.7% of the total antidepressant prescriptions were for this class. The most commonly prescribed SSRI drugs were citalopram hydrobromide (23.0% of all prescriptions) and fluoxetine (14.0%). There were 442,192 prescriptions for TCAs, constituting 31.6% of all antidepressant prescriptions. The most commonly prescribed TCAs were amitriptyline (13.5% of all prescriptions) and dosulepin (10.3%). The group of other antidepressants contributed 13.5% of the total prescriptions. The most commonly prescribed drugs within this group were venlafaxine (6.3% of all prescriptions) and mirtazapine (5.9%). MAOI drugs were the least commonly prescribed class, constituting only 0.16% of the total number of prescriptions issued. The 10 most commonly prescribed antidepressant drugs constituted 93.6% of all prescriptions: these were citalopram hydrobromide, fluoxetine hydrochloride, amitriptyline hydrochloride, dosulepin hydrochloride, paroxetine hydrochloride, venlafaxine hydrochloride, sertraline hydrochloride, mirtazapine, lofepramine and escitalopram. As there were only slightly fewer prescriptions for trazodone hydrochloride, the 11 most commonly prescribed drugs were considered separately in some analyses; these constituted 96.0% of all prescriptions.

Figure 3 shows the total number of prescriptions during follow-up for the 11 most commonly prescribed antidepressant drugs issued over the study period.

TABLE 4 Total number of prescriptions received during follow-up for each antidepressant class and drug name, and numbers of patients with one or more prescriptions for each drug

Antidepressant class	Drug name	No. of prescriptions issued		No. of patients who received at least one prescription	
		<i>n</i>	%	<i>n</i>	% ^a
TCA (any)		442,192	31.62	29,085	53.82
	Amitriptyline hydrochloride	188,283	13.46	16,440	30.42
	Amoxapine	4	0.00	2	0.00
	Clomipramine hydrochloride	6425	0.46	543	1.00
	Desipramine	2	0.00	2	0.00
	Dosulepin hydrochloride	144,658	10.34	10,402	19.25
	Doxepin	6031	0.43	434	0.80
	Imipramine	24	0.00	8	0.01
	Imipramine hydrochloride	7218	0.52	859	1.59
	Lofepramine	43,570	3.12	5517	10.21
	Maprotiline hydrochloride	321	0.02	20	0.04
	Mianserin hydrochloride	1840	0.13	156	0.29
	Nortriptyline	4956	0.35	565	1.05
	Protriptyline hydrochloride	115	0.01	15	0.03
	Trazodone hydrochloride	33,675	2.41	2573	4.76
	Trimipramine	5055	0.36	314	0.58
	Viloxazine hydrochloride	15	0.00	4	0.01
MAOI (any)		2203	0.16	108	0.20
	Isocarboxazid	390	0.03	7	0.01
	Moclobemide	665	0.05	75	0.14
	Phenelzine	376	0.03	24	0.04
	Tranylcypromine	806	0.06	14	0.03
SSRI (any)		764,659	54.68	42,575	78.79
	Citalopram hydrobromide	321,495	22.99	22,029	40.77
	Citalopram hydrochloride	1730	0.12	283	0.52
	Escitalopram	36,014	2.58	3233	5.98
	Fluoxetine hydrochloride	196,393	14.04	17,354	32.11
	Fluvoxamine maleate	484	0.03	68	0.13
	Paroxetine hydrochloride	120,475	8.62	7519	13.91
	Sertraline hydrochloride	88,068	6.30	6525	12.07
Other (any)		189,305	13.54	10,485	19.40
	Duloxetine	3017	0.22	327	0.61
	Flupentixol	13,140	0.94	1698	3.14
	L-Tryptophan	20	0.00	5	0.01
	Mirtazapine	81,756	5.85	5258	9.73
	Nefazodone hydrochloride	1529	0.11	163	0.30
	Reboxetine	1420	0.10	171	0.32
	Tryptophan	79	0.01	6	0.01
	Venlafaxine hydrochloride	88,344	6.32	4686	8.67
<i>Total</i>		<i>1,398,359</i>	<i>100.00</i>	<i>54,038</i>	<i>100.00</i>

a Percentages are out of 54,038 patients with one or more prescriptions for an antidepressant drug.

Note: percentages add to more than 100%, as some patients were prescribed drugs from more than one class.

Figure 4 shows the number of prescriptions for each antidepressant class, by year of prescription. There was a steep increase in the proportion of prescriptions which were for an SSRI over time, with a corresponding reduction for TCAs. There was also an increase for the group of other antidepressants over time. In terms of the first antidepressant prescribed, the proportion of patients for whom the first antidepressant prescribed was a TCA fell from 65.7% in 1996 to 18.7% in 2007, whereas the proportion for whom it was an SSRI increased from 29.9% in 1996 to 75.0% in 2007. The proportion of patients in whom the first antidepressant prescribed was in the group of other antidepressants increased from 4.0% in 1996 to 8.0% in 2004 and then decreased to 5.9% in 2007.

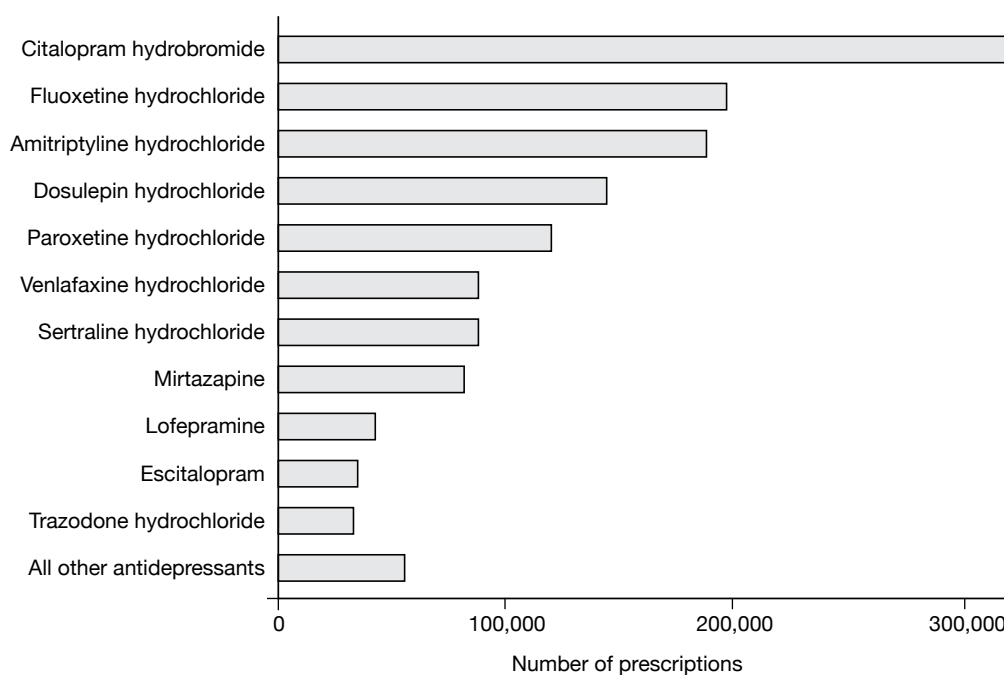


FIGURE 3 Total number of prescriptions during follow-up for the 11 commonly prescribed antidepressant drugs.

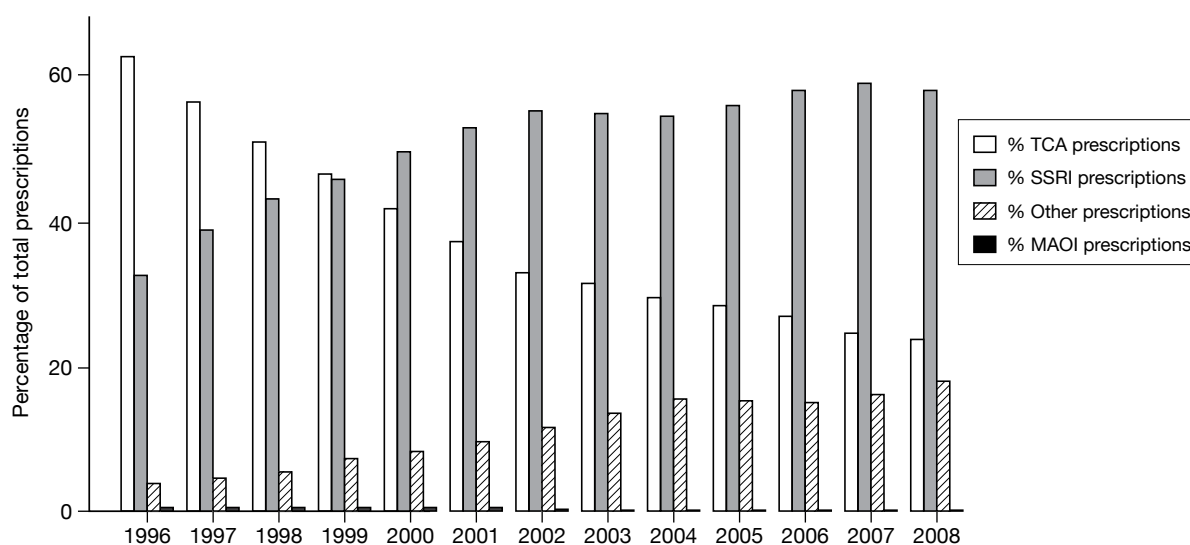


FIGURE 4 Percentages of prescriptions for each antidepressant class by year of prescription.

For the 11 most commonly prescribed antidepressant drugs, the proportions of total prescriptions that were for the TCAs amitriptyline, dosulepin and lofepramine all decreased over time, while they increased for the SSRIs citalopram hydrobromide, fluoxetine hydrochloride and escitalopram (data not shown). The proportion of prescriptions that was for the SSRI paroxetine hydrochloride decreased from 13.3% in 1996 to 4.0% in 2008, and stayed fairly constant throughout this period for the SSRI sertraline hydrochloride (at around 6.3%) and the TCA trazodone hydrochloride (at around 2.4%). In the group of other antidepressants the proportion prescribed increased for mirtazapine from 1996 to 2008 and increased for venlafaxine hydrochloride from 1.2% in 1996 to 9.1% in 2004, after which it declined to 5.6% in 2008.

Antidepressant treatment by baseline characteristics

The baseline characteristics according to the class of antidepressant first prescribed, excluding the combined group, are shown in *Table 5*. There were significant differences between the groups (excluding MAOIs owing to small numbers) for all baseline characteristics except for obsessive-compulsive disorder and anticonvulsant treatment, although absolute differences were generally small. The most marked differences were that, compared with the treated groups, the untreated group had a higher proportion of men, a higher proportion of patients aged 85 years and over, higher proportions of patients with CHD, diabetes, dementia and epilepsy/seizures at baseline, lower proportions treated with antipsychotics and hypnotics/anxiolytics and a higher proportion treated with statins. Comparing treated groups directly there was a higher proportion of men in the SSRI group than in the other groups and a lower proportion in the TCA group. There were fewer people aged 85 years and over in the TCA and MAOI groups. Patients in the TCA group tended to be less likely to have comorbidities than patients in the SSRI group. For example, 17.4% of patients in the TCA group had CHD compared with 20.6% in the SSRI group; they were also less likely to be treated with antihypertensive drugs, aspirin or statins than patients in the SSRI group.

TABLE 5 Baseline characteristics of patients according to the class of antidepressant first prescribed

Characteristic	First antidepressant class prescribed									
	No antidepressant		TCA		MAOI		SSRI		Other	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Gender										
Female	4201	62.63	14,929	70.95	21	67.74	19,252	64.68	2028	66.27
Male	2507	37.37	6114	29.05	10	32.26	10,511	35.32	1032	33.73
Age group (years)										
65–74	2771	41.31	11,585	55.05	20	64.52	15,397	51.73	1484	48.50
75–84	2653	39.55	7335	34.86	10	32.26	10,355	34.79	1100	35.95
85+	1284	19.14	2123	10.09	1	3.23	4011	13.48	476	15.56
Mean age (years) (SD)										
Overall	76.74 (8.00)		74.30 (7.12)		72.39 (5.74)		75.02 (7.64)		75.52 (7.80)	
Female	77.19 (8.20)		74.33 (7.23)		71.10 (4.91)		75.16 (7.83)		75.70 (7.99)	
Male	75.98 (7.60)		74.23 (6.86)		75.10 (6.64)		74.77 (7.28)		75.16 (7.40)	
Depression severity (index diagnosis)										
Mild	4361	65.01	14,954	71.06	18	58.06	20,732	69.66	2127	69.51
Moderate	2124	31.66	5105	24.26	12	38.71	7630	25.64	730	23.86
Severe	223	3.32	984	4.68	1	3.23	1401	4.71	203	6.63
Depression before age 65 years										
Yes	880	13.12	3220	15.30	13	41.94	4349	14.61	451	14.74
Mean BMI in kg/m ² (SD)	26.80 (4.85)		26.62 (4.65)		25.76 (4.15)		26.48 (4.70)		26.21 (4.64)	

TABLE 5 Baseline characteristics of patients according to the class of antidepressant first prescribed (*continued*)

Characteristic	First antidepressant class prescribed									
	No antidepressant		TCA		MAOI		SSRI		Other	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Smoking										
Non-smoker	3588	59.36	11,891	59.17	14	48.28	16,332	57.41	1753	60.51
Ex-smoker	1343	22.22	4487	22.33	7	24.14	6536	22.98	606	20.92
Current smoker	1,113	18.41	3720	18.51	8	27.59	5580	19.61	538	18.57
Comorbidities										
CHD										
Yes	1581	23.57	3655	17.37	4	12.90	6128	20.59	595	19.44
Diabetes										
Yes	1003	14.95	1857	8.82	3	9.68	3023	10.16	271	8.86
Hypertension										
Yes	2739	40.83	7600	36.12	7	22.58	12,083	40.60	1189	38.86
Stroke/TIA										
Yes	770	11.48	1788	8.50	1	3.23	3535	11.88	336	10.98
Any cancer										
Yes	572	8.53	1545	7.34	3	9.68	2666	8.96	235	7.68
Dementia										
Yes	215	3.21	171	0.81	0	0.00	629	2.11	74	2.42
Epilepsy/seizures										
Yes	144	2.15	282	1.34	0	0.00	468	1.57	56	1.83
Parkinson's disease										
Yes	111	1.65	216	1.03	1	3.23	471	1.58	66	2.16
Hypothyroidism										
Yes	495	7.38	1288	6.12	1	3.23	1979	6.65	186	6.08
Obsessive-compulsive disorder										
Yes	10	0.15	45	0.21	0	0.00	56	0.19	8	0.26
Medications										
Anticonvulsants										
Yes	165	2.46	604	2.87	0	0.00	790	2.65	102	3.33
Antihypertensives										
Yes	3205	47.78	10,077	47.89	11	35.48	15,483	52.02	1528	49.93
Antipsychotic drugs										
Yes	410	6.11	1951	9.27	3	9.68	2576	8.66	382	12.48
Aspirin										
Yes	2104	31.37	5365	25.50	3	9.68	9497	31.91	867	28.33
Hypnotics/anxiolytics										
Yes	866	12.91	5582	26.53	10	32.26	7076	23.77	813	26.57
Lithium										
Yes	54	0.81	38	0.18	1	3.23	35	0.12	19	0.62
NSAIDs										
Yes	3262	48.63	12,596	59.86	14	45.16	17,065	57.34	1617	52.84
Statins										
Yes	1428	21.29	2538	12.06	0	0.00	5784	19.43	510	16.67

SD, standard deviation.

Values are numbers (*n*) and column percentages (%), unless stated otherwise.

Antidepressant dose

Table 6 shows the doses prescribed in terms of DDDs by antidepressant class. Dose could not be calculated for 160,170 (11.5%) of the 1,398,359 prescriptions issued during the study period either because dosing directions were not recorded or were unclear or for certain drugs a DDD value was not available. Prescribed doses tended to be lowest for TCAs, with 70.0% of prescriptions being for ≤ 0.5 DDD, compared with 13.8% for SSRIs. Doses prescribed were highest for MAOIs.

Table 7 summarises doses prescribed for the 11 most commonly prescribed drugs. The median doses were below the DDD values for all of the TCAs, except lofepramine.

Total number and duration of prescriptions for each antidepressant class

Table 8 shows the number of prescriptions received by patients for each antidepressant class and the median total duration of treatment, both for the whole follow-up period and for the first year of treatment. Of the 29,085 patients who had one or more prescriptions for a TCA during follow-up, one-quarter had only one TCA prescription; this proportion was the same among the 10,485 patients with prescriptions for other antidepressants, whereas 20.2% of the 42,575 patients who had one or more prescriptions for an SSRI had only one SSRI prescription during follow-up. Among the patients with one or more TCA prescriptions, the median duration of use during follow-up was 127 days; it was 117 days for MAOIs, 206 days for SSRIs and 172 days for

TABLE 6 Doses prescribed by antidepressant class in DDDs

DDD prescribed	Antidepressant class								Total	
	TCA		MAOI		SSRI		Other			
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
≤0.5	250,208	69.97	214	12.10	96,870	13.80	27,912	19.20	375,204	31.09
>0.5/≤1	75,922	21.23	601	33.99	505,093	71.95	77,286	53.16	658,902	54.60
>1/≤1.5	26,139	7.31	81	4.58	25,037	3.57	33,511	23.05	84,768	7.02
>1.5	5308	1.48	872	49.32	75,021	10.69	6664	4.58	87,865	7.28
Total	357,577		1768		702,021		145,373		1,206,739	

Values are numbers (*n*) and column percentages (%).

TABLE 7 Doses prescribed and DDDs for the 11 most commonly prescribed antidepressant drugs

Antidepressant drug	DDDs	Dose prescribed (mg/day)			
		Median	IQR	Minimum	Maximum
Amitriptyline hydrochloride (TCA)	75	25	20 to 50	5	225
Dosulepin hydrochloride (TCA)	150	75	50 to 75	13	300
Lofepramine (TCA)	105	140	70 to 140	35	280
Trazodone hydrochloride (TCA)	300	100	50 to 150	25	600
Citalopram hydrobromide (SSRI)	20	20	10 to 20	5	80
Escitalopram (SSRI)	10	10	10 to 10	3	50
Fluoxetine hydrochloride (SSRI)	20	20	20 to 20	10	180
Paroxetine hydrochloride (SSRI)	20	20	20 to 20	5	90
Sertraline hydrochloride (SSRI)	50	50	50 to 100	25	300
Mirtazapine (other)	30	30	15 to 30	8	105
Venlafaxine hydrochloride (other)	100	75	75 to 150	19	450

TABLE 8 Number (*n*) of prescriptions and column percentages (%) for each antidepressant class received by patients during total follow-up and the first year of treatment

	Antidepressant class							
	TCA		MAOI		SSRI		Other	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
<i>Total no. of prescriptions for each class in follow-up</i>								
1	7338	25.23	25	23.15	8597	20.19	2645	25.23
2–3	5980	20.56	23	21.30	7215	16.95	1553	14.81
4–6	3782	13.00	17	15.74	5221	12.26	1198	11.43
6–12	3148	10.82	10	9.26	5060	11.88	1102	10.51
13–24	3517	12.09	11	10.19	6686	15.70	1586	15.13
25–36	1677	5.77	3	2.78	3414	8.02	770	7.34
37+	3643	12.53	19	17.59	6382	14.99	1631	15.56
Total patients	29,085	100.00	108	100.00	42,575	100.00	10,485	100.00
<i>Total duration of prescriptions during follow-up (days)</i>								
Median (IQR)	127 (46 to 504)		117 (52 to 532)		206 (56 to 672)		172 (45 to 629)	
<i>No. of prescriptions in the first year of treatment for each class^a</i>								
1	7178	36.51	8	25.81	7146	27.35	901	33.48
2–3	4628	23.54	7	22.58	4699	17.99	449	16.69
4–6	2842	14.46	5	16.13	4042	15.47	367	13.64
6–12	3417	17.38	10	32.26	6459	24.72	553	20.55
13+	1595	8.11	1	3.23	3780	14.47	421	15.64
Total patients	19,660	100.00	31	100.00	26,126	100.00	2,691	100.00
<i>Total duration of prescriptions during the first year of treatment (days)^a</i>								
Median (IQR)	84 (28 to 224)		224 (56 to 300)		174 (56 to 343)		224 (56 to 364)	

a Restricted to those with at least 1-year of follow-up after first prescription.

the group of other antidepressants. In the first year of treatment the median duration of use was lowest for TCAs and highest for MAOIs and the group of other antidepressants.

Changes between antidepressant classes

Table 9 shows whether patients had prescriptions from only one class, or changed to another class during follow-up, according to the class of the first antidepressant prescribed. For example, in patients whose first antidepressant was a TCA, then 41.9% had prescriptions only for TCAs during follow-up and 58.1% also had prescriptions from other classes of antidepressants. In patients whose first prescription was for an SSRI, then 67.7% had prescriptions only for SSRIs during follow-up, and 32.3% had prescriptions for other antidepressants. Among those patients who changed from a TCA, the majority of patients changed to an SSRI (10,797, 88.3%). Among patients who changed from an SSRI, 6521 (67.8%) changed to a TCA and 3080 (32.0%) changed to a drug from the group of other antidepressants, and among those patients who changed from the group of other antidepressants, 541 (33.7%) changed to a TCA and 1062 (66.2%) changed to an SSRI.

These differences may reflect, in part, differing amounts of follow-up between the classes, as TCAs were more likely to be prescribed as a first antidepressant earlier in the study period. An additional analysis was therefore carried out looking at changes within 1 year restricted

to patients who had at least 1 year's follow-up (*Table 10*). For patients who were prescribed a TCA as their first antidepressant, 20.1% had prescriptions for other classes of antidepressants within 1 year of their first TCA prescription. Among patients whose first prescription was an SSRI, 15.7% had prescriptions for other classes of antidepressants within 1 year of their first prescription. The highest rate of switching occurred in the group receiving other antidepressants, of whom 30.4% had prescriptions for other antidepressant classes during their first year of treatment. Among those patients who changed from a TCA within 1 year, the majority changed to an SSRI (3446, 87.4%). Among those patients who changed from an SSRI, 2717 (66.3%) changed to a TCA and 1371 (33.5%) changed to a drug from the group of other antidepressants. Among those patients who changed from the group of other antidepressants, 280 (34.5%) changed to a TCA and 532 (65.5%) to an SSRI.

Table 11 distinguishes patients who did not switch class, but had only one prescription in their first year of treatment. Among patients who were prescribed a TCA as their first antidepressant, 27.6% had only one prescription in the year and 20.1% had prescriptions for other classes of antidepressants during the year. This compares with 20.8% and 15.7%, respectively, for SSRIs and 19.7% and 30.4%, respectively, for other antidepressants. Among all patients who switched classes within the first year, 52% switched after only one prescription. The proportions who switched classes within the first year of treatment were similar in male and female patients, and by age group (data not shown).

Table 12 shows whether patients switched or only had one prescription within their first year of treatment by individual drug. The proportion of patients who did not switch, but only had one prescription in the first year of treatment was the highest for amitriptyline hydrochloride (31.3%) and the lowest for mirtazapine (16.8%). The proportion of patients who switched from the first

TABLE 9 Changes in antidepressant class during study follow-up according to first class prescribed

Class of first antidepressant drug prescribed	Had prescriptions from another class during follow-up				Total
	No change		Changed		
	<i>n</i>	Row %	<i>n</i>	Row %	
TCA	8811	41.87	12,232	58.13	21,043
MAOI	9	29.03	22	70.97	31
SSRI	20,148	67.69	9615	32.31	29,763
Other	1456	47.58	1604	52.42	3060
<i>Total</i>	<i>30,424</i>	<i>56.45</i>	<i>23,473</i>	<i>43.55</i>	<i>53,897</i>

TABLE 10 Changes in antidepressant class during the first year of treatment in patients with at least 1 year's follow-up

Class of first antidepressant drug prescribed	Had prescriptions from another class within 1 year				Total
	No switch within 1 year		Switch within 1 year		
	<i>n</i>	Row %	<i>n</i>	Row %	
TCA	15,653	79.87	3944	20.13	19,597
MAOI	26	83.87	5	16.13	31
SSRI	21,970	84.29	4096	15.71	26,066
Other	1859	69.60	812	30.40	2671
<i>Total</i>	<i>39,508</i>	<i>81.69</i>	<i>8,857</i>	<i>18.31</i>	<i>48,365</i>

TABLE 11 Changes in antidepressant class and single prescriptions during the first year of treatment in patients with at least 1 year's follow-up

Class of first antidepressant drug prescribed	No switch (two or more prescriptions)		No switch (only one prescription)		Switch		Total
	<i>n</i>	Row %	<i>n</i>	Row %	<i>n</i>	Row %	
TCA	10,237	52.24	5416	27.64	3944	20.13	19,597
MAOI	20	64.52	6	19.35	5	16.13	31
SSRI	16,538	63.45	5,432	20.84	4096	15.71	26,066
Other	1332	49.87	527	19.73	812	30.40	2671
<i>Total</i>	<i>28,127</i>	<i>58.16</i>	<i>11,381</i>	<i>23.53</i>	<i>8857</i>	<i>18.31</i>	<i>48,365</i>

TABLE 12 Changes in antidepressant drug and single prescriptions during the first year of treatment in patients with at least 1 year's follow-up

First drug prescribed	No switch (two or more prescriptions)		No switch (only one prescription)		Switch		Total
	<i>n</i>	Row %	<i>n</i>	Row %	<i>n</i>	Row %	<i>n</i>
TCAs							
Amitriptyline hydrochloride	3894	44.41	2740	31.25	2134	24.34	8768
Dosulepin hydrochloride	3329	52.24	1534	24.07	1510	23.69	6373
Lofepramine	1021	40.04	691	27.10	838	32.86	2550
Trazodone hydrochloride	319	45.70	137	19.63	242	34.67	698
SSRIs							
Citalopram hydrobromide	5498	57.82	1944	20.45	2066	21.73	9508
Escitalopram	587	52.98	237	21.39	284	25.63	1108
Fluoxetine hydrochloride	4827	54.23	1937	21.76	2137	24.01	8901
Paroxetine hydrochloride	2209	55.71	770	19.42	986	24.87	3965
Sertraline hydrochloride	1349	53.38	529	20.93	649	25.68	2527
Others							
Mirtazapine	473	57.06	139	16.77	217	26.18	829
Venlafaxine hydrochloride	528	53.77	191	19.45	263	26.78	982
All other antidepressants							
	882	40.91	532	24.68	742	34.42	2156
Total	24,916	51.52	11,381	23.53	12,068	24.95	48,365

drug they were prescribed within a year was the highest for trazodone hydrochloride (34.7%) and lofepramine (32.9%) and the lowest for citalopram hydrobromide (21.7%).

Practice variation in antidepressant prescribing

Table 13 shows variation in practice prescribing by antidepressant class and for the 11 most commonly prescribed drugs across the 570 practices included in the study. The median number of study patients in each practice was 77 (IQR 40 to 131) with a range of 1 to 436. Across practices the median proportion of TCA prescriptions out of all prescriptions for antidepressant drugs was 30.3%, but this ranged from 0% to 100% (IQR 22.6% to 39.4%). The median percentage of SSRI prescriptions was 54.9%, but this also ranged from 0% to 100% (IQR 47.2% to 62.9%). There was considerable variation between practices for all of the individual drugs.

Severity of depression by gender and age band

Table 14 shows the level of severity of the initial diagnosis of depression according to age group and gender. The distribution of the severity of depression was similar in all age bands, and in men and women.

Follow-up details

Table 15 gives details of person-years of follow-up for the 60,746 patients in the study cohort. The total number of person-years of follow-up was 305,188, with a mean per patient of 5.0 years [standard deviation (SD) 3.3 years] and a median of 4.6 years (IQR 2.2 years to 7.4 years).

TABLE 13 Variation in practice prescribing by antidepressant class and the 11 most commonly prescribed drugs

	Percentage of total antidepressant prescriptions					
	Median	IQR	Minimum	Maximum	Mean	SD
Antidepressant class						
TCAs	30.29	22.60 to 39.41	0.00	100.00	31.21	13.48
MAOIs	0.00	0.00 to 0.00	0.00	13.25	0.16	0.93
SSRIs	54.94	47.23 to 62.86	0.00	100.00	54.46	13.34
Other class	12.19	7.95 to 18.24	0.00	93.75	14.17	10.25
Antidepressant drugs						
Amitriptyline hydrochloride (TCA)	11.71	7.28 to 17.45	0.00	72.46	13.39	9.06
Dosulepin hydrochloride (TCA)	7.50	2.87 to 15.25	0.00	100.00	10.10	9.92
Lofepramine (TCA)	1.87	0.48 to 4.07	0.00	38.83	3.09	3.89
Trazodone hydrochloride (TCA)	0.65	0.00 to 2.88	0.00	33.38	2.25	3.91
Citalopram hydrobromide (SSRI)	20.87	13.15 to 28.72	0.00	59.74	21.59	11.51
Escitalopram (SSRI)	1.09	0.05 to 3.55	0.00	100.00	3.13	6.85
Fluoxetine hydrochloride (SSRI)	12.97	7.29 to 19.24	0.00	60.98	14.13	9.11
Paroxetine hydrochloride (SSRI)	6.97	3.55 to 12.07	0.00	46.12	8.68	7.30
Sertraline hydrochloride (SSRI)	4.64	1.43 to 9.91	0.00	57.25	6.76	7.27
Mirtazapine (other)	4.65	2.18 to 8.26	0.00	61.54	6.20	6.34
Venlafaxine hydrochloride (other)	5.14	1.82 to 8.69	0.00	87.50	6.63	7.58
All others	2.67	0.91 to 5.37	0.00	70.68	4.04	5.10
All antidepressant prescriptions (n)	1962	945 to 3380	12	12,207	2453	1979.27

TABLE 14 Level of severity of index depression according to age group and gender

	Depression severity					
	Mild		Moderate		Severe	
	n	Row %	n	Row %	n	Row %
Age band at baseline (years)						
65–74	22,338	71.27	7481	23.87	1522	4.86
75–84	14,609	67.96	5949	27.67	939	4.37
85+	5334	67.45	2209	27.93	365	4.62
Gender						
Female	28,414	70.13	10,288	25.39	1814	4.48
Male	13,867	68.55	5351	26.45	1012	5.00

Table 16 shows the number of patients who had the outcomes of interest during follow-up and the numbers who had these outcomes at baseline. The most common outcome during follow-up was death (29.4% of the cohort), followed by falls (20.2%), fractures (10.1%) and stroke/TIA (9.9%). A total of 43 people committed suicide. Only four patients had antidepressant poisoning recorded during follow-up, so this outcome was excluded from further analysis.

TABLE 15 Total person-years of follow-up by gender and age group for study cohort

Age band (years)	Male	Female	Total
65–74	38,182	84,317	122,498
75–84	40,547	92,720	133,268
85+	12,341	37,082	49,422
<i>Total</i>	<i>91,070</i>	<i>214,118</i>	<i>305,188</i>

TABLE 16 Numbers of patients (%) who had the outcomes of interest during the follow-up period or at baseline

Outcome	Had outcome at baseline		Had outcome during follow-up ^a	
	<i>n</i>	%	<i>n</i>	%
Deaths (all causes)	–		17,834	29.36
Sudden cardiac death	–		84	0.14
Suicide	–		43	0.07
Attempted suicide/self-harm	1107	1.82	507	0.85
MI	4216	6.94	2376	4.20
Stroke/TIA	6448	10.61	5369	9.89
Epilepsy/seizures	953	1.57	505	0.84
Upper GI bleeding	1251	2.06	1365	2.29
Falls	4979	8.20	11,251	20.18
Fractures	7839	12.90	5330	10.07
RTAs	963	1.59	423	0.71
ADRs	471	0.78	833	1.38
Hyponatraemia	341	0.56	1114	1.84
Antidepressant poisoning	4	0.01	4	0.01

a Events during follow-up are first events in patients without the outcome at baseline.

Results of time-varying analyses for the study outcomes

Results of analyses for all-cause mortality

Incidence rates for all-cause mortality

All 60,746 patients in the cohort contributed to the analyses of overall mortality. In the follow-up period 17,834 (29.4%) of these patients died, giving a crude mortality rate of 584.4 per 10,000 person-years (95% CI 575.9 to 593.0 person-years). Mortality rates were higher in men than in women and increased steeply with increasing age (*Table 17*).

Mortality rates by antidepressant class are shown in *Table 18*. These exclude patients who had taken MAOIs at any time during follow-up, owing to small numbers. The highest rates occurred in patients having combined prescriptions, then in patients taking the group of other antidepressants.

Hazard ratios for all-cause mortality

Table 19 shows the HRs for mortality according to antidepressant class, both unadjusted and adjusted for the potential confounding variables listed in the table footnotes. This shows increased HRs for all classes of antidepressant drugs after adjusting for potential confounding

TABLE 17 Incidence rates of mortality in study cohort by gender and age band

Age band (years)	Deaths	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	1571	84,317	186.3	177.3 to 195.8
75–84	4091	92,720	441.2	427.9 to 455.0
85+	4814	37,082	1298.2	1262.1 to 1335.4
65+	10,476	214,118	489.3	480.0 to 498.7
Men				
65–74	1551	38,182	406.2	386.5 to 426.9
75–84	3425	40,547	844.7	816.9 to 873.5
85+	2382	12,341	1930.2	1854.3 to 2009.3
65+	7358	91,070	808.0	789.7 to 826.6
Both sexes				
65–74	3122	122,498	254.9	246.1 to 264.0
75–84	7516	133,268	564.0	551.4 to 576.9
85+	7196	49,422	1456.0	1422.8 to 1490.1
65+	17,834	305,188	584.4	575.9 to 593.0

TABLE 18 Incidence rates of mortality in study cohort by antidepressant class

Antidepressant class	Deaths	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	8210	170,864	480.5	470.2 to 491.0
TCAAs	2337	45,957	508.5	488.3 to 529.6
SSRIs	5782	70,893	815.6	794.8 to 836.9
Other antidepressants	1268	14,489	875.2	828.3 to 924.7
Combination of antidepressants	216	2163	998.8	874.1 to 1141.3

variables. There were significant differences between the classes ($p < 0.001$). The adjusted HR was highest for combined prescriptions, with an 84% increase in mortality rate compared with no antidepressant use, and then the group of other antidepressants in which there was a 66% increase in mortality rate. In a direct comparison with TCAs, the adjusted HRs were 1.32 (95% CI 1.26 to 1.39) for SSRIs and 1.43 (95% CI 1.33 to 1.54) for the group of other antidepressants.

The results of the dose analyses (Table 20) show that the mortality rate was significantly increased for all classes at all dose levels except for lower doses of TCAs (≤ 1.0 DDDs), with evidence of a dose–response relationship for TCAs and SSRIs, but not for the group of other antidepressants.

TABLE 19 Hazard ratios for mortality by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Not currently on antidepressants	1.00			1.00		
TCAs	0.99	0.95 to 1.04	0.748	1.16	1.10 to 1.22	<0.001
SSRIs	1.61	1.55 to 1.66	<0.001	1.54	1.48 to 1.59	<0.001
Other antidepressants	1.77	1.66 to 1.87	<0.001	1.66	1.56 to 1.77	<0.001
Combination of antidepressants	2.02	1.76 to 2.31	<0.001	1.84	1.59 to 2.13	<0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive–compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 20 Adjusted HRs for mortality by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	<i>p</i> -value
Not currently on antidepressants	1.00		
TCAs			
≤ 0.5 DDDs	1.05	0.98 to 1.12	0.149
$> 0.5/\leq 1.0$ DDDs	1.28	1.15 to 1.43	<0.001
> 1.0 DDDs	1.43	1.22 to 1.66	<0.001
Test for trend			<0.001
SSRIs			
≤ 0.5 DDDs	1.48	1.38 to 1.60	<0.001
$> 0.5/\leq 1.0$ DDDs	1.46	1.40 to 1.52	<0.001
> 1.0 DDDs	1.78	1.64 to 1.93	<0.001
Test for trend			<0.001
Others			
≤ 0.5 DDDs	1.76	1.55 to 2.01	<0.001
$> 0.5/\leq 1.0$ DDDs	1.67	1.52 to 1.83	<0.001
> 1.0 DDDs	1.77	1.55 to 2.04	<0.001
Test for trend			0.696

a Adjusted for: gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive–compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Table 21 shows the effects of duration of use and time since stopping an antidepressant on mortality rates. For TCAs the mortality rate was significantly increased in the first 28 days after starting the drug (adjusted HR 1.24, 95% CI 1.06 to 1.45), but was significantly reduced after 85 days of use (adjusted HR 0.60, 95% CI 0.56 to 0.66). The HR was significantly increased in the first 84 days after starting SSRIs, but was significantly reduced after 85 days of use (adjusted HR 0.75, 95% CI 0.71 to 0.80). For the group of other antidepressants the mortality rate was significantly increased in the first 28 days after starting (adjusted HR 2.10, 95% CI 1.73 to 2.56), but was significantly reduced after 85 days of use (adjusted HR 0.81, 95% CI 0.73 to 0.90). The HRs were significantly increased throughout the 182 days after stopping TCAs, SSRIs and the group of other antidepressants, but decreased with time.

There were significant interactions for mortality between antidepressant class and age, gender, and use of NSAIDs and antihypertensive drugs at baseline (all $p < 0.01$). The HRs for all classes of antidepressant drugs were slightly higher for people aged 65–74 years than for those aged 75 and over; the HR for SSRIs was somewhat higher in men than in women, whereas the HR for other antidepressants was slightly lower in men. The HRs for all classes of antidepressant drugs were higher in people taking NSAIDs at baseline and the HR for the class of other antidepressant drugs was slightly higher in people taking antihypertensive drugs at baseline (data not shown).

TABLE 21 Adjusted HRs for mortality by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
1–28 days	1.24	1.06 to 1.45	0.008
29–84 days	0.86	0.70 to 1.04	0.120
85+ days	0.60	0.56 to 0.66	<0.001
Stopped 1–28 days	6.80	6.27 to 7.37	<0.001
Stopped 29–84 days	2.75	2.50 to 3.03	<0.001
Stopped 85–182 days	1.29	1.15 to 1.45	<0.001
SSRIs			
1–28 days	1.86	1.66 to 2.07	<0.001
29–84 days	1.41	1.26 to 1.57	<0.001
85+ days	0.75	0.71 to 0.80	<0.001
Stopped 1–28 days	11.33	10.71 to 11.98	<0.001
Stopped 29–84 days	4.45	4.17 to 4.76	<0.001
Stopped 85–182 days	1.87	1.72 to 2.03	<0.001
Others			
1–28 days	2.10	1.73 to 2.56	<0.001
29–84 days	1.15	0.90 to 1.48	0.259
85+ days	0.81	0.73 to 0.90	<0.001
Stopped 1–28 days	13.46	12.11 to 14.96	<0.001
Stopped –84 days	5.34	4.67 to 6.11	<0.001
Stopped 85–182 days	2.07	1.72 to 2.50	<0.001

a Adjusted for: gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Table 22 shows the HRs for mortality according to individual antidepressant drugs, both unadjusted and adjusted for the potential confounding variables listed in the table footnotes. There were significant differences between the different drugs ($p < 0.001$), with significantly increased HRs for all the antidepressant drugs except for dosulepin after adjusting for confounding variables. The highest HRs among these 11 drugs were for trazodone, which was associated with an 82% increased mortality rate compared with no antidepressant use (adjusted HR 1.82, 95% CI 1.59 to 2.08) and mirtazapine (adjusted HR 1.76, 95% CI 1.62 to 1.91).

Absolute risk of death

Table 23 shows the absolute risk of mortality over 1, 2 and 5 years of treatment, using the adjusted HRs presented in Tables 19 and 22, which were significant at $p < 0.01$, to calculate adjusted absolute risks and numbers of extra deaths per 10,000 treated patients compared with no antidepressant treatment by antidepressant class and individual drug. The results by antidepressant class show that the group of other antidepressants is associated with the highest absolute risks and numbers of extra cases. For individual drugs, trazodone and mirtazapine are associated with the highest number of additional deaths, assuming causality.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in Table 24. For all classes of antidepressants, mortality rates were significantly increased throughout use and during the 182-day period after stopping; however, the self-controlled case-series analysis may produce unreliable results when the outcome under investigation is a fatal one.⁵⁷

Summary of results for all-cause mortality

Mortality rates were significantly increased for all classes of antidepressants compared with no use of antidepressants, with highest rates for the class of other antidepressant drugs. There was some evidence of a dose–response relationship for TCAs and SSRIs, but not for the group of other antidepressants. Among the 11 most commonly prescribed antidepressant drugs, trazodone and mirtazapine were associated with the highest HRs. Mortality rates tended to be highest in the first 28 days of starting an antidepressant, but were reduced after 85 days of use. Rates remained increased during 182 days after stopping antidepressants.

TABLE 22 Unadjusted and adjusted HRs for mortality for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	0.94	0.88 to 1.00	0.065	1.10	1.03 to 1.18	0.008
Dosulepin hydrochloride (TCA)	0.80	0.73 to 0.86	<0.001	1.03	0.95 to 1.13	0.469
Lofepramine (TCA)	1.48	1.33 to 1.64	<0.001	1.51	1.35 to 1.69	<0.001
Trazodone hydrochloride (TCA)	2.12	1.88 to 2.40	<0.001	1.82	1.59 to 2.08	<0.001
Citalopram hydrobromide (SSRI)	1.76	1.68 to 1.84	<0.001	1.55	1.48 to 1.63	<0.001
Escitalopram (SSRI)	1.44	1.27 to 1.64	<0.001	1.45	1.27 to 1.66	<0.001
Fluoxetine hydrochloride (SSRI)	1.64	1.55 to 1.72	<0.001	1.66	1.57 to 1.76	<0.001
Paroxetine hydrochloride (SSRI)	1.16	1.08 to 1.26	<0.001	1.24	1.14 to 1.35	<0.001
Sertraline hydrochloride (SSRI)	1.58	1.45 to 1.71	<0.001	1.47	1.35 to 1.61	<0.001
Mirtazapine (other)	2.07	1.90 to 2.24	<0.001	1.76	1.62 to 1.91	<0.001
Venlafaxine hydrochloride (other)	1.67	1.54 to 1.83	<0.001	1.66	1.51 to 1.82	<0.001

a Adjusted for: gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive–compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 23 Absolute and excess risks of mortality by antidepressant class and 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	7.04	10.85	21.66			
TCAs	8.12	12.48	24.68	109	163	302
SSRIs	10.61	16.18	31.29	357	533	962
Other antidepressants	11.43	17.39	33.37	439	654	1171
Antidepressant drug						
Not currently on antidepressants	7.04	10.85	21.66			
Amitriptyline hydrochloride (TCA)	7.72	11.88	23.58	69	103	191
Dosulepin hydrochloride (TCA)	7.26	11.18	22.28	NS	NS	NS
Lofepramine (TCA)	10.43	15.91	30.81	339	506	915
Trazodone hydrochloride (TCA)	12.44	18.87	35.88	540	801	1422
Citalopram hydrobromide (SSRI)	10.69	16.29	31.48	365	544	982
Escitalopram (SSRI)	10.06	15.37	29.86	302	451	819
Fluoxetine hydrochloride (SSRI)	11.42	17.38	33.36	439	653	1169
Paroxetine hydrochloride (SSRI)	8.68	13.32	26.20	164	247	454
Sertraline hydrochloride (SSRI)	10.20	15.57	30.23	316	472	856
Mirtazapine (other)	12.05	18.29	34.91	501	744	1324
Venlafaxine hydrochloride (other)	11.40	17.35	33.30	436	649	1164

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 19.

Results of analyses for sudden cardiac death

Incidence rates of sudden cardiac death

All 60,746 patients in the study cohort contributed to the analyses of sudden cardiac death. During the follow-up period, 84 (0.14%) of these patients had a sudden cardiac death, giving a crude incidence rate of 2.8 per 10,000 person-years (95% CI 2.2 to 3.4 per 10,000 person-years). Rates were higher in men than in women and tended to increase with increasing age (Table 25).

Sudden cardiac death rates by antidepressant class are shown in Table 26. These rates are not adjusted for patient characteristics and exclude patients who had taken MAOIs during follow-up. The highest sudden cardiac death rate occurred in patients taking the group of other antidepressants than in patients having combined prescriptions.

Hazard ratios for sudden cardiac death

Table 27 shows HRs for sudden cardiac death according to antidepressant class. There was an increased HR for the group of other antidepressant drugs (adjusted HR 2.25, 95% CI 1.05 to 4.83), but this was not statistically significant at $p < 0.01$. There were no significant differences between the classes ($p = 0.50$); however, numbers were small. In a direct comparison with TCAs, the adjusted HRs were 0.89 (95% CI 0.45 to 1.75) for SSRIs and 1.66 (95% CI 0.69 to 3.97) for the group of other antidepressant drugs.

Tests of interaction, and analyses of dose, duration and individual drugs were not carried out for sudden cardiac death owing to small patient numbers.

TABLE 24 Incidence rate ratios for mortality by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCAs			
1–28 days	3.99	3.43 to 4.65	<0.001
29–84 days	5.22	4.62 to 5.91	<0.001
85+ days	8.43	7.50 to 9.48	<0.001
Stopped 1–28 days	6.01	5.29 to 6.82	<0.001
Stopped 29–84 days	3.66	3.26 to 4.12	<0.001
Stopped 85–182 days	2.19	1.95 to 2.46	<0.001
SSRIs			
1–28 days	7.87	7.10 to 8.72	<0.001
29–84 days	12.04	11.12 to 13.02	<0.001
85+ days	16.26	15.02 to 17.60	<0.001
Stopped 1–28 days	13.29	12.20 to 14.47	<0.001
Stopped 29–84 days	6.11	5.60 to 6.68	<0.001
Stopped 85–182 days	3.29	3.00 to 3.60	<0.001
Others			
1–28 days	5.99	4.79 to 7.51	<0.001
29–84 days	8.65	7.17 to 10.42	<0.001
85+ days	18.59	15.59 to 22.17	<0.001
Stopped 1–28 days	11.75	9.63 to 14.34	<0.001
Stopped 29–84 days	5.82	4.73 to 7.16	<0.001
Stopped 85–182 days	3.31	2.66 to 4.12	<0.001

IRR, incidence rate ratio.

TABLE 25 Incidence rates of sudden cardiac death in study cohort by gender and age band

Age band (years)	Sudden cardiac deaths	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	9	84,317	1.1	0.6 to 2.1
75–84	17	92,720	1.8	1.1 to 3.0
85+	18	37,082	4.9	3.1 to 7.7
65+	44	214,118	2.1	1.5 to 2.8
Men				
65–74	9	38,182	2.4	1.2 to 4.5
75–84	26	40,547	6.4	4.4 to 9.4
85+	5	12,341	4.1	1.7 to 9.7
65+	40	91,070	4.4	3.2 to 6.0
Both sexes				
65–74	18	122,498	1.5	0.9 to 2.3
75–84	43	133,268	3.2	2.4 to 4.4
85+	23	49,422	4.7	3.1 to 7.0
65+	84	305,188	2.8	2.2 to 3.4

TABLE 26 Incidence rates of sudden cardiac death in study cohort by antidepressant class

Antidepressant class	Sudden cardiac deaths	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	40	170,863	2.3	1.7 to 3.2
TCAs	14	45,957	3.1	1.8 to 5.1
SSRIs	21	70,893	3.0	1.9 to 4.5
Other antidepressants	8	14,489	5.5	2.8 to 11.0
Combination of antidepressants	1	2163	4.6	0.7 to 32.8

TABLE 27 Hazard ratios for sudden cardiac death by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCAs	1.25	0.67 to 2.33	0.475	1.36	0.73 to 2.53	0.333
SSRIs	1.23	0.72 to 2.11	0.451	1.21	0.70 to 2.07	0.496
Other antidepressants	2.30	1.07 to 4.92	0.032	2.25	1.05 to 4.83	0.036
Combination of antidepressants	1.99	0.27 to 14.5	0.496	1.91	0.26 to 13.92	0.523

a Adjusted for gender, age (5-year bands), CHD, diabetes, hypertension, statins, aspirin and antihypertensives.

Absolute risk of sudden cardiac death

Table 28 shows the absolute risk of sudden cardiac death by antidepressant class over 1, 2 and 5 years of treatment. There were no excess risks by class which were significant at $p < 0.01$.

Self-controlled case-series analyses

The case-series analyses are not presented for sudden cardiac death owing to small patient numbers.

Summary of results for sudden cardiac death

Sudden cardiac death rates were not significantly increased for any class of antidepressant drugs compared with no use of antidepressant drugs. Numbers were too small to examine interactions or effects of dose, duration or individual drugs.

Results of analyses for suicide

Incidence rates of suicide

All 60,746 patients in the study cohort contributed to the analyses of suicide. During follow-up 43 (0.07%) of these patients committed suicide, giving a crude incidence rate of 1.4 per 10,000 person-years (95% CI 1.0 to 1.9 per 10,000 person-years). Rates were higher in men than in women below the age of 85 years, and there was no clear change in rates with increasing age (Table 29).

Suicide incidence rates by antidepressant class are shown in Table 30. These rates are not adjusted for patient characteristics and exclude patients who had taken MAOIs during follow-up. The highest suicide rates occurred in patients taking the group of other antidepressant drugs than in patients having combined prescriptions.

TABLE 28 Absolute and excess risks of sudden cardiac death by antidepressant class

Antidepressant class	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Not currently on antidepressants	0.04	0.04	0.12			
TCAs	0.05	0.06	0.17	NS	NS	NS
SSRIs	0.04	0.05	0.15	NS	NS	NS
Other antidepressants	0.08	0.10	0.28	NS	NS	NS

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in *Table 27*.

TABLE 29 Incidence rates of suicide in study cohort by gender and age band

Age band (years)	Suicides	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	5	84,316	0.6	0.3 to 1.4
75–84	9	92,719	1.0	0.5 to 1.9
85+	2	37,081	0.5	0.1 to 2.2
65+	16	214,117	0.8	0.5 to 1.2
Men				
65–74	10	38,181	2.6	1.4 to 4.9
75–84	17	40,547	4.2	2.6 to 6.7
85+	0	12,341	0.0	–
65+	27	91,068	3.0	2.0 to 4.3
Both sexes				
65–74	15	122,497	1.2	0.7 to 2.0
75–84	26	133,266	2.0	1.3 to 2.9
85+	2	49,422	0.4	0.1 to 1.6
65+	43	305,185	1.4	1.0 to 1.9

Hazard ratios for suicide

Table 31 shows the HRs for suicide according to antidepressant class. This shows significantly increased HRs for all classes of antidepressant drugs after adjusting for potential confounding variables. There were no significant differences between the classes ($p = 0.16$); however, numbers were small. In a direct comparison with TCAs, the adjusted HRs were 1.14 (95% CI 0.51 to 2.57) for SSRIs and 2.64 (95% CI 1.00 to 6.97) for the group of other antidepressant drugs.

Tests of interaction and analyses of dose, duration and individual drugs were not carried out for suicide owing to small patient numbers.

Absolute risk of suicide

Table 32 shows the absolute risk of suicide by antidepressant class over 1, 2 and 5 years of treatment. Absolute risks and numbers of extra cases are greatest for the group of other antidepressant drugs.

TABLE 30 Incidence rates of suicide in study cohort by antidepressant class

Antidepressant class	Suicides	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	7	170,863	0.4	0.2 to 0.9
TCAs	9	45,955	2.0	1.0 to 3.8
SSRIs	17	70,891	2.4	1.5 to 3.9
Other antidepressants	8	14,489	5.5	2.8 to 11.0
Combination of antidepressants	1	2163	4.6	0.7 to 32.8

TABLE 31 Hazard ratios for suicide by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCAs	3.91	1.43 to 10.69	0.008	4.27	1.56 to 11.70	0.005
SSRIs	4.83	1.97 to 11.83	0.001	4.87	1.99 to 11.96	0.001
Other antidepressants	12.97	4.69 to 35.89	<0.001	11.29	4.06 to 31.35	<0.001
Combination of antidepressants	13.03	1.60 to 106.29	0.017	12.11	1.48 to 98.81	0.020

a Adjusted for gender, age (5-year bands), depression severity, previous attempted suicide and lithium.

TABLE 32 Absolute and excess risks of suicide by antidepressant class

Antidepressant class	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Not currently on antidepressants	0.01	0.02	0.03			
TCAs	0.04	0.08	0.13	3	6	10
SSRIs	0.04	0.09	0.14	3	7	11
Other antidepressants	0.09	0.20	0.33	8	18	30

Note: absolute risks and excess risks are adjusted for confounders listed in Table 31.

Self-controlled case-series analyses

The case-series analyses are not presented for suicide owing to small patient numbers.

Summary of results for suicide

All classes of antidepressant drugs were associated with significantly increased suicide rates compared with no current use of antidepressant drugs. Numbers were too small to examine interactions or effects of dose, duration or individual drugs.

Results of analyses for attempted suicide/self-harm

Incidence rates of attempted suicide/self-harm

A total of 59,639 patients were included in the analyses of incident attempted suicide/self-harm during follow-up, excluding the 1107 patients who had attempted suicide/self-harm by the baseline date. During the follow-up period, 507 (0.85%) of these patients attempted suicide/self-harm, giving a crude incidence rate of 17.0 per 10,000 person-years (95% CI 15.6 to 18.6 per

10,000 person-years). The rates were higher in men than in women and there was little change in rates with increasing age (*Table 33*).

Attempted suicide/self-harm incidence rates by antidepressant class are shown in *Table 34*. These rates exclude patients who had taken MAOIs during follow-up. The highest attempted suicide/self-harm rates occurred in patients having prescriptions for the group of other antidepressant drugs, followed by patients having combined prescriptions.

Hazard ratios for attempted suicide/self-harm

Table 35 shows the HRs for attempted suicide/self-harm according to antidepressant class. This shows increased HRs for all classes of antidepressant drugs, with only small changes after adjusting for potential confounding variables. There were significant differences between the classes ($p < 0.001$). The HR was highest for the group of other antidepressant drugs, with more than a fivefold increase in attempted suicide/self-harm rate compared with no antidepressant use, and for combined prescriptions, which were associated with a more than fourfold increase in attempted suicide/self-harm rate. In a direct comparison with TCAs, there were adjusted HRs of 1.27 (95% CI 0.97 to 1.66) for SSRIs and 3.04 (95% CI 2.21 to 4.17) for the group of other antidepressant drugs.

TABLE 33 Incidence rates of attempted suicide/self-harm in study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	125	81,505	15.3	12.9 to 18.3
75–84	116	90,955	12.8	10.6 to 15.3
85+	50	36,568	13.7	10.4 to 18.0
65+	291	209,028	13.9	12.4 to 15.6
Men				
65–74	95	37,241	25.5	20.9 to 31.2
75–84	96	39,791	24.1	19.8 to 29.5
85+	25	12,120	20.6	13.9 to 30.5
65+	216	89,152	24.2	21.2 to 27.7
Both sexes				
65–74	220	118,746	18.5	16.2 to 21.1
75–84	212	130,746	16.2	14.2 to 18.6
85+	75	48,688	15.4	12.3 to 19.3
65+	507	298,180	17.0	15.6 to 18.6

TABLE 34 Incidence rates of attempted suicide/self-harm in study cohort by antidepressant class

Antidepressant class	Events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	150	167,507	9.0	7.6 to 10.5
TCAs	89	44,890	19.8	16.1 to 24.4
SSRIs	178	69,255	25.7	22.2 to 29.8
Other antidepressants	79	13,683	57.7	46.3 to 72.0
Combination of antidepressants	8	2059	38.9	19.4 to 77.7

The results of the dose analyses are shown in *Table 36*. This shows that, although the risk of attempted suicide/self-harm tended to increase as dose increased in all classes, the tests for trend were not statistically significant.

Table 37 shows the effects of duration of use and time since stopping an antidepressant on attempted suicide/self-harm, according to antidepressant class. For TCAs the attempted suicide/self-harm rate was highest in the first 28 days after starting the drug, with no significant increase in risk after 29 days of use. The HR was significantly increased in the first 28 days after

TABLE 35 Hazard ratios for attempted suicide/self-harm by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCAs	1.67	1.27 to 2.18	<0.001	1.70	1.28 to 2.25	<0.001
SSRIs	2.22	1.77 to 2.78	<0.001	2.16	1.71 to 2.71	<0.001
Other antidepressants	5.80	4.41 to 7.63	<0.001	5.16	3.90 to 6.83	<0.001
Combination of antidepressants	4.60	2.25 to 9.37	<0.001	4.15	2.03 to 8.48	<0.001

a Adjusted for: gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 36 Adjusted HRs for attempted suicide/self-harm by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
≤ 0.5 DDDs	1.51	1.07 to 2.15	0.020
> 0.5/≤ 1.0 DDDs	1.76	1.01 to 3.06	0.046
> 1.0 DDDs	2.03	0.94 to 4.35	0.070
Test for trend			0.282
SSRIs			
≤ 0.5 DDDs	2.19	1.41 to 3.41	0.001
> 0.5/≤ 1.0 DDDs	1.87	1.44 to 2.44	<0.001
> 1.0 DDDs	2.93	1.87 to 4.60	<0.001
Test for trend			0.133
Others			
≤ 0.5 DDDs	4.14	2.23 to 7.69	<0.001
> 0.5/≤ 1.0 DDDs	5.49	3.77 to 8.01	<0.001
> 1.0 DDDs	6.63	3.99 to 11.03	<0.001
Test for trend			0.110

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 37 Adjusted HRs for attempted suicide/self-harm by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
1–28 days	7.11	4.66 to 10.83	<0.001
29–84 days	1.69	0.81 to 3.53	0.164
85+ days	1.10	0.72 to 1.68	0.659
Stopped 1–28 days	4.14	2.35 to 7.31	<0.001
Stopped 29–84 days	1.31	0.63 to 2.72	0.464
Stopped 85–182 days	2.05	1.18 to 3.54	0.011
SSRIs			
1–28 days	12.31	8.84 to 17.14	<0.001
29–84 days	1.96	1.11 to 3.46	0.020
85+ days	0.98	0.68 to 1.40	0.894
Stopped 1–28 days	5.91	3.76 to 9.30	<0.001
Stopped 29–84 days	3.51	2.24 to 5.48	<0.001
Stopped 85–182 days	1.04	0.53 to 2.07	0.905
Others			
1–28 days	17.12	10.58 to 27.71	<0.001
29–84 days	6.63	3.34 to 13.16	<0.001
85+ days	3.99	2.69 to 5.92	<0.001
Stopped 1–28 days	17.26	9.26 to 32.16	<0.001
Stopped 29–84 days	5.87	2.57 to 13.37	<0.001
Stopped 85–182 days	3.36	1.24 to 9.13	0.017

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

stopping TCAs. For SSRIs the attempted suicide/self-harm rate was highest in the first 28 days after starting the drug, but was not significantly increased after 85 days of use. The HR was significantly increased in the first 84 days after stopping SSRIs, but not between 85 and 182 days after stopping. For the group of other antidepressant drugs, the attempted suicide/self-harm rate was significantly increased throughout use and was significantly increased in the first 84 days after stopping, with some indication of an increase between 85 and 182 days after stopping.

There was a significant interaction between antidepressant class and CHD at baseline ($p=0.006$), with higher HRs for attempted suicide in patients without CHD at baseline (adjusted HRs: TCAs 1.99, 95% CI 1.46 to 2.72; SSRIs 2.38, 95% CI 1.82 to 3.10; other antidepressant drugs 6.40, 95% CI 4.72 to 8.69) than in patients with CHD at baseline (adjusted HRs: TCAs 0.98, 95% CI 0.49 to 1.97; SSRIs 1.64, 95% CI 1.01 to 2.69; other antidepressant drugs 1.76, 95% CI 0.73 to 4.27). There were no other significant interactions for attempted suicide/self-harm.

There were significantly ($p<0.01$) increased HRs for all individual antidepressant drugs (except for amitriptyline, escitalopram and paroxetine) after adjusting for potential confounding variables (Table 38). There were significant differences in the attempted suicide/self-harm rates

TABLE 38 Unadjusted and adjusted HRs for attempted suicide/self-harm for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.03	0.67 to 1.60	0.879	1.07	0.69 to 1.67	0.761
Dosulepin hydrochloride (TCA)	1.94	1.34 to 2.82	0.001	1.87	1.26 to 2.77	0.002
Lofepramine (TCA)	2.49	1.45 to 4.25	0.001	2.58	1.48 to 4.50	0.001
Trazodone hydrochloride (TCA)	4.56	2.53 to 8.22	<0.001	4.70	2.60 to 8.49	<0.001
Citalopram hydrobromide (SSRI)	2.88	2.20 to 3.77	<0.001	2.70	2.04 to 3.58	<0.001
Escitalopram (SSRI)	2.18	1.07 to 4.45	0.032	2.08	1.02 to 4.27	0.045
Fluoxetine hydrochloride (SSRI)	2.06	1.49 to 2.86	<0.001	2.08	1.49 to 2.90	<0.001
Paroxetine hydrochloride (SSRI)	1.14	0.67 to 1.94	0.628	1.14	0.66 to 1.99	0.640
Sertraline hydrochloride (SSRI)	1.99	1.20 to 3.30	0.007	2.07	1.25 to 3.44	0.005
Mirtazapine (other)	7.03	4.92 to 10.05	<0.001	6.11	4.24 to 8.80	<0.001
Venlafaxine hydrochloride (other)	5.25	3.58 to 7.70	<0.001	4.60	3.11 to 6.80	<0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

between the different antidepressant drugs ($p < 0.001$), with the highest HRs for mirtazapine, which was associated with a more than sixfold increase in the attempted suicide/self-harm rate compared with no antidepressant use, and trazodone and venlafaxine, which were associated with a more than fourfold increase.

Absolute risk of attempted suicide/self-harm

Table 39 shows the absolute risks of attempted suicide/self-harm over 1, 2 and 5 years of treatment and the number of extra cases for significant associations at $p < 0.01$. The results by antidepressant class show that the group of other antidepressant drugs are associated with the highest absolute risks and numbers of extra cases. For individual drugs, mirtazapine, trazodone and venlafaxine are associated with the highest number of additional cases of attempted suicide/self-harm.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in Table 40. The attempted suicide/self-harm rate was significantly increased during the first 28 days of use for TCAs and the group of other antidepressant drugs, and during the first 84 days of use for SSRIs. The attempted suicide/self-harm rate was significantly increased in the first 28 days and 85–182 days after stopping for TCAs, and in the first 84 days after stopping for SSRIs.

Summary of results for attempted suicide/self-harm

All classes of antidepressant drug were associated with an increased risk of attempted suicide/self-harm risk compared with no current use of antidepressant drugs. The risk varied by antidepressant class, being higher for the group of other antidepressant drugs. The risk tended to increase as dose increased in all classes. There were increased HRs for all 11 most commonly prescribed antidepressant drugs, except for amitriptyline, escitalopram and paroxetine. Mirtazapine, trazodone and venlafaxine were associated with the highest HRs. Attempted suicide/self-harm rates tended to be highest in the first 28 days of starting an antidepressant, and

TABLE 39 Absolute and excess risks of attempted suicide/self-harm by antidepressant class and for 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	0.25	0.36	0.55			
TCA	0.43	0.62	0.93	18	25	38
SSRIs	0.55	0.78	1.18	29	42	63
Other antidepressants	1.30	1.86	2.81	105	150	226
Antidepressant drug						
Not currently on antidepressants	0.25	0.35	0.54			
Amitriptyline hydrochloride (TCA)	0.27	0.39	0.59	NS	NS	NS
Dosulepin hydrochloride (TCA)	0.48	0.67	1.02	23	32	49
Lofepramine (TCA)	0.66	0.93	1.41	41	58	88
Trazodone hydrochloride (TCA)	1.20	1.69	2.56	95	134	203
Citalopram hydrobromide (SSRI)	0.68	0.96	1.45	43	60	92
Escitalopram (SSRI)	0.47	0.66	1.01	NS	NS	NS
Fluoxetine hydrochloride (SSRI)	0.53	0.75	1.14	28	40	61
Paroxetine hydrochloride (SSRI)	0.29	0.41	0.63	NS	NS	NS
Sertraline hydrochloride (SSRI)	0.53	0.75	1.14	28	40	60
Mirtazapine (other)	1.56	2.20	3.33	131	185	279
Venlafaxine hydrochloride (other)	1.17	1.65	2.50	92	130	197

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 35.

also in the first 28 days after stopping. There were inconsistencies in the patterns of risk between the cohort analyses and case-series analysis, suggesting some indication bias for the group of other antidepressant drugs.

Results of analyses for myocardial infarction outcome

Incidence rates of myocardial infarction

A total of 56,530 patients were included in the analyses of incident MI during follow-up, excluding the 4216 patients who had had a MI by the baseline date. During the follow-up period, 2376 (4.2%) of these patients had an incident MI, giving a crude incidence rate of 84.3 per 10,000 person-years (95% CI 80.9 to 87.7 per 10,000 person-years). The rates were higher in men than women and increased with increasing age (Table 41).

Myocardial infarction incidence rates by antidepressant class are shown in Table 42. These rates exclude patients who had taken MAOIs during follow-up. The highest MI rates occurred in patients taking SSRIs.

Table 43 shows the HRs for MI according to antidepressant class. This shows HRs were only significantly increased for SSRIs, which were associated with a 15% increase in MI rate compared with no antidepressant use after adjusting for potential confounding variables. The differences between the classes were not, however, statistically significant ($p = 0.72$). In a direct comparison with TCAs, there were adjusted HRs of 1.06 (95% CI 0.92 to 1.21) for SSRIs and 0.95 (95% CI 0.76 to 1.19) for the group of other antidepressant drugs.

TABLE 40 Incidence rate ratios for attempted suicide/self-harm by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCA			
1–28 days	6.00	3.74 to 9.60	<0.001
29–84 days	2.02	0.80 to 5.11	0.136
85+ days	1.89	0.85 to 4.21	0.120
Stopped 1–28 days	2.87	1.57 to 5.25	0.001
Stopped 29–84 days	1.47	0.75 to 2.89	0.257
Stopped 85–182 days	2.14	1.28 to 3.55	0.003
SSRIs			
1–28 days	12.77	9.12 to 17.88	<0.001
29–84 days	3.47	1.93 to 6.25	<0.001
85+ days	1.05	0.59 to 1.88	0.872
Stopped 1–28 days	4.58	2.78 to 7.56	<0.001
Stopped 29–84 days	3.17	1.90 to 5.29	<0.001
Stopped 85–182 days	1.90	1.08 to 3.36	0.026
Others			
1–28 days	3.20	1.68 to 6.06	<0.001
29–84 days	0.98	0.35 to 2.74	0.970
85+ days	0.38	0.16 to 0.86	0.020
Stopped 1–28 days	2.42	1.07 to 5.48	0.035
Stopped 29–84 days	1.56	0.61 to 4.01	0.355
Stopped 85–182 days	0.39	0.09 to 1.69	0.211

IRR, incidence rate ratio.

The results of the dose analyses are shown in *Table 44*. The risk of MI tended to increase with dose for TCAs and SSRIs; however, the tests for trend were not statistically significant. The risk was significantly increased only for SSRIs at > 1.0 DDDs.

Table 45 shows the effects of duration of use and time since stopping an antidepressant on MI risk. For TCAs and the group of other antidepressant drugs there was no association during the first 84 days of use, but the MI rate was significantly reduced from 85 days after starting medication. For SSRIs the MI rate was highest in the first 28 days after starting medication, but was significantly reduced from 85 days after starting. There was a significant increase in the first 84 days after stopping TCAs, SSRIs and the group of other antidepressant drugs, but not after 85 days.

There were no significant interactions for MI.

Table 46 shows the HRs for MI for individual antidepressant drugs. The only significant association was for fluoxetine, with a 31% increased rate compared with no antidepressant use; however, overall there were no significant differences between the drugs ($p = 0.65$).

TABLE 41 Incidence rates of MI in study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	355	80,872	43.9	39.6 to 48.7
75–84	665	87,270	76.2	70.6 to 82.2
85+	427	34,580	123.5	112.3 to 135.8
65+	1447	202,723	71.4	67.8 to 75.2
Men				
65–74	309	33,561	92.1	82.4 to 102.9
75–84	435	34,964	124.4	113.3 to 136.7
85+	185	10,735	172.3	149.2 to 199.0
65+	929	79,260	117.2	109.9 to 125.0
Both sexes				
65–74	664	114,434	58.0	53.8 to 62.6
75–84	1100	122,234	90.0	84.8 to 95.5
85+	612	45,316	135.1	124.8 to 146.2
65+	2376	281,983	84.3	80.9 to 87.7

TABLE 42 Incidence rates of MI in study cohort by antidepressant class

Antidepressant class	First events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	1264	157,723	80.1	75.8 to 84.7
TCA	362	43,054	84.1	75.9 to 93.2
SSRI	614	64,978	94.5	87.3 to 102.3
Other antidepressants	110	13,469	81.7	67.8 to 98.5
Combination of antidepressants	16	1974	81.1	49.7 to 132.3

TABLE 43 Hazard ratios for MI by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCA	1.02	0.91 to 1.15	0.688	1.09	0.96 to 1.23	0.179
SSRI	1.16	1.05 to 1.27	0.004	1.15	1.04 to 1.27	0.008
Other antidepressant drugs	1.01	0.83 to 1.23	0.915	1.04	0.85 to 1.27	0.733
Combination of antidepressants	1.01	0.62 to 1.66	0.964	1.03	0.62 to 1.72	0.906

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 44 Adjusted HRs for MI by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCA s			
≤ 0.5 DDDs	1.05	0.91 to 1.23	0.495
> 0.5/≤ 1.0 DDDs	1.10	0.84 to 1.43	0.495
> 1.0 DDDs	1.30	0.90 to 1.88	0.166
TCA: test for trend			0.323
SSRI s			
≤ 0.5 DDDs	1.17	0.93 to 1.47	0.186
> 0.5/≤ 1.0 DDDs	1.12	1.00 to 1.26	0.048
> 1.0 DDDs	1.37	1.08 to 1.73	0.009
SSRI: test for trend			0.240
≤ 0.5 DDDs	0.96	0.58 to 1.57	0.857
Others			
> 0.5/≤ 1.0 DDDs	1.04	0.77 to 1.41	0.782
> 1.0 DDDs	1.00	0.63 to 1.60	0.986
Others: test for trend			0.598

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Absolute risk of myocardial infarction

Table 47 shows the absolute risk of MI over 1, 2 and 5 years of treatment by antidepressant class and individual drug. The results by class show that the absolute risks and numbers of extra cases are slightly increased for SSRIs.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in Table 48. For TCAs there were no significant associations during use. The MI rate was significantly increased in the first 28 days after starting an SSRI, but not after 28 days of use. For the group of other antidepressant drugs there was some indication of a reduced risk after 28 days of use. For TCAs, rates were significantly increased in the first 28 days after stopping, and for SSRIs and other antidepressant drugs they were significantly increased in the first 84 days after stopping.

Summary of results for myocardial infarction

Myocardial infarction risk did not differ significantly between the classes of antidepressant drugs, although it was significantly increased for SSRIs compared with no use of antidepressants drugs. Among the most commonly prescribed drugs, only fluoxetine was associated with a significantly increased HR, but overall there were no significant differences between the drugs. MI rates tended to be highest in the first 28 days of starting an SSRI antidepressant and also in the first 28 days after stopping.

TABLE 45 Adjusted HRs for MI by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
1–28 days	0.96	0.65 to 1.42	0.839
29–84 days	0.81	0.51 to 1.26	0.345
85+ days	0.77	0.65 to 0.91	0.003
Stopped 1–28 days	3.74	2.95 to 4.76	<0.001
Stopped 29–84 days	1.87	1.45 to 2.40	<0.001
Stopped 85–182 days	1.07	0.82 to 1.41	0.600
SSRIs			
1–28 days	1.46	1.09 to 1.95	0.012
29–84 days	1.18	0.87 to 1.59	0.288
85+ days	0.71	0.61 to 0.81	<0.001
Stopped 1–28 days	5.97	5.01 to 7.12	<0.001
Stopped 29–84 days	1.82	1.44 to 2.29	<0.001
Stopped 85–182 days	1.02	0.79 to 1.31	0.902
Others			
1–28 days	1.21	0.65 to 2.26	0.555
29–84 days	0.91	0.45 to 1.83	0.794
85+ days	0.63	0.47 to 0.85	0.003
Stopped 1–28 days	4.69	3.04 to 7.23	<0.001
Stopped 29–84 days	2.53	1.59 to 4.04	<0.001
Stopped 85–182 days	0.83	0.41 to 1.66	0.596

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Results of analyses for stroke/transient ischaemic attack

Incidence rates of stroke/transient ischaemic attack

A total of 54,298 patients were included in the analyses of stroke/TIA during follow-up, excluding the 6448 patients who had had a stroke/TIA by the baseline date. During the follow-up period, 5369 (9.9%) of these patients had an incident stroke/TIA, giving a crude incidence rate of 202.3 per 10,000 person-years 95% CI (197.0 to 207.8 per 10,000 person-years). Rates were higher in men than in women and increased with increasing age (*Table 49*).

Stroke/TIA incidence rates by antidepressant class are shown in *Table 50*. These exclude patients who had taken MAOIs during follow-up. The highest rates occurred in patients having combined prescriptions than in patients taking the group of other antidepressant drugs.

Hazard ratios for stroke/transient ischaemic attack

Table 51 shows HRs for stroke/TIA according to antidepressant class. This shows that SSRIs and the group of other antidepressant drugs were associated with significantly increased HRs. There

TABLE 46 Unadjusted and adjusted HRs for MI for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.04	0.88 to 1.23	0.659	1.10	0.93 to 1.31	0.257
Dosulepin hydrochloride (TCA)	0.99	0.82 to 1.20	0.915	1.07	0.88 to 1.29	0.527
Lofepramine (TCA)	1.15	0.85 to 1.57	0.369	1.18	0.86 to 1.61	0.300
Trazodone hydrochloride (TCA)	1.06	0.68 to 1.65	0.784	1.04	0.66 to 1.64	0.864
Citalopram hydrobromide (SSRI)	1.11	0.96 to 1.28	0.164	1.10	0.95 to 1.28	0.198
Escitalopram (SSRI)	1.10	0.75 to 1.61	0.628	1.31	0.89 to 1.93	0.166
Fluoxetine hydrochloride (SSRI)	1.30	1.11 to 1.51	0.001	1.31	1.12 to 1.53	0.001
Paroxetine hydrochloride (SSRI)	1.17	0.96 to 1.43	0.120	1.10	0.90 to 1.36	0.347
Sertraline hydrochloride (SSRI)	0.95	0.73 to 1.25	0.730	0.89	0.67 to 1.19	0.427
Mirtazapine (other)	1.06	0.79 to 1.42	0.698	1.11	0.82 to 1.49	0.494
Venlafaxine hydrochloride (other)	1.04	0.79 to 1.36	0.801	1.04	0.78 to 1.39	0.779

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 47 Absolute and excess risks of MI by antidepressant class and 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	1.00	1.83	4.06			
TCAs	1.09	1.99	4.41	NS	NS	NS
SSRIs	1.15	2.10	4.65	15	27	59
Other antidepressants	1.04	1.90	4.20	NS	NS	NS
Antidepressant drug						
Not currently on antidepressants	1.00	1.83	4.06			
Amitriptyline hydrochloride (TCA)	1.11	2.02	4.47	NS	NS	NS
Dosulepin hydrochloride (TCA)	1.07	1.95	4.32	NS	NS	NS
Lofepramine (TCA)	1.18	2.16	4.77	NS	NS	NS
Trazodone hydrochloride (TCA)	1.04	1.90	4.22	NS	NS	NS
Citalopram hydrobromide (SSRI)	1.11	2.02	4.46	NS	NS	NS
Escitalopram (SSRI)	1.32	2.40	5.29	NS	NS	NS
Fluoxetine hydrochloride (SSRI)	1.31	2.39	5.29	31	56	123
Paroxetine hydrochloride (SSRI)	1.11	2.02	4.47	NS	NS	NS
Sertraline hydrochloride (SSRI)	0.89	1.63	3.62	NS	NS	NS
Mirtazapine (other)	1.11	2.03	4.49	NS	NS	NS
Venlafaxine hydrochloride (other)	1.05	1.91	4.23	NS	NS	NS

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 43.

TABLE 48 Incidence rate ratios for MI by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCAs			
1–28 days	1.19	0.83 to 1.71	0.342
29–84 days	1.11	0.72 to 1.70	0.634
85+ days	0.87	0.62 to 1.22	0.430
Stopped 1–28 days	2.49	1.87 to 3.33	<0.001
Stopped 29–84 days	1.28	0.94 to 1.76	0.123
Stopped 85–182 days	1.14	0.86 to 1.51	0.350
SSRIs			
1–28 days	1.44	1.10 to 1.88	0.008
29–84 days	1.01	0.73 to 1.39	0.955
85+ days	1.03	0.84 to 1.26	0.774
Stopped 1–28 days	3.49	2.80 to 4.34	<0.001
Stopped 29–84 days	1.76	1.38 to 2.24	<0.001
Stopped 85–182 days	1.20	0.93 to 1.55	0.150
Others			
1–28 days	1.11	0.56 to 2.18	0.766
29–84 days	0.55	0.20 to 1.49	0.241
85+ days	0.54	0.32 to 0.93	0.026
Stopped 1–28 days	3.98	2.45 to 6.48	<0.001
Stopped 29–84 days	2.80	1.72 to 4.56	<0.001
Stopped 85–182 days	1.14	0.60 to 2.17	0.679

IRR, incidence rate ratio.

TABLE 49 Incidence rates of stroke/TIA in study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	820	78,380	104.6	97.7 to 112.0
75–84	1662	80,959	205.3	195.7 to 215.4
85+	1126	30,176	373.1	352.0 to 395.6
65+	3608	189,515	190.4	184.3 to 196.7
Men				
65–74	511	33,473	152.7	140.0 to 166.5
75–84	881	32,763	268.9	251.7 to 287.3
85+	369	9659	382.0	345.0 to 423.1
65+	1761	75,895	232.0	221.4 to 243.1
Both sexes				
65–74	1331	111,853	119.0	112.8 to 125.6
75–84	2543	113,722	223.6	215.1 to 232.5
85+	1495	39,835	375.3	356.8 to 394.8
65+	5369	265,410	202.3	197.0 to 207.8

TABLE 50 Incidence rates of stroke/TIA in study cohort by antidepressant class

Antidepressant class	First events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	2811	149,821	187.6	180.8 to 194.7
TCAs	791	40,564	195.0	181.9 to 209.1
SSRIs	1384	60,109	230.3	218.4 to 242.7
Other antidepressants	317	12,391	255.8	229.2 to 285.6
Combination of antidepressants	48	1807	265.7	200.2 to 352.6

TABLE 51 Hazard ratios for stroke/TIA by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCAs	1.01	0.93 to 1.10	0.792	1.02	0.93 to 1.11	0.703
SSRIs	1.19	1.12 to 1.27	<0.001	1.17	1.10 to 1.26	<0.001
Other antidepressants	1.35	1.21 to 1.52	<0.001	1.37	1.22 to 1.55	<0.001
Combination of antidepressants	1.45	1.09 to 1.92	0.011	1.42	1.05 to 1.91	0.022

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

were significant differences between the classes ($p < 0.001$). The HR was highest for combined prescriptions, with a 42% increase in stroke/TIA rate compared with no antidepressant use, and then for the group of other antidepressant drugs in which there was a 37% increase. In a direct comparison with TCAs, the adjusted HRs were 1.15 (95% CI 1.05 to 1.26) for SSRIs and 1.35 (95% CI 1.18 to 1.54) for the group of other antidepressant drugs.

The results of the dose analyses are shown in *Table 52*. This shows little evidence of dose-response relationships.

Table 53 shows the effects of duration of use and time since stopping an antidepressant on stroke/TIA risk. For TCAs there was no association during the first 84 days of use, but the rate of stroke/TIA was significantly reduced from 85 days after starting the drug. For SSRIs the rate was significantly increased in the first 28 days after starting, but was significantly reduced from 85 days after starting. For the group of other antidepressant drugs, the stroke/TIA rate was significantly increased in the first 28 days after starting. The HR was significantly increased in the first 84 days after stopping TCAs, SSRIs and the group of other antidepressant drugs.

There were no significant interactions for stroke/TIA between antidepressant class and age, gender, CHD, hypertension or use of aspirin, NSAIDs, antihypertensive drugs or hypnotics/anxiolytics at baseline.

Table 54 shows the HRs for individual antidepressant drugs. There were significantly increased HRs for citalopram, mirtazapine and venlafaxine (at $p < 0.01$) after adjusting for potential confounding variables. There were significant differences between the drugs ($p < 0.001$), with the highest HRs associated with venlafaxine, where the stroke/TIA rate was increased by 51% compared with no antidepressant use, and mirtazapine, where there was a 38% increase.

TABLE 52 Adjusted HRs for stroke/TIA by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
≤ 0.5 DDDs	0.98	0.88 to 1.09	0.713
> 0.5/≤ 1.0 DDDs	1.03	0.86 to 1.24	0.727
> 1.0 DDDs	1.30	1.01 to 1.68	0.041
Test for trend			0.143
SSRIs			
≤ 0.5 DDDs	1.20	1.03 to 1.39	0.017
> 0.5/≤ 1.0 DDDs	1.14	1.05 to 1.23	0.001
> 1.0 DDDs	1.37	1.17 to 1.62	< 0.001
Test for trend			0.158
Others			
≤ 0.5 DDDs	1.65	1.29 to 2.11	< 0.001
> 0.5/≤ 1.0 DDDs	1.43	1.20 to 1.70	< 0.001
> 1.0 DDDs	1.37	1.04 to 1.80	0.025
Test for trend			0.233

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Absolute risk of stroke/transient ischaemic attack

Table 55 shows the absolute risk of stroke/TIA over 1, 2 and 5 years of treatment and number of extra cases for the significant associations at $p < 0.01$. The results show that the group of other antidepressant drugs is associated with the highest absolute risks and number of extra cases. Of the individual drugs, venlafaxine and mirtazapine are associated with the highest number of additional cases.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in Table 56. There was a reduction in the stroke/TIA rate after the first 84 days of use of TCAs, but this was not significant at $p < 0.01$. For SSRIs, the rate was significantly increased in the first 28 days after starting, but was significantly reduced from 85 days after starting treatment. For the group of other antidepressant drugs, there were no significant associations during drug use. For TCAs and SSRIs, rates were significantly increased in the first 84 days after stopping and for the group of other antidepressant drugs rates were significantly increased in the first 28 days after stopping.

Summary of results for stroke/transient ischaemic attack

Selective serotonin reuptake inhibitors and the group of other antidepressant drugs were associated with a significantly increased stroke/TIA risk compared with no use of antidepressant drugs, but TCAs were not. There was little evidence of a dose-response relationship. Among the most commonly prescribed antidepressant drugs, the highest HRs were associated with venlafaxine and mirtazapine. Rates tended to be highest in the first 28 days of starting an antidepressant and in the first 28 days after stopping. There was an association with a reduced

TABLE 53 Adjusted HRs for stroke/TIA by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCA s			
1–28 days	1.19	0.94 to 1.51	0.148
29–84 days	0.89	0.67 to 1.18	0.422
85+ days	0.78	0.70 to 0.88	<0.001
Stopped 1–28 days	3.05	2.56 to 3.63	<0.001
Stopped 29–84 days	1.58	1.32 to 1.89	<0.001
Stopped 85–182 days	1.09	0.91 to 1.30	0.344
SSRI s			
1–28 days	1.79	1.50 to 2.15	<0.001
29–84 days	1.15	0.94 to 1.42	0.169
85+ days	0.84	0.77 to 0.92	<0.001
Stopped 1–28 days	4.05	3.52 to 4.66	<0.001
Stopped 29–84 days	2.00	1.73 to 2.33	<0.001
Stopped 85–182 days	1.19	1.01 to 1.39	0.034
Others			
1–28 days	1.87	1.33 to 2.64	<0.001
29–84 days	1.49	1.03 to 2.15	0.035
85+ days	0.92	0.77 to 1.09	0.335
Stopped 1–28 days	6.29	4.87 to 8.12	<0.001
Stopped 29–84 days	2.52	1.83 to 3.46	<0.001
Stopped 85–182 days	1.33	0.92 to 1.93	0.134

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 54 Unadjusted and adjusted HRs for stroke/TIA for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.00	0.89 to 1.12	0.980	1.01	0.90 to 1.13	0.901
Dosulepin hydrochloride (TCA)	0.90	0.79 to 1.03	0.124	0.95	0.83 to 1.09	0.487
Lofepamine (TCA)	1.33	1.10 to 1.62	0.004	1.26	1.02 to 1.54	0.028
Trazodone hydrochloride (TCA)	1.34	1.02 to 1.75	0.034	1.10	0.82 to 1.48	0.523
Citalopram hydrobromide (SSRI)	1.25	1.14 to 1.37	<0.001	1.22	1.11 to 1.34	<0.001
Escitalopram (SSRI)	1.07	0.83 to 1.40	0.598	1.21	0.93 to 1.59	0.152
Fluoxetine hydrochloride (SSRI)	1.16	1.04 to 1.29	0.006	1.16	1.03 to 1.29	0.011
Paroxetine hydrochloride (SSRI)	1.10	0.96 to 1.26	0.173	1.08	0.93 to 1.24	0.314
Sertraline hydrochloride (SSRI)	1.29	1.10 to 1.52	0.001	1.22	1.03 to 1.44	0.021
Mirtazapine (other)	1.42	1.19 to 1.68	<0.001	1.38	1.15 to 1.65	<0.001
Venlafaxine hydrochloride (other)	1.45	1.23 to 1.70	<0.001	1.51	1.28 to 1.78	<0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 55 Absolute and excess risks of stroke/TIA by antidepressant class and for 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	2.23	4.04	9.09			
TCA	2.26	4.10	9.23	NS	NS	NS
SSRI	2.61	4.72	10.57	38	68	148
Other antidepressants	3.04	5.49	12.24	81	146	316
Antidepressant drug						
Not currently on antidepressants	2.23	4.04	9.09			
Amitriptyline hydrochloride (TCA)	2.24	4.07	9.15	NS	NS	NS
Dosulepin hydrochloride (TCA)	2.12	3.85	8.67	NS	NS	NS
Lofepramine (TCA)	2.79	5.04	11.27	NS	NS	NS
Trazodone hydrochloride (TCA)	2.45	4.44	9.95	NS	NS	NS
Citalopram hydrobromide (SSRI)	2.71	4.90	10.96	48	86	187
Escitalopram (SSRI)	2.70	4.88	10.93	NS	NS	NS
Fluoxetine hydrochloride (SSRI)	2.57	4.65	10.43	NS	NS	NS
Paroxetine hydrochloride (SSRI)	2.39	4.34	9.74	NS	NS	NS
Sertraline hydrochloride (SSRI)	2.70	4.89	10.95	NS	NS	NS
Mirtazapine (other)	3.06	5.53	12.31	83	149	323
Venlafaxine hydrochloride (other)	3.34	6.03	13.40	112	200	431

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 51.

risk of stroke/TIA for TCAs and SSRIs after 85 days of use. There were some differences in the pattern of risks between the cohort and case-series analyses.

Results of analyses for falls

Incidence rates of falls

A total of 55,767 patients were included in the analyses of falls during follow-up, excluding the 4979 patients who had had a fall by the baseline date. During the follow-up period 11,251 (20.2%) of these patients had an incident fall, giving a crude incidence rate of 436.3 per 10,000 person-years (95% CI 428.3 to 444.4 per 10,000 person-years). Rates were higher in women than in men and increased steeply with increasing age (Table 57).

Falls rates by antidepressant class are shown in Table 58, excluding patients who had taken MAOIs during follow-up. The highest rates occurred in patients having combined prescriptions, followed by patients taking SSRIs.

Hazard ratios for falls

Table 59 shows the HRs for falls according to antidepressant class. This shows significantly increased HRs for all classes of antidepressant drugs, with only small changes after adjusting for potential confounding variables. There were significant differences between the classes ($p < 0.001$). The HR was highest for combined prescriptions, with a 70% increase in falls rate compared with no antidepressant use, and for SSRIs where there was a 66% increase. In a direct comparison with TCAs, there were adjusted HRs of 1.27 (95% CI 1.20 to 1.35) for SSRIs and 1.07 (95% CI 0.97 to 1.17) for the group of other antidepressant drugs.

TABLE 56 Incidence rate ratios for stroke/TIA by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCAs			
1–28 days	1.05	0.83 to 1.34	0.686
29–84 days	1.19	0.93 to 1.53	0.171
85+ days	0.79	0.65 to 0.96	0.020
Stopped 1–28 days	1.73	1.40 to 2.14	<0.001
Stopped 29–84 days	1.35	1.11 to 1.64	0.002
Stopped 85–182 days	1.14	0.95 to 1.36	0.153
SSRIs			
1–28 days	1.38	1.17 to 1.63	<0.001
29–84 days	0.98	0.80 to 1.18	0.806
85+ days	0.68	0.60 to 0.78	<0.001
Stopped 1–28 days	1.79	1.49 to 2.14	<0.001
Stopped 29–84 days	1.42	1.20 to 1.68	<0.001
Stopped 85–182 days	1.16	1.00 to 1.36	0.057
Others			
1–28 days	1.37	0.93 to 2.03	0.114
29–84 days	0.82	0.50 to 1.36	0.450
85+ days	0.87	0.65 to 1.16	0.349
Stopped 1–28 days	2.36	1.62 to 3.43	<0.001
Stopped 29–84 days	1.11	0.71 to 1.73	0.660
Stopped 85–182 days	1.24	0.86 to 1.80	0.250

IRR, incidence rate ratio.

TABLE 57 Incidence rates of falls in study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	1777	76,536	232.2	221.6 to 243.2
75–84	3972	75,358	527.1	511.0 to 543.7
85+	2544	24,836	1024.3	985.3 to 1064.9
65+	8293	176,730	469.3	459.3 to 479.5
Men				
65–74	585	36,174	161.7	149.1 to 175.4
75–84	1502	35,613	421.8	401.0 to 443.6
85+	871	9,385	928.1	868.5 to 991.8
65+	2958	81,172	364.4	351.5 to 377.8
Both sexes				
65–74	2362	112,710	209.6	201.3 to 218.2
75–84	5474	110,971	493.3	480.4 to 506.5
85+	3415	34,221	997.9	965.0 to 1032.0
65+	11251	257,902	436.3	428.3 to 444.4

TABLE 58 Incidence rates of falls in study cohort by antidepressant class

Antidepressant class	Events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	5208	145,407	358.2	348.6 to 368.0
TCA	1704	39,465	431.8	411.8 to 452.8
SSRI	3575	58,600	610.1	590.4 to 630.4
Other antidepressants	631	11,990	526.3	486.8 to 569.0
Combination of antidepressants	117	1716	681.9	568.9 to 817.4

TABLE 59 Hazard ratios for falls by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCA	1.20	1.14 to 1.27	<0.001	1.30	1.23 to 1.38	<0.001
SSRI	1.71	1.64 to 1.79	<0.001	1.66	1.58 to 1.73	<0.001
Other antidepressants	1.45	1.34 to 1.58	<0.001	1.39	1.28 to 1.52	<0.001
Combination of antidepressants	1.80	1.50 to 2.16	<0.001	1.70	1.42 to 2.05	<0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Table 60 shows that the fall rate was significantly increased for all classes at all dose levels, with risk tending to increase as dose increased in all classes.

Table 61 shows the effects of duration of use and time since stopping an antidepressant on fall risk. For TCAs, SSRIs and the group of other antidepressants, the fall rate was highest in the first 28 days after starting treatment. The HRs were significantly increased in the first 84 days after stopping, but not between 85 and 182 days after stopping across all groups.

There was a significant interaction for falls between antidepressant class and gender ($p = 0.002$), with slightly higher HRs for men than women across the classes of antidepressant drugs. There were no other significant interactions for falls.

Table 62 shows the HRs for individual antidepressant drugs. This shows that all antidepressant drugs were associated with significantly increased HRs. There were significant differences between the different drugs ($p < 0.001$). Citalopram, venlafaxine, escitalopram, fluoxetine and sertraline had slightly higher HRs than the other drugs.

Absolute risk of falls

Table 63 shows the absolute risk of falls over 1, 2 and 5 years of treatment. The results show that SSRIs are associated with the highest absolute risks and number of extra cases. For individual drugs, citalopram, venlafaxine, escitalopram, fluoxetine and sertraline are associated with the highest number of extra cases.

TABLE 60 Adjusted HRs for falls by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
≤ 0.5 DDDs	1.26	1.17 to 1.35	<0.001
> 0.5/≤ 1.0 DDDs	1.52	1.35 to 1.70	<0.001
> 1.0 DDDs	1.52	1.27 to 1.82	<0.001
Test for trend			0.003
SSRIs			
≤ 0.5 DDDs	1.49	1.35 to 1.63	<0.001
> 0.5/≤ 1.0 DDDs	1.66	1.57 to 1.74	<0.001
> 1.0 DDDs	1.89	1.71 to 2.09	<0.001
Test for trend			0.001
Others			
≤ 0.5 DDDs	1.33	1.09 to 1.60	0.004
> 0.5/≤ 1.0 DDDs	1.34	1.18 to 1.52	<0.001
> 1.0 DDDs	1.82	1.53 to 2.15	<0.001
Test for trend			0.040

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in *Table 64*. The fall rate was significantly increased during all periods of use for all three classes of antidepressants, with SSRIs having the highest rate ratios. For TCAs, rates were significantly increased in the first 84 days after stopping, but for SSRIs rates remained significantly increased during 182 days after stopping. For the group of other antidepressants, there were no significant increases after stopping.

Summary of results for falls

All classes of antidepressant drug were associated with significant increases in fall risk, compared with no use of antidepressants. The risk varied by antidepressant class, being higher for SSRIs. The risk tended to increase as dose increased in all classes. All of the most commonly prescribed antidepressant drugs were associated with an increased rate of falls, with citalopram, venlafaxine, escitalopram, fluoxetine and sertraline having slightly higher HRs than the other drugs. Fall rates tended to be highest in the first 28 days after starting an antidepressant and also in the first 28 days after stopping.

Results of analyses for fractures

Incidence rates of fractures

A total of 52,907 patients were included in the analyses of fracture during follow-up, excluding the 7839 patients who had had a fracture by the baseline date. During the follow-up period, 5330 (10.1%) of these patients sustained an incident fracture, giving a crude incidence rate of 210.1 per 10,000 person-years (95% CI 204.5 to 215.8 per 10,000 person-years). Rates were higher in women than in men and increased with increasing age (*Table 65*).

TABLE 61 Adjusted HRs for falls by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
1–28 days	1.48	1.26 to 1.75	<0.001
29–84 days	1.16	0.96 to 1.41	0.115
85+ days	1.10	1.03 to 1.19	0.009
Stopped 1–28 days	3.62	3.20 to 4.09	<0.001
Stopped 29–84 days	1.47	1.27 to 1.69	<0.001
Stopped 85–182 days	1.08	0.94 to 1.24	0.266
SSRIs			
1–28 days	2.23	1.97 to 2.52	<0.001
29–84 days	2.20	1.97 to 2.46	<0.001
85+ days	1.38	1.31 to 1.46	<0.001
Stopped 1–28 days	5.03	4.58 to 5.53	<0.001
Stopped 29–84 days	1.47	1.29 to 1.66	<0.001
Stopped 85–182 days	1.09	0.97 to 1.24	0.157
Others			
1–28 days	1.86	1.45 to 2.38	<0.001
29–84 days	1.33	1.01 to 1.76	0.046
85+ days	1.12	1.00 to 1.25	0.051
Stopped 1–28 days	5.23	4.27 to 6.42	<0.001
Stopped 29–84 days	1.71	1.29 to 2.26	<0.001
Stopped 85–182 days	0.84	0.59 to 1.19	0.324

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Fracture rates by antidepressant class are shown in *Table 66*. These exclude patients who had taken MAOIs during follow-up. The highest rates occurred in patients having combined prescriptions.

Hazard ratios for fractures

Table 67 shows HRs for fractures according to antidepressant class. This shows significantly increased HRs for all classes of antidepressant drugs, with only small changes after adjusting for potential confounding variables. There were significant differences between the classes ($p < 0.001$). The HR was highest for combined prescriptions, with more than a doubling of the fracture rate compared with no antidepressant use, and than for the group of other antidepressants, in which there was a 64% increase. In a direct comparison with TCAs, there were adjusted HRs of 1.26 (95% CI 1.15 to 1.37) for SSRIs and 1.31 (95% CI 1.15 to 1.50) for other antidepressants.

The results of the dose analyses (*Table 68*) show that the risk of fracture was significantly increased for all classes at all dose levels, but there was a significant dose-response relationship only for TCAs.

TABLE 62 Unadjusted and adjusted HRs for falls for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.26	1.17 to 1.36	<0.001	1.32	1.22 to 1.42	<0.001
Dosulepin hydrochloride (TCA)	1.06	0.97 to 1.16	0.226	1.24	1.13 to 1.36	<0.001
Lofepramine (TCA)	1.38	1.19 to 1.59	<0.001	1.34	1.15 to 1.55	<0.001
Trazodone hydrochloride (TCA)	1.63	1.36 to 1.96	<0.001	1.55	1.29 to 1.87	<0.001
Citalopram hydrobromide (SSRI)	2.00	1.89 to 2.11	<0.001	1.76	1.66 to 1.86	<0.001
Escitalopram (SSRI)	1.81	1.55 to 2.11	<0.001	1.66	1.42 to 1.94	<0.001
Fluoxetine hydrochloride (SSRI)	1.58	1.48 to 1.70	<0.001	1.64	1.52 to 1.76	<0.001
Paroxetine hydrochloride (SSRI)	1.31	1.19 to 1.44	<0.001	1.45	1.31 to 1.59	<0.001
Sertraline hydrochloride (SSRI)	1.71	1.55 to 1.90	<0.001	1.63	1.46 to 1.81	<0.001
Mirtazapine (other)	1.37	1.21 to 1.56	<0.001	1.19	1.05 to 1.36	0.009
Venlafaxine hydrochloride (other)	1.61	1.44 to 1.80	<0.001	1.68	1.49 to 1.88	<0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 63 Absolute and excess risks of falls by antidepressant class and 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	3.46	6.34	15.54			
TCAs	4.49	8.19	19.75	103	184	421
SSRIs	5.67	10.28	24.38	220	394	884
Other antidepressants	4.79	8.72	20.95	133	238	542
Antidepressant drug						
Not currently on antidepressants	3.46	6.34	15.54			
Amitriptyline hydrochloride (TCA)	4.54	8.27	19.95	108	193	441
Dosulepin hydrochloride (TCA)	4.28	7.80	18.89	81	146	335
Lofepramine (TCA)	4.61	8.40	20.24	115	206	471
Trazodone hydrochloride (TCA)	5.32	9.67	23.05	186	333	751
Citalopram hydrobromide (SSRI)	6.01	10.88	25.68	255	454	1015
Escitalopram (SSRI)	5.70	10.33	24.50	223	399	896
Fluoxetine hydrochloride (SSRI)	5.60	10.16	24.13	214	382	859
Paroxetine hydrochloride (SSRI)	4.97	9.04	21.66	150	270	612
Sertraline hydrochloride (SSRI)	5.57	10.11	24.01	211	377	847
Mirtazapine (other)	4.11	7.51	18.21	65	116	267
Venlafaxine hydrochloride (other)	5.74	10.40	24.65	227	406	911

Note: absolute risks and excess risks are adjusted for confounders listed in Table 59.

TABLE 64 Incidence rate ratios for falls by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCA s			
1–28 days	1.58	1.33 to 1.87	<0.001
29–84 days	1.75	1.46 to 2.11	<0.001
85+ days	1.60	1.39 to 1.85	<0.001
Stopped 1–28 days	1.45	1.20 to 1.74	<0.001
Stopped 29–84 days	1.23	1.05 to 1.44	0.010
Stopped 85–182 days	1.06	0.92 to 1.22	0.442
SSR is			
1–28 days	2.65	2.37 to 2.97	<0.001
29–84 days	3.07	2.75 to 3.42	<0.001
85+ days	2.22	2.03 to 2.42	<0.001
Stopped 1–28 days	1.88	1.62 to 2.18	<0.001
Stopped 29–84 days	1.25	1.07 to 1.44	0.004
Stopped 85–182 days	1.24	1.09 to 1.40	0.001
Others			
1–28 days	2.26	1.71 to 2.98	<0.001
29–84 days	1.60	1.14 to 2.24	0.007
85+ days	1.73	1.40 to 2.15	<0.001
Stopped 1–28 days	1.47	1.00 to 2.16	0.051
Stopped 29–84 days	1.37	0.99 to 1.89	0.058
Stopped 85–182 days	0.94	0.67 to 1.31	0.702

IRR, incidence rate ratio.

TABLE 65 Incidence rates of fracture in study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	1104	72,552	152.2	143.5 to 161.4
75–84	2049	73,702	278.0	266.2 to 290.3
85+	1187	26,402	449.6	424.7 to 475.9
65+	4340	172,657	251.4	244.0 to 259.0
Men				
65–74	291	34,200	85.1	75.9 to 95.5
75–84	457	36,170	126.4	115.3 to 138.5
85+	242	10,700	226.2	199.4 to 256.5
65+	990	81,070	122.1	114.7 to 130.0
Both sexes				
65–74	1395	106,752	130.7	124.0 to 137.7
75–84	2506	109,872	228.1	219.3 to 237.2
85+	1429	37,102	385.2	365.7 to 405.7
65+	5330	253,726	210.1	204.5 to 215.8

TABLE 66 Incidence rates of fractures in the study cohort by antidepressant class

Antidepressant class	Events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	2507	142,664	175.7	169.0 to 182.7
TCA's	809	38,575	209.7	195.8 to 224.7
SSRIs	1597	58,170	274.5	261.4 to 288.3
Other antidepressants	341	11,883	287.0	258.1 to 319.1
Combination of antidepressants	67	1737	385.7	303.6 to 490.1

TABLE 67 Hazard ratios for fractures by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCA's	1.23	1.13 to 1.33	<0.001	1.26	1.16 to 1.37	<0.001
SSRIs	1.61	1.51 to 1.72	<0.001	1.58	1.48 to 1.68	<0.001
Other antidepressants	1.64	1.46 to 1.84	<0.001	1.64	1.46 to 1.84	<0.001
Combination of antidepressants	2.11	1.65 to 2.69	<0.001	2.08	1.62 to 2.66	<0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, falls, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics

TABLE 68 Adjusted HRs for fracture by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCA's			
≤ 0.5 DDDs	1.16	1.04 to 1.28	0.006
> 0.5/≤ 1.0 DDDs	1.40	1.18 to 1.66	<0.001
> 1.0 DDDs	1.59	1.23 to 2.04	<0.001
Test for trend			0.001
SSRIs			
≤ 0.5 DDDs	1.42	1.23 to 1.64	<0.001
SSRIs > 0.5/≤ 1.0 DDDs	1.57	1.46 to 1.69	<0.001
SSRIs > 1.0 DDDs	1.63	1.39 to 1.90	<0.001
Test for trend			0.337
Others			
≤ 0.5 DDDs	1.44	1.10 to 1.89	0.008
Others > 0.5/≤ 1.0 DDDs	1.67	1.41 to 1.98	<0.001
Others > 1.0 DDDs	2.16	1.71 to 2.71	<0.001
Test for trend			0.130

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, falls, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Table 69 shows the effect of duration and time since stopping an antidepressant on fracture rates. For TCAs the fracture rate was highest in the first 28 days after starting and was not significantly increased after 28 days of use. For SSRIs the rate was significantly increased throughout use. For the group of other antidepressant drugs, the fracture rate was highest in the first 28 days after starting the drug, and was still significantly increased after 85 days of use. The rate was significantly increased in the first 84 days after stopping for TCAs, SSRIs and the group of other antidepressant drugs.

There were no significant interactions for fractures.

Table 70 shows the HRs for individual antidepressant drugs. There were significantly increased HRs (at $p < 0.01$) for all antidepressant drugs, except trazodone and escitalopram, after adjusting for potential confounding variables. There were significant differences between the drugs ($p < 0.001$), with venlafaxine, citalopram and sertraline having the highest HRs.

Absolute risk of fracture

Table 71 shows the absolute risk of fracture over 1, 2 and 5 years of treatment and numbers of extra cases for the significant associations at $p < 0.01$. The results by class show that the group of other antidepressant drugs is associated with the highest absolute risks and number of

TABLE 69 Adjusted HRs for fractures by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
1–28 days	1.62	1.28 to 2.04	<0.001
29–84 days	1.19	0.91 to 1.56	0.210
85+ days	1.01	0.91 to 1.13	0.822
Stopped 1–28 days	3.68	3.09 to 4.38	<0.001
Stopped 29–84 days	1.44	1.18 to 1.77	<0.001
Stopped 85–182 days	1.26	1.05 to 1.51	0.015
SSRIs			
1–28 days	1.71	1.40 to 2.09	<0.001
29–84 days	1.76	1.47 to 2.11	<0.001
85+ days	1.29	1.19 to 1.40	<0.001
Stopped 1–28 days	5.68	4.99 to 6.46	<0.001
Stopped 29–84 days	1.72	1.45 to 2.04	<0.001
Stopped 85–182 days	1.06	0.89 to 1.27	0.520
Others			
1–28 days	1.83	1.26 to 2.66	0.002
29–84 days	1.45	0.98 to 2.16	0.065
85+ days	1.37	1.18 to 1.59	<0.001
Stopped 1–28 days	6.74	5.18 to 8.77	<0.001
Stopped 29–84 days	1.82	1.23 to 2.70	0.003
Stopped 85–182 days	1.32	0.88 to 1.97	0.180

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, falls, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 70 Unadjusted and adjusted HRs for fractures for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.21	1.08 to 1.35	0.001	1.22	1.09 to 1.36	0.001
Dosulepin hydrochloride (TCA)	1.13	0.99 to 1.28	0.071	1.23	1.07 to 1.40	0.003
Lofepramine (TCA)	1.53	1.26 to 1.87	<0.001	1.46	1.19 to 1.80	<0.001
Trazodone hydrochloride (TCA)	1.01	0.72 to 1.40	0.965	0.97	0.70 to 1.35	0.848
Citalopram hydrobromide (SSRI)	1.78	1.63 to 1.93	<0.001	1.62	1.48 to 1.77	<0.001
Escitalopram (SSRI)	1.40	1.09 to 1.79	0.008	1.29	1.00 to 1.65	0.049
Fluoxetine hydrochloride (SSRI)	1.48	1.33 to 1.64	<0.001	1.58	1.42 to 1.75	<0.001
Paroxetine hydrochloride (SSRI)	1.34	1.17 to 1.53	<0.001	1.46	1.27 to 1.68	<0.001
Sertraline hydrochloride (SSRI)	1.70	1.46 to 1.97	<0.001	1.60	1.37 to 1.87	<0.001
Mirtazapine (other)	1.57	1.32 to 1.87	<0.001	1.46	1.23 to 1.74	<0.001
Venlafaxine hydrochloride (other)	1.77	1.52 to 2.06	<0.001	1.87	1.60 to 2.19	<0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, falls, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 71 Absolute and excess risks of fractures by antidepressant class and for 11 antidepressant drugs

Antidepressant class	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Not currently on antidepressants	1.76	3.26	8.06			
TCAs	2.18	4.03	9.90	42	77	184
SSRIs	2.74	5.05	12.31	98	179	425
Other antidepressants	2.85	5.26	12.79	109	200	473
Antidepressant drug						
Not currently on antidepressants	1.76	3.26	8.06			
Amitriptyline hydrochloride (TCA)	2.14	3.96	9.72	38	69	166
Dosulepin hydrochloride (TCA)	2.15	3.99	9.80	40	73	174
Lofepramine (TCA)	2.56	4.73	11.56	80	147	350
Trazodone hydrochloride (TCA)	1.70	3.16	7.81	NS	NS	NS
Citalopram hydrobromide (SSRI)	2.83	5.23	12.71	107	196	465
Escitalopram (SSRI)	2.26	4.18	10.25	NS	NS	NS
Fluoxetine hydrochloride (SSRI)	2.76	5.10	12.42	100	184	436
Paroxetine hydrochloride (SSRI)	2.56	4.74	11.57	80	147	351
Sertraline hydrochloride (SSRI)	2.80	5.17	12.58	104	191	452
Mirtazapine (other)	2.56	4.74	11.57	80	147	351
Venlafaxine hydrochloride (other)	3.26	6.01	14.53	150	275	647

Note: absolute risks and excess risks are adjusted for confounders listed in Table 67.

extra cases. Among the individual drugs, venlafaxine is associated with the highest number of additional cases.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in *Table 72*. For TCAs, the rates were significantly increased during the first 84 days of use, but not after 85 days. Rates were increased throughout all periods of SSRI use. For the group of other antidepressant drugs, rates were significantly increased only from 85 days after starting treatment. Rates decreased with time after stopping TCAs and SSRIs, but remained elevated for other antidepressant drugs.

Summary of results for fractures

All classes of antidepressant drug were associated with a significantly increased fracture risk, compared with no use of antidepressant drugs. The risk varied by antidepressant class, being higher for SSRIs and the group of other antidepressant drugs than for with TCAs; however, there was a significant dose-response relationship only for TCAs. All of the most commonly prescribed antidepressant drugs, except trazodone and escitalopram, were associated with an increased fracture risk, with venlafaxine, citalopram and sertraline having the highest rates. Rates tended to be highest in the first 28 days of starting an antidepressant and also in the first 28 days after stopping.

TABLE 72 Incidence rate ratios for fractures by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCAs			
1–28 days	1.64	1.31 to 2.05	<0.001
29–84 days	1.70	1.33 to 2.17	<0.001
85+ days	1.19	0.97 to 1.46	0.098
Stopped 1–28 days	1.63	1.27 to 2.09	<0.001
Stopped 29–84 days	1.20	0.96 to 1.51	0.108
Stopped 85–182 days	1.27	1.06 to 1.53	0.011
SSRIs			
1–28 days	1.52	1.25 to 1.83	<0.001
29–84 days	1.98	1.66 to 2.35	<0.001
85+ days	1.69	1.49 to 1.92	<0.001
Stopped 1–28 days	1.71	1.39 to 2.12	<0.001
Stopped 29–84 days	1.29	1.06 to 1.57	0.011
Stopped 85–182 days	1.02	0.85 to 1.24	0.800
Others			
1–28 days	1.71	1.12 to 2.62	0.014
29–84 days	1.22	0.73 to 2.02	0.447
85+ days	1.63	1.22 to 2.17	0.001
Stopped 1–28 days	1.78	1.08 to 2.94	0.025
Stopped 29–84 days	1.17	0.71 to 1.93	0.545
Stopped 85–182 days	1.87	1.32 to 2.65	<0.001

IRR, incidence rate ratio.

Results of analyses for upper gastrointestinal bleeding

Incidence rates of upper gastrointestinal bleeding

A total of 59,495 patients were included in the analyses of upper GI bleeding during follow-up, excluding the 1251 patients who had had an upper GI bleed by the baseline date. During the follow-up period, 1365 (2.29%) of these patients had an incident upper GI bleed, giving a crude incidence rate of 46.0 per 10,000 person-years (95% CI 43.6 to 48.5 per 10,000 person-years). Rates were higher in men than in women and increased with increasing age (*Table 73*).

Upper GI bleed incidence rates by antidepressant class are shown in *Table 74*. These exclude patients who had taken MAOIs during follow-up. The highest rate occurred in patients having combined prescriptions.

Hazard ratios for upper gastrointestinal bleed

Table 75 shows HRs for upper GI bleed according to antidepressant class. This shows significantly increased HRs for TCAs, SSRIs and the group of other antidepressant drugs, with only small changes after adjusting for potential confounding variables. There were no significant differences between the classes ($p = 0.74$). In a direct comparison with TCAs, the adjusted HRs were 0.95 (95% CI 0.80 to 1.12) for SSRIs and 1.06 (95% CI 0.82 to 1.38) for the group of other antidepressant drugs.

TABLE 73 Incidence rates of upper GI bleeding in the study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	186	82,928	22.4	19.4 to 25.9
75–84	368	90,554	40.6	36.7 to 45.0
85+	258	35,732	72.2	63.9 to 81.6
65+	812	209,213	38.8	36.2 to 41.6
Men				
65–74	158	37,113	42.6	36.4 to 49.8
75–84	258	38,745	66.6	58.9 to 75.2
85+	137	11,658	117.5	99.4 to 138.9
65+	553	87,516	63.2	58.1 to 68.7
Both sexes				
65–74	344	120,041	28.7	25.8 to 31.9
75–84	626	129,298	48.4	44.8 to 52.4
85+	395	47,390	83.4	75.5 to 92.0
65+	1365	296,729	46.0	43.6 to 48.5

TABLE 74 Incidence rates of upper GI bleed in study cohort by antidepressant class

Antidepressant class	Events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	671	166,182	40.4	37.4 to 43.6
TCAs	229	44,746	51.2	45.0 to 58.3
SSRIs	365	68,803	53.1	47.9 to 58.8
Other antidepressants	79	14,105	56.0	44.9 to 69.8
Combination of antidepressants	14	2086	67.1	39.8 to 113.4

Table 76 shows that although the risk of upper GI bleed was significantly increased for some dose categories; there were no significant trends with dose.

Table 77 shows the effects of duration of use and time since stopping an antidepressant. For TCAs the upper GI bleed rate was significantly increased in the first 28 days after starting, but not during the remaining period of use. The HR was also significantly increased in the first 84 days after stopping TCAs, but not between 85 and 182 days after stopping. The HR was significantly increased in the first 28 days after stopping SSRIs, but not for the remaining period after stopping.

TABLE 75 Hazard ratios for upper GI bleed by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCAs	1.21	1.04 to 1.41	0.014	1.29	1.10 to 1.51	0.002
SSRIs	1.27	1.11 to 1.44	<0.001	1.22	1.07 to 1.40	0.004
Other antidepressants	1.36	1.08 to 1.72	0.009	1.37	1.08 to 1.74	0.010
Combination of antidepressants	1.63	0.96 to 2.76	0.072	1.44	0.82 to 2.56	0.208

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 76 Adjusted HRs for upper GI bleed by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
≤ 0.5 DDDs	1.23	1.01 to 1.49	0.042
> 0.5/≤ 1.0 DDDs	1.69	1.25 to 2.28	0.001
> 1.0 DDDs	0.45	0.19 to 1.09	0.077
Test for trend			0.428
SSRIs			
≤ 0.5 DDDs	1.45	1.10 to 1.91	0.007
> 0.5/≤ 1.0 DDDs	1.19	1.01 to 1.39	0.033
> 1.0 DDDs	1.21	0.87 to 1.70	0.263
Test for trend			0.482
Others			
≤ 0.5 DDDs	1.01	0.54 to 1.90	0.964
> 0.5/≤ 1.0 DDDs	1.53	1.10 to 2.14	0.012
> 1.0 DDDs	1.56	0.95 to 2.57	0.078
Test for trend			0.185

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 77 Adjusted HRs for upper GI bleed by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
1–28 days	1.92	1.29 to 2.85	0.001
29–84 days	1.22	0.73 to 2.03	0.443
85+ days	0.92	0.74 to 1.15	0.476
stopped 1–28 days	4.03	2.92 to 5.56	<0.001
stopped 29–84 days	2.00	1.42 to 2.82	<0.001
stopped 85–182 days	1.26	0.87 to 1.81	0.218
SSRIs			
1–28 days	1.58	1.09 to 2.29	0.017
29–84 days	1.25	0.84 to 1.86	0.266
85+ days	0.97	0.82 to 1.16	0.760
Stopped 1–28 days	4.73	3.62 to 6.18	<0.001
Stopped 29–84 days	1.49	1.05 to 2.12	0.026
Stopped 85–182 days	1.28	0.93 to 1.77	0.130
Others			
1–28 days	1.71	0.85 to 3.46	0.135
29–84 days	0.62	0.20 to 1.92	0.403
85+ days	1.28	0.95 to 1.71	0.102
Stopped 1–28 days	4.60	2.53 to 8.36	<0.001
Stopped 29–84 days	1.62	0.72 to 3.63	0.241
Stopped 85–182 days	1.46	0.69 to 3.09	0.318

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

For the group of other antidepressant drugs, the upper GI bleed rate was significantly increased only in the first 28 days after stopping medication, but not in the other time periods.

There were no significant interactions for upper GI bleed.

Table 78 shows the HRs for upper GI bleed for individual antidepressant drugs. There were significantly ($p < 0.01$) increased HRs for venlafaxine, amitriptyline and citalopram after adjusting for potential confounding variables; however, there were no significant differences between the different drugs overall ($p = 0.44$). Although trazodone had the highest HR, it was not significant at $p < 0.01$.

Absolute risk of upper gastrointestinal bleed

Table 79 shows the absolute risk of upper GI bleed over 1, 2 and 5 years of treatment and the number of extra cases for the significant associations at $p < 0.01$. The results show similar absolute risks and the number of extra cases for the three classes of antidepressant drugs. Among the

TABLE 78 Unadjusted and adjusted HRs for upper GI bleed for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.30	1.06 to 1.60	0.011	1.38	1.11 to 1.70	0.003
Dosulepin hydrochloride (TCA)	1.08	0.84 to 1.39	0.527	1.21	0.93 to 1.56	0.152
Lofepramine (TCA)	1.24	0.82 to 1.87	0.302	1.21	0.79 to 1.85	0.387
Trazodone hydrochloride (TCA)	1.90	1.20 to 2.99	0.006	1.79	1.12 to 2.87	0.015
Citalopram hydrobromide (SSRI)	1.41	1.19 to 1.69	<0.001	1.34	1.12 to 1.61	0.001
Escitalopram (SSRI)	1.13	0.68 to 1.89	0.631	1.07	0.62 to 1.86	0.811
Fluoxetine hydrochloride (SSRI)	1.15	0.93 to 1.43	0.202	1.15	0.92 to 1.44	0.217
Paroxetine hydrochloride (SSRI)	1.24	0.95 to 1.61	0.108	1.15	0.87 to 1.53	0.329
Sertraline hydrochloride (SSRI)	1.08	0.77 to 1.53	0.660	1.04	0.73 to 1.49	0.825
Mirtazapine (other)	1.09	0.73 to 1.61	0.681	1.05	0.71 to 1.56	0.809
Venlafaxine hydrochloride (other)	1.67	1.24 to 2.26	0.001	1.71	1.26 to 2.33	0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 79 Absolute and excess risks of upper GI bleed by antidepressant class and for 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	0.42	0.78	2.02			
TCAs	0.54	1.00	2.60	12	22	58
SSRIs	0.51	0.95	2.46	9	17	44
Other antidepressants	0.57	1.06	2.76	15	29	74
Antidepressant drug						
Not currently on antidepressants	0.42	0.78	2.02			
Amitriptyline hydrochloride (TCA)	0.58	1.07	2.77	16	29	75
Dosulepin hydrochloride (TCA)	0.51	0.94	2.44	NS	NS	NS
Lofepramine (TCA)	0.51	0.94	2.44	NS	NS	NS
Trazodone hydrochloride (TCA)	0.75	1.39	3.60	NS	NS	NS
Citalopram hydrobromide (SSRI)	0.56	1.04	2.71	14	27	69
Escitalopram (SSRI)	0.45	0.83	2.16	NS	NS	NS
Fluoxetine hydrochloride (SSRI)	0.48	0.89	2.33	NS	NS	NS
Paroxetine hydrochloride (SSRI)	0.48	0.89	2.33	NS	NS	NS
Sertraline hydrochloride (SSRI)	0.44	0.81	2.11	NS	NS	NS
Mirtazapine (other)	0.44	0.82	2.12	NS	NS	NS
Venlafaxine hydrochloride (other)	0.72	1.33	3.44	30	55	142

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 75.

individual drugs, venlafaxine is associated with the highest numbers of additional cases of upper GI bleed compared with no treatment.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in *Table 80*. The upper GI bleed rate was significantly increased ($p < 0.01$) for TCAs during the first 28 days of use and marginally for the remaining period of use ($p < 0.05$). The rates were significantly increased throughout use for SSRIs. The rates were significantly increased after 85 days of use for the group of other antidepressant drugs. For all three classes, the rates were significantly increased in the first 28 days after stopping then decreased with time, with no significant increase between 85 and 182 days after stopping for TCAs and after 28 days for SSRIs and other antidepressant drugs.

Summary of results for upper gastrointestinal bleeding

All classes of antidepressant drug were associated with a significantly increased risk of upper GI bleeding compared with no use of antidepressant drugs, with no significant differences in risk between the classes. There was no evidence of a dose–response relationship in any class. There were no significant differences between the most commonly prescribed antidepressant drugs. Rates tended to be highest in the first 28 days of starting an antidepressant. Rates were also increased in the first 28 days after stopping for all classes, but were no longer increased after 85 days.

TABLE 80 Incidence rate ratios for upper GI bleed by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCAs			
1–28 days	2.92	2.05 to 4.15	<0.001
29–84 days	1.73	1.05 to 2.86	0.033
85+ days	1.48	1.00 to 2.18	0.049
Stopped 1–28 days	2.16	1.40 to 3.34	0.001
Stopped 29–84 days	1.90	1.31 to 2.76	0.001
Stopped 85–182 days	1.14	0.77 to 1.69	0.517
SSRIs			
1–28 days	1.96	1.40 to 2.75	<0.001
29–84 days	1.81	1.27 to 2.60	0.001
85+ days	1.46	1.12 to 1.90	0.005
Stopped 1–28 days	2.61	1.86 to 3.67	<0.001
Stopped 29–84 days	1.38	0.94 to 2.02	0.098
Stopped 85–182 days	1.33	0.95 to 1.85	0.095
Others			
1–28 days	2.24	1.14 to 4.40	0.019
29–84 days	1.41	0.56 to 3.53	0.467
85+ days	2.21	1.26 to 3.90	0.006
Stopped 1–28 days	2.75	1.27 to 5.95	0.010
Stopped 29–84 days	1.02	0.37 to 2.77	0.975
Stopped 85–182 days	1.46	0.71 to 3.02	0.304

IRR, incidence rate ratio.

Results of analyses for epilepsy/seizures

Incidence rates of epilepsy/seizures

A total of 59,793 patients were included in the analyses of incident epilepsy/seizures during follow-up, excluding the 953 patients who had recorded diagnoses of epilepsy/seizures by the baseline date. During the follow-up period, 505 (0.84%) of these patients had incident epilepsy/seizures, giving a crude incidence rate of 16.9 per 10,000 person-years (95% CI 15.5 to 18.4 per 10,000 person-years). The rates were higher in men than in women and increased slightly with increasing age (*Table 81*).

Epilepsy/seizures incidence rates by antidepressant class are shown in *Table 82*. These rates exclude patients who had taken MAOIs during follow-up. The highest epilepsy/seizure rates occurred in patients having combined prescriptions, followed by patients taking the group of other antidepressant drugs or SSRIs.

Hazard ratios for epilepsy/seizures

Table 83 shows the HRs for epilepsy/seizures according to antidepressant class. This shows significantly increased HRs for SSRIs and the group of other antidepressant drugs after adjustment for potential confounding variables. There were significant differences between the

TABLE 81 Incidence rates of epilepsy/seizures in study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	107	82,887	12.9	10.7 to 15.6
75–84	129	91,127	14.2	11.9 to 16.8
85+	66	36,491	18.1	14.2 to 23.0
65+	302	210,505	14.4	12.8 to 16.1
Men				
65–74	74	37,342	19.8	15.8 to 24.9
75–84	98	39,601	24.8	20.3 to 30.2
85+	31	12,060	25.7	18.1 to 36.6
65+	203	89,004	22.8	19.9 to 26.2
Both sexes				
65–74	181	120,229	15.1	13.0 to 17.4
75–84	227	130,728	17.4	15.3 to 19.8
85+	97	48,551	20.0	16.4 to 24.4
65+	505	299,508	16.9	15.5 to 18.4

TABLE 82 Incidence rates of epilepsy/seizures in study cohort by antidepressant class

Antidepressant class	Events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	223	176,455	12.6	11.1 to 14.4
TCAs	58	41,623	13.9	10.8 to 18.0
SSRIs	177	65,074	27.2	23.5 to 31.5
Other antidepressants	39	13,498	28.9	21.1 to 39.6
Combination of antidepressants	8	2069	38.7	19.3 to 77.3

classes ($p < 0.001$). In a direct comparison with TCAs, there were adjusted HRs of 1.80 (95% CI 1.32 to 2.43) for SSRIs and 2.20 (95% CI 1.46 to 3.30) for the group of other antidepressant drugs.

Table 84 shows that the risk of epilepsy/seizures was significantly increased for SSRIs and the group of other antidepressant drugs at dose levels above 0.5 DDDs. There was a significant trend with increasing dose for SSRIs and TCAs, but not for the group of other antidepressant drugs.

Table 85 shows the effects of duration of use and time since stopping an antidepressant on epilepsy/seizures risk. The epilepsy/seizures rate was increased in the first 28 days after starting

TABLE 83 Hazard ratios for epilepsy/seizures by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Not currently on antidepressants	1.00			1.00		
TCAs	0.99	0.74 to 1.32	0.921	1.02	0.76 to 1.38	0.892
SSRIs	1.98	1.62 to 2.43	<0.001	1.83	1.49 to 2.26	<0.001
Other antidepressants	2.32	1.67 to 3.24	<0.001	2.24	1.60 to 3.15	<0.001
Combination of antidepressants	3.13	1.54 to 6.35	0.002	2.61	1.23 to 5.55	0.013

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, hypnotics/anxiolytics.

TABLE 84 Adjusted HRs for epilepsy/seizures by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	<i>p</i> -value
Not currently on antidepressants	1.00		
TCAs			
≤ 0.5 DDDs	0.68	0.44 to 1.07	0.094
> 0.5/≤ 1.0 DDDs	1.20	0.65 to 2.21	0.560
> 1.0 DDDs	2.14	1.05 to 4.36	0.036
Test for trend			0.010
SSRIs			
≤ 0.5 DDDs	1.26	0.74 to 2.15	0.789
> 0.5/≤ 1.0 DDDs	1.83	1.43 to 2.35	<0.001
> 1.0 DDDs	3.40	2.29 to 5.05	<0.001
Test for trend			<0.001
Others			
≤ 0.5 DDDs	1.84	0.81 to 4.15	0.144
> 0.5/≤ 1.0 DDDs	2.46	1.53 to 3.94	<0.001
> 1.0 DDDs	3.11	1.64 to 5.89	<0.001
Test for trend			0.331

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, hypnotics/anxiolytics.

TABLE 85 Adjusted HRs for epilepsy/seizures by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
1–28 days	2.31	1.16 to 4.59	0.017
29–84 days	1.20	0.52 to 2.77	0.670
85+ days	0.79	0.51 to 1.22	0.280
Stopped 1–28 days	2.99	1.60 to 5.58	0.001
Stopped 29–84 days	1.06	0.46 to 2.41	0.894
Stopped 85–182 days	2.12	1.27 to 3.54	0.004
SSRIs			
1–28 days	1.40	0.68 to 2.89	0.366
29–84 days	1.75	1.01 to 3.04	0.046
85+ days	1.69	1.31 to 2.17	<0.001
Stopped 1–28 days	8.35	5.81 to 12.00	<0.001
Stopped 29–84 days	1.59	0.88 to 2.88	0.126
Stopped 85–182 days	1.80	1.11 to 2.92	0.017
Others			
1–28 days	4.35	1.91 to 9.91	<0.001
29–84 days	0.59	0.08 to 4.21	0.596
85+ days	1.73	1.08 to 2.75	0.022
Stopped 1–28 days	8.79	4.11 to 18.81	<0.001
Stopped 29–84 days	5.91	2.77 to 12.64	<0.001
Stopped 85–182 days	0.65	0.09 to 4.65	0.668

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives and hypnotics/anxiolytics.

TCAs; however, this was not significant at $p < 0.01$. The HR was significantly increased in the first 28 days and between 85 and 182 days after stopping TCAs, but not between 29 and 84 days after stopping. For SSRIs the epilepsy/seizures rates were significantly increased after 85 days of use. The HR was highest in the first 28 days after stopping SSRIs. For the group of other antidepressant drugs, the epilepsy/seizures rate was significantly increased in the first 28 days after starting the drug and in the first 84 days after stopping, but not from 85 days after stopping.

There were no significant interactions for epilepsy/seizures.

Table 86 shows the HRs for individual antidepressant drugs. This shows significantly ($p < 0.01$) increased HRs for citalopram, paroxetine, sertraline and venlafaxine. There were significant differences between the drugs ($p = 0.003$), with the highest HRs for venlafaxine where there was a threefold increase in the epilepsy/seizures rate compared with no current antidepressant use, and sertraline (2.7-fold increase).

TABLE 86 Unadjusted and adjusted HRs for epilepsy/seizures for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.14	0.77 to 1.67	0.511	1.17	0.79 to 1.74	0.440
Dosulepin hydrochloride (TCA)	0.44	0.22 to 0.85	0.015	0.50	0.26 to 0.98	0.042
Lofepramine (TCA)	1.23	0.61 to 2.50	0.566	1.37	0.67 to 2.79	0.388
Trazodone hydrochloride (TCA)	1.55	0.64 to 3.77	0.332	1.46	0.60 to 3.55	0.406
Citalopram hydrobromide (SSRI)	2.03	1.55 to 2.66	<0.001	1.79	1.35 to 2.36	<0.001
Escitalopram (SSRI)	1.88	0.93 to 3.82	0.080	1.75	0.86 to 3.57	0.123
Fluoxetine hydrochloride (SSRI)	1.58	1.14 to 2.21	0.007	1.49	1.06 to 2.09	0.022
Paroxetine hydrochloride (SSRI)	1.96	1.34 to 2.87	<0.001	2.04	1.38 to 3.01	<0.001
Sertraline hydrochloride (SSRI)	2.96	2.01 to 4.34	<0.001	2.68	1.80 to 3.99	<0.001
Mirtazapine (other)	1.76	1.00 to 3.07	0.049	1.59	0.90 to 2.79	0.110
Venlafaxine hydrochloride (other)	3.00	1.98 to 4.54	<0.001	2.99	1.95 to 4.57	<0.001

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives and hypnotics/anxiolytics.

Absolute risk of epilepsy/seizures

Table 87 shows the absolute risk of epilepsy/seizures over 1, 2 and 5 years of treatment and numbers of extra cases for the significant associations at $p < 0.01$. The results by class show that the group of other antidepressant drugs is associated with the highest absolute risks and number of extra cases. Among the individual drugs, venlafaxine and sertraline are associated with the highest number of additional cases.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in Table 88. The epilepsy/seizure rate was significantly increased for TCAs only during the first 28 days of use and only after 28 days of use for SSRIs. The rate ratios for the group of other antidepressant drugs were not significantly increased throughout use, although CIs were wide. For TCAs and SSRIs, rates were significantly increased in the first 28 days after stopping and then decreased with time. For the group of other antidepressant drugs, rates were highest in the 29–84 days after stopping, but this was not significant at $p < 0.01$.

Summary of results for epilepsy/seizures

The risk of epilepsy/seizures varied by antidepressant class, and was significantly increased for SSRIs, and the group of other antidepressant drugs compared with no current use of antidepressant drugs, but not for TCAs. The risk tended to increase as dose increased in all classes. Among the most commonly prescribed antidepressant drugs, venlafaxine and sertraline were associated with the highest rates. Epilepsy/seizures rates tended to be highest in the first 28 days of starting an antidepressant.

Results of analyses for road traffic accidents

Incidence rates of road traffic accidents

A total of 59,783 patients were included in the analyses of incident RTAs during follow-up, excluding the 963 patients who had had a RTA recorded by the baseline date. During follow-up,

TABLE 87 Absolute and excess risks of epilepsy/seizures by antidepressant class and for 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	0.21	0.39	0.68			
TCA	0.21	0.40	0.69	NS	NS	NS
SSRI	0.38	0.71	1.24	17	32	56
Other antidepressants	0.46	0.87	1.51	26	48	84
Antidepressant drug						
Not currently on antidepressants	0.21	0.39	0.68			
Amitriptyline hydrochloride (TCA)	0.24	0.46	0.79	NS	NS	NS
Dosulepin hydrochloride (TCA)	0.10	0.19	0.34	NS	NS	NS
Lofepramine (TCA)	0.28	0.53	0.93	NS	NS	NS
Trazodone hydrochloride (TCA)	0.30	0.57	0.99	NS	NS	NS
Citalopram hydrobromide (SSRI)	0.37	0.69	1.21	16	30	53
Escitalopram (SSRI)	0.36	0.68	1.18	NS	NS	NS
Fluoxetine hydrochloride (SSRI)	0.31	0.58	1.01	NS	NS	NS
Paroxetine hydrochloride (SSRI)	0.42	0.79	1.38	21	40	70
Sertraline hydrochloride (SSRI)	0.55	1.04	1.80	34	65	113
Mirtazapine (other)	0.33	0.62	1.07	NS	NS	NS
Venlafaxine hydrochloride (other)	0.61	1.16	2.01	41	77	133

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 83.

423 (0.71%) of these patients had a RTA recorded giving a crude incidence rate of 14.2 per 10,000 person-years (95% CI 12.9 to 15.6 per 10,000 person-years). Rates were higher in men than in women and decreased with increasing age (Table 89).

Road traffic accident incidence rates by antidepressant class are shown in Table 90. These rates exclude patients who had taken MAOIs during follow-up. The highest RTA rates occurred in patients having combined prescriptions.

Hazard ratios for road traffic accidents

Table 91 shows the HRs for RTAs according to antidepressant class. There were no significant HRs and no significant differences between the classes ($p=0.62$). In a direct comparison with TCAs, the adjusted HRs were 1.03 (95% CI 0.74 to 1.44) for SSRIs and 0.78 (95% CI 0.43 to 1.40) for other antidepressant drugs.

There was no association between RTAs and either dose of antidepressant or with duration of use, although RTA rates were significantly increased during the first 28 days after stopping TCAs and SSRIs (data not shown).

Table 92 shows the HRs for RTAs for individual antidepressant drugs. This table shows no significant HRs for any of these antidepressant drugs (at $p<0.01$) and there were no significant differences between the different drugs overall ($p=0.33$).

TABLE 88 Incidence rate ratios for epilepsy/seizures by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCAs			
1–28 days	2.65	1.27 to 5.55	0.010
29–84 days	1.69	0.61 to 4.70	0.314
85+ days	1.56	0.78 to 3.13	0.208
Stopped 1–28 days	5.20	2.87 to 9.44	<0.001
Stopped 29–84 days	2.18	1.09 to 4.36	0.028
Stopped 85–182 days	1.48	0.74 to 2.94	0.268
SSRIs			
1–28 days	1.69	0.93 to 3.08	0.083
29–84 days	2.99	1.86 to 4.81	<0.001
85+ days	2.49	1.73 to 3.59	<0.001
Stopped 1–28 days	3.61	2.21 to 5.90	<0.001
Stopped 29–84 days	1.22	0.62 to 2.41	0.568
Stopped 85–182 days	1.37	0.78 to 2.38	0.274
Others			
1–28 days	2.77	0.97 to 7.87	0.057
29–84 days	0.90	0.12 to 6.69	0.921
85+ days	2.06	0.90 to 4.71	0.086
Stopped 1–28 days	1.08	0.15 to 7.91	0.938
Stopped 29–84 days	3.26	1.27 to 8.33	0.014
Stopped 85–182 days	1.53	0.47 to 5.00	0.482

IRR, incidence rate ratio.

TABLE 89 Incidence rates of RTAs in the study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	120	82,565	14.5	12.2 to 17.4
75–84	134	91,131	14.7	12.4 to 17.4
85+	20	36,543	5.5	3.5 to 8.5
65+	274	210,239	13.0	11.6 to 14.7
Men				
65–74	76	37,050	20.5	16.4 to 25.7
75–84	60	39,649	15.1	11.8 to 19.5
85+	13	12,107	10.7	6.2 to 18.5
65+	149	88,806	16.8	14.3 to 19.7
Both sexes				
65–74	196	119,615	16.4	14.3 to 18.9
75–84	194	130,780	14.8	12.9 to 17.1
85+	33	48,650	6.8	4.8 to 9.5
65+	423	299,045	14.2	12.9 to 15.6

TABLE 90 Incidence rates of RTAs in study cohort by antidepressant class

Antidepressant class	Events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	252	167,255	15.1	13.3 to 17.1
TCA	56	45,112	12.4	9.6 to 16.1
SSRI	96	69,506	13.8	11.3 to 16.9
Other antidepressants	15	14,261	10.5	6.3 to 17.5
Combination of antidepressants	4	2099	19.1	7.2 to 50.8

TABLE 91 Hazard ratios for RTAs by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCA	0.83	0.62 to 1.11	0.205	0.86	0.64 to 1.15	0.307
SSRI	0.92	0.72 to 1.16	0.473	0.89	0.70 to 1.13	0.328
Other antidepressants	0.71	0.42 to 1.19	0.189	0.67	0.39 to 1.14	0.140
Combination of antidepressants	1.32	0.49 to 3.55	0.580	1.34	0.50 to 3.60	0.565

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 92 Unadjusted and adjusted HRs for RTAs for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	0.85	0.56 to 1.29	0.453	0.84	0.55 to 1.27	0.412
Dosulepin hydrochloride (TCA)	0.48	0.26 to 0.88	0.018	0.50	0.27 to 0.92	0.027
Lofepramine (TCA)	1.00	0.47 to 2.12	0.995	1.13	0.53 to 2.41	0.744
Trazodone hydrochloride (TCA)	1.36	0.56 to 3.31	0.492	1.53	0.63 to 3.70	0.351
Citalopram hydrobromide (SSRI)	1.07	0.77 to 1.48	0.688	1.01	0.72 to 1.41	0.956
Escitalopram (SSRI)	1.06	0.44 to 2.57	0.901	0.98	0.40 to 2.38	0.958
Fluoxetine hydrochloride (SSRI)	0.77	0.50 to 1.18	0.231	0.70	0.45 to 1.09	0.118
Paroxetine hydrochloride (SSRI)	0.83	0.49 to 1.40	0.480	0.90	0.54 to 1.53	0.709
Sertraline hydrochloride (SSRI)	0.87	0.46 to 1.64	0.670	0.89	0.47 to 1.68	0.727
Mirtazapine (other)	0.46	0.17 to 1.23	0.123	0.45	0.17 to 1.21	0.114
Venlafaxine hydrochloride (other)	0.80	0.40 to 1.62	0.532	0.72	0.34 to 1.53	0.391

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Absolute risk of road traffic accidents

Table 93 shows the absolute risk of having a RTA over 1, 2 and 5 years of treatment. There were no excess risks which were significant at $p < 0.01$. The results show that the absolute risks are low and similar for all classes and individual drugs.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in Table 94. There were no significant associations.

Summary of results for road traffic accidents

Increased risk of RTAs is not associated with any class of antidepressant drug or with any individual drug.

Results of analyses for adverse drug reactions

Incidence rates of adverse drug reactions

A total of 60,275 patients were included in the analyses of ADRs (including bullous eruptions) during follow-up, excluding the 471 patients who had had an ADR recorded by the baseline date. During the follow-up period, 833 (1.38%) of these patients had an incident ADR giving a crude incidence rate of 27.7 per 10,000 person-years (95% CI 25.9 to 29.7 per 10,000 person-years). Rates were higher in women than in men and there was little change with increasing age (Table 95).

Adverse drug reaction incidence rates by antidepressant class are shown in Table 96. These rates exclude patients who had taken MAOIs during follow-up. The highest ADR rates occurred in patients taking SSRIs, followed by patients taking TCAs.

TABLE 93 Absolute and excess risks of RTAs by antidepressant class and for 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	0.16	0.32	0.77			
TCAs	0.13	0.28	0.66	NS	NS	NS
SSRIs	0.14	0.29	0.68	NS	NS	NS
Other antidepressants	0.10	0.21	0.51	NS	NS	NS
Antidepressant drug						
Not currently on antidepressants	0.16	0.32	0.77			
Amitriptyline hydrochloride (TCA)	0.13	0.27	0.65	NS	NS	NS
Dosulepin hydrochloride (TCA)	0.08	0.16	0.39	NS	NS	NS
Lofepramine (TCA)	0.18	0.37	0.88	NS	NS	NS
Trazodone hydrochloride (TCA)	0.24	0.49	1.17	NS	NS	NS
Citalopram hydrobromide (SSRI)	0.16	0.33	0.78	NS	NS	NS
Escitalopram (SSRI)	0.15	0.32	0.75	NS	NS	NS
Fluoxetine hydrochloride (SSRI)	0.11	0.23	0.54	NS	NS	NS
Paroxetine hydrochloride (SSRI)	0.14	0.29	0.70	NS	NS	NS
Sertraline hydrochloride (SSRI)	0.14	0.29	0.69	NS	NS	NS
Mirtazapine (other)	0.07	0.15	0.35	NS	NS	NS
Venlafaxine hydrochloride (other)	0.11	0.23	0.56	NS	NS	NS

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 91.

TABLE 94 Incidence rate ratios for RTAs by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCA s			
1–28 days	0.18	0.02 to 1.26	0.083
29–84 days	1.49	0.64 to 3.48	0.355
85+ days	1.21	0.58 to 2.50	0.613
Stopped 1–28 days	1.74	0.84 to 3.57	0.133
Stopped 29–84 days	0.39	0.12 to 1.21	0.103
Stopped 85–182 days	1.58	0.96 to 2.60	0.070
SSR Is			
1–28 days	1.05	0.51 to 2.15	0.896
29–84 days	1.27	0.64 to 2.52	0.494
85+ days	0.80	0.47 to 1.36	0.410
Stopped 1–28 days	0.73	0.27 to 1.98	0.537
Stopped 29–84 days	0.70	0.31 to 1.60	0.399
Stopped 85–182 days	1.17	0.68 to 1.99	0.575
Others			
1–28 days	1.13	0.15 to 8.35	0.902
29–84 days	0.00	–	0.988
85+ days	1.52	0.37 to 6.25	0.561
Stopped 1–28 days	1.45	0.2 to 10.69	0.716
Stopped 29–84 days	1.70	0.41 to 7.18	0.467
Stopped 85–182 days	1.77	0.54 to 5.86	0.348

IRR, incidence rate ratio.

TABLE 95 Incidence rates of ADRs in the study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	253	83,093	30.5	26.9 to 34.4
75–84	276	90,961	30.3	27.0 to 34.1
85+	107	36,417	29.4	24.3 to 35.5
65+	636	210,472	30.2	28.0 to 32.7
Men				
65–74	82	37,764	21.7	17.5 to 27.0
75–84	84	39,993	21.0	17.0 to 26.0
85+	31	12,175	25.5	17.9 to 36.2
65+	197	89,932	21.9	19.1 to 25.2
Both sexes				
65–74	335	120,857	27.7	24.9 to 30.9
75–84	360	130,955	27.5	24.8 to 30.5
85+	138	48,592	28.4	24.0 to 33.6
65+	833	300,404	27.7	25.9 to 29.7

IRR, incidence rate ratio.

TABLE 96 Incidence rates of ADRs in study cohort by antidepressant class

Antidepressant class	Events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	417	167,913	24.8	22.6 to 27.3
TCAs	139	45,405	30.6	25.9 to 36.2
SSRIs	231	69,890	33.1	29.1 to 37.6
Other antidepressants	37	14,280	25.9	18.8 to 35.8
Combination of antidepressants	5	2123	23.6	9.8 to 56.6

Hazard ratios for adverse drug reactions

Table 97 shows the HRs for ADRs according to antidepressant class. There were no significant HRs for any class of antidepressant drugs after adjusting for potential confounding variables and no significant difference between the classes ($p = 0.60$).

Table 98 shows that the risk of an ADR was not significantly increased for any class at any dose level at $p < 0.01$, although there was some indication of an increase ($p = 0.02$) with high doses of TCAs (> 1.0 DDDs).

Table 99 shows the effects of duration of use and time since stopping an antidepressant on ADR risk. There were significantly increased risks for all classes of antidepressant in the first 28 days after starting and significant decreases in risk for TCAs and SSRIs after 85 days of use. HRs were also significantly increased in the first 28 days after stopping TCAs and SSRIs, but not after 28 days.

There was a significant interaction between antidepressant class and CHD at baseline ($p = 0.008$), with an indication that HRs for TCAs and SSRIs were somewhat higher in people without CHD at baseline, but for the group of other antidepressant drugs the HR was higher for people with CHD at baseline. There were no other significant interactions.

Table 100 shows the HRs for individual antidepressant drugs. There was some evidence of differences between the different drugs ($p = 0.05$), with significantly increased HRs for lofepramine and sertraline after adjusting for potential confounding variables.

Absolute risk of adverse drug reactions

Table 101 shows the absolute risk of ADR over 1, 2 and 5 years of treatment. The absolute risks are low and similar for all classes and individual drugs, except for lofepramine and sertraline, which are associated with the highest numbers of additional cases.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in *Table 102*. ADR rates were significantly increased for all classes of antidepressant in the first 28 days after starting the drugs and remained significantly increased for SSRIs up to 84 days after starting. Rates were significantly increased in the first 28 days after stopping TCAs, but not SSRIs or the group of other drugs.

Summary of results for adverse drug reactions

Adverse drug reaction rates were not associated with any class of antidepressant drug overall, although rates were increased in the first 28 days of starting an antidepressant. Among the most commonly prescribed antidepressant drugs only lofepramine and sertraline were associated with an increased risk of ADRs.

TABLE 97 Hazard ratios for ADRs by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCAs	1.09	0.89 to 1.32	0.407	1.06	0.86 to 1.29	0.596
SSRIs	1.20	1.02 to 1.42	0.030	1.16	0.98 to 1.37	0.087
Other antidepressants	1.00	0.71 to 1.40	0.987	0.95	0.68 to 1.34	0.783
Combination of antidepressants	0.93	0.38 to 2.24	0.865	0.85	0.35 to 2.06	0.723

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 98 Adjusted HRs for ADRs by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
≤ 0.5 DDDs	0.98	0.76 to 1.26	0.885
> 0.5/≤ 1.0 DDDs	0.77	0.46 to 1.27	0.300
> 1.0 DDDs	1.85	1.10 to 3.12	0.020
Test for trend			0.158
SSRIs			
≤ 0.5 DDDs	1.28	0.91 to 1.80	0.162
> 0.5/≤ 1.0 DDDs	1.11	0.91 to 1.35	0.291
> 1.0 DDDs	1.12	0.73 to 1.72	0.600
Test for trend			0.660
Others			
≤ 0.5 DDDs	0.57	0.21 to 1.52	0.258
> 0.5/≤ 1.0 DDDs	1.05	0.65 to 1.71	0.835
> 1.0 DDDs	1.03	0.49 to 2.17	0.945
Test for trend			0.134

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Results of analyses for hyponatraemia

Incidence rates of hyponatraemia

A total of 60,405 patients were included in the analyses of hyponatraemia during follow-up, excluding the 341 patients who had hyponatraemia recorded by the baseline date. During the follow-up period, 1114 (1.84%) of these patients had incident hyponatraemia, giving a crude incidence rate of 37.0 per 10,000 person-years (95% CI 34.9 to 39.2 per 10,000 person-years). The rates were similar in men and women, and increased with increasing age (*Table 103*).

TABLE 99 Adjusted HRs for ADRs by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCA s			
1–28 days	4.13	2.99 to 5.70	<0.001
29–84 days	0.90	0.44 to 1.83	0.767
85+ days	0.45	0.31 to 0.65	<0.001
Stopped 1–28 days	3.59	2.39 to 5.40	<0.001
Stopped 29–84 days	1.34	0.82 to 2.20	0.243
Stopped 85–182 days	1.20	0.77 to 1.86	0.415
SSRI s			
1–28 days	4.86	3.68 to 6.42	<0.001
29–84 days	1.30	0.80 to 2.10	0.286
85+ days	0.68	0.53 to 0.86	0.002
Stopped 1–28 days	2.68	1.76 to 4.07	<0.001
Stopped 29–84 days	1.15	0.71 to 1.86	0.565
Stopped 85–182 days	0.85	0.53 to 1.35	0.482
Others			
1–28 days	3.25	1.77 to 5.95	<0.001
29–84 days	0.61	0.15 to 2.46	0.489
85+ days	0.72	0.45 to 1.14	0.164
Stopped 1–28 days	1.23	0.31 to 4.96	0.768
Stopped 29–84 days	1.18	0.38 to 3.69	0.772
Stopped 85–182 days	0.59	0.15 to 2.38	0.461

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Hyponatraemia incidence rates by antidepressant class are shown in *Table 104*. These rates exclude patients who had taken MAOIs during follow-up. The highest rates occurred in patients taking SSRIs, followed by patients taking combined prescriptions or the group of other antidepressant drugs.

Hazard ratios for hyponatraemia

Table 105 shows the HRs for hyponatraemia according to antidepressant class. There were significant differences between the classes ($p = 0.002$). The only significant adjusted HR was for SSRIs, which was associated with a 52% increase in hyponatraemia rate compared with no antidepressant use. In a direct comparison with TCAs, the adjusted HRs were 1.44 (95% CI 1.19 to 1.75) for SSRIs and 1.21 (95% 0.90 to 1.64) for other antidepressant drugs.

Table 106 shows that the risk of hyponatraemia was significantly increased for SSRIs at lower doses, but decreased as the dose of SSRI increased (test for trend, $p = 0.014$).

TABLE 100 Unadjusted and adjusted HRs for ADRs for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.02	0.77 to 1.35	0.889	0.96	0.72 to 1.27	0.758
Dosulepin hydrochloride (TCA)	0.89	0.64 to 1.24	0.484	0.88	0.63 to 1.24	0.482
Lofepramine (TCA)	2.10	1.43 to 3.09	<0.001	2.11	1.42 to 3.13	<0.001
Trazodone hydrochloride (TCA)	1.06	0.50 to 2.25	0.870	1.05	0.50 to 2.21	0.905
Citalopram hydrobromide (SSRI)	1.22	0.97 to 1.54	0.090	1.12	0.88 to 1.41	0.361
Escitalopram (SSRI)	1.25	0.69 to 2.28	0.467	1.10	0.60 to 2.01	0.755
Fluoxetine hydrochloride (SSRI)	1.20	0.92 to 1.56	0.169	1.19	0.91 to 1.55	0.199
Paroxetine hydrochloride (SSRI)	0.90	0.62 to 1.31	0.574	0.93	0.63 to 1.37	0.730
Sertraline hydrochloride (SSRI)	1.60	1.12 to 2.28	0.010	1.60	1.12 to 2.29	0.010
Mirtazapine (other)	1.12	0.69 to 1.82	0.639	1.02	0.63 to 1.66	0.941
Venlafaxine hydrochloride (other)	0.88	0.53 to 1.47	0.626	0.88	0.52 to 1.47	0.619

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 101 Absolute and excess risks of ADRs by antidepressant class and for 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	0.26	0.45	1.18			
TCAs	0.28	0.47	1.24	NS	NS	NS
SSRIs	0.30	0.52	1.36	NS	NS	NS
Other antidepressants	0.25	0.43	1.12	NS	NS	NS
Antidepressant drug						
Not currently on antidepressants	0.26	0.45	1.18			
Amitriptyline hydrochloride (TCA)	0.25	0.43	1.13	NS	NS	NS
Dosulepin hydrochloride (TCA)	0.23	0.39	1.04	NS	NS	NS
Lofepramine (TCA)	0.55	0.94	2.47	29	49	129
Trazodone hydrochloride (TCA)	0.27	0.47	1.23	NS	NS	NS
Citalopram hydrobromide (SSRI)	0.29	0.50	1.31	NS	NS	NS
Escitalopram (SSRI)	0.29	0.49	1.30	NS	NS	NS
Fluoxetine hydrochloride (SSRI)	0.31	0.53	1.40	NS	NS	NS
Paroxetine hydrochloride (SSRI)	0.24	0.42	1.10	NS	NS	NS
Sertraline hydrochloride (SSRI)	0.42	0.71	1.88	16	27	70
Mirtazapine (other)	0.27	0.45	1.20	NS	NS	NS
Venlafaxine hydrochloride (other)	0.23	0.39	1.03	NS	NS	NS

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 97.

TABLE 102 Incidence rate ratios for ADRs by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCAs			
1–28 days	7.02	5.09 to 9.68	<0.001
29–84 days	2.19	1.15 to 4.19	0.018
85+ days	0.99	0.50 to 1.96	0.973
Stopped 1–28 days	2.14	1.29 to 3.54	0.003
Stopped 29–84 days	1.55	0.96 to 2.52	0.076
Stopped 85–182 days	0.71	0.39 to 1.27	0.243
SSRIs			
1–28 days	7.39	5.62 to 9.72	<0.001
29–84 days	2.36	1.46 to 3.79	<0.001
85+ days	1.57	1.05 to 2.35	0.027
Stopped 1–28 days	1.61	0.96 to 2.70	0.072
Stopped 29–84 days	1.29	0.78 to 2.12	0.316
Stopped 85–182 days	0.97	0.60 to 1.57	0.896
Others			
1–28 days	4.50	2.20 to 9.22	<0.001
29–84 days	0.68	0.09 to 5.00	0.709
85+ days	0.97	0.32 to 2.97	0.962
Stopped 1–28 days	0.92	0.22 to 3.87	0.911
Stopped 29–84 days	1.71	0.60 to 4.89	0.314
Stopped 85–182 days	0.67	0.16 to 2.78	0.583

IRR, incidence rate ratio.

TABLE 103 Incidence rates of hyponatraemia in study cohort by gender and age band

Age band (years)	First events	Person-years	Rate per 10,000 person-years	95% CI
Women				
65–74	159	83,861	19.0	16.2 to 22.2
75–84	404	91,235	44.3	40.2 to 48.8
85+	251	36,064	69.6	61.5 to 78.8
65+	814	211,160	38.6	36.0 to 41.3
Men				
65–74	74	37,949	19.5	15.5 to 24.5
75–84	166	40,005	41.5	35.6 to 48.3
85+	60	12,098	49.6	38.5 to 63.9
65+	300	90,052	33.3	29.8 to 37.3
Both sexes				
65–74	233	121,810	19.1	16.8 to 21.8
75–84	570	131,239	43.4	40.0 to 47.2
85+	311	48,162	64.6	57.8 to 72.2
65+	1114	301,212	37.0	34.9 to 39.2

TABLE 104 Incidence rates of hyponatraemia in study cohort by antidepressant class

Antidepressant class	Events	Person-years	Rate per 10,000 person-years	95% CI
Not currently on antidepressants	503	168,648	29.8	27.3 to 32.6
TCAs	155	45,439	34.1	29.1 to 39.9
SSRIs	383	70,031	54.7	49.5 to 60.5
Other antidepressants	62	14,151	43.8	34.2 to 56.2
Combination of antidepressants	10	2132	46.9	25.2 to 87.2

TABLE 105 Hazard ratios for hyponatraemia by antidepressant class, unadjusted and adjusted for confounders

Antidepressant class	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
TCAs	0.99	0.82 to 1.18	0.875	1.05	0.87 to 1.27	0.580
SSRIs	1.62	1.42 to 1.86	<0.001	1.52	1.33 to 1.75	<0.001
Other antidepressants	1.38	1.06 to 1.80	0.016	1.28	0.98 to 1.67	0.072
Combination of antidepressants	1.48	0.79 to 2.78	0.217	1.38	0.74 to 2.59	0.310

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 106 Adjusted HRs for hyponatraemia by antidepressant class and dose

Antidepressant class and dose category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
≤ 0.5 DDDs	1.01	0.80 to 1.27	0.949
> 0.5/≤ 1.0 DDDs	0.86	0.54 to 1.37	0.530
> 1.0 DDDs	1.49	0.86 to 2.60	0.156
Test for trend			0.442
SSRIs			
≤ 0.5 DDDs	1.95	1.53 to 2.48	<0.001
> 0.5/≤ 1.0 DDDs	1.46	1.25 to 1.71	<0.001
> 1.0 DDDs	1.07	0.71 to 1.61	0.754
Test for trend			0.014
Others			
≤ 0.5 DDDs	1.27	0.71 to 2.25	0.420
> 0.5/≤ 1.0 DDDs	1.45	1.00 to 2.11	0.053
> 1.0 DDDs	1.06	0.53 to 2.13	0.870
Test for trend			0.428

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

Table 107 shows the effects of duration of use and time since stopping an antidepressant on hyponatraemia risk. There were significantly increased risks for all classes of antidepressant in the first 28 days after starting, the risk remained increased for SSRIs between 29 and 84 days after starting, and there were significant decreases in risk for TCAs and SSRIs after 85 days of use. There were increased risks for all classes of antidepressant in the first 28 days after stopping, and the risk remained significantly increased for TCAs between 29 and 84 days after stopping.

There were no significant interactions for hyponatraemia.

Table 108 shows the HRs for individual antidepressant drugs. This shows significantly increased HRs (at $p < 0.01$) for escitalopram, fluoxetine and citalopram after adjusting for potential confounding variables. There were significant differences between the different drugs ($p < 0.001$). The highest HR was for escitalopram (the hyponatraemia rate was doubled compared with no antidepressant use), then fluoxetine (70% increase) and citalopram (65% increase).

Absolute risk of hyponatraemia

Table 109 shows the absolute risk of hyponatraemia over 1, 2 and 5 years of treatment, and numbers of extra cases for the significant associations at $p < 0.01$. The results by class show that

TABLE 107 Adjusted HRs for hyponatraemia by antidepressant class, duration of use and time since stopping

Antidepressant class and duration category	Adjusted ^a		
	HR	95% CI	p-value
Not currently on antidepressants	1.00		
TCAs			
1–28 days	2.55	1.76 to 3.70	<0.001
29–84 days	0.68	0.32 to 1.44	0.311
85+ days	0.67	0.50 to 0.89	0.005
Stopped 1–28 days	4.14	2.89 to 5.91	<0.001
Stopped 29–84 days	1.80	1.18 to 2.73	0.006
Stopped 85–182 days	0.91	0.56 to 1.46	0.684
SSRIs			
1–28 days	7.72	6.19 to 9.63	<0.001
29–84 days	2.17	1.54 to 3.05	<0.001
85+ days	0.75	0.61 to 0.92	0.006
Stopped 1–28 days	4.20	3.08 to 5.72	<0.001
Stopped 29–84 days	1.22	0.79 to 1.88	0.367
Stopped 85–182 days	1.01	0.68 to 1.50	0.966
Others			
1–28 days	6.33	4.21 to 9.53	<0.001
29–84 days	0.74	0.24 to 2.29	0.597
85+ days	0.62	0.39 to 0.97	0.035
Stopped 1–28 days	4.47	2.31 to 8.67	<0.001
Stopped 29–84 days	1.01	0.32 to 3.15	0.983
Stopped 85–182 days	1.76	0.83 to 3.72	0.139

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 108 Unadjusted and adjusted HRs for hyponatraemia for 11 antidepressant drugs

Antidepressant drug	Unadjusted			Adjusted ^a		
	HR	95% CI	p-value	HR	95% CI	p-value
Not currently on antidepressants	1.00			1.00		
Amitriptyline hydrochloride (TCA)	1.11	0.87 to 1.42	0.382	1.17	0.92 to 1.49	0.211
Dosulepin hydrochloride (TCA)	0.72	0.52 to 1.00	0.054	0.83	0.59 to 1.16	0.268
Lofepramine (TCA)	0.92	0.55 to 1.53	0.739	0.93	0.55 to 1.59	0.791
Trazodone hydrochloride (TCA)	1.73	1.02 to 2.95	0.043	1.51	0.87 to 2.62	0.143
Citalopram hydrobromide (SSRI)	1.96	1.64 to 2.33	<0.001	1.65	1.38 to 1.97	<0.001
Escitalopram (SSRI)	2.48	1.68 to 3.66	<0.001	2.08	1.40 to 3.09	<0.001
Fluoxetine hydrochloride (SSRI)	1.66	1.35 to 2.04	<0.001	1.70	1.38 to 2.09	<0.001
Paroxetine hydrochloride (SSRI)	0.94	0.67 to 1.31	0.696	1.04	0.74 to 1.47	0.823
Sertraline hydrochloride (SSRI)	1.06	0.72 to 1.57	0.761	1.00	0.68 to 1.49	0.986
Mirtazapine (other)	1.37	0.91 to 2.04	0.127	1.06	0.71 to 1.61	0.765
Venlafaxine hydrochloride (other)	1.47	1.01 to 2.12	0.042	1.53	1.06 to 2.22	0.023

a Adjusted for gender, age (5-year bands), year, depression severity, depression before age 65 years, smoking status, Townsend deprivation score, CHD, diabetes, hypertension, stroke, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder, statins, NSAIDs, antipsychotics, aspirin, antihypertensives, anticonvulsants and hypnotics/anxiolytics.

TABLE 109 Absolute and excess risks of hyponatraemia by antidepressant class and for 11 antidepressant drugs

Antidepressant class/drug	Absolute risk (%)			Extra cases per 10,000 treated		
	1 year	2 years	5 years	1 year	2 years	5 years
Antidepressant class						
Not currently on antidepressants	0.29	0.56	1.36			
TCAs	0.30	0.59	1.43	NS	NS	NS
SSRIs	0.44	0.86	2.06	15	29	70
Other antidepressants	0.37	0.72	1.73	NS	NS	NS
Antidepressant drug						
Not currently on antidepressants	0.29	0.56	1.36			
Amitriptyline hydrochloride (TCA)	0.33	0.66	1.59	NS	NS	NS
Dosulepin hydrochloride (TCA)	0.24	0.47	1.12	NS	NS	NS
Lofepramine (TCA)	0.27	0.52	1.27	NS	NS	NS
Trazodone hydrochloride (TCA)	0.43	0.85	2.05	NS	NS	NS
Citalopram hydrobromide (SSRI)	0.47	0.93	2.23	18	36	87
Escitalopram (SSRI)	0.59	1.17	2.80	31	60	144
Fluoxetine hydrochloride (SSRI)	0.49	0.96	2.30	20	39	94
Paroxetine hydrochloride (SSRI)	0.30	0.59	1.41	NS	NS	NS
Sertraline hydrochloride (SSRI)	0.29	0.57	1.36	NS	NS	NS
Mirtazapine (other)	0.31	0.60	1.45	NS	NS	NS
Venlafaxine hydrochloride (other)	0.44	0.86	2.08	NS	NS	NS

NS, not statistically significant.

Note: absolute risks and excess risks are adjusted for confounders listed in Table 105.

SSRIs are associated with the highest absolute risks and numbers of extra cases. For individual drugs, escitalopram is associated with the highest number of additional cases.

Self-controlled case-series analyses

The results of the self-controlled case-series analyses are shown in *Table 110*. The hyponatraemia rates were significantly increased for TCAs and the group of other antidepressant drugs only in the first 28 days after starting the drugs and in the first 28 days after stopping. The SSRIs rates were significantly increased throughout use and remained significantly increased during the first 84 days after stopping.

Summary of results for hyponatraemia

Hyponatraemia risk was significantly associated only with use of SSRIs overall; however, there were increased risks for all classes of antidepressant in the first 28 days after starting the drugs. The risk of hyponatraemia tended to decrease as SSRI dose increased. Among the most commonly prescribed antidepressant drugs, there were significantly increased HRs for escitalopram, fluoxetine and citalopram.

TABLE 110 Incidence rate ratios for hyponatraemia by antidepressant class-risk periods using case-series analysis

Exposure risk period	IRR	95% CI	p-value
Baseline period	1.00		
TCAs			
1–28 days	3.19	2.12 to 4.81	<0.001
29–84 days	1.32	0.64 to 2.71	0.452
85+ days	1.44	0.87 to 2.37	0.160
Stopped 1–28 days	2.16	1.37 to 3.39	0.001
Stopped 29–84 days	1.28	0.78 to 2.08	0.329
Stopped 85–182 days	1.09	0.69 to 1.73	0.706
SSRIs			
1–28 days	13.14	10.59 to 16.29	<0.001
29–84 days	5.97	4.31 to 8.28	<0.001
85+ days	2.09	1.48 to 2.95	<0.001
Stopped 1–28 days	3.88	2.71 to 5.57	<0.001
Stopped 29–84 days	1.84	1.21 to 2.80	0.005
Stopped 85–182 days	1.15	0.75 to 1.78	0.523
Others			
1–28 days	3.63	2.03 to 6.51	<0.001
29–84 days	0.65	0.16 to 2.67	0.550
85+ days	0.78	0.38 to 1.59	0.494
Stopped 1–28 days	2.64	1.29 to 5.43	0.008
Stopped 29–84 days	0.70	0.22 to 2.25	0.549
Stopped 85–182 days	1.28	0.58 to 2.81	0.544

IRR, incidence rate ratio.

Overall summary of results across all outcomes

Table 111 shows the adjusted HRs for all 13 outcomes by antidepressant class. Use of a combination of antidepressant drugs had the highest HRs for many of the outcomes. There were significant differences between the three main classes of antidepressant drugs and their associations with the adverse outcomes for seven of the outcomes. For these outcomes, SSRIs had the highest HRs for falls and hyponatraemia; the group of other antidepressant drugs had the highest HRs for overall mortality, attempted suicide/self-harm, stroke/TIA, fracture and epilepsy/seizures; and TCAs did not have the highest HR for any of the outcomes. The results of complete case analyses where we also adjusted for BMI were very similar. The proportional hazards assumption of the Cox proportional hazards model was reasonable for most outcomes, based on a graphical evaluation, although there was some indication of convergence for stroke/TIA, upper GI bleed and hyponatraemia towards the end of the follow-up period.

Table 112 shows the adjusted HRs for 11 outcomes according to individual antidepressant drugs. There were significant differences between the drugs for seven outcomes; of these, venlafaxine had the highest HR for three outcomes (stroke/TIA, fracture and epilepsy/seizures) and trazodone had the highest HR for one outcome (all-cause mortality), as did citalopram (falls), escitalopram (hyponatraemia) and mirtazapine (attempted suicide). Amitriptyline, dosulepin, fluoxetine, lofepramine, paroxetine and sertraline did not have the highest HRs for any of these seven outcomes. There was some indication ($p=0.05$) of a difference between the drugs for ADRs, with lofepramine having the highest HR for this outcome.

Table 113 shows the number of extra cases per 10,000 patients treated over 1 year for the 13 outcomes according to antidepressant class and individual drug. Overall, the number of extra cases were highest for all-cause mortality, falls, fractures and attempted suicide/self-harm, and generally low for the other outcomes.

TABLE 111 Adjusted HRs for all 13 outcomes according to antidepressant class

Outcome	HRs (95% CI)			
	TCAs	SSRIs	Other antidepressants	Combination of antidepressants
All-cause mortality	1.16 (1.10 to 1.22)	1.54 (1.48 to 1.59)	1.66 (1.56 to 1.77)	1.84 (1.59 to 2.13)
Sudden cardiac death	1.36 (0.73 to 2.53)	1.21 (0.70 to 2.07)	2.25 (1.05 to 4.83)	1.91 (0.26 to 13.92)
Suicide	4.27 (1.56 to 11.70)	4.87 (1.99 to 11.96)	11.29 (4.06 to 31.35)	12.11 (1.48 to 98.81)
Attempted suicide/self-harm	1.70 (1.28 to 2.25)	2.16 (1.71 to 2.71)	5.16 (3.90 to 6.83)	4.15 (2.03 to 8.48)
MI	1.09 (0.96 to 1.23)	1.15 (1.04 to 1.27)	1.04 (0.85 to 1.27)	1.03 (0.62 to 1.72)
Stroke/TIA	1.02 (0.93 to 1.11)	1.17 (1.10 to 1.26)	1.37 (1.22 to 1.55)	1.42 (1.05 to 1.91)
Falls	1.30 (1.23 to 1.38)	1.66 (1.58 to 1.73)	1.39 (1.28 to 1.52)	1.70 (1.42 to 2.05)
Fractures	1.24 (1.14 to 1.35)	1.56 (1.46 to 1.67)	1.63 (1.45 to 1.83)	2.08 (1.63 to 2.66)
Upper GI bleed	1.29 (1.10 to 1.51)	1.22 (1.07 to 1.40)	1.37 (1.08 to 1.74)	1.44 (0.82 to 2.56)
Epilepsy/seizures	1.02 (0.76 to 1.38)	1.83 (1.49 to 2.26)	2.24 (1.60 to 3.15)	2.61 (1.23 to 5.55)
RTAs	0.86 (0.64 to 1.15)	0.89 (0.70 to 1.13)	0.67 (0.39 to 1.14)	1.34 (0.50 to 3.60)
ADRs	1.06 (0.86 to 1.29)	1.16 (0.98 to 1.37)	0.95 (0.68 to 1.34)	0.85 (0.35 to 2.06)
Hyponatraemia	1.05 (0.87 to 1.27)	1.52 (1.33 to 1.75)	1.28 (0.98 to 1.67)	1.38 (0.74 to 2.59)

TABLE 112 Adjusted HRs for 11 outcomes according to antidepressant drug

Outcome	TCAs				SSRIs				Other class				p-value ^a
	Amitriptyline	Dosulepin	Lofepramine	Trazodone	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Mirtazapine	Venlafaxine		
All-cause mortality	1.10 ^b	1.03	1.51 ^b	1.82 ^b	1.55 ^b	1.45 ^b	1.66 ^b	1.24 ^b	1.47 ^b	1.76 ^b	1.66 ^b	<0.001	
Attempted suicide	1.07	1.87 ^b	2.58 ^b	4.70 ^b	2.70 ^b	2.08	2.08 ^b	1.14	2.07 ^b	6.11 ^b	4.60 ^b	<0.001	
MI	1.10	1.07	1.18	1.04	1.10	1.31	1.31 ^b	1.10	0.89	1.11	1.04	0.650	
Stroke/TIA	1.01	0.95	1.26	1.10	1.22 ^b	1.21	1.16	1.08	1.22	1.38 ^b	1.51 ^b	<0.001	
Falls	1.32 ^b	1.24 ^b	1.34 ^b	1.55 ^b	1.76 ^b	1.66 ^b	1.64 ^b	1.45 ^b	1.63 ^b	1.19 ^b	1.68 ^b	<0.001	
Fractures	1.22 ^b	1.23 ^b	1.46 ^b	0.97	1.62 ^b	1.29	1.58 ^b	1.46 ^b	1.60 ^b	1.46 ^b	1.87 ^b	<0.001	
Upper GI bleed	1.38 ^b	1.21	1.21	1.79	1.34 ^b	1.07	1.15	1.15	1.04	1.05	1.71 ^b	0.440	
Epilepsy/seizures	1.17	0.50	1.37	1.46	1.79 ^b	1.75	1.49	2.04 ^b	2.68 ^b	1.59	2.99 ^b	0.003	
RTAs	0.84	0.50	1.13	1.53	1.01	0.98	0.70	0.90	0.89	0.45	0.72	0.330	
ADRs	0.96	0.88	2.11 ^b	1.05	1.12	1.10	1.19	0.93	1.60 ^b	1.02	0.88	0.050	
Hyponatraemia	1.17	0.83	0.93	1.51	1.65 ^b	2.08 ^b	1.70 ^b	1.04	1.00	1.06	1.53	<0.001	

^a The *p*-value from a direct comparison of the 11 drugs.^b *p*<0.01.

TABLE 113 Number of extra cases per 10,000 patients treated over 1 year for the 13 outcomes according to antidepressant class and individual drug

Antidepressant class/drug	Extra cases per 10,000 treated in 1 year compared with no antidepressant use												
	All-cause mortality	Sudden cardiac death	Suicide	Attempted suicide	MI	Stroke/TIA	Falls	Fractures	Upper GI bleed	Epilepsy/seizures	RTAs	ADRs	Hypotonaemia
Antidepressant class													
TCA	109	NS	3	18	NS	NS	103	42	12	NS	NS	NS	NS
SSRI	357	NS	3	29	15	38	220	98	9	15	NS	NS	15
Other antidepressants	439	NS	8	105	NS	81	133	109	15	18	NS	NS	NS
Antidepressant drug													
Amitriptyline hydrochloride	69			NS	NS	NS	108	38	16	NS	NS	NS	NS
Dosulepin hydrochloride	NS			23	NS	NS	81	40	NS	NS	NS	NS	NS
Lofepamine	339			41	NS	NS	115	80	NS	NS	NS	29	NS
Trazodone hydrochloride	540			95	NS	NS	186	NS	NS	NS	NS	NS	NS
Citalopram hydrobromide	365			43	NS	48	255	107	14	16	NS	NS	18
Escitalopram	302			22	NS	NS	223	NS	NS	NS	NS	NS	31
Fluoxetine hydrochloride	439			28	31	NS	214	100	NS	NS	NS	NS	20
Paroxetine hydrochloride	164			NS	NS	NS	150	80	NS	21	NS	NS	NS
Sertraline hydrochloride	316			28	NS	48	211	104	NS	34	NS	16	NS
Mirtazapine	501			131	NS	83	65	80	NS	NS	NS	NS	NS
Venlafaxine hydrochloride	436			92	NS	112	227	150	30	41	NS	NS	NS

NS, not statistically significant at $p < 0.01$.

Results of health economic analyses

Patients

Given the objective of estimating costs for the first 5 years post diagnosis, the exclusion of patients who were diagnosed after 1 January 2004, those who moved practice before 5 years, and those who were initially prescribed more than one type of antidepressant resulted in the identification of 37,268 eligible patients (base-case analysis). When costs were estimated for a 1-year follow-up period data, were available for 58,657 patients (sensitivity analysis).

Levels of resource use

The number of patients (of the 37,268 eligible patients) who were first prescribed each of the 11 most commonly prescribed antidepressant drugs, within 12 months of diagnosis, are shown in *Table 114*. It can be seen that amitriptyline (TCA) was the most commonly first prescribed antidepressant for the 5-year post-diagnosis period based on patients who were diagnosed before 1 January 2004 and who did not move practice within 5 years, with 6231 of the eligible patients initially receiving a prescription for this drug within 12 months of diagnosis. Citalopram was the

TABLE 114 Number of patients first prescribed the antidepressant drug in question and for whom data were available for 5 years post diagnosis

First antidepressant drug prescribed	No. of patients	No. of prescriptions per user		
		Minimum	Maximum	Mean
Not prescribed antidepressants	4811 (8599)	–	–	–
Amitriptyline hydrochloride (TCA)	6231 (8647)	1 (1)	207 (91)	10.53 (3.84)
Dosulepin hydrochloride (TCA)	5143 (6461)	1 (1)	284 (86)	11.93 (4.46)
Lofepamine (TCA)	2123 (2675)	1 (1)	217 (54)	7.08 (3.61)
Trazodone hydrochloride (TCA)	490 (734)	1 (1)	245 (53)	12.64 (5.04)
Citalopram hydrobromide (SSRI)	4654 (10,066)	1 (1)	263 (100)	15.49 (5.96)
Escitalopram (SSRI)	320 (1201)	1 (1)	137 (50)	11.13 (5.29)
Fluoxetine hydrochloride (SSRI)	5576 (9489)	1 (1)	258 (60)	11.51 (4.75)
Paroxetine hydrochloride (SSRI)	3474 (4058)	1 (1)	242 (55)	13.21 (4.93)
Sertraline hydrochloride (SSRI)	1760 (2662)	1 (1)	245 (53)	13.43 (5.35)
Mirtazapine (other)	312 (888)	1 (1)	253 (64)	16.32 (6.31)
Venlafaxine hydrochloride (other)	709 (1033)	1 (1)	402 (92)	17.49 (5.97)
TCAs	14973 (19,737)	1 (1)	284 (91)	11.44 (4.35)
SSRIs	15819 (27,544)	1 (1)	263 (100)	14.54 (5.74)
Other antidepressants	1665 (27,77)	1 (1)	402 (92)	13.94 (5.52)

Figures for 1 year post diagnosis are shown in parentheses.

most commonly first prescribed antidepressant over the 1-year post-diagnosis period, based on patients who were diagnosed before 1 January 2008 and who did not move practice within 1 year. Figures for the remaining antidepressant drugs are also shown in *Table 114*, where it should be noted that 4811 of the eligible patients did not receive any antidepressant prescriptions within the 5-year period.

Patients often received prescriptions for more than one different antidepressant within the first 5 years post diagnosis. *Table 115* shows the total number of prescriptions for all antidepressant drugs for patients initially prescribed each of the 11 antidepressant drugs. For example, patients who were first prescribed amitriptyline (TCA) within 12 months of diagnosis received an average of 18.68 antidepressant prescriptions over 5 years (range 1–407). Looking at *Table 114*, it can be seen that approximately one-half of these prescriptions were for amitriptyline (mean 10.53), which shows that a number of patients who originally started on amitriptyline switched to other antidepressant drugs within the 5-year post-diagnosis period.

The number of visits to practice nurses, community nurses and GPs are shown in *Tables 116–118*. For example, those initially prescribed amitriptyline (TCA) visited the practice nurse on average 13.4 times over the 5-year post-diagnosis period, compared with 5.2 visits to community nurses and 50.9 to GPs. On average, those not prescribed any antidepressant drugs had the fewest GP and practice nurse visits, although this was not always the case for community nurse visits.

Dosage

The estimated weighted-average dose for each type of chemical, across all prescriptions, in both our study data set and for the Prescription Cost Analysis database⁶⁰ are shown in *Table 119*. It can be seen that patients within our study cohort (all of whom were aged ≥ 65 years) received, on average, a slightly lower dose than the mean from the Prescription Cost Analysis database.

TABLE 115 Overall number of all antidepressant prescriptions in the 5-year post-diagnosis period for patients prescribed each drug^a

First antidepressant drug prescribed	No. of antidepressant prescriptions		
	Minimum	Maximum	Mean
Not prescribed antidepressants	—	—	—
Amitriptyline hydrochloride (TCA)	1 (1)	407 (117)	18.68 (4.93)
Dosulepin hydrochloride (TCA)	1 (1)	319 (86)	20.10 (5.53)
Lofepramine (TCA)	1 (1)	264 (54)	18.14 (5.30)
Trazodone hydrochloride (TCA)	1 (1)	245 (66)	23.27 (7.02)
Citalopram hydrobromide (SSRI)	1 (1)	417 (100)	23.32 (7.10)
Escitalopram (SSRI)	1 (1)	145 (50)	18.48 (6.51)
Fluoxetine hydrochloride (SSRI)	1 (1)	389 (81)	19.33 (5.98)
Paroxetine hydrochloride (SSRI)	1 (1)	327 (73)	22.05 (6.12)
Sertraline hydrochloride (SSRI)	1 (1)	245 (53)	21.55 (6.49)
Mirtazapine (other)	1 (1)	253 (67)	25.78 (7.65)
Venlafaxine hydrochloride (other)	1 (1)	402 (92)	26.42 (7.20)
TCAs	1 (1)	407 (117)	19.43 (5.29)
SSRIs	1 (1)	417 (100)	21.33 (6.48)
Other antidepressants	1 (1)	402 (92)	23.90 (6.94)

a Figures for 1 year post diagnosis are shown in parentheses.

TABLE 116 Total number of practice nurse visits within the 5-year post-diagnosis period^a

First antidepressant drug prescribed	Number of practice nurse visits		
	Minimum	Maximum	Mean
Not prescribed antidepressants	0 (0)	177 (115)	9.40 (2.67)
Amitriptyline hydrochloride (TCA)	0 (0)	419 (93)	13.44 (2.81)
Dosulepin hydrochloride (TCA)	0 (0)	249 (89)	10.97 (2.02)
Lofepramine (TCA)	0 (0)	348 (102)	10.28 (1.99)
Trazodone hydrochloride (TCA)	0 (0)	154 (61)	10.14 (2.78)
Citalopram hydrobromide (SSRI)	0 (0)	547 (176)	12.68 (3.06)
Escitalopram (SSRI)	0 (0)	118 (64)	12.37 (2.95)
Fluoxetine hydrochloride (SSRI)	0 (0)	271 (76)	11.30 (2.70)
Paroxetine hydrochloride (SSRI)	0 (0)	227 (73)	10.79 (1.98)
Sertraline hydrochloride (SSRI)	0 (0)	145 (139)	10.39 (2.43)
Mirtazapine (other)	0 (0)	74 (51)	9.82 (2.81)
Venlafaxine hydrochloride (other)	0 (0)	193 (51)	11.47 (2.32)
TCAs	0 (0)	419 (102)	11.86 (2.40)
SSRIs	0 (0)	547 (1.76)	11.51 (2.71)
Other antidepressants	0 (0)	193 (52)	11.10 (2.48)

a Figures for 1 year post diagnosis are shown in parentheses.

However, for simplicity, the mean unit costs were based on the weighted average (at the individual chemical level) within the Prescription Cost Analysis database.⁶⁰ Further justification for this was provided by the fact that the cost/mg does not vary systematically according to dosage⁵² (the cost/mg reduces with dose for some drugs, whereas it increases for others).

TABLE 117 Total number of community nurse visits within the 5-year post-diagnosis period^a

First antidepressant drug prescribed	No. of community nurse visits		
	Minimum	Maximum	Mean
Not prescribed antidepressants	0 (0)	624 (287)	4.24 (1.14)
Amitriptyline hydrochloride (TCA)	0 (0)	578 (172)	5.16 (1.10)
Dosulepin hydrochloride (TCA)	0 (0)	327 (161)	3.97 (0.68)
Lofepamine (TCA)	0 (0)	219 (73)	3.31 (0.69)
Trazodone hydrochloride (TCA)	0 (0)	222 (57)	4.92 (1.38)
Citalopram hydrobromide (SSRI)	0 (0)	565 (227)	5.51 (1.48)
Escitalopram (SSRI)	0 (0)	273 (72)	5.53 (1.17)
Fluoxetine hydrochloride (SSRI)	0 (0)	393 (168)	4.56 (1.15)
Paroxetine hydrochloride (SSRI)	0 (0)	305 (101)	3.36 (0.66)
Sertraline hydrochloride (SSRI)	0 (0)	204 (138)	4.11 (1.02)
Mirtazapine (other)	0 (0)	129 (256)	4.81 (2.11)
Venlafaxine hydrochloride (other)	0 (0)	161 (308)	5.33 (1.59)
TCAs	0 (0)	578 (172)	4.37 (0.88)
SSRIs	0 (0)	565 (227)	4.54 (1.19)
Other antidepressants	0 (0)	257 (308)	4.28 (1.42)

a Figures for 1 year post diagnosis are shown in parentheses.

TABLE 118 Total number of GP visits within the 5-year post-diagnosis period^a

First antidepressant drug prescribed	No. of GP visits		
	Minimum	Maximum	Mean
Not prescribed antidepressants	0 (0)	294 (115)	33.96 (9.30)
Amitriptyline hydrochloride (TCA)	0 (0)	429 (110)	50.92 (13.42)
Dosulepin hydrochloride (TCA)	0 (0)	625 (97)	42.46 (9.37)
Lofepamine (TCA)	0 (0)	283 (105)	42.71 (10.08)
Trazodone hydrochloride (TCA)	0 (0)	291 (96)	48.35 (11.87)
Citalopram hydrobromide (SSRI)	0 (0)	328 (97)	49.22 (9.37)
Escitalopram (SSRI)	1 (0)	230 (90)	54.60 (14.58)
Fluoxetine hydrochloride (SSRI)	0 (0)	528 (136)	44.19 (11.96)
Paroxetine hydrochloride (SSRI)	0 (0)	266 (105)	44.27 (9.78)
Sertraline hydrochloride (SSRI)	0 (0)	413 (84)	45.08 (11.23)
Mirtazapine (other)	0 (0)	222 (118)	50.91 (14.43)
Venlafaxine hydrochloride (other)	0 (0)	277 (88)	48.78 (11.82)
TCAs	0 (0)	625 (144)	45.86 (10.64)
SSRIs	0 (0)	528 (136)	45.23 (12.22)
Other antidepressants	0 (0)	277 (118)	46.73 (12.18)

a Figures for 1 year post diagnosis are shown in parentheses.

Unit costs

The unit cost (per prescription), at the level of the individual chemical, for each of the different antidepressant drugs was extracted from the Prescription Cost Analysis database.⁶⁰ Figures for the 11 most commonly prescribed antidepressant drugs are shown in *Table 120*, where it can be seen that the prescription costs vary between £1.64 [amitriptyline (TCA)] and £39.29 [lofepramine (TCA)] per prescription. In terms of visit costs, Curtis⁶² estimated the unit cost for

TABLE 119 Mean dosage (mg) in the study database compared with the Prescription Cost Analysis database⁶⁰

	Mean prescription dosage (mg) in study database	Mean prescription dosage (mg) in the Prescription Cost Analysis database ⁶⁰
Amitriptyline hydrochloride (TCA)	20.77	21.89
Dosulepin hydrochloride (TCA)	45.37	50.20
Lofepramine (TCA)	70.00	70.00
Trazodone hydrochloride (TCA)	75.15	87.66
Citalopram hydrobromide (SSRI)	17.85	19.92
Escitalopram (SSRI)	10.66	12.45
Fluoxetine hydrochloride (SSRI)	20.02	20.56
Paroxetine hydrochloride (SSRI)	21.02	21.58
Sertraline hydrochloride (SSRI)	61.80	69.42
Mirtazapine (other)	27.79	28.90
Venlafaxine hydrochloride (other)	79.38	95.46

TABLE 120 Unit cost per prescription, as reported in the Prescription Cost Analysis database⁶⁰

	Unit cost per prescription (£)
Amitriptyline hydrochloride (TCA)	1.64
Dosulepin hydrochloride (TCA)	2.90
Lofepramine (TCA)	39.29
Trazodone hydrochloride (TCA)	11.67
Citalopram hydrobromide (SSRI)	1.73
Escitalopram (SSRI)	19.79
Fluoxetine hydrochloride (SSRI)	2.43
Paroxetine hydrochloride (SSRI)	6.89
Sertraline hydrochloride (SSRI)	2.74
Mirtazapine (other)	12.15
Venlafaxine hydrochloride (other)	34.79

a visit to a practice nurse to be £11.00 compared with £36.00 for a GP consultation and £26.00 for a home visit by a community nurse (costs were estimated at 2007–8 financial year levels). These unit costs include salary costs, employers' costs (national insurance and superannuation), qualifications, overheads and travel (if applicable).⁶² Owing to the fact that these costs are estimated to the nearest pound (and not pence), when estimating costs over a 1-year period, pence values are not reported as these are equivalent to zero (discounting means that this is not the case over the 5-year period).

Prescription costs

Mean total prescription costs over the 5-year study period, for the 11 most commonly prescribed antidepressant drugs, were estimated using the prescription numbers and unit costs (as reported in *Tables 114* and *120*, respectively) and are shown in *Table 121*. Amitriptyline (TCA) had the lowest mean cost over the 5-year period (£16.44) and venlafaxine (other) had the highest mean cost (£578.05), and there was wide variation across different patients who were initially prescribed the same drug. Figures for the 1-year post-diagnosis period are also shown in *Table 121*, where it can be seen that the rankings, in terms of lowest (1) to highest (11) cost, are broadly similar to those over a 5-year period.

TABLE 121 Total prescription costs for the drug in question within the 5-year post-diagnosis period^a

Antidepressant drug	Minimum (£)	Maximum (£)	Mean (£)	Ranked cost ^b
Not prescribed antidepressants	–	–	–	
Amitriptyline hydrochloride (TCA)	1.64 (1.64)	319.26 (149.41)	16.44 (6.31)	1 (1)
Dosulepin hydrochloride (TCA)	2.90 (2.90)	747.48 (249.40)	32.98 (12.94)	4 (4)
Lofepamine (TCA)	39.29 (39.29)	7941.47 (2121.85)	268.01 (141.81)	10 (9)
Trazodone hydrochloride (TCA)	11.67 (11.67)	2662.67 (618.77)	141.08 (58.87)	7 (7)
Citalopram hydrobromide (SSRI)	1.73 (1.73)	424.49 (173.31)	25.55 (10.32)	2 (2)
Escitalopram (SSRI)	19.79 (19.79)	2520.27 (989.71)	211.04 (184.81)	9 (10)
Fluoxetine hydrochloride (SSRI)	2.43 (2.43)	585.50 (145.73)	26.72 (11.53)	3 (3)
Paroxetine hydrochloride (SSRI)	6.89 (6.89)	1510.94 (378.93)	85.45 (33.96)	6 (6)
Sertraline hydrochloride (SSRI)	2.74 (2.74)	634.45 (145.44)	35.18 (14.69)	5 (5)
Mirtazapine (other)	12.15 (12.15)	2869.04 (777.78)	188.34 (76.71)	8 (8)
Venlafaxine hydrochloride (other)	34.79 (34.79)	12,827.79 (320.42)	578.05 (207.85)	11 (11)
TCAs	1.64 (1.64)	7,941.47 (2121.85)	74.08 (33.66)	
SSRIs	1.73 (1.73)	2520.27 (989.71)	49.02 (20.89)	
Other antidepressants	3.08 (3.08)	12,827.79 (3200.42)	331.82 (119.59)	

a Figures for 1 year post diagnosis are shown in parentheses.

b 1 = lowest cost, 11 = highest cost.

When the mean total prescription costs for all antidepressant drugs were estimated over the 5- and 1-year post-diagnosis period, it can be seen (*Table 122*) that the rank ordering of lowest (1) to highest (11) cost was broadly similar across the 11 most commonly prescribed antidepressant drugs. When these figures were collated across different classes of antidepressant drugs (TCAs, SSRIs and other antidepressant drugs), the mean cost was estimated to be lowest for SSRIs and highest for other antidepressant drugs.

We assessed whether those patients who changed practices (within the 5-year period) had different costs to those who remained with the same practice for the whole 5-year period. Of those who were otherwise eligible for the base-case analysis, but who changed practices, 5334 had a cost over 1 year, the mean value of which was estimated to be £40.22. Conversely, the 37,268 who were included in the base-case analysis had a mean cost of £35.87 over 1 year.

The total costs associated with practice nurse, community nurse and GP visits are reported in *Tables 123–125*, respectively. It can be seen that total costs for both practice nurse and community nurse visits are broadly comparable, although there is variation across antidepressant drugs. Conversely, GP visit costs are substantially higher, varying between a mean of £1145.35 over 5 years for those who received no antidepressant prescriptions and £1707.58 for those prescribed escitalopram (SSRI).

When the costs associated with practice nurse, community nurse and GP visits were summed, the total visit cost over 5 years varied between an average of £1344.49 for those who received no antidepressant drugs and £1969.39 for those prescribed escitalopram (SSRI) (*Table 126*). There was also wide variation across different patients who were initially prescribed the same drug.

When the total prescription costs for all antidepressant drugs were added to the total visit costs, in order to estimate the overall visit plus prescription cost, of the 11 most commonly prescribed

TABLE 122 Total prescription cost for all antidepressant drugs (within the 5-year post-diagnosis period) for patients prescribed each drug^a

Antidepressant drug	Minimum (£)	Maximum (£)	Mean (£)	Ranked cost
Not prescribed antidepressants	–	–	–	
Amitriptyline hydrochloride (TCA)	1.64 (1.64)	7800.59 (1,599.62)	40.13 (15.34)	1 (1)
Dosulepin hydrochloride (TCA)	2.90 (2.90)	7703.10 (2,719.20)	60.79 (22.49)	2 (2)
Lofepramine (TCA)	39.29 (39.29)	8271.83 (2,121.85)	308.08 (153.09)	10 (10)
Trazodone hydrochloride (TCA)	11.67 (11.67)	2662.67 (1,415.31)	196.10 (80.48)	7 (7)
Citalopram hydrobromide (SSRI)	1.73 (1.73)	10,406.06 (1,599.62)	69.11 (24.29)	3 (3)
Escitalopram (SSRI)	19.79 (19.79)	3101.71 (989.71)	249.58 (116.98)	8 (9)
Fluoxetine hydrochloride (SSRI)	2.43 (2.43)	4644.71 (1,867.28)	69.34 (25.92)	4 (4)
Paroxetine hydrochloride (SSRI)	6.89 (6.89)	10,448.22 (1,302.64)	135.07 (48.04)	6 (6)
Sertraline hydrochloride (SSRI)	2.74 (2.74)	2441.36 (1,466.55)	75.48 (30.14)	5 (5)
Mirtazapine (other)	12.15 (12.15)	2869.04 (1,589.73)	251.44 (94.25)	9 (8)
Venlafaxine hydrochloride (other)	34.79 (34.79)	12,827.79 (3,200.42)	602.81 (216.35)	11 (11)
TCAs	1.64 (1.64)	8271.83 (2,719.20)	95.98 (40.75)	
SSRIs	1.73 (1.73)	10,448.22 (1,867.28)	88.22 (33.08)	
Other antidepressants	3.08 (3.08)	12,827.79 (3,200.42)	359.26 (128.84)	

^a Figures for 1 year post diagnosis are shown in parentheses.

TABLE 123 Total costs associated with practice nurse visits within the 5-year post-diagnosis period^a

Antidepressant drug	Total costs associated with practice nurse visits		
	Minimum (£)	Maximum (£)	Mean (£)
Not prescribed antidepressants	0 (0)	1841.81 (1265)	96.49 (29.24)
Amitriptyline hydrochloride (TCA)	0 (0)	4236.66 (1023)	137.60 (30.96)
Dosulepin hydrochloride (TCA)	0 (0)	2523.37 (979)	112.25 (22.21)
Lofepramine (TCA)	0 (0)	3607.07 (1122)	105.05 (21.94)
Trazodone hydrochloride (TCA)	0 (0)	1545.66 (671)	103.86 (30.53)
Citalopram hydrobromide (SSRI)	0 (0)	5716.46 (1936)	130.35 (33.61)
Escitalopram (SSRI)	0 (0)	1191.42 (704)	127.41 (32.46)
Fluoxetine hydrochloride (SSRI)	0 (0)	2790.60 (836)	115.97 (29.67)
Paroxetine hydrochloride (SSRI)	0 (0)	2371.77 (803)	110.46 (21.75)
Sertraline hydrochloride (SSRI)	0 (0)	1,488.86 (1529)	106.51 (26.73)
Mirtazapine (other)	0 (0)	729.48 (561)	101.16 (30.92)
Venlafaxine hydrochloride (other)	0 (0)	2005.76 (572)	117.97 (25.47)
TCAs	0 (0)	4236.66 (1122)	121.29 (26.35)
SSRIs	0 (0)	5716.46 (1936)	118.14 (29.77)
Other antidepressants	0 (0)	2005.76 (572)	113.99 (27.25)

^a Figures for 1 year post diagnosis are shown in parentheses.

antidepressant drugs, dosulepin (TCA) was estimated to have the lowest (1) mean cost (£1632.39) and venlafaxine (other) the highest (11; £2399.04) (*Table 127*). The mean cost for the different classes of antidepressant drugs ranged between £1807.58 for SSRIs and £2035.23 for other antidepressant drugs.

TABLE 124 Total costs associated with community nurse visits within the 5-year post-diagnosis period^a

Antidepressant drug	Total costs associated with community nurse visits		
	Minimum (£)	Maximum (£)	Mean (£)
Not prescribed antidepressants	0 (0)	14,605.77 (7462)	102.65 (29.53)
Amitriptyline hydrochloride (TCA)	0 (0)	14,075.80 (4472)	124.64 (28.51)
Dosulepin hydrochloride (TCA)	0 (0)	7684.30 (4186)	95.24 (17.67)
Lofepamine (TCA)	0 (0)	5208.10 (1898)	79.61 (17.91)
Trazodone hydrochloride (TCA)	0 (0)	5479.25 (1482)	119.14 (35.99)
Citalopram hydrobromide (SSRI)	0 (0)	13,810.28 (5902)	133.23 (38.42)
Escitalopram (SSRI)	0 (0)	6649.84 (1872)	134.40 (30.55)
Fluoxetine hydrochloride (SSRI)	0 (0)	9577.72 (4368)	110.20 (29.79)
Paroxetine hydrochloride (SSRI)	0 (0)	7559.93 (2626)	81.09 (17.11)
Sertraline hydrochloride (SSRI)	0 (0)	4950.92 (3588)	99.79 (26.48)
Mirtazapine (other)	0 (0)	3260.28 (6656)	117.20 (54.90)
Venlafaxine hydrochloride (other)	0 (0)	4053.24 (8008)	129.61 (29.53)
TCAs	0 (0)	14,075.80 (4472)	105.32 (22.80)
SSRIs	0 (0)	13,810.28 (5902)	109.92 (30.87)
Other antidepressants	0 (0)	6070.45 (8008)	103.78 (36.99)

a Figures for 1 year post diagnosis are shown in parentheses.

TABLE 125 Total costs associated with GP visits within the 5-year post-diagnosis period^a

Antidepressant drug	Total costs associated with GP visits		
	Minimum (£)	Maximum (£)	Mean (£)
Not prescribed antidepressants	0 (0)	9800.19 (4140)	1145.35 (334.70)
Amitriptyline hydrochloride (TCA)	0 (0)	14,749.99 (5184)	1685.53 (422.24)
Dosulepin hydrochloride (TCA)	0 (0)	20,631.76 (3492)	1364.22 (337.32)
Lofepamine (TCA)	0 (0)	9543.30 (3780)	1355.88 (362.77)
Trazodone hydrochloride (TCA)	0 (0)	9794.84 (3456)	1512.14 (427.39)
Citalopram hydrobromide (SSRI)	0 (0)	10,801.56 (3960)	1593.10 (483.06)
Escitalopram (SSRI)	32.47 (0)	7691.73 (3240)	1707.58 (524.98)
Fluoxetine hydrochloride (SSRI)	0 (0)	17,702.75 (4896)	1440.51 (430.38)
Paroxetine hydrochloride (SSRI)	0 (0)	8956.14 (3780)	1444.79 (352.05)
Sertraline hydrochloride (SSRI)	0 (0)	7858.29 (3024)	1439.86 (404.34)
Mirtazapine (other)	0 (0)	6691.40 (3024)	1553.25 (519.49)
Venlafaxine hydrochloride (other)	0 (0)	9320.32 (3168)	1548.64 (425.48)
TCAs	0 (0)	20,631.76 (5184)	1514.67 (382.99)
SSRIs	0 (0)	17,702.75 (4896)	1491.30 (439.74)
Other antidepressants	0 (0)	9320.32 (4248)	1458.20 (438.30)

a Figures for 1 year post diagnosis are shown in parentheses.

The costs presented do not control for potential differences between patients prescribed different antidepressant drugs. Thus, we sought to control for the patient characteristics, baseline comorbidities and use of certain drugs at baseline as detailed in *Chapter 2*. Complete data were available for each of these variables with the exception of smoking status (2097 had missing data) and Townsend score (1090 had missing data), so 2069 of the 37,268 eligible patients were excluded from subsequent analyses. All subsequently presented 5-year costs are thereby based

TABLE 126 Total visit costs (for practice nurse, community nurse and GP) within the 5-year post-diagnosis period^a

Antidepressant drug	Total visit costs (practice nurse, community nurse and GP)		
	Minimum (£)	Maximum (£)	Mean (£)
Not prescribed antidepressants	0 (0)	21,993.03 (7697)	1344.49 (393.58)
Amitriptyline hydrochloride (TCA)	0 (0)	21,765.24 (5564)	1947.76 (481.71)
Dosulepin hydrochloride (TCA)	0 (0)	20,702.63 (4797)	1571.60 (377.20)
Lofepramine (TCA)	0 (0)	10,912.18 (4642)	1540.55 (402.63)
Trazodone hydrochloride (TCA)	0 (0)	12,518.13 (3630)	1735.14 (493.91)
Citalopram hydrobromide (SSRI)	0 (0)	17,606.22 (6417)	1856.68 (555.09)
Escitalopram (SSRI)	32.47 (0)	9220.75 (3240)	1969.39 (587.99)
Fluoxetine hydrochloride (SSRI)	0 (0)	20,695.92 (6153)	1666.68 (489.84)
Paroxetine hydrochloride (SSRI)	0 (0)	10,446.79 (4563)	1636.34 (390.92)
Sertraline hydrochloride (SSRI)	0 (0)	9686.08 (4769)	1646.15 (457.55)
Mirtazapine (other)	0 (0)	8715.47 (7229)	1771.60 (605.30)
Venlafaxine hydrochloride (other)	0 (0)	12,882.21 (8091)	1796.22 (492.23)
TCAs	0 (0)	21,765.24 (5564)	1741.29 (432.15)
SSRIs	0 (0)	20,695.92 (6417)	1719.36 (500.38)
Other antidepressants	0 (0)	13,610.63 (8091)	1675.97 (502.54)

^a Figures for 1 year post diagnosis are shown in parentheses.

TABLE 127 Overall visit plus prescription cost within the 5-year post-diagnosis period^a

Antidepressant drug	Total visits plus prescription costs			Ranked cost
	Minimum (£)	Maximum (£)	Mean (£)	
Not prescribed antidepressants	0.00 (0.00)	21,993.03 (7697.00)	1344.49 (393.58)	
Amitriptyline hydrochloride (TCA)	1.64 (1.64)	21,771.80 (5565.64)	1987.90 (497.05)	8 (4)
Dosulepin hydrochloride (TCA)	2.90 (2.90)	20,731.63 (4802.33)	1632.39 (399.68)	1 (1)
Lofepramine (TCA)	39.29 (39.29)	11,030.06 (5108.97)	1848.63 (555.72)	5 (6)
Trazodone hydrochloride (TCA)	11.67 (11.67)	12,589.96 (3641.67)	1931.24 (574.38)	7 (7)
Citalopram hydrobromide (SSRI)	1.73 (1.73)	17,607.95 (6439.53)	1925.80 (579.38)	6 (8)
Escitalopram (SSRI)	87.17 (19.79)	9240.55 (3420.30)	2218.98 (704.97)	10 (10)
Fluoxetine hydrochloride (SSRI)	2.43 (2.43)	20,925.47 (6174.86)	1736.03 (515.76)	3 (5)
Paroxetine hydrochloride (SSRI)	6.89 (6.89)	13,211.86 (4718.43)	1771.42 (438.95)	4 (2)
Sertraline hydrochloride (SSRI)	2.74 (2.74)	9702.55 (4887.00)	1721.64 (487.69)	2 (3)
Mirtazapine (other)	84.15 (12.15)	9501.16 (7800.19)	2023.04 (699.56)	9 (9)
Venlafaxine hydrochloride (other)	34.79 (34.79)	15,934.83 (9726.00)	2399.04 (708.58)	11 (11)
TCAs	1.64 (1.64)	21,771.80 (5565.64)	1837.26 (472.89)	
SSRIs	1.73 (1.73)	20,925.47 (6439.53)	1807.58 (533.45)	
Other antidepressants	3.08 (3.08)	15,934.83 (9726.00)	2035.23 (631.38)	

^a Figures for 1 year post diagnosis are shown in parentheses.

on 35,217 patients (base case) and, for similar reasons, 1-year costs are based on 55,907 patients (sensitivity analysis).

The incremental cost estimates from the regression analysis, i.e. the mean incremental total prescription cost for all antidepressant drugs compared with prescription of no antidepressant drugs over the 5-year study period, after controlling for other factors, are presented in *Table 128*.

TABLE 128 Mean incremental total prescription costs (for all antidepressant drugs) within the 5-year post-diagnosis period^a

Antidepressant drug	Mean incremental cost (£)	Ranked cost
Amitriptyline hydrochloride (TCA)	46.36 (15.34)	1 (1)
Citalopram hydrobromide (SSRI)	66.89 (24.29)	3 (3)
Dosulepin hydrochloride (TCA)	66.48 (22.49)	2 (2)
Escitalopram (SSRI)	232.45 (116.98)	8 (9)
Fluoxetine hydrochloride (SSRI)	72.96 (25.92)	4 (4)
Lofepramine (TCA)	314.32 (153.09)	10 (10)
Mirtazapine (other)	241.40 (94.25)	9 (8)
Paroxetine hydrochloride (SSRI)	142.83 (48.04)	6 (6)
Sertraline hydrochloride (SSRI)	77.36 (30.14)	5 (5)
Trazodone hydrochloride (TCA)	193.49 (80.48)	7 (7)
Venlafaxine hydrochloride (other)	611.14 (216.35)	11 (11)
TCA's	100.62 (40.75)	
SSRIs	90.30 (33.08)	
Other antidepressants	364.95 (128.84)	

a Figures for 1 year post diagnosis are shown in parentheses.

All cost differences were significant ($p < 0.001$) when the 11 most commonly prescribed antidepressant drugs were compared with no antidepressant prescriptions, with the adjusted R^2 -value ranging between 0.021 [paroxetine (SSRI)] and 0.070 [venlafaxine (other)]. The mean incremental cost ranged between £46.36 for amitriptyline (TCA) and £611.14 for venlafaxine (other), and the ranking [from lowest (1) to highest cost] was identical to that when other factors were not controlled for (see Table 122). The mean incremental cost for the different classes of antidepressant drugs ranged from £90.30 for SSRIs to £364.95 for the group of other antidepressant drugs. Incremental costs for the 1-year post-diagnosis period are also shown in Table 128.

Sensitivity analysis

When the overall visit plus prescription costs were adjusted for differences between patients prescribed different antidepressant drugs, all cost differences were significant ($p < 0.001$) when the 11 most commonly prescribed antidepressant drugs were compared with those patients who were prescribed no antidepressant prescriptions. Also, the adjusted R^2 -value ranged between 0.122 [escitalopram (SSRI)] and 0.125 [venlafaxine (other)], and venlafaxine (other) was again found to have the highest mean incremental cost. However, fluoxetine (SSRI) was now found to have the lowest mean incremental cost (£217.30) and the incremental costs were higher, after the inclusion of visit costs, than when only prescription costs were assessed (Table 129).

Levels of cost-effectiveness

We now estimate the incremental number of adverse events for each of the 11 most commonly prescribed antidepressant drugs, and for the antidepressant classes, compared with no antidepressant drugs. Additionally, we also estimate the incremental cost per averted event (ICER) for those antidepressant drugs that are located on the efficiency frontier. These analyses are presented for each of the 13 adverse events in turn (the results of the sensitivity analysis are presented in Appendix 2). Finally, summary ICER results for both the base-case and sensitivity analyses, over the 5- and 1-year periods, are presented.

TABLE 129 Mean incremental costs, in terms of overall visit plus prescription cost for (all antidepressant drugs), within the 5-year post-diagnosis period^a

Antidepressant drug	Mean incremental cost (£)	Ranked cost
Amitriptyline hydrochloride (TCA)	498.75 (141.50)	8 (6)
Citalopram hydrobromide (SSRI)	280.95 (123.03)	4 (4)
Dosulepin hydrochloride (TCA)	248.61 (95.26)	3 (1)
Escitalopram (SSRI)	345.79 (198.39)	6 (7)
Fluoxetine hydrochloride (SSRI)	217.30 (116.15)	1 (3)
Lofepramine (TCA)	536.83 (260.59)	9 (10)
Mirtazapine (other)	330.97 (212.18)	5 (9)
Paroxetine hydrochloride (SSRI)	370.12 (140.95)	7 (5)
Sertraline hydrochloride (SSRI)	235.88 (109.16)	2 (2)
Trazodone hydrochloride (TCA)	541.30 (209.75)	10 (8)
Venlafaxine hydrochloride (other)	851.55 (309.09)	11 (11)
TCAs	425.51 (146.06)	
SSRIs	272.70 (125.55)	
Other antidepressants	526.56 (226.11)	

^a Figures for 1 year post diagnosis are shown in parentheses.

Mortality

The absolute risk of mortality when patients were not prescribed antidepressant drugs was estimated to be 21.66% over 5 years (see *Table 23*). However, of the 4811 patients who were prescribed no antidepressant drugs, 1691 (35.1%) died within 5 years of being diagnosed with depression, which meant that the mean follow-up time over which costs were estimated was 3.95 years. Consequently, when account was taken of this, and deaths in future years were discounted, the expected mortality rate for those who were prescribed no antidepressant drugs, was estimated to be to 0.1626 per patient over 5 years. Similar methods were used to estimate the expected mortality rate and the incremental number of deaths for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over 5 years, and for each of the different classes of antidepressant drugs. These values are presented in *Table 130*.

The values for the incremental number of deaths were subsequently combined with the previously estimated incremental costs [the base-case incremental total prescription costs (for all antidepressant drugs) reported in *Table 128*] in order to estimate the efficiency frontier. Amitriptyline (TCA) had the lowest mean prescription cost (of all antidepressant drugs) (hereafter referred to as *lowest cost*) and was also estimated to be associated with fewer deaths than lofepramine (TCA), trazodone (TCA), citalopram (SSRI), escitalopram (SSRI), fluoxetine (SSRI), paroxetine (SSRI), sertraline (SSRI) mirtazapine (other) and venlafaxine (other). Consequently, amitriptyline was deemed to dominate these nine antidepressant drugs. The remaining antidepressant [dosulepin (TCA)] made up the efficiency frontier. Amitriptyline had the lowest cost; dosulepin had a mean incremental cost of £20.12 compared with amitriptyline, but was associated with 0.0110 fewer deaths. This equated to an incremental cost per averted death (mean incremental cost/incremental number of deaths) (ICER) of £1829 per averted death. With regard to the different classes of antidepressant drugs (see *Table 130*), SSRIs had the lowest cost and dominated other antidepressant drugs. The mean cost was on average higher for those patients prescribed a TCA than for those prescribed an SSRI, but TCAs were estimated to be associated with fewer deaths, giving an incremental cost per averted death of £264 for TCAs, compared with SSRIs.

TABLE 130 Differences in incremental cost, incremental number of deaths and incremental cost per averted death

Antidepressant drug	Incremental mean cost (£)	Incremental no. of deaths	Difference in incremental mean cost (£)	Difference in incremental no. of deaths	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0401	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0291	20.12	0.011	1828.79
Lofepramine (TCA)	314.32	0.0888			
Trazodone hydrochloride (TCA)	193.49	0.1146			
Citalopram hydrobromide (SSRI)	66.89	0.0836			
Escitalopram (SSRI)	232.45	0.0600			
Fluoxetine hydrochloride (SSRI)	72.96	0.1010			
Paroxetine hydrochloride (SSRI)	142.83	0.0551			
Sertraline hydrochloride (SSRI)	77.36	0.0776			
Mirtazapine (other)	241.40	0.1000			
Venlafaxine hydrochloride (other)	611.14	0.0989			
TCAs	100.62	0.0474	10.32	0.0391	263.96
SSRIs	90.30	0.0865	LC		LC
Other antidepressants	364.95	0.1039			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

Sudden cardiac death

The estimated incremental number of sudden cardiac deaths for each of the 11 most commonly prescribed antidepressant drugs over the 5-year follow-up period are presented in *Table 131*. A negative incremental number of sudden cardiac deaths, as, for example for trazodone (TCA), can be explained by the fact that the estimated absolute risk of a sudden cardiac death is lower for these antidepressants than for no antidepressant drugs. Of the 11 most commonly prescribed antidepressant drugs amitriptyline (TCA) had the lowest cost. After excluding dominated options, citalopram (SSRI) was estimated to have an incremental cost per averted sudden cardiac death of £32,791 compared with amitriptyline; fluoxetine (SSRI) was estimated to have an incremental cost per averted sudden cardiac death of £56,882 compared with citalopram; and trazodone (TCA) was estimated to have an incremental cost per averted sudden cardiac death of £138,536 compared with fluoxetine. In terms of class, SSRIs had the lowest cost and dominated both TCAs and other antidepressant drugs.

Suicide

The estimated incremental number of suicides that would be expected for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 132*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, paroxetine (SSRI) was estimated to have an incremental cost per averted suicide of £228,598 compared with amitriptyline. When looking at the different classes, SSRIs had the lowest cost and TCAs were estimated to have an incremental cost per averted suicide of £48,339 compared with SSRIs.

Attempted suicide/self-harm

The estimated incremental number of attempted suicides for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 133*. Amitriptyline (TCA) had the lowest absolute risk, as well as the lowest incremental number of attempted suicides and lowest cost (compared with those not prescribed

TABLE 131 Differences in incremental cost, incremental number of sudden cardiac deaths and incremental cost per averted sudden cardiac death

Antidepressant drug	Incremental mean cost (£)	Incremental no. of sudden cardiac deaths	Difference in incremental mean cost (£)	Difference in incremental no. of sudden cardiac deaths	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0007	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0011			
Lofepamine (TCA)	314.32	0.0001			
Trazodone hydrochloride (TCA)	193.49	-0.0009	120.53	0.0009	138,535.53
Citalopram hydrobromide (SSRI)	66.89	0.0000	20.53	0.0006	32,790.81
Escitalopram (SSRI)	232.45	-0.0009			
Fluoxetine hydrochloride (SSRI)	72.96	-0.0001	6.07	0.0001	56,882.32
Paroxetine hydrochloride (SSRI)	142.83	0.0008			
Sertraline hydrochloride (SSRI)	77.36	0.0001			
Mirtazapine (other)	241.40	0.0015			
Venlafaxine hydrochloride (other)	611.14	0.0017			
TCAs	100.62	0.0005			
SSRIs	90.30	0.0001	LC		Dominates
Other antidepressants	364.95	0.0014			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (-) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

TABLE 132 Differences in incremental cost, incremental number of suicides and incremental cost per averted suicide

Antidepressant drug	Incremental mean cost (£)	Incremental no. of suicides	Difference in incremental mean cost (£)	Difference in incremental no. of suicides	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0002	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0013			
Lofepamine (TCA)	314.32	0.0027			
Trazodone hydrochloride (TCA)	193.49	0.0027			
Citalopram hydrobromide (SSRI)	66.89	0.0014			
Escitalopram (SSRI)	232.45	-0.0002			
Fluoxetine hydrochloride (SSRI)	72.96	0.0022			
Paroxetine hydrochloride (SSRI)	142.83	-0.0002	96.47	0.0004	228,598.47
Sertraline hydrochloride (SSRI)	77.36	0.0006			
Mirtazapine (other)	241.40	0.0036			
Venlafaxine hydrochloride (other)	611.14	0.0025			
TCAs	100.62	0.0010	10.32	0.0002	48,339.10
SSRIs	90.30	0.0012	LC		LC
Other antidepressants	364.95	0.0028			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (-) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

antidepressant drugs). Consequently, amitriptyline was deemed to dominate all of the other 10 most commonly prescribed antidepressant drugs, when estimating the cost per attempted suicide averted. When looking at the different classes, SSRIs had the lowest cost and TCAs were

TABLE 133 Differences in incremental cost, incremental number of attempted suicides and incremental cost per averted attempted suicide/self-harm

Antidepressant drug	Incremental mean cost (£)	Incremental no. of attempted suicides	Difference in incremental mean cost (£)	Difference in incremental no. of attempted suicides	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0010	LC		D
Dosulepin hydrochloride (TCA)	66.48	0.0048			
Lofepramine (TCA)	314.32	0.0075			
Trazodone hydrochloride (TCA)	193.49	0.0158			
Citalopram hydrobromide (SSRI)	66.89	0.0073			
Escitalopram (SSRI)	232.45	0.0035			
Fluoxetine hydrochloride (SSRI)	72.96	0.0050			
Paroxetine hydrochloride (SSRI)	142.83	0.0012			
Sertraline hydrochloride (SSRI)	77.36	0.0050			
Mirtazapine (other)	241.40	0.0210			
Amitriptyline hydrochloride (TCA)	46.36	0.0010	LC		D
TCAs	100.62	0.0039	10.32	0.0014	7596.58
SSRIs	90.30	0.0053	LC		LC
Other antidepressants	364.95	0.0184			

D, dominates; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

estimated to be associated with an incremental cost per averted attempted suicide of £7597 compared with SSRIs.

Myocardial infarction

The estimated incremental number of MIs for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 134*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, sertraline (SSRI) was estimated to have an incremental cost per averted MI of £3227 compared with amitriptyline. When looking at the different classes of antidepressant drugs, SSRIs had the lowest cost and other antidepressant drugs were estimated to be associated with an incremental cost per averted MI of £79,799.

Stroke/transient ischaemic attack

The estimated incremental number of strokes/TIAs for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 135*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, dosulepin (TCA) was estimated to have an incremental cost per averted stroke/TIA of £4961 compared with amitriptyline. When looking at the different classes of antidepressant drugs, SSRIs had the lowest cost and TCAs were estimated to be associated with an incremental cost per averted stroke/TIA of £1833.

Falls

The estimated incremental number of falls for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are shown in *Table 136*. Amitriptyline (TCA) had the lowest cost, yet other antidepressant drugs were associated with fewer expected falls. After excluding dominated options, dosulepin (TCA) had an incremental

TABLE 134 Differences in incremental cost, incremental number of averted MIs and incremental cost per averted MI

Antidepressant drug	Incremental mean cost (£)	Incremental no. of MIs	Difference in incremental mean cost (£)	Difference in incremental no. of MIs	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0079	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0067			
Lofepamine (TCA)	314.32	0.0085			
Trazodone hydrochloride (TCA)	193.49	0.0021			
Citalopram hydrobromide (SSRI)	66.89	0.0044			
Escitalopram (SSRI)	232.45	0.0090			
Fluoxetine hydrochloride (SSRI)	72.96	0.0113			
Paroxetine hydrochloride (SSRI)	142.83	0.0067			
Sertraline hydrochloride (SSRI)	77.36	−0.0017	31.01	0.01	3226.98
Mirtazapine (other)	241.40	0.0033			
Venlafaxine hydrochloride (other)	611.14	0.0027			
TCAs	100.62	0.0070			
SSRIs	90.30	0.0065	LC		LC
Other antidepressants	364.95	0.0031	274.65	0.0034	79,799.09

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (−) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

TABLE 135 Differences in incremental cost, incremental number of averted strokes/TIAs and incremental cost per averted stroke/TIA

Antidepressant drug	Incremental mean cost (£)	Incremental no/ of strokes/TIAs	Difference in incremental mean cost (£)	Difference in incremental no. of strokes/TIAs	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0105	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0064	20.12	0.0041	4961.16
Lofepamine (TCA)	314.32	0.0238			
Trazodone hydrochloride (TCA)	193.49	0.0087			
Citalopram hydrobromide (SSRI)	66.89	0.0175			
Escitalopram (SSRI)	232.45	0.0132			
Fluoxetine hydrochloride (SSRI)	72.96	0.0142			
Paroxetine hydrochloride (SSRI)	142.83	0.0128			
Sertraline hydrochloride (SSRI)	77.36	0.0188			
Mirtazapine (other)	241.40	0.0244			
Venlafaxine hydrochloride (other)	611.14	0.0370			
TCAs	100.62	0.0103	10.32	0.0056	1832.83
SSRIs	90.30	0.0160	LC		LC
Other antidepressants	364.95	0.0296			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

cost per averted fall of £2234 compared with amitriptyline (TCA) and mirtazapine (other) had an incremental cost per averted fall of £6868 compared with dosulepin (TCA). When looking at the different classes of antidepressant drugs, SSRIs had the lowest cost and TCAs were estimated to be associated with an incremental cost per averted fall of £396.

TABLE 136 Differences in incremental cost, incremental number of averted falls and incremental cost per averted fall

Antidepressant drug	Incremental mean cost (£)	Incremental no. of falls	Difference in incremental mean cost (£)	Difference in incremental no. of falls	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0549	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0459	20.12	0.009	2234.36
Lofepramine (TCA)	314.32	0.0486			
Trazodone hydrochloride (TCA)	193.49	0.0614			
Citalopram hydrobromide (SSRI)	66.89	0.0842			
Escitalopram (SSRI)	232.45	0.0660			
Fluoxetine hydrochloride (SSRI)	72.96	0.0741			
Paroxetine hydrochloride (SSRI)	142.83	0.0634			
Sertraline hydrochloride (SSRI)	77.36	0.0742			
Mirtazapine (other)	241.40	0.0204	174.92	0.0255	6868.42
Venlafaxine hydrochloride (other)	611.14	0.0769			
TCAs	100.62	0.0514	10.32	0.0261	395.62
SSRIs	90.30	0.0775	LC		LC
Other antidepressants	364.95	0.0507			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

Fractures

The estimated incremental number of fractures for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 137*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, trazodone (TCA) was estimated to have an incremental cost per averted fracture of £6342 compared with amitriptyline. When looking at the different classes, SSRIs had the lowest cost and TCAs were estimated to be associated with an incremental cost per averted fracture of £750.

Upper gastrointestinal bleed

The estimated incremental number of upper GI bleeds for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 138*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, the estimated incremental costs per averted upper GI bleed were £23 for dosulepin (TCA) compared with amitriptyline, £2527 for fluoxetine (SSRI) compared with dosulepin, £2655 for sertraline (SSRI) compared with fluoxetine and £215,955 for mirtazapine (other) compared with sertraline. Escitalopram (SSRI) was estimated to be subject to extended dominance (it was estimated to be associated with more upper GI bleeds than the other antidepressant drugs, but had a higher ICER, i.e. combinations of sertraline (SSRI) and mirtazapine (other) would be estimated to be associated with a lower cost and fewer upper GI bleeds. When looking at the different classes, SSRIs had the lowest cost and were estimated to dominate both TCAs and other antidepressant drugs.

Epilepsy/seizures

The estimated incremental number of epilepsy/seizure cases for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 139*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, dosulepin (TCA) was estimated to have an incremental cost per averted epilepsy/seizure of £5159 compared with amitriptyline. When looking at the different classes, SSRIs had the lowest cost and TCAs had an incremental cost per averted epilepsy/seizure case of £2594 compared with SSRIs.

TABLE 137 Differences in incremental cost, incremental number of averted fractures and incremental cost per averted fracture

Antidepressant drug	Incremental mean cost (£)	Incremental no. of fractures	Difference in incremental mean cost (£)	Difference in incremental no. of fractures	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0231	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0238			
Lofepamine (TCA)	314.32	0.0338			
Trazodone hydrochloride (TCA)	193.49	-0.0001	147.14	0.0232	6342.21
Citalopram hydrobromide (SSRI)	66.89	0.0389			
Escitalopram (SSRI)	232.45	0.0159			
Fluoxetine hydrochloride (SSRI)	72.96	0.0376			
Paroxetine hydrochloride (SSRI)	142.83	0.0356			
Sertraline hydrochloride (SSRI)	77.36	0.0395			
Mirtazapine (other)	241.40	0.0265			
Venlafaxine hydrochloride (other)	611.14	0.0536			
TCAs	100.62	0.0237	10.32	0.0138	750.28
SSRIs	90.30	0.0375	LC		LC
Other antidepressants	364.95	0.0417			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (-) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressant drugs.

TABLE 138 Differences in incremental cost, incremental number of averted upper GI bleed and incremental cost per averted upper GI bleed

Antidepressant drug	Incremental mean cost (£)	Incremental no. of upper GI bleeds	Difference in incremental mean cost (£)	Difference in incremental no. of upper GI bleeds	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0086	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0058	20.12	0.8800	22.89
Lofepamine (TCA)	314.32	0.0047			
Trazodone hydrochloride (TCA)	193.49	0.0126			
Citalopram hydrobromide (SSRI)	66.89	0.0060			
Escitalopram (SSRI)	232.45	0.0009			ED
Fluoxetine hydrochloride (SSRI)	72.96	0.0032	6.48	0.0026	2527.25
Paroxetine hydrochloride (SSRI)	142.83	0.0041			
Sertraline hydrochloride (SSRI)	77.36	0.0015	4.4	0.0000	2655.44
Mirtazapine (other)	241.40	0.0008	164.04	0.0000	215,954.79
Venlafaxine hydrochloride (other)	611.14	0.0118			
TCAs	100.62	0.0070			
SSRIs	90.30	0.0044	LC		D
Other antidepressants	364.95	0.0069			

D, dominates; ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (-) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

Road traffic accidents

The estimated incremental number of RTAs for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 140*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, dosulepin (TCA) was estimated to have an incremental cost per averted RTA of £9009 compared with amitriptyline, and mirtazapine (other) was estimated to have an incremental cost per averted RTA of £240,044 compared with dosulepin. When looking at the different classes, SSRIs had the lowest cost and TCAs were estimated to be associated with an incremental cost per averted RTA of £204,943.

Adverse drug reactions

The estimated incremental number of ADRs for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 141*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, dosulepin (TCA) had a mean incremental cost of £28,209 per averted ADR and venlafaxine (other) had an incremental cost of £637,960 per averted ADR. Those prescribed SSRIs had the lowest cost. The incremental cost per averted ADR was £39,280 for TCAs compared with SSRIs and £164,896 for the group of other antidepressant drugs compared with TCAs.

Hyponatraemia

The estimated incremental number of hyponatraemia cases for each of the 11 most commonly prescribed antidepressant drugs (after discounting) over the 5-year follow-up period are presented in *Table 142*. Amitriptyline (TCA) had the lowest cost and, after excluding dominated options, dosulepin (TCA) was estimated to have an incremental cost per averted hyponatraemia case of £5087 compared with amitriptyline. When looking at the different classes, SSRIs had the lowest cost and TCAs were estimated to be associated with an incremental cost per averted hyponatraemia case of £2433.

TABLE 139 Differences in incremental cost, incremental number of averted epilepsy/seizure cases and incremental cost per averted epilepsy/seizure case

Antidepressant drug	Incremental mean cost (£)	Incremental no. of epilepsy/seizure cases	Difference in incremental mean cost (£)	Difference in incremental no. of epilepsy/seizure cases	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0017	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0022	20.12	0.0039	5158.97
Lofepramine (TCA)	314.32	0.0025			
Trazodone hydrochloride (TCA)	193.49	0.0026			
Citalopram hydrobromide (SSRI)	66.89	0.0044			
Escitalopram (SSRI)	232.45	0.0039			
Fluoxetine hydrochloride (SSRI)	72.96	0.0029			
Paroxetine hydrochloride (SSRI)	142.83	0.0064			
Sertraline hydrochloride (SSRI)	77.36	0.0094			
Mirtazapine (other)	241.4	0.0031			
Venlafaxine hydrochloride (other)	611.14	0.0109			
TCAs	100.62	0.0008	10.32	0.0040	2593.95
SSRIs	90.30	0.0048	LC		LC
Other antidepressants	364.95	0.0070			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (–) value indicates that fewer events were predicted for those taking a particular antidepressant compared with those who were prescribed no antidepressants.

TABLE 140 Differences in incremental cost, incremental number of RTAs and incremental cost per averted RTA

Antidepressant drug	Incremental mean cost (£)	Incremental no. of RTAs	Difference in incremental mean cost (£)	Difference in incremental no. of RTAs	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	−0.0002	LC		LC
Dosulepin hydrochloride (TCA)	66.48	−0.0024	20.12	0.0022	9008.60
Lofepamine (TCA)	314.32	0.0013			
Trazodone hydrochloride (TCA)	193.49	0.0033			
Citalopram hydrobromide (SSRI)	66.89	0.0003			
Escitalopram (SSRI)	232.45	−0.0002			
Fluoxetine hydrochloride (SSRI)	72.96	−0.0015			
Paroxetine hydrochloride (SSRI)	142.83	0.0000			
Sertraline hydrochloride (SSRI)	77.36	−0.0003			
Mirtazapine (other)	241.40	−0.0032	174.92	0.0007	240,043.92
Venlafaxine hydrochloride (other)	611.14	−0.0014			
TCAs	100.62	−0.0002			
SSRIs	90.30	−0.0003	LC		LC
Other antidepressants	364.95	−0.0017	274.65	0.0013	204,943.04

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (−) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

TABLE 141 Differences in incremental cost, incremental number of ADRs and incremental cost per averted ADR

Antidepressant drug	Incremental mean cost (£)	Incremental no. of ADRs	Difference in incremental mean cost (£)	Difference in incremental no. of ADRs	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0008	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0001	20.12	0.0007	28,209.46
Lofepamine (TCA)	314.32	0.0113			
Trazodone hydrochloride (TCA)	193.49	0.0007			
Citalopram hydrobromide (SSRI)	66.89	0.0014			
Escitalopram (SSRI)	232.45	0.0008			
Fluoxetine hydrochloride (SSRI)	72.96	0.0022			
Paroxetine hydrochloride (SSRI)	142.83	0.0003			
Sertraline hydrochloride (SSRI)	77.36	0.0061			
Mirtazapine (other)	241.40	0.0002			
Venlafaxine hydrochloride (other)	611.14	0.0007	544.66	0.0009	637,960.00
TCAs	100.62	0.0017	10.32	0.0003	39,280.15
SSRIs	90.30	0.0020	LC		LC
Other antidepressants	364.95	0.0001	264.33	0.0016	164,896.44

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (−) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

Summary

The ICER values for each of the adverse events for those antidepressant drugs located on the efficiency frontier are presented in *Table 143* (base-case analysis: prescription costs for all antidepressant drugs) and *Table 144* [sensitivity analysis: overall costs (total visit costs and

TABLE 142 Differences in incremental cost, incremental number of averted hyponatraemia cases and incremental cost per averted hyponatraemia case

Antidepressant drug	Incremental mean cost (£)	Incremental no. of hyponatraemia cases	Difference in incremental mean cost (£)	Difference in incremental no. of hyponatraemia cases	ICER (£)
Amitriptyline hydrochloride (TCA)	46.36	0.0034	LC		LC
Dosulepin hydrochloride (TCA)	66.48	0.0005	20.12	0.004	5087.28
Lofepramine (TCA)	314.32	0.0001			
Trazodone hydrochloride (TCA)	193.49	0.0056			
Citalopram hydrobromide (SSRI)	66.89	0.0072			
Escitalopram (SSRI)	232.45	0.0107			
Fluoxetine hydrochloride (SSRI)	72.96	0.008			
Paroxetine hydrochloride (SSRI)	142.83	0.0015			
Sertraline hydrochloride (SSRI)	77.36	0.0006			
Mirtazapine (other)	241.4	0.0007			
Venlafaxine hydrochloride (other)	611.14	0.0061			
TCAs	100.62	0.0020	10.32	0.0042	2433.15
SSRIs	90.30	0.0062	LC		LC
Other antidepressants	364.95	0.0036			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (–) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

total prescription costs)] for the 5-year post-diagnosis period. None of the 11 most commonly prescribed antidepressant drugs was estimated to be consistently the most cost-effective across the different types of adverse events; this was the case for both prescription costs and overall costs, and for both 1- and 5-year time periods. Moreover, as it is unclear what one would be willing to pay to avert an adverse event, one cannot determine the most cost-effective antidepressant for averting different adverse events (with the exception of where dominance occurs). That said, when focusing on prescription costs over the 5-year perspective, patients prescribed amitriptyline (TCA) had the lowest mean cost and this drug also had the lowest predicted number of attempted suicides (i.e. here it dominated other options). Dosulepin (TCA) was the other drug that was located, more often than not, on the efficiency frontier (this was the case for ADRs, epilepsy/seizures, falls, hyponatraemia, mortality, RTAs, stroke/TIA and upper GI bleeds) and, therefore, could potentially be cost-effective if one were willing to pay the specific values to avoid the different adverse events. Additionally, escitalopram (SSRI) and lofepramine (TCA) were always dominated by at least one other option, for each of the 13 adverse events. Conversely, when looking at overall costs (total visit cost and the total prescription cost) (see *Appendix 2* for results) over the 5-year perspective, those prescribed fluoxetine (SSRI) had the lowest mean cost. However, fluoxetine (SSRI) never dominated any of the other options, and dosulepin (TCA) was again located, more often than not, on the efficiency frontier (this was the case for ADRs, epilepsy/seizures, falls, fractures, hyponatraemia, mortality, RTAs and stroke/TIA). Moreover, escitalopram (SSRI), citalopram (SSRI) and lofepramine (TCA) were always dominated by at least one other option, for each of the 13 adverse events. Additionally, it should be noted that these 5-year perspective results are in line with those for the 1-year period (sensitivity analysis: see *Tables 145* and *146*, respectively), although dosulepin (TCA) was located on the efficiency frontier on a greater number of occasions for overall costs for the 1-year perspective as it was estimated to have the lowest cost. Finally, given that there is variation in levels of cost-effectiveness within classes, it is difficult to conclude that a particular class of drugs are more cost-effective than another in terms of these adverse events.

TABLE 143 Base-case: levels of cost-effectiveness when assessing the incremental cost [the mean incremental prescription cost (for all antidepressant drugs)] per adverse event averted, for each of the 11 antidepressants and each class of antidepressants, over a 5-year period

	Mortality	Sudden cardiac death	Suicide	Attempted suicide	MI	Stroke/TIA	Falls	Fractures	Upper GI bleed	Epilepsy/seizures	RTA	ADR	Hyponatraemia
Amitriptyline hydrochloride (TCA)	LC	LC	LC	D	LC	LC	LC	LC	LC	LC	LC	LC	LC
Dosulepin hydrochloride (TCA)	1829				4961	2234			23	5159	9009	28,209	5087
Lofepramine (TCA)													
Trazodone hydrochloride (TCA)		138,536						6342					
Citalopram hydrobromide (SSRI)		32,791											
Escitalopram (SSRI)									ED				
Fluoxetine hydrochloride (SSRI)		56,882							2527				
Paroxetine hydrochloride (SSRI)			228,598										
Sertraline hydrochloride (SSRI)					3227				2655				
Mirtazapine (other)						6868			215,955		240,044		
Venlafaxine hydrochloride (other)												637,960	
TCAs	264		48,339	7597		1833	396	750		2594		39,280	2433
SSRIs	LC	D	LC	LC	LC	LC	LC	LC	D	LC	LC	LC	LC
Other antidepressants					79,799						204,943	164,896	

D, dominates; ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; results rounded to the nearest pound (£).

TABLE 144 Sensitivity analysis: levels of cost-effectiveness when assessing the incremental cost [the mean incremental total visit cost and the total prescription cost (for all antidepressant drugs)] per adverse event averted, for each of the 11 antidepressants and each class of antidepressants, over a 5-year period

	Mortality	Sudden cardiac death	Suicide	Attempted suicide	MI	Stroke/TIA	Falls	Fractures	Upper GI bleed	Epilepsy/seizures	RTA	ADR	Hyponatraemia
Amitriptyline hydrochloride (TCA)				882,758				ED					
Dosulepin hydrochloride (TCA)	435			ED	ED	3993	1109	2260		6210	32,854	15,090	10,914
Lofepamine (TCA)		372,401											
Trazodone hydrochloride (TCA)								12,240					
Citalopram hydrobromide (SSRI)													
Escitalopram (SSRI)					ED								
Fluoxetine hydrochloride (SSRI)	LC	LC	LC	LC	LC	LC	LC	LC	LC	LC	LC	LC	LC
Paroxetine hydrochloride (SSRI)			158,763	39,865									
Sertraline hydrochloride (SSRI)	ED		12,123		1428				961				2532
Mirtazapine (other)							3234		125,188		113,029		
Venlafaxine hydrochloride (other)												706,227	
TCA's	3908		715,767	112,484		27,139	5858	11,109		38,409		ED	36,028
SSRIs	LC	D	LC	LC	LC	LC	LC	LC	D	LC	LC	LC	LC
Other antidepressants					73,758						189,427	136,063	

D, dominates; ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; results rounded to the nearest pound (£).

TABLE 145 Base-case: levels of cost-effectiveness, when assessing the incremental cost [the mean incremental prescription cost (for all antidepressant drugs)] per adverse event averted, for each of the 11 antidepressants and each class of antidepressants, over a 1-year period

	Mortality	Sudden cardiac death	Suicide	Attempted suicide	MI	Stroke/TIA	Falls	Fracture	Upper GI bleed	Epilepsy/seizures	RTA	ADR	Hyponatraemia
Amitriptyline hydrochloride (TCA)	LC	LC	LC	D	LC	LC	LC	LC	LC	LC	LC	LC	LC
Dosulepin hydrochloride (TCA)	1300				ED	4968	2,297		7	4499	11,851	32,723	6345
Lofepramine (TCA)													
Trazodone hydrochloride (TCA)		171,388						13,466					
Citalopram hydrobromide (SSRI)		37,843											
Escitalopram (SSRI)													
Fluoxetine hydrochloride (SSRI)		86,674							ED				
Paroxetine hydrochloride (SSRI)			246,675										
Sertraline hydrochloride (SSRI)					5858				9522				
Mirtazapine (other)							20,653		1,423,810		637,171		
Venlafaxine hydrochloride (other)												2,840,352	
TCA's	355		88,010	8207	24,566	2834	760	1609		4997	ED	41,939	6386
SSRIs	LC	D	LC	LC	LC	LC	LC	LC	D	LC	LC	LC	LC
Other antidepressants					121,278						292,702	278,602	

D, dominates; ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; results rounded to the nearest pound (£).

TABLE 146 Sensitivity analysis: levels of cost-effectiveness, when assessing the incremental cost [the mean incremental total visit cost and the total prescription cost (for all antidepressant drugs)] per adverse event averted, for each of the 11 antidepressants and each class of antidepressants, over a 1-year period

	Mortality	Sudden cardiac death	Suicide	Attempted suicide	MI	Stroke/TIA	Falls	Fracture	Upper GI bleed	Epilepsy/seizures	RTA	ADR	Hyponatraemia
Amitriptyline hydrochloride (TCA)				23,339				ED					
Dosulepin hydrochloride (TCA)	D	LC	LC	LC	LC	D	LC	LC	LC	D	LC	LC	D
Lofepamine (TCA)		30,8907						23,968					
Trazodone hydrochloride (TCA)													
Citalopram hydrobromide (SSRI)													
Escitalopram (SSRI)													
Fluoxetine hydrochloride (SSRI)		58,384											
Paroxetine hydrochloride (SSRI)			112,872	ED					17,581				
Sertraline hydrochloride (SSRI)			69,588		7166								
Mirtazapine (other)							34,230		2,327,655		1,056,032		
Venlafaxine hydrochloride (other)												3,148,619	
TCA's	945		234,451	21,863	65,441	7548	2025	4286		13,312	ED	111,721	17,012
SSRIs	LC	D	LC	LC	LC	LC	LC	LC	D	LC	LC	LC	LC
Other antidepressants					112,264						312,544	257,897	

D, dominates; ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; results rounded to the nearest pound (£).

Chapter 4

Discussion

Summary of the main findings

Findings by antidepressant class

All classes of antidepressant drugs were associated with significantly increased rates of all-cause mortality, suicide, attempted suicide/self-harm, falls, fracture and upper GI bleeds compared with periods of no use of antidepressant drugs in this cohort of older people who had been diagnosed with depression. There were significant differences between the three main classes of antidepressant drugs and their associations with 7 of the 13 adverse outcomes examined; all-cause mortality, attempted suicide/self-harm, stroke/TIA, falls, fracture, epilepsy/seizures and hyponatraemia. For these outcomes, SSRIs was associated with the highest rates for falls and hyponatraemia, and the group of other antidepressant drugs was associated with the highest rates for overall mortality, attempted suicide/self-harm, stroke/TIA, fracture and epilepsy/seizures. TCAs did not have the highest rates for any of these outcomes.

The rates of sudden cardiac death, suicide, MI, upper GI bleeds, RTAs and ADRs were not significantly different between the different antidepressant classes.

Patients who had been prescribed combined antidepressant drugs from different classes or different drugs within a class had the highest overall rates for several of the adverse outcomes: all-cause mortality, suicide, stroke/TIA, falls, fracture, upper GI bleed, epilepsy/seizures and RTAs.

Findings for individual antidepressant drugs

There were significant differences between the associations of the most commonly prescribed individual drugs and seven of the adverse outcomes: all-cause mortality, attempted suicide/self-harm, stroke/TIA, falls, fracture, epilepsy/seizures and hyponatraemia. Patients who had been prescribed trazodone had the highest rate of all-cause mortality and one of the highest rates of attempted suicide/self-harm. Mirtazapine was associated with the highest rate of attempted suicide/self-harm and one of the highest rates for all-cause mortality and stroke/TIA. Patients prescribed venlafaxine had higher rates of stroke/TIA, fracture and epilepsy/seizures than patients prescribed the other drugs, and one of the highest rates for all-cause mortality, attempted suicide/self-harm and falls. Citalopram was associated with the highest rate of falls, but rates were similar for all of the SSRIs. There were significantly increased risks of hyponatraemia associated with three SSRIs (citalopram, escitalopram and fluoxetine), but not paroxetine or sertraline. Amitriptyline and dosulepin were associated with the lowest rates for several of these outcomes.

There were no significant differences between individual drugs for MI, upper GI bleeds and RTAs. There was some evidence of a difference between individual drugs for ADRs, with lofepramine and sertraline being associated with the highest rates. The number of cases of sudden cardiac death and suicide were too small to enable comparisons of individual drugs.

Findings according to dose and duration of use

There was considerable variation in the prescribed doses between the antidepressant classes, and between individual drugs. TCAs tended to have the lowest prescribed doses, with nearly 70% of

prescriptions being ≤ 0.5 of a DDD, compared with 14% for SSRIs and 19% for the class of other antidepressant drugs.

There was evidence of a dose–response relationship with mortality rates for TCAs and SSRIs, but not for the group of other antidepressant drugs. The rate of falls tended to increase as dose increased in all classes, whereas the fracture rate increased significantly as dose increased for TCAs, but less markedly for SSRIs and other antidepressant drugs. The rates of epilepsy/seizures tended to increase as dose increased in all classes, although the trend was not significant for the group of other antidepressant drugs. Hyponatraemia was significantly associated only with use of SSRIs; however, the rate was highest for low doses of SSRIs and decreased as SSRI dose increased. There were no significant dose–response relationships for any class for ADRs, although there was some indication of an increased rate associated with high doses of TCAs.

Although TCAs had the lowest prescribed doses, when comparisons were made within separate categories of dose (≤ 0.5 DDDs, 0.5–1.0 DDDs and > 1.0 DDDs) TCAs tended to be associated with lower adjusted HRs for all-cause mortality, attempted suicide/self-harm, stroke/TIA and epilepsy/seizures within each dose category. There is also some evidence suggesting that low-dose TCAs are similar to higher-dose TCAs in terms of reducing symptoms of depression.^{3,68}

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, MI, stroke/TIA, ADRs and hyponatraemia, there was some evidence that rates were reduced after 85 days of use.

For most outcomes risks were no longer increased from 85 days after stopping antidepressant treatment; however, they remained increased for overall mortality and epilepsy/seizures.

The high rates in the first 28 days after stopping may reflect a direct effect of withdrawal from the antidepressant drug, but are more likely, given the similar pattern for many outcomes, to reflect patients stopping the drugs because of an onset of symptoms or after being admitted to hospital or a residential home following an adverse event that may be recorded at a later date. In addition, these findings are hard to interpret as we cannot tell the precise date when patients stopped taking antidepressant medication, as they may not have taken all of the tablets in their last prescription.

Findings on patterns of antidepressant prescribing

Selective serotonin reuptake inhibitors were the most commonly prescribed drug class in the cohort; more than three-quarters of treated patients were prescribed an SSRI during follow-up, compared with 54% for TCAs and 19% for the other class of antidepressant drugs. Very few patients were prescribed a MAOI (0.2%). There was a steep increase in the proportion of prescriptions that were for SSRIs over the study period, with a corresponding reduction for TCAs. There was also an increase for the group of other antidepressant drugs and a slight reduction in MAOI prescribing. These trends, are likely to reflect the availability of new SSRIs and other antidepressant drugs, and concerns that TCAs have more side effects and are more toxic in overdose than SSRIs, as well as recommendations in guidelines. MAOIs have never been recommended for older people because of possible interaction effects with other medicines that older people, in particular, are likely to take and with certain foods.

Patients who had been prescribed SSRIs were slightly less likely than patients prescribed TCAs or other antidepressant drugs to either stop after a single prescription or switch to another drug class in the year following their first prescription: 37% for SSRIs, 48% for TCAs, 50% for the group of other antidepressant drugs. Among the individual antidepressant drugs, the proportions of patients who either stopped after a single prescription or switched to another drug in the year

following their first prescription were lowest for citalopram (42%) and mirtazapine (43%), and highest for lofepramine (60%), amitriptyline (56%) and trazodone (54%).

Findings from analyses of costs

It was difficult to conclude that one particular class was more cost-effective than another in terms of adverse events avoided. Although SSRIs were estimated to have the lowest mean cost, they often had higher estimated adverse event rates than other classes (sudden cardiac death and upper GI bleed were the exceptions). Conversely, TCAs were often estimated to be associated with lower adverse event rates (this was the case for attempted suicide, epilepsy/seizures, falls, fractures, MI, stroke/TIA and suicide), but higher costs. However, as it is unclear what one would be willing to pay to avert the different types of adverse events it is difficult to assess whether the provision of TCAs would constitute value for money. The group of other antidepressant drugs was dominated, however, by either SSRIs or TCAs for 10 of the 13 adverse events, as they had higher mean cost and adverse event rates (the exceptions were ADRs, hyponatraemia and RTAs).

In terms of individual drugs, amitriptyline was estimated to have the lowest prescription costs (for all antidepressant drugs), although when practice/community nurse and GP visits (which far outweigh prescription costs) were included fluoxetine had the lowest cost. Venlafaxine was estimated to have the highest mean cost from both these perspectives. Dominance occurred only with regard to attempted suicide, for which amitriptyline was estimated to have both the lowest prescription cost and adverse event rate. In all other cases, the most cost-effective drug in terms of adverse events avoided was estimated to be dependent on what one would be willing to pay to avert an adverse event, which is an unknown factor. That said, in the base-case analysis, as it appeared on the efficiency frontier, dosulepin was estimated to be potentially cost-effective for 8 of the 13 types of adverse events. Finally, it should be noted that the conclusions drawn from the results of the sensitivity analyses, where costs were conducted over a 1-year period and additionally included visit costs, were similar to those discussed above.

Strengths of the study

This study has a number of strengths. It is a large study, comprising over 60,000 patients over the age of 65 years who had been diagnosed with depression, followed up for up to 13 years, with a mean length of follow-up of 5.0 years. This study size enabled us to detect associations with relatively rare adverse events, which would not be possible with clinical trials of antidepressant drugs which are smaller and have shorter follow-up periods and so are generally underpowered to detect effects on adverse events unless they are very common.

The study had broad inclusion criteria and so the findings are generalisable to the population of older people diagnosed with depression in primary care. This, again, 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 medication for other conditions. In addition, we included all eligible patients, as individual consent to participate was not required, which reduces selection bias and increases external validity compared with clinical trials or many cohort and case-control studies, and for which patients need to consent to participate, which may lead to a highly selected group participating in the study. As it has been shown that practices within the QResearch database are generally representative of those within England and Wales,⁴² this will also increase the generalisability of results.

The data on the database are recorded prospectively, so all information on prescriptions for antidepressant drugs and potential confounding variables was recorded before occurrence of any adverse event. This means that recall bias will not have occurred in this study, which can be

a problem in case-control studies collecting information after the occurrence of adverse events. We were able to adjust our analyses for a number of potential confounding variables, including comorbidities and use of other medications.

We had details of all prescriptions for antidepressant drugs issued in primary care throughout the follow-up period, so were able to carry out detailed 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 is collected only at the start of the study.

The detailed information about the number of GP and nurse visits enabled us to assess whether patients prescribed certain antidepressant drugs were more likely to visit these health-care professionals, for example to renew prescriptions or to have their symptoms monitored. The collation of such detailed information may not have been possible with other study designs or would be susceptible to recall bias.

Limitations of the study

The main concerns from observational studies such as this one are indication and ascertainment bias. Indication bias occurs when patients are prescribed medication for a condition that is itself associated with the outcome of interest. This means that apparent associations with a medication may be in fact owing to the condition for which it was prescribed rather than the medication itself. To reduce this bias we restricted our study cohort to patients with a recorded GP diagnosis of depression, as depression itself is associated with many adverse outcomes.^{69–72} There are still likely to be systematic differences between those who are treated and those who are not. The latter are more likely to have less severe and chronic depression, and to express a preference for psychological treatment, and they may have poorer physical health, such that they are considered too frail for antidepressant medication. We adjusted the analyses for many of factors that could differ between groups and which are risk factors for the adverse outcomes, including age, gender, severity of depression, a number of comorbidities and use of other medications. Generally, the adjustment did not have a large effect on the results (this was the case for both adverse events and costs), as there were no big differences in these factors according to whether or not antidepressant medication was prescribed. However, although we adjusted for severity of the initial diagnosis of depression, we were able to use only a crude measure, as we did not have a detailed depression severity score. We cannot therefore exclude the possible effect of residual confounding on our results.

Another concern in direct comparisons of drugs is channelling bias, whereby different antidepressant drugs might be prescribed according to various patient characteristics. An example of this would be preferentially prescribing SSRIs rather than TCAs to frail patients who were at greater risk of falling.²⁰ 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 a large number of other confounders. This bias would be less likely to apply to comparisons between individual drugs within a class than to comparisons between classes, and we have found differences between individual drugs within classes for some of the outcomes.

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. For these reasons we also carried out a self-controlled case-series analysis, which can largely remove the problems of residual confounding and selection and indication bias.⁵⁷ This is a within-patients comparison, which implicitly removes the effects of all

patient 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.⁵⁷ This means that factors such as patient frailty or level of physical activity, which may not be recorded on the database, are implicitly accounted for, and, as the analysis compares outcome rates across different periods of exposure in treated patients rather than comparing treated with untreated patients, the issue of indication bias arising from the cohort analyses discussed above is reduced. The results from the case-series analyses were generally in accordance with the findings from the cohort analyses, although there were some differences for attempted suicide/self-harm and stroke/TIA, suggesting possible indication bias. However, case-series analyses are less valid when the adverse event is a fatal one, so we do not consider the findings of high increase in mortality rates from the case-series analysis to be reliable.

The main remaining bias is due to changes in severity of depression over time. The presence and severity of depression can vary considerably over time, particularly after starting antidepressant treatment, and our analysis was not able to accommodate this. This is a source of bias in both the cohort analyses and the case-series analysis, which implicitly adjusts only for confounders which do not change over time. As antidepressant prescribing and the presence and severity of depression change over time and will be highly correlated, it is difficult to separate their effects in these analyses. This could explain why increases 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 impact on direct comparisons between classes or individual antidepressant drugs than on comparisons with non-use of antidepressant drugs. So, for example, where analyses show similar increases for all classes of antidepressant use compared with periods of non-use we cannot be sure that these are not due to the effects of depression itself, but where there are differences between classes or individual drugs these are more likely to be direct effects of the drugs.

The outcome measures we used were not specifically validated in this study, although some have been validated in other UK primary care databases and we would expect similar levels of validity in QResearch. We included information from death certificates to identify additional patients with the outcomes, and this will have reduced misclassification. However, some outcomes may be more likely to be recorded by a GP if a patient is known to be taking antidepressant drugs which could increase the HRs – this could be the case for ADRs, for example. In addition, patients taking antidepressant drugs visit their GPs and practice nurses more frequently, and this could lead to additional tests for certain outcomes (hyponatraemia) and an increased likelihood of reporting more minor events, such as some ADRs or some falls. This is an ascertainment bias, and could affect comparisons with the group not currently taking antidepressant drugs; however, the numbers of visits to GPs and practice nurses were similar for each class of antidepressant drugs, so the direct comparisons between classes should be less affected by this source of bias. We restricted our analyses to first events for each outcome, as it is difficult to distinguish whether subsequent recorded events are new events or reviews of previous events; this also reduces confounding effects due to previous events, but does mean we were unable to assess the effects of antidepressant medication in people with previous events.

The data on prescriptions for antidepressant drugs are likely to be reliably recorded; however, prescriptions in secondary care may not be included. As the majority of people with depression are treated in primary care, this should not have much of an effect on our results. Furthermore, we do not know whether prescriptions dispensed were actually taken, and there is research showing that adherence with antidepressant medication is low in patients with depression;^{73,74} for example, one study in older people found that nearly one-third of patients were not fully adherent with their medication.⁷³ This would tend to reduce the HRs comparing drug use with

non-use, but if the adherence with medication varies by drug class or individual drugs then this may distort direct comparisons between drugs.

There were some missing data in our study, for example smoking status was missing for 5% of the cohort. We did not adjust for BMI, which was missing for 28% of the cohort in our main analyses; however, there were only small differences when we did adjust for BMI in a complete case analysis.

In our analyses we treated antidepressant use as a time-varying exposure, as this relates the rate of events to the antidepressant currently being used, rather than basing results on the first antidepressant prescribed, for example. This is particularly important given the large amount of switching between antidepressant drugs during the follow-up period; however, we did not directly account for changes in dose or previous switches between antidepressant drugs in the models owing to the complex patterns of antidepressant use over time.

We have presented absolute as well as relative rates for the outcomes studied; however, we did not account for death as a competing risk in our analyses so the estimates of absolute rates will tend to overestimate the true values.

With regard to the health economic analysis, one limitation was that we were unable to estimate costs from the NHS and Personal Social Services viewpoint as, among other things, levels of resource use in secondary care are not routinely recorded in the QResearch database. The collation of secondary-care costs would have enabled us to estimate and include the costs associated with adverse events. Their inclusion would have been likely to mean that antidepressant drugs that had a low adverse event rate would have had relatively lower overall costs, which may have led to improvements in the cost-effectiveness of such antidepressant drugs in terms of adverse events.

Estimation of the cost per adverse event averted is in line with previous cost-effectiveness studies;⁷⁵ however, a weakness of this technique is that, as it is unclear what one would be willing to pay to avert the different types of adverse events, it is difficult to make recommendations with regard to cost-effectiveness. Thus, in the absence of dominance we have been able to identify only those antidepressants that are potentially cost-effective, as they appear on the efficiency frontier. This limitation could potentially be overcome by seeking to estimate the loss in utility associated with each of the different types of adverse events, as discussed in the subsequent section on the implications for further research.

Finally, it should be reiterated that the above analyses focus on adverse events. This is justified on the basis that different antidepressant classes have largely similar efficacy.³⁻⁷ A further limitation of this study, however, is that efficacy data for the different antidepressant drugs are not available in the QResearch database.

Interpretation of the study findings in light of previous research

All-cause mortality

There is a complex picture in relation to antidepressants and mortality in the literature with differential effects according to age, gender, underlying physical morbidity, response of depression to antidepressant treatment and class of antidepressant.

A cohort study from Finland found that current use of all antidepressant drugs and each class of antidepressant (SSRIs, TCAs and other antidepressant drugs) was associated with a reduced

mortality rate compared with no current use or one antidepressant prescription only.⁷⁶ Another cohort study in Finland of subjects hospitalised because of a suicide attempt also found reduced mortality during use of all antidepressant drugs;⁷⁷ however, in this study only 5% of the sample was aged 65 years or older and the analysis did not control for physical comorbidity, although it did control for the number of previous suicide attempts.

In a cohort study from Sweden, antidepressant treatment in patients over 65 years of age was associated with increased all-cause mortality and mortality from cardiovascular disease.²⁸ The analysis controlled for baseline comorbidity but not for gender, current or past depression, suicidal ideation or self-harm. A cohort of union members found that antidepressant drugs were not associated with an increase in all-cause mortality after adjustment for confounding variables;⁷⁸ however, this study contained few people aged over 65 years.

A more complex picture emerges in a French prospective study of non-institutionalised patients aged over 65 years.²⁹ After adjustment for confounders there was a difference in the effects of antidepressant drugs according to gender and severity of depression. In men, antidepressant drugs were associated with increased mortality, especially in those with severe depression. In women, use of antidepressant drugs was not associated with increased mortality and the only increase was in women with severe depression who were not taking antidepressant drugs. There was no increase in mortality in men or women who were on antidepressant drugs but not currently depressed.²⁹ Given that both mild and especially severe depression increased mortality, there is a possibility that the increase in mortality in men taking antidepressant drugs is due to indication bias, whereby antidepressant drugs were prescribed for depression, which is the cause of increased mortality rather than the treatment itself.

This observation has support from prospective studies. In one study, severe depression in the first 2 weeks of hospitalisation for an acute coronary syndrome and failure to improve from depression after treatment with the SSRI antidepressant sertraline or placebo was associated with a twofold increase in mortality rate in the following 7 years.⁷⁹ Persistent depression was associated with poor adherence to antidepressant drugs. The sample included a substantial proportion of older people and the effects were not age or gender dependent. Both major and minor depression at the time of acute MI reduced survival in the ENRICHED (Enhancing Recovery in Coronary Heart Disease) study.⁸⁰ In women with suspected CHD, an analysis that controlled for cardiovascular risk factors and severity of depression and anxiety symptoms showed that a combination of antidepressant drugs and sedatives was associated with increased all-cause mortality compared with antidepressant drugs alone, sedatives alone or neither antidepressant drugs nor sedatives.⁸¹ All of these data point to the severity of depression and its response to treatment or the ability to tolerate antidepressant drugs to be predictive of mortality rather than antidepressant drugs themselves.

Many of these studies were carried out in people at high risk of cardiovascular disease and in the elderly. In a primary-care population that contained mostly people of middle age, there were no significant differences between mortality rates for six antidepressant drugs after adjustment for age and gender.⁸²

In summary, the literature shows that the severity of depression and its previous course, gender, response to antidepressant treatment and the ability to tolerate and adhere to antidepressant treatment seem to be more likely to be associated with mortality rather than the effects of antidepressant treatment alone. In our study we found that increased rates of mortality were particularly associated with the group of other antidepressant drugs and SSRIs during the first 28 days of use of antidepressant drugs, with a reduced risk after 85 days of use. This pattern could

reflect the effects of an improvement in severity of depression after starting treatment, and a subsequent reduction in mortality rates.

Sudden cardiac death

Few studies have looked specifically at the relationship between sudden cardiac death and antidepressant use. One study using data from the Nurses' Health Study³⁰ found an increased risk of sudden cardiac death among those with depression, and, more specifically, there was more than a threefold increase among those treated with antidepressant drugs. The risk did not differ by class of antidepressant and was independent of a proxy measure for severity of clinical depression. In another study an elevated risk of sudden cardiac death was observed for TCA doses of more than 100 mg (amitriptyline equivalents) compared with non-users of antidepressant drugs but not with lower doses of TCAs or SSRIs.⁸³ A nested case-control study in another UK primary-care data set found that venlafaxine was not associated with an increased risk of sudden cardiac death when compared with fluoxetine, dosulepin or citalopram.⁸⁴

Other associations indirectly provide some evidence of an association between antidepressant use and sudden cardiac death. In a study of survival among patients with heart failure,⁸⁵ antidepressant drugs were associated with increased mortality rates after adjustment for depression severity. However, the study was not large enough to look at mortality specific to antidepressant class. Compared with other antidepressant drugs, SSRI use was found to be associated with increased mortality among patients with coronary artery bypass grafting.⁸⁶ No studies have been restricted to older patients.

In our study the number of sudden cardiac deaths was small and we are unable to draw firm conclusions on any associations with antidepressant treatment.

Suicide

Twenty per cent of fatal self-poisonings (whether there was suicide intent or not) involve antidepressant drugs,^{87,88} although there are lower rates of detectable antidepressant drugs in the over-85-year age group, possibly reflecting lower rates of antidepressant prescribing at this age. Among suicides involving people with a recent physician-recorded diagnosis of depression, around one-third had detectable antidepressant drugs at the time of death.⁸⁹ Sedatives, rather than antidepressant drugs, are found more often in older suicide victims.⁹⁰ A study of suicides in older people found that the commonest methods of suicide were hanging in men and drug overdose in women.⁹¹

There is some evidence that tricyclic antidepressant drugs, with the exception of lofepramine, may result in a higher relative mortality from overdose of that antidepressant than MAOIs, other antidepressant drugs and particularly SSRI antidepressant drugs.⁹²⁻⁹⁸ A national study relating primary-care prescription data to mortality data in England, Scotland and Wales⁹³ found that amoxapine, dosulepin, amitriptyline, trimipramine and nortriptyline were particularly associated with high mortality from overdose, whereas fluoxetine, lofepramine, paroxetine, mianserin and fluvoxamine were associated with a lower mortality from overdose.

Arguably the more important question is whether antidepressant drugs in general and specific classes of antidepressant drugs or individual antidepressant drugs are associated with changes in suicide rates. A number of ecological studies have shown that the suicide rate has decreased as prescribing rates for SSRI antidepressant drugs have increased, but they do not fully account for the decline that started before SSRI antidepressant drugs were introduced.⁹⁹⁻¹⁰⁵ There are mixed results concerning whether use of tricyclic antidepressant drugs has changed suicide rate with claims both that they have increased¹⁰² and decreased rates.¹⁰⁶⁻¹⁰⁸ Most studies claim that

the largest effects are in the elderly, but absolute risk reductions in suicide with antidepressant drugs in the elderly are low,¹⁰⁹ perhaps contributing to only 10% of the decline in elderly suicides because of underprescribing of effective doses of antidepressant drugs.¹¹⁰ However, a study in England found no clear relationship between antidepressant drugs or class of antidepressant and suicide.¹¹¹ Furthermore, most ecological studies do not adequately correct for risk factors for suicide, such as gender, age, alcohol use, previous suicide attempts, previous depression, divorce and unemployment, and, when they do, the relationship between antidepressant use and suicide may disappear.¹¹²

Meta-analyses of RCTs of antidepressant drugs in adults have tended to show no effect of antidepressant drugs overall or class of antidepressant drugs on suicide rates.^{113–115} Record linkage studies also tend to show no effect of antidepressant drugs overall, SSRIs or tricyclic antidepressant drugs on suicide.^{116–117} However, a national cohort study in Finland found that SSRIs were associated with slightly decreased suicide rates, whereas TCAs and other antidepressant drugs had no effect.⁷⁷ Among specific antidepressant agents, fluoxetine was associated with decreased suicide rates and venlafaxine with increased suicide rates. In a case–control study with an analysis confined to the over-65-year age group, there was an increased risk of suicide, and particularly suicide by violent means, in the first month of SSRI antidepressant treatment compared with other antidepressant drugs.¹¹⁸ After the first month, use of SSRIs was not associated with an increased risk of suicide. These results were not confirmed in a study of suicidal thoughts in the elderly, which declined in the first 2 weeks of treatment with antidepressant drugs.¹¹⁹ A cohort study of elderly patients dispensed SSRIs found that the risk of suicide was not higher during periods of SSRI use than when antidepressant drugs were not being used.¹²⁰ Other studies have shown the emergence of new suicidal ideation and worsening of existing suicidal thoughts in 8–23% of patients in the first month of treatment, which usually subside in subsequent months with SSRIs and TCAs, particularly in men and retired people.^{121,122}

In summary, there is little evidence from the literature that use of SSRI antidepressant drugs increases suicide rates in the elderly, but some evidence that they may reduce rates, although numbers are small in absolute terms and some studies are not adequately controlled for confounding variables. The evidence for the effects of TCAs is less clear, and there is an absence of evidence concerning other antidepressant drugs and specific antidepressant agents. There is a possible risk of increased suicide in the first month of antidepressant treatment, particularly for SSRI antidepressant drugs, but this subsides in subsequent months.

We found that suicide rates were significantly associated with all classes of antidepressant drugs compared with non-use of antidepressant drugs, with highest rates associated with the group of other antidepressant drugs. The number of suicides in our study was small, so we were unable to carry out detailed analyses of individual drugs, dose or duration.

Attempted suicide/self-harm

There has been growing concern about the potential of antidepressant drugs to increase suicidality, especially in children, adolescents and young adults,¹²³ but there is also concern about these effects in the elderly, who have the highest suicide rates.¹¹⁹ Often suicidality is considered from the perspectives of suicidal ideation and suicidal behaviour, such as self-harm and mortality, but these are not necessarily on a continuum of severity of suicidality because suicides are more common in males and the elderly and self-harm is more common in females and younger adults.⁷⁷ Therefore, antidepressant drugs may have effects on suicidal ideation and self-harm that do not necessarily translate into an increased risk of suicide, so a complex picture emerges in relation to antidepressant drugs and suicidality.¹¹⁷ On the other hand, self-harm is an important clinical outcome in its own right as it often results in hospital admission.¹²⁴

The most comprehensive meta-analysis of suicidal behaviour or ideation using individual patient data from randomised controlled trials registered with the US Food and Drug Administration (FDA) found that age has an important mediating effect in relation to antidepressant drugs and suicidal behaviour and ideation.¹²⁵ In the group aged 65 years and over, antidepressant drugs reduced suicidal behaviour and ideation, especially in patients with a diagnosis of a major depressive episode. The biggest reductions in suicidal behaviour and ideation were in the group aged 75 years and over. There were no significant differences between drugs in adults overall. Typically, these trials exclude patients who are actively suicidal, which reduces their generalisability.

An earlier meta-analysis of study using FDA-registered RCTs comparing SSRIs and other antidepressant drugs with placebo or a comparator group of older antidepressant drugs (amitriptyline, imipramine or trazodone) found no significant differences in attempted suicide rates between the groups.¹¹³ There was no analysis by age group.

An analysis of data from RCTs submitted to the UK Medicines and Healthcare products Regulatory Agency (MHRA) showed weak evidence of an increase in self-harm with SSRI antidepressant drugs versus placebo;¹²⁶ however, this increase was not reflected in suicidal ideation or suicides. There was no analysis by age group. Meta-analyses of RCT data of the single agents fluoxetine,^{127,128} sertraline¹²⁹ and duloxetine¹³⁰ showed no change in self-harm compared with placebo or tricyclic antidepressant drugs. No analyses were performed by age and the studies involved few elderly participants.

In a nationwide cohort study in Finland of patients hospitalised for attempted suicide, all classes of antidepressant were associated with an increased rate of future attempted suicide when compared with no antidepressant use.⁷⁷ However, these increases were not reflected in increases in suicides or mortality. The sample included a relatively small number of patients over the age of 65 years. A sample of psychiatric outpatients with depressive episodes found a 50% decrease in self-harm over 6 months with antidepressant treatment.¹³¹ In a case-control study of attempted suicide,¹³² antidepressant use was associated with a reduced risk, whereas discontinuation, initiation and titration of dose up or down were associated with an increased risk of attempted suicide that did not diminish for 8 weeks. There was no analysis by age or gender.

In another large study of antidepressant drugs mostly prescribed by primary-care physicians, the risk of a suicide attempt was highest in the month before starting an antidepressant and progressively declined in the next 6 months.¹³³ The pattern was similar in those aged over 50 years and in younger age groups. In contrast with some other studies, in this study the risk of suicide attempts in the first month after treatment was higher in patients on TCAs and trazodone than in those on SSRIs and other antidepressant drugs.

In a case-control study using the UK General Practice Research Database (GPRD), patients with depression taking the TCAs amitriptyline or dosulepine or SSRIs fluoxetine or paroxetine showed an increase in suicidal ideation and behaviour in the first 3 months after starting the antidepressant compared with patients who were not prescribed antidepressant drugs.¹⁴ These findings were more marked in the first month of treatment, and on days 1–9 in particular. There were no differences in the results between the four antidepressant drugs. However, there were relatively few patients aged over 60 years and none was older than 69 years. The results were similar in a nested case-control study using a GP database in New Zealand, where use of SSRI antidepressant drugs was associated with an increase in self-harm but not suicide once age, gender and the presence of depression and suicidal ideation was controlled.¹³⁴

In another study also using the UK GPRD, but with a much larger sample of patients over the age of 60 years, rates of self-harm were not increased with use of SSRIs or other antidepressant drugs compared with TCAs.¹⁵ There were no differences between specific antidepressant agents, but the prescription of more than one antidepressant was associated with increased rates of self-harm. Another case-control study confined to patients who received psychiatric in-patient care for depression in the USA did not find an association between antidepressant drugs and self-harm in adults under 65 years,¹²³ although there were trends for more suicide attempts with venlafaxine and mirtazapine. No patients in this study were over the age of 64 years.

A problem with naturalistic studies is that antidepressant treatment may be inadequate, in terms of dosage and duration, to measure the antisuicidal effects of antidepressant drugs, particularly in patients who are at known high risk of self-harm.¹³⁵ These concerns may be less with the elderly, for whom a previous history of self-harm is not so closely associated with further self-harm.^{135,136} Furthermore, most studies do not adequately control for risk factors such as previous suicide attempts, previous depression, medical and psychiatric comorbidity other than depression, alcohol use disorders and marital status.¹³⁷

Around 20–30% of non-fatal self-poisoning episodes presenting to general hospitals involve antidepressant drugs.¹³⁸ In a study of patients with antidepressant overdose presenting to one Edinburgh hospital, the likelihood of self-harm was decreased by sertaline and amitriptyline, and increased by mirtazapine, venlafaxine and trazodone.¹²⁴ There was no analysis by age, so it is unclear how the findings relate to the elderly.

In conclusion, there are relatively few data on antidepressant drugs and self-harm in people over 65 years. The data suggest that in people over 65 years with depressive episodes antidepressant drugs tend to be associated with either reductions or no change in rates of self-harm, with no clear evidence of differences between classes of antidepressant drugs or specific antidepressant agents. Our findings of increased rates of attempted suicide for all classes of antidepressant drugs, which were most marked in the 28 days after an antidepressant prescription, suggest an effect of depression itself rather than a direct causal effect; however, the findings of particularly increased rates for mirtazapine, venlafaxine and trazodone compared with other antidepressant drugs are in accordance, to some extent, with the study by Bateman and colleagues¹²⁴ and warrant further investigation.

Myocardial infarction

A case-control study of patients with MI, aged between 40 and 75 years, found SSRI use (but not TCA or atypical antidepressant use) to be protective against MI.¹³⁹ A slight protective effect of current use of SSRIs on acute MI was also found in a study using GPRD data,¹⁴⁰ but not for other antidepressant drugs. However, recent past SSRI use was associated with a slightly raised risk. Among a large cohort of people who were hospitalised in Finland for a suicide attempt, SSRIs were associated with a lower rate of cardiovascular deaths.⁷⁷

In a Danish case-control study¹⁷ there was a protective effect of all classes of antidepressant on MI, but only when restricted to those with a history of cardiovascular disease. In a cohort study of 136,293 post menopausal women, antidepressant use was not associated with incident CHD (defined as fatal plus non-fatal MI or death due to definite or possible CHD).³² This was one of the few studies to have adjusted for severity of depression.

Another study using GPRD data found antidepressant drugs to be associated with an elevated risk of MI, but this was not specific to any antidepressant class.¹⁸ The authors argued that this

association is most likely to be explained by the nature of depression itself (indication bias) and health utilisation rather than by the antidepressant drugs themselves. However, a large cohort study carried out in North America found a twofold increased risk of MI in those prescribed TCAs, with no elevated risk among those treated with SSRIs.⁷⁸ One study confined to older people found that SSRI users were at increased risk of MI compared with non-users after adjusting for depression.¹⁴¹ A case-control study found no association between risk of ischaemic heart disease and use of SSRIs or the TCAs amitriptyline and lofepramine after adjustment for confounders, but dosulepin (formerly known as dothiepin) was associated with an increased risk which increased with the number of prescriptions.¹⁶

Overall, there are no clear findings in the literature for MI risk and antidepressant use in older people. While some studies have provided evidence of increased risk of MI with antidepressant use,^{17,18,78,141} others have found that antidepressant drugs confer a protective effect,^{77,139,140} with others finding no association.³² Increased risk has been observed as being restricted to TCAs,⁷⁸ SSRIs¹⁴¹ or across classes^{17,18} or restricted to particular drugs.¹⁶ Evidence of a protective effect is largely limited to SSRIs.^{139,140}

Our study found no clear evidence of a difference in myocardial risk between antidepressant classes, although there was some indication of an increased risk associated with SSRIs, mostly confined to fluoxetine and occurring during the first 28 days of use.

Stroke

There have been a number of trials of antidepressant treatment for post-stroke depression, but few have looked at stroke outcomes.¹⁴² In a cohort of post menopausal women, after adjusting for severity of depression, use of SSRIs and the group of other antidepressant drugs were associated with an increased risk of stroke, with other antidepressant drugs having the highest HR.³² SSRIs were a risk factor for haemorrhagic stroke in particular. In a case-control study of patients with depression, the risk of stroke was increased for all antidepressant classes compared with no antidepressant use.³¹

In a Finnish study of subjects who were hospitalised for suicide attempts, there was reduced mortality among those treated with SSRIs, due to a decrease in cerebrovascular-related deaths.⁷⁷ A Danish case-control study¹⁴³ found no association between antidepressant use and intracerebral haemorrhage or ischaemic stroke, although there was some evidence of an increased risk of intracerebral haemorrhage among those taking both SSRIs and NSAIDs.

A comparison of antidepressant drugs in terms of their degree of serotonin reuptake inhibition found no difference in the risk of haemorrhagic stroke across groups (including non-users).¹⁴⁴ Data from the Framingham Heart Study indicated that depressive symptoms were predictive of stroke/TIA among only those aged < 65 years, but revealed no evidence to support an association between antidepressant use and stroke.¹⁴⁵ In a matched case-control study there was no evidence of an increased risk of haemorrhagic stroke among SSRI users.¹⁴⁶ An analysis of GPRD data found no evidence of an increased risk of intracranial haemorrhage among users of antidepressant drugs,¹⁴⁷ although the level of antidepressant use was not high enough to exclude the possibility of anything other than fairly large effects.

Findings from previous studies are therefore inconsistent, but some suggest a possible increase in risk among users of antidepressant drugs. Our study findings showed a significantly increased risk of stroke/TIA associated with SSRIs and the group of other antidepressant drugs.

Falls

There is a large literature on the risk of falls in relation to antidepressant drugs among older people,^{148,149} with some studies suggesting that the risk for TCAs is similar to that for SSRIs,^{150,151} while others suggest that SSRIs have the highest risk.¹⁵² Few studies have examined effects of individual drugs. Sedation, insomnia and impaired sleep, nocturia, impaired postural reflexes and increased reaction times, postural hypotension, and cardiac rhythm and movement disorders have all been proposed as contributing factors to falls in patients who are taking antidepressant drugs; however, it is difficult to distinguish whether these are due to antidepressant treatment or effects of depression itself.

A review of 78 studies¹⁴⁸ found that although there are extensive data for TCAs and SSRIs, there are few data for other antidepressant drugs. The effects of TCAs and SSRIs on the risk of falls were found to be generally similar across studies. There were insufficient data to exonerate any individual antidepressant or class of antidepressant drugs as a potential cause of falls. The authors reported that the magnitude of the increased risk of falling with an antidepressant is about the same as the excess risk found in patients with untreated depression.

A large meta-analysis of RCTs and observational studies of falls in patients older than 60 years found that antidepressant drugs had the strongest association with falls risk out of a number of different types of medication reviewed.¹⁴⁹ This analysis did not distinguish by class or individual drug.

A cross-sectional survey of patients aged 60 years and over¹⁵² found that use of antidepressant drugs – SSRIs in particular – was strongly associated with the risk of falls, regardless of the presence of depressive symptoms. Another cross-sectional survey of patients aged 65 and over¹⁵³ found that SSRIs were significantly associated with the risk of falls but that other antidepressant drugs were not; however, only a small number of patients were taking other antidepressant drugs.

A cohort study of patients aged 60 years and over¹⁵⁴ found that SSRIs were associated with over a twofold increase in risk of falls and injurious falls, but there was no significant increase in risk for non-SSRI antidepressant drugs. A cohort study of nursing home residents¹⁵¹ found that patients taking TCAs had a twofold increased rate of falling compared with non-antidepressant users, and SSRIs were associated with an 80% increase; however, trazodone was not associated with an increased falls rate. The study found dose–response effects for TCAs and SSRIs, and a persistent effect throughout treatment.

Our finding of an increased rate of falls for all antidepressant drugs, being slightly higher for SSRIs, is in general accordance with other studies, as are our findings of a dose–response effect and a persistent effect during treatment.

Fracture

A case–control study and case-series analysis²⁰ found that both SSRIs and TCAs were associated with an increased risk of hip fracture, which was most marked in the first 15 days of treatment. The case-series analysis showed lower effects than the case–control study, suggesting that the case–control study was subject to some indication bias. The increased risk with SSRIs and TCAs remained throughout the treatment period, but decreased more steeply for TCAs.

A case–control study of hip fracture in people over 65 years old¹⁹ found more than a twofold increased risk for SSRIs and for secondary amine TCAs (nortriptyline, protriptyline and

desipramine), and a 50% increase for tertiary amine TCAs (amitriptyline, clomipramine, doxepin, imipramine and trimipramine). Risks were higher for current use than for former use, and for new current users than for continuous current users, in all three drug classes.

A cohort study of patients aged 55 years and over¹⁵⁵ found that the risk of non-vertebral fractures increased by over twofold among patients taking SSRIs compared with past antidepressant users, and there was a 50% increase for TCAs users, which was not statistically significant. The association increased with prolonged use for SSRIs but decreased for TCAs. Another cohort study of patients aged 50 years and over¹⁵⁶ found that daily SSRI use was associated with a twofold increased rate of low-trauma fractures, but there was no statistically significant effect for TCAs (HR 1.2, 95% CI 0.7 to 2.2). This study also found an increased risk of falling among SSRI users, and a reduced bone mineral density. A case-control study that examined individual drugs in the group of other antidepressant drugs as well as TCAs and SSRIs found dose-response relationships for some TCAs and SSRIs but not for other drugs.¹⁵⁷

The increased risk of fracture associated with antidepressant use may be due to an increased risk of falls, but there is also evidence of reduced bone mineral density in SSRIs users. For example, a study of 5995 men aged 65 years and older¹⁵⁸ found that bone mineral density was lower among those reporting current SSRI use, but not among users of other antidepressant drugs. A cohort study of older women found that use of SSRIs but not of TCAs was associated with an increased rate of bone loss at the hip.¹⁵⁹

Overall findings from the literature suggest that SSRIs and TCAs are associated with increased fracture rates, with possibly somewhat higher rates for SSRI use than for TCAs. There is little evidence for other antidepressant drugs. Our findings of a more marked and prolonged increase in risk for SSRIs, compared with TCAs, are in general agreement with this. Our finding of an increased risk associated with the group of other antidepressant drugs warrants confirmation in other studies.

Upper gastrointestinal bleeds

In a systematic review comparing SSRIs with TCAs in the treatment of depression in older people there was some suggestion that GI problems were more common in those patients who were treated with classical TCAs, although the number of adverse outcomes was too low to be conclusive.¹⁶⁰ In the absence of trials of sufficient size to identify differences in rare adverse outcomes, studies examining associations between antidepressant use and GI bleeding have been largely confined to cohort studies^{24–26} and case-control studies.^{27,161–163} Whereas some studies have found an increased risk of GI bleeds to be associated with antidepressant use,^{24,27,161} others have found no evidence for an effect.^{25,163} There is conflicting evidence as to whether^{25,26,162} or not²⁷ that risk is increased in the presence of NSAID use.

Much of the evidence is not specific to older age groups; however, in a retrospective cohort of Canadians aged 65 years and over, the risk of GI bleeding increased with higher levels of inhibition of serotonin reuptake,²⁴ and was greatest in the oldest age groups and those with previous upper GI bleeding. Among adults admitted to hospital, a modest increased risk of GI bleeding was found with antidepressant use, but this was restricted to the group of other antidepressant drugs rather than TCAs or SSRIs.¹⁶¹ A case-control study found that SSRIs overall were associated with an increased risk of upper GI tract bleeding, and also found a particularly increased risk for venlafaxine.¹⁶²

In a study of medication data, combined use of SSRIs and NSAIDs strongly increased the risk of GI adverse effects.²⁵ A study of hospitalisation data in Denmark reported similar findings of an increased risk of upper GI bleeding with use of SSRIs, which was increased by concurrent

use of NSAIDs or low-dose aspirin.²⁶ There is some evidence that this risk is attenuated with the use of acid-suppressing agents.¹⁶² In contrast, a case-control study of incident cases of upper GI bleeds found no evidence of an increased risk of GI bleeding for SSRI use and no evidence of an interaction with NSAIDs.¹⁶³ A case-control analysis of GPRD data estimated that individually SSRIs and NSAIDs doubled the risk of GI bleeding but that this risk was not substantially increased when these drugs were prescribed together.²⁷ The relationship between antidepressant drugs and GI bleeding did not differ between those above and below 80 years.

In our study we found similar increased risks for all classes of antidepressant drugs. Our finding of a particularly increased risk associated with venlafaxine is in agreement with the findings of de Abajo and colleagues.¹⁶² Unlike some other studies, we did not find a significant interaction with use of NSAIDs or aspirin.

Epilepsy/seizures

Antidepressant drugs can result in seizures as an ADR and as a complication of an overdose.¹⁶⁴ Both are more likely in people with a history of epilepsy and with other disorders of the brain that might be associated with seizures, such as stroke. Depressive episodes are more likely in those with epilepsy and with other disorders of the brain than in the general population, so antidepressant drugs are used in more than 10% of people with these conditions.¹⁶⁵ Polypharmacy of drugs with the potential to induce seizures, including SSRIs and TCAs, increased two- or threefold in women and men with epilepsy, respectively, from age 34 to 85 years.¹⁶⁵ There are also claims that depression itself can increase the risk of seizures in people over the age of 65 years independently of taking antidepressant drugs.¹⁶⁶

Interrogation of the World Health Organization (WHO) Program for International Drug Monitoring database of ADRs shows a 12-fold variation in the reporting of seizures as a proportion of ADRs.¹⁶⁷ In general, tetracyclic drugs have higher rates of seizures than tricyclic drugs and these, in turn, have higher rates of seizures than SSRI antidepressant drugs.^{33,168}

Other literature also points to different potentials for specific drugs to induce seizures within classes of antidepressant. Desipramine and dosulepin may be more proconvulsant than other tricyclic antidepressant drugs.^{169,170} However, there are exceptions, with the growing realisation that escitalopram and citalopram may have a proconvulsive effect compared with other SSRI antidepressant drugs.¹⁷¹ A review of consecutive overdose patients admitted to one Edinburgh hospital also suggested that citalopram and venlafaxine are proconvulsants.¹⁷² Paradoxically, doxepin (TCA) and fluoxetine (SSRI) may have anticonvulsant effects,^{173,174} although there are no randomised controlled trials supporting these claims. However, nothing in the literature points to differential effects of age on the capacity for an antidepressant to produce a seizure unless there is polypharmacy or a greater risk due to underlying medical problems.

Our analyses found that the risk of epilepsy/seizures varied by antidepressant class and was increased for SSRIs and the group of other antidepressant drugs compared with no use of antidepressant drugs, but not for TCAs. Of individual drugs, venlafaxine had the highest rates. There is limited support for these findings in the literature.

Road traffic accidents

Studies that have tested the effects of antidepressant drugs on driving performance have found that sedating antidepressant drugs have a similar effect to alcohol.²¹

A study that examined risk factors for vehicle crashes specifically in older people¹⁷⁵ found that the use of antidepressant drugs increased the risk of a crash in men but not in women, with an approximate doubling in risk. Another study in older people found that current use of TCAs

increased the risk of a motor vehicle crash in men and women, and that the risk increased with dose and was substantial for high doses.¹⁷⁶ A case-control study also found an increased risk in older drivers taking TCAs.¹⁷⁷

In studies across all ages, a Norwegian study found similar increased risks for sedating (including TCAs and mirtazapine) and non-sedating antidepressant drugs (including SSRIs and venlafaxine).¹⁷⁸ In a self-controlled case-series study, Gibson and colleagues⁵¹ found that use of SSRIs for more than 4 weeks was associated with an increased risk of a motor vehicle crash, but shorter-term use was not, nor was the use of TCAs. Other studies have found no associations with antidepressant use.^{179,180}

Many of these studies have been unable to distinguish between effects of antidepressant use and direct effects of depression itself on risk of a crash, or account for possible changes in driving patterns that may occur in people with depression. Our findings of no association with RTAs for antidepressant medication in a study restricted to people diagnosed with depression suggests that at least part of the increased risk in other studies may be due to depression itself rather than its treatment.

Adverse drug reactions

A Swedish death registry study reported that antidepressant drugs account for approximately 7% of all fatal ADRs.¹⁸¹ Antidepressant drugs also have the highest Adverse Drug Reaction Hospitalization index based on a 7-year study of 454,520 events reported to a national drug poisoning data system related to commonly implicated therapeutic agents,³⁴ although this is across all age groups rather than the elderly.

The German drug safety programme in psychiatry reported an assessment of severe or new ADRs in patients treated with antidepressant drugs.¹⁸² The overall incidence of severe ADRs was 1.4% for exposed patients. Rates were higher for TCAs and lower for MAOIs and SSRIs. In particular, TCAs were associated with known risks, such as toxic delirium, grand mal seizures, and hepatic, urological, allergic and cardiovascular reactions. In SSRI-treated patients, psychic and neurological ADRs were most common, followed by GI, dermatological and endocrinological/electrolyte reactions, with agitation, hyponatraemia, increased liver enzymes, nausea, and the serotonin syndrome as the main unwanted symptoms. Venlafaxine was associated with adverse central nervous systems and somatic symptoms, such as severe agitation, diarrhoea, increased liver enzymes, hypertension and hyponatraemia. Mirtazapine was mostly connected with increased liver enzymes, cutaneous oedema and collapse.

A large multinational case-control study, conducted in Europe between 1997 and 2001, evaluated the risk of medications to induce severe cutaneous adverse reactions.¹⁸³ An association was found for sertraline (odds ratio 11, 95% CI 2.7 to 46) based on six cases and five controls. No association was found for fluoxetine or other SSRIs, although the authors mentioned the need to monitor fluoxetine closely.

We found little evidence of any difference between drugs for ADRs, although there was some indication of an increased risk for TCAs at high doses and for lofepramine and sertraline.

Hyponatraemia

Reviews of hyponatraemia^{184,185} have concluded that SSRIs cause hyponatraemia more frequently than other antidepressant drugs. The incidence of hyponatraemia caused by SSRIs was reported to vary widely from 0.5% to 32%, usually occurring within the first few weeks of treatment and returning to normal within 2 weeks after drug withdrawal. Older age was an important risk factor

for the development of hyponatraemia associated with SSRIs. However, a review of the risks and benefits of newer antidepressant drugs concluded that there is a lack of data on hyponatraemia.¹⁸⁶

A case-control study²³ found that SSRIs were associated with a threefold increased risk of hyponatraemia compared with non-use, and that hyponatraemia was more common in older patients. Another study by the same authors found that serotonergic antidepressant drugs (SSRIs and venlafaxine) were associated with the development of hyponatraemia, with the highest risk occurring in the first 2 weeks.¹⁸⁷

A study to determine risk factors associated with hyponatraemia during treatment with antidepressant drugs using the WHO database for spontaneous reporting of ADRs²² found that the risk for hyponatraemia during treatment with antidepressant drugs was highest in women, in the elderly, during the summer, and during the first weeks of treatment.

A study of elderly patients in a psychogeriatric inpatient unit¹⁸⁸ reported that the odds of hyponatraemia were increased in patients taking either an SSRI or venlafaxine compared with patients not taking these drugs, with venlafaxine having the larger risk.

There is fairly consistent evidence from these studies of an increased risk of hyponatraemia with SSRI use, and the findings of our study are in accordance with this, although we found increased risks only for the SSRIs citalopram, escitalopram and fluoxetine, but not paroxetine or sertraline. We also found some evidence of an increased risk associated with venlafaxine. As in other studies, the highest risks occurred during the first few weeks of starting the antidepressant and were no longer increased a few weeks after stopping treatment.

Analyses of costs

A draft National Clinical Practice Guideline¹⁸⁹ undertook a literature review to identify economic evaluations, comparing different antidepressant drugs, and identified nine studies. The report concluded that the pharmacoeconomic data were piecemeal as no study had compared all relevant antidepressant drugs in a single evaluation and went on to develop a cost-utility model to compare 10 antidepressant drugs.¹⁸⁹ It is difficult to make comparisons with any of these nine previous studies as they sought to identify the most cost-effective antidepressant, where successful treatment/QALY gain was the measure of effect, whereas the measures of effect within our analyses were the different adverse events (estimated number averted with different drugs). In terms of costs, the National Clinical Practice Guideline estimated that of the drugs assessed citalopram/fluoxetine had the lowest unit cost and venlafaxine the highest, which is in line with our estimates;¹⁸⁹ however, it did point out that venlafaxine has recently been released in generic form, and that escitalopram will be shortly. This means that the price for these drugs will fall in the future, which may have implications for estimates of cost-effectiveness.

Chapter 5

Conclusions

Implications for health care

The finding that SSRIs and drugs in the group of other antidepressant drugs were not associated with a reduced risk of any of the adverse outcomes compared with TCAs and may even be associated with an increased risk for certain outcomes implies that a careful evaluation of benefits and adverse outcomes is needed when prescribing antidepressant drugs to older people, which should include consideration of TCAs and tailoring of drugs to individual patients.

In this study, mirtazapine, venlafaxine and trazodone were associated with higher rates than the other antidepressant drugs for a number of outcomes, including all-cause mortality and attempted suicide/self-harm. Venlafaxine was also associated with the highest rates of stroke/TIA, fracture and epilepsy/seizures. These risks should be considered when prescribing these drugs.

There was evidence from the current study that use of a combination of antidepressant drugs was associated with an increased risk for many of the adverse events studied. Although this may reflect increased severity of depression and lack of response to monotherapy, it is a matter of concern, and use of a higher dose of a single antidepressant should be considered as an alternative to combined treatment where appropriate.

This study found that rates of most outcomes were highest in the first 28 days after starting an antidepressant, which would support careful monitoring during the first weeks after prescribing antidepressant drugs in older people.

The evidence suggests that all classes of antidepressant drugs are associated with an increased risk of falls and fracture in older people. These risks should be considered when prescribing these drugs.

There is fairly consistent evidence of an increased risk of hyponatraemia associated with SSRI use; we found increased risks associated with citalopram, escitalopram and fluoxetine but not with paroxetine or sertraline. We also found some evidence of an increased risk with venlafaxine. These risks should be considered when prescribing these drugs.

Implications for further research

There are few randomised trials of antidepressant drugs in older people, particularly in a primary-care setting, with sufficient size and length of follow-up to assess adverse outcomes as well as benefits. Thus, there is a need for a long-term randomised trial of antidepressant drugs in older people with depression in primary care comparing benefits and risks of more common adverse events between an SSRI and a low-dose TCA.

As all observational studies are susceptible to indication biases and residual confounding, and as it is particularly difficult in observational studies of antidepressant drugs to separate the effects of treatment from the effects of depression itself and changes in severity of depression, there is

a need for meta-analyses of randomised controlled trials of antidepressant drugs in relation to adverse events in older people to be carried out to confirm these findings.

Some of our findings are unexpected, and there is limited information in the literature on some of these adverse events in older people, particularly for individual drugs. Research is needed to confirm our findings using other data sources of older people in a community setting.

Further studies are needed to develop algorithms to individualise the risks associated with antidepressant use so that patients at highest risk of these adverse events can be monitored closely.

A number of adverse events have been examined within this study, but it is unclear which of the different adverse events it is most important to avert, what the overall loss is expected to be for the different types of antidepressant drugs, and what one would be willing to pay to avert an adverse event. Further research might be conducted with a view to estimate the loss in utility (disutility) associated with each of the different types of adverse events. This would enable calculation of expected QALY loss associated with the different types of antidepressant drugs for each adverse event. When combined with cost information this would enable one to estimate the incremental cost per loss in QALY averted, i.e. level of cost-effectiveness associated with different antidepressant drugs.

Conclusions

There are associations between use of antidepressant drugs and a number of adverse events in people with depression aged 65 years and older. These associations vary by antidepressant class and between individual drugs. There is no evidence that SSRIs or drugs in the group of other antidepressant drugs are associated with a reduced risk of any of the adverse outcomes compared with TCAs, and they may even be associated with an increased risk for certain outcomes. The risks of prescribing different antidepressant drugs need to be weighed against the potential benefits of these drugs. Limitations of this study include possible indication bias, and residual confounding.

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Contribution of authors

Carol Coupland (Associate Professor of Medical Statistics) was the chief investigator of the study and was involved in the conception and design of the study, carrying out statistical analysis, interpretation of data, reviewing the literature, and drafting and revising the report.

Paula Dhiman (Research Statistician) was involved in the design of the study, data checking, statistical analysis, interpreting data and reviewing the literature.

Garry Barton (Senior Lecturer in Health Economics) conducted the health-economic analyses, and was involved in interpretation of data, reviewing the literature and drafting the report.

Richard Morriss (Professor of Psychiatry and Community Mental Health) was involved in the conception and design of the study, interpretation of data, reviewing the literature, and drafting the report.

Antony Arthur (Senior Lecturer in Elder Care) was involved in the conception and design of the study, interpretation of data, reviewing the literature, and drafting the report.

Tracey Sach (Senior Lecturer in Health Economics) was involved in the conception and design of the study, health-economic analyses, interpretation of data, and drafting the report.

Julia Hippisley-Cox (Professor of Clinical Epidemiology and General Practice) was involved in the conception and design of the study, extraction of the data, interpretation of data, reviewing the literature and drafting the report.

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Appendix 1

Read codes used for depression and severity

Read codes used for identification of patients diagnosed with depression and their severity classification. The severity classification uses codes published by Martinez and colleagues¹⁵ and some additional classification by a member of the study team (RM).

Read code	Read code description	Severity
1465	H/O – depression	Mild
1B17	Depressed	Mild
1B17-1	C/O – feeling depressed	Mild
E1121	Single major depressive episode, mild	Mild
E1126	Single major depressive episode, in full remission	Mild
E1131	Recurrent major depressive episodes, mild	Mild
E1136	Recurrent major depressive episodes, in full remission	Mild
E118	Seasonal affective disorder	Mild
E2003	Anxiety with depression	Mild
E204	Neurotic depression reactive type	Mild
E2112	Depressive personality disorder	Mild
E290	Brief depressive reaction	Mild
E2B0	Postviral depression	Mild
Eu320	[X]Mild depressive episode	Mild
Eu320-99	Mild depression	Mild
Eu32-1	[X]Single episode of depressive reaction	Mild
Eu32-2	[X]Single episode of psychogenic depression	Mild
Eu324	[X]Mild depression	Mild
Eu32y	[X]Other depressive episodes	Mild
Eu32y-2	[X]Single episode of masked depression NOS	Mild
Eu32z-1	[X]Depression NOS	Mild
Eu32z-2	[X]Depressive disorder NOS	Mild
Eu32z-4	[X]Reactive depression NOS	Mild
Eu330	[X]Recurrent depressive disorder, current episode mild	Mild
Eu33-1	[X]Recurrent episodes of depressive reaction	Mild
Eu33-2	[X]Recurrent episodes of psychogenic depression	Mild
Eu33-3	[X]Recurrent episodes of reactive depression	Mild
Eu33-4	[X]Seasonal depressive disorder	Mild
Eu33-5	[X]SAD – seasonal affective disorder	Mild
Eu341	[X]Dysthymia	Mild
Eu341-1	[X]Depressive neurosis	Mild
Eu3y1-1	[X]Recurrent brief depressive episodes	Mild
Eu412-1	[X]Mild anxiety depression	Mild
R007z-3	[D]Postoperative depression	Mild
2257	O/E – depressed	Moderate
E002	Senile dementia with depressive or paranoid features	Moderate
E0021	Senile dementia with depression	Moderate

Read code	Read code description	Severity
E002z	Senile dementia with depressive or paranoid features NOS	Moderate
E112	Single major depressive episode	Moderate
E1122	Single major depressive episode, moderate	Moderate
E112-2	Endogenous depression first episode	Moderate
E1123	Single major depressive episode, severe, without psychosis	Moderate
E112-3	Endogenous depression first episode	Moderate
E1125	Single major depressive episode, partial or unspec remission	Moderate
E112z	Single major depressive episode NOS	Moderate
E1132	Recurrent major depressive episodes, moderate	Moderate
E1135	Recurrent major depressive episodes, partial/unspec remission	Moderate
E1137	Recurrent depression	Moderate
E115-1	Manic-depressive – now depressed	Moderate
E11y	Other and unspecified manic-depressive psychoses	Moderate
E11y2	Atypical depressive disorder	Moderate
E11z2	Masked depression	Moderate
E291	Prolonged depressive reaction	Moderate
E2B	Depressive disorder NEC	Moderate
E2B1	Chronic depression	Moderate
Eu32	[X]Depressive episode	Moderate
Eu321	[X]Moderate depressive episode	Moderate
Eu321-99	Moderate depression	Moderate
Eu322-3	[X]Single episode vital depression without psychotic symptoms	Moderate
Eu32y-1	[X]Atypical depression	Moderate
Eu32z	[X]Depressive episode, unspecified	Moderate
Eu32z-3	[X]Prolonged single episode of reactive depression	Moderate
Eu33	[X]Recurrent depressive disorder	Moderate
Eu331	[X]Recurrent depressive disorder, current episode moderate	Moderate
Eu332-1	[X]Endogenous depression without psychotic symptoms	Moderate
Eu332-2	[X]Major depression, recurrent without psychotic symptoms	Moderate
Eu332-3	[X]Manic-depressive psychosis, depressed, no psychotic symptoms	Moderate
Eu332-4	[X]Vital depression, recurrent without psychotic symptoms	Moderate
Eu334	[X]Recurrent depressive disorder, currently in remission	Moderate
Eu33y	[X]Other recurrent depressive disorders	Moderate
Eu33z	[X]Recurrent depressive disorder, unspecified	Moderate
Eu33z-1	[X]Monopolar depression NOS	Moderate
Eu341-4	[X]Persistent anxiety depression	Moderate
Eu3y0-1	[X]Mixed affective episode	Moderate
Eu412	[X]Mixed anxiety and depressive disorder	Moderate
ZV111-1	[V]Personal history of manic-depressive psychosis	Moderate
E0013	Presenile dementia with depression	Severe
E11-2	Depressive psychoses	Severe
E1120	Single major depressive episode, unspecified	Severe
E112-1	Agitated depression	Severe
E1124	Single major depressive episode, severe, with psychosis	Severe
E112-4	Endogenous depression	Severe
E113	Recurrent major depressive episode	Severe
E1130	Recurrent major depressive episodes, unspecified	Severe
E113-1	Endogenous depression – recurrent	Severe
E1133	Recurrent major depressive episodes, severe, no psychosis	Severe
E1134	Recurrent major depressive episodes, severe, with psychosis	Severe

Read code	Read code description	Severity
E113z	Recurrent major depressive episode NOS	Severe
E11y0	Unspecified manic–depressive psychoses	Severe
E130	Reactive depressive psychosis	Severe
E130–1	Psychotic reactive depression	Severe
E135	Agitated depression	Severe
Eu322	[X]Severe depressive episode without psychotic symptoms	Severe
Eu322–1	[X]Single episode agitated depression without psychotic symptoms	Severe
Eu322–2	[X]Single episode major depression without psychotic symptoms	Severe
Eu322–99	Severe depression	Severe
Eu323	[X]Severe depressive episode with psychotic symptoms	Severe
Eu323–1	[X]Single episode of major depression and psychotic symptoms	Severe
Eu323–2	[X]Single episode of psychogenic depressive psychosis	Severe
Eu323–3	[X]Single episode of psychotic depression	Severe
Eu323–4	[X]Single episode of reactive depressive psychosis	Severe
Eu332	[X]Recurrent depressive disorder, current episode severe without psychotic symptoms	Severe
Eu333	[X]Recurrent depressive disorder, current episode severe with psychotic symptoms	Severe
Eu333–1	[X]Endogenous depression with psychotic symptoms	Severe
Eu333–2	[X]Manic-depressive psychosis, depressed type + psychotic symptoms	Severe
Eu333–3	[X]Recurrent severe episodes/major depression + psychotic symptom	Severe
Eu333–5	[X]Recurrent severe episodes of psychotic depression	Severe
Eu333–6	[X]Recurrent severe episodes/reactive depressive psychosis	Severe
ZV111–2	[V]Personal history of manic–depressive psychosis	Severe

NEC, not elsewhere classified; NOS, not otherwise specified.

Appendix 2

Cost-effectiveness analysis – sensitivity analysis

Levels of cost-effectiveness

Mortality

Sensitivity analysis was performed with regard to the incremental cost, in order to assess whether results were robust to the inclusion of visit costs. The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of deaths figures (see *Table 130*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, dosulepin (TCA) had an incremental cost per averted death of £435 compared with fluoxetine (*Table 147*). With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and TCAs were estimated to have an incremental cost per averted death of £3909 compared with SSRIs (see *Table 147*).

Sudden cardiac death

The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of sudden cardiac death figures (see *Table 131*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, trazodone (TCA) had an incremental cost per averted sudden cardiac death of £372,401 compared with fluoxetine (*Table 148*). With regard to the different

TABLE 147 Differences in incremental cost, incremental number of deaths and incremental cost per averted death

Antidepressant drug	Incremental mean cost (£)	Incremental no. of deaths	Difference in incremental mean cost (£)	Difference in incremental no. of deaths	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0000			
Dosulepin hydrochloride (TCA)	248.61	0.0291	31.30	0.0719	435.13
Lofepramine (TCA)	536.83	0.0888			
Trazodone hydrochloride (TCA)	541.30	0.1146			
Citalopram hydrobromide (SSRI)	280.95	0.0836			
Escitalopram (SSRI)	345.79	0.0600			
Fluoxetine hydrochloride (SSRI)	217.30	0.1010	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0551			
Sertraline hydrochloride (SSRI)	235.88	0.0776			ED
Mirtazapine (other)	330.97	0.1000			
Venlafaxine hydrochloride (other)	851.55	0.0989			
TCAs	425.51	0.0474	152.81	0.0391	3908.54
SSRIs	272.70	0.0865	LC		LC
Other antidepressants	526.56	0.1039			

ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

TABLE 148 Differences in incremental cost, incremental number of averted ADRs and incremental cost per averted sudden cardiac death

Antidepressant drug	Incremental mean cost (£)	Incremental no. of sudden cardiac deaths	Difference in incremental mean cost (£)	Difference in incremental no. of sudden cardiac deaths	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0007			
Dosulepin hydrochloride (TCA)	248.61	0.0011			
Lofepramine (TCA)	536.83	0.0001			
Trazodone hydrochloride (TCA)	541.30	−0.0009	324.00	0.0009	372,400.56
Citalopram hydrobromide (SSRI)	280.95	0.0000			
Escitalopram (SSRI)	345.79	−0.0009			
Fluoxetine hydrochloride (SSRI)	217.30	−0.0001	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0008			
Sertraline hydrochloride (SSRI)	235.88	0.0001			
Mirtazapine (other)	330.97	0.0015			
Venlafaxine hydrochloride (other)	851.55	0.0017			
TCA	425.51	0.0005			
SSRIs	272.70	0.0001	LC		D
Other antidepressants	526.56	0.0014			

D, dominates; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (−) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

classes of antidepressant drugs, SSRIs had the lowest cost and dominated both TCAs and other antidepressants (see *Table 148*).

Suicide

The incremental costs, in terms of overall visit plus prescription cost for (all antidepressant drugs) (reported in *Table 129*) were combined with the previously reported incremental number of suicide figures. Fluoxetine (SSRI) had the lowest mean cost (see *Table 132*) and, after excluding dominated options, sertraline (SSRI) had an incremental cost per averted suicide of £12,123 compared with fluoxetine, and paroxetine (SSRI) had an incremental cost per averted suicide of £158,763 compared with sertraline (*Table 149*). With regard to the different classes of antidepressant drugs SSRIs had the lowest cost and TCAs had an incremental cost per averted suicide of £715,767 compared with SSRIs (see *Table 149*).

Attempted suicide/self-harm

The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of attempted suicide figures (see *Table 133*). Fluoxetine (SSRI) had the lowest mean cost, and, after excluding dominated options, paroxetine had an incremental cost per averted attempted suicide of £39,865 compared with fluoxetine (*Table 150*). Amitriptyline was estimated to have an incremental cost per averted attempted suicide of £882,758 compared with paroxetine (see *Table 150*). With regard to the different classes of antidepressant drugs, other antidepressants were dominated by SSRIs and TCAs were estimated to have an incremental cost per averted attempted suicide of £112,484 compared with SSRIs (see *Table 150*).

TABLE 149 Differences in incremental cost, incremental number of suicides and incremental cost per averted suicide

Antidepressant drug	Incremental mean cost (£)	Incremental no. of suicides	Difference in incremental mean cost (£)	Difference in incremental no. of suicides	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0002			
Dosulepin hydrochloride (TCA)	248.61	0.0013			
Lofepamine (TCA)	536.83	0.0027			
Trazodone hydrochloride (TCA)	541.30	0.0027			
Citalopram hydrobromide (SSRI)	280.95	0.0014			
Escitalopram (SSRI)	345.79	−0.0002			
Fluoxetine hydrochloride (SSRI)	217.30	0.0022	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	−0.0002	134.24	0.0008	158,763.22
Sertraline hydrochloride (SSRI)	235.88	0.0006	18.58	0.0015	12,123.51
Mirtazapine (other)	330.97	0.0036			
Venlafaxine hydrochloride (other)	851.55	0.0025			
TCAs	425.51	0.0010	152.81	0.0002	715,766.57
SSRIs	272.70	0.0012	LC		LC
Other antidepressants	526.56	0.0028			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (−) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

TABLE 150 Differences in incremental cost, incremental number of attempted suicide and incremental cost per averted attempted suicide/self-harm

Antidepressant drug	Incremental mean cost (£)	Incremental no. of attempted suicides	Difference in incremental mean cost (£)	Difference in incremental no. of attempted suicides	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0010	128.63	0.0001	882,758.26
Dosulepin hydrochloride (TCA)	248.61	0.0048			ED
Lofepamine (TCA)	536.83	0.0075			
Trazodone hydrochloride (TCA)	541.30	0.0158			
Citalopram hydrobromide (SSRI)	280.95	0.0073			
Escitalopram (SSRI)	345.79	0.0035			ED
Fluoxetine hydrochloride (SSRI)	217.30	0.0050	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0012	152.82	0.0038	39,865.25
Sertraline hydrochloride (SSRI)	235.88	0.0050			
Mirtazapine (other)	330.97	0.0210			
Venlafaxine hydrochloride (other)	851.55	0.0156			
TCAs	425.51	0.0039	152.81	0.0014	112,484.12
SSRIs	272.70	0.0053	LC		LC
Other antidepressants	526.56	0.0184			

ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

Myocardial infarction

The incremental costs, in terms of overall visit plus prescription cost for (all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of MI figures (see *Table 134*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, sertraline (SSRI) had an incremental cost per averted MI of £1428 compared with fluoxetine (*Table 151*). With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and other antidepressants were estimated to have an incremental cost per averted MI of £73,358 compared with SSRIs (see *Table 151*).

Stroke/transient ischaemic attack

The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of stroke/TIA figures (see *Table 135*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, dosulepin (TCA) had an incremental cost per averted stroke/TIA of £3993 compared with fluoxetine (*Table 152*). With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and other antidepressants were estimated to have an incremental cost per averted stroke/TIA of £27,139 compared with SSRIs (see *Table 152*).

Falls

The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*) were combined with the previously reported incremental number of falls figures (see *Table 136*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, dosulepin (TCA) had an incremental cost per averted fall of £1109 compared with fluoxetine and mirtazapine (other) had an incremental cost per averted fall of £3234 compared with dosulepin (*Table 153*). With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and TCAs were estimated to have an incremental cost per averted fall of £5858 compared with SSRIs (see *Table 153*).

TABLE 151 Differences in incremental cost, incremental number of averted MIs and incremental cost per averted MI

Antidepressant drug	Incremental mean cost (£)	Incremental no. of MIs	Difference in incremental mean cost (£)	Difference in incremental no. of MIs	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0079			
Dosulepin hydrochloride (TCA)	248.61	0.0067			ED
Lofepamine (TCA)	536.83	0.0085			
Trazodone hydrochloride (TCA)	541.30	0.0021			
Citalopram hydrobromide (SSRI)	280.95	0.0044			
Escitalopram (SSRI)	345.79	0.0090			
Fluoxetine hydrochloride (SSRI)	217.30	0.0113	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0067			
Sertraline hydrochloride (SSRI)	235.88	−0.0017	18.58	0.013	1428.02
Mirtazapine (other)	330.97	0.0033			
Venlafaxine hydrochloride (other)	851.55	0.0027			
TCAs	425.51	0.0070			
SSRIs	272.70	0.0065	LC		LC
Other antidepressants	526.56	0.0031	253.85	0.0034	73,757.69

ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (−) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

TABLE 152 Differences in incremental cost, incremental number of averted strokes and incremental cost per averted stroke/TIAs

Antidepressant drug	Incremental mean cost (£)	Incremental no. of strokes/TIAs	Difference in incremental mean cost (£)	Difference in incremental no. of strokes/TIAs	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0105			
Dosulepin hydrochloride (TCA)	248.61	0.0064	31.30	0.0078	3992.93
Lofepramine (TCA)	536.83	0.0238			
Trazodone hydrochloride (TCA)	541.30	0.0087			
Citalopram hydrobromide (SSRI)	280.95	0.0175			
Escitalopram (SSRI)	345.79	0.0132			
Fluoxetine hydrochloride (SSRI)	217.30	0.0142	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0128			
Sertraline hydrochloride (SSRI)	235.88	0.0188			
Mirtazapine (other)	330.97	0.0244			
Venlafaxine hydrochloride (other)	851.55	0.0370			
TCAs	425.51	0.0103	152.81	0.0056	27,139.05
SSRIs	272.70	0.0160	LC		LC
Other antidepressants	526.56	0.0296			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

TABLE 153 Differences in incremental cost, incremental number of averted falls and incremental cost per averted fall

Antidepressant drug	Incremental mean cost (£)	Incremental no. of falls	Difference in incremental mean cost (£)	Difference in incremental no. of falls	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0549			
Dosulepin hydrochloride (TCA)	248.61	0.0459	31.30	0.0282	1109.34
Lofepramine (TCA)	536.83	0.0486			
Trazodone hydrochloride (TCA)	541.30	0.0614			
Citalopram hydrobromide (SSRI)	280.95	0.0842			
Escitalopram (SSRI)	345.79	0.0660			
Fluoxetine hydrochloride (SSRI)	217.30	0.0741	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0634			
Sertraline hydrochloride (SSRI)	235.88	0.0742			
Mirtazapine (other)	330.97	0.0204	82.36	0.0255	3234.11
Venlafaxine hydrochloride (other)	851.55	0.0769			
TCAs	425.51	0.0514	152.81	0.0261	5858.06
SSRIs	272.70	0.0775	LC		LC
Other antidepressants	526.56	0.0507			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

Fractures

The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of fractures figures (see *Table 137*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, dosulepin (TCA) had an incremental cost per averted fracture

of £2260 compared with fluoxetine and trazodone (TCA) had an incremental cost per averted fall of £12,240 compared with dosulepin (*Table 154*). With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and TCAs were estimated to have an incremental cost per averted fracture of £11,109 compared with SSRIs (see *Table 154*).

Upper gastrointestinal bleed

The incremental costs, in terms of overall visit plus prescription cost for (all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of upper GI bleed figures (see *Table 138*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, sertraline (SSRI) had an incremental cost per averted upper GI bleed of £961 compared with fluoxetine, and mirtazapine (other) had an incremental cost per averted upper GI bleed of £125,188 compared with sertraline (*Table 155*). With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and dominated both TCAs and other antidepressants (see *Table 155*).

Epilepsy/seizures

The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of epilepsy/seizure figures (see *Table 139*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, dosulepin (TCA) had an incremental cost per averted epilepsy/seizure of £6211 compared with fluoxetine (*Table 156*). With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and TCAs were estimated to have an incremental cost per averted epilepsy/seizure of £38,409 compared with SSRIs (see *Table 156*).

Road traffic accident

The incremental costs, in terms of overall visit plus prescription cost for (all antidepressant drugs) (reported in *Table 129*) were combined with the previously reported incremental number of RTA figures (see *Table 140*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, dosulepin (TCA) had an incremental cost per averted RTA of

TABLE 154 Differences in incremental cost, incremental number of averted fractures and incremental cost per averted fracture

Antidepressant drug	Incremental mean cost (£)	Incremental no. of fractures	Difference in incremental mean cost (£)	Difference in incremental no. of fractures	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0231			ED
Dosulepin hydrochloride (TCA)	248.61	0.0238	31.30	0.0139	2260.05
Lofepamine (TCA)	536.83	0.0338			
Trazodone hydrochloride (TCA)	541.30	0.0001	292.70	0.0239	12,240.01
Citalopram hydrobromide (SSRI)	280.95	0.0389			
Escitalopram (SSRI)	345.79	0.0159			
Fluoxetine hydrochloride (SSRI)	217.30	0.0376	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0356			
Sertraline hydrochloride (SSRI)	235.88	0.0395			
Mirtazapine (other)	330.97	0.0265			
Venlafaxine hydrochloride (other)	851.55	0.0536			
TCAs	425.51	0.0237	152.81	0.0138	11,109.49
SSRIs	272.70	0.0375	LC		LC
Other antidepressants	526.56	0.0417			

ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

TABLE 155 Differences in incremental cost, incremental number of averted upper GI bleed and incremental cost per averted upper GI bleed

Antidepressant drug	Incremental mean cost (£)	Incremental no. of upper GI bleeds	Difference in incremental mean cost (£)	Difference in incremental no. of upper GI bleeds	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0086			
Dosulepin hydrochloride (TCA)	248.61	0.0058			
Lofepamine (TCA)	536.83	0.0047			
Trazodone hydrochloride (TCA)	541.30	0.0126			
Citalopram hydrobromide (SSRI)	280.95	0.0060			
Escitalopram (SSRI)	345.79	0.0009			
Fluoxetine hydrochloride (SSRI)	217.30	0.0032	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0041			
Sertraline hydrochloride (SSRI)	235.88	0.0015	18.58	0.0193	961.12
Mirtazapine (other)	330.97	0.0008	95.09	0.0008	125,188.46
Venlafaxine hydrochloride (other)	851.55	0.0118			
TCAs	425.51	0.0070			
SSRIs	272.70	0.0044	LC		D
Other antidepressants	526.56	0.0069			

D, dominates; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option.

TABLE 156 Differences in incremental cost, incremental number of averted epilepsy/seizure cases and incremental cost per averted epilepsy/seizure case

Antidepressant drug	Incremental mean cost (£)	Incremental no. of epilepsy/seizure cases	Difference in incremental mean cost (£)	Difference in incremental no. of epilepsy/seizure cases	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0017			
Dosulepin hydrochloride (TCA)	248.61	-0.0022	31.30	0.0050	6210.77
Lofepamine (TCA)	536.83	0.0025			
Trazodone hydrochloride (TCA)	541.30	0.0026			
Citalopram hydrobromide (SSRI)	280.95	0.0044			
Escitalopram (SSRI)	345.79	0.0039			
Fluoxetine hydrochloride (SSRI)	217.30	0.0029	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0064			
Sertraline hydrochloride (SSRI)	235.88	0.0094			
Mirtazapine (other)	330.97	0.0031			
Venlafaxine hydrochloride (other)	851.55	0.0109			
TCAs	425.51	0.0008	152.81	0.0040	38,409.14
SSRIs	272.70	0.0048	LC		LC
Other antidepressants	526.56	0.0070			

No values are reported when the drug in question is dominated by at least one other option; a negative (-) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

£32,854 compared with fluoxetine (*Table 157*) and mirtazapine (other) had an incremental cost per averted RTA of £113,029 compared with dosulepin. With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and other antidepressants were estimated to have an incremental cost per averted RTA of £189,427 compared with SSRIs (see *Table 157*).

Adverse drug reactions

The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of ADR figures (see *Table 141*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, dosulepin had an incremental cost per averted ADR of £15,090 compared with fluoxetine (*Table 158*). Venlafaxine was estimated to have an incremental cost per averted ADR of £706,227 compared with dosulepin. With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and other antidepressants were estimated to have an incremental cost per averted ADR of £136,063 compared with SSRIs (see *Table 158*).

Hyponatraemia

The incremental costs, in terms of overall visit plus prescription costs (for all antidepressant drugs) (reported in *Table 129*), were combined with the previously reported incremental number of hyponatraemia figures (see *Table 142*). Fluoxetine (SSRI) had the lowest mean cost and, after excluding dominated options, sertraline (SSRI) had an incremental cost per averted case of hyponatraemia of £2532 compared with fluoxetine, and dosulepin (TCA) had an incremental cost per averted hyponatraemia case of £10,914 compared with sertraline (SSRI) (*Table 159*). With regard to the different classes of antidepressant drugs, SSRIs had the lowest cost and TCAs were estimated to have an incremental cost per averted hyponatraemia case of £36,028 compared with SSRIs (see *Table 159*).

TABLE 157 Differences in incremental cost, incremental number of RTAs and incremental cost per averted RTA

Antidepressant drug	Incremental mean cost (£)	Incremental no. of RTAs	Difference in incremental mean cost (£)	Difference in incremental no. of RTAs	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	−0.0002			
Dosulepin hydrochloride (TCA)	248.61	−0.0024	31.30	0.0010	32,854.05
Lofepramine (TCA)	536.83	0.0013			
Trazodone hydrochloride (TCA)	541.30	0.0033			
Citalopram hydrobromide (SSRI)	280.95	0.0003			
Escitalopram (SSRI)	345.79	−0.0002			
Fluoxetine hydrochloride (SSRI)	217.30	−0.0015	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0000			
Sertraline hydrochloride (SSRI)	235.88	−0.0003			
Mirtazapine (other)	330.97	−0.0032	82.36	0.0007	113,028.70
Venlafaxine hydrochloride (other)	851.55	−0.0014			
TCAs	425.51	−0.0002			
SSRIs	272.70	−0.0003	LC		LC
Other antidepressants	526.56	−0.0017	253.85	0.0013	189,427.28

No values are reported when the drug in question is dominated by at least one other option; a negative (−) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

TABLE 158 Differences in incremental cost, incremental number of ADRs and incremental cost per averted ADR

Antidepressant drug	Incremental mean cost (£)	Incremental no. of ADRs	Difference in incremental mean cost (£)	Difference in incremental no. of ADRs	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0008			
Dosulepin hydrochloride (TCA)	248.61	0.0001	31.30	0.0021	15,090.47
Lofepamine (TCA)	536.83	0.0113			
Trazodone hydrochloride (TCA)	541.30	0.0007			
Citalopram hydrobromide (SSRI)	280.95	0.0014			
Escitalopram (SSRI)	345.79	0.0008			
Fluoxetine hydrochloride (SSRI)	217.30	0.0022	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0003			
Sertraline hydrochloride (SSRI)	235.88	0.0061			
Mirtazapine (other)	330.97	0.0002			
Venlafaxine hydrochloride (other)	851.55	0.0007	602.94	0.0009	706,227.34
TCAs	425.51	0.0017			ED
SSRIs	272.70	0.0020	LC		LC
Other antidepressants	526.56	0.0001	253.85	0.0019	136,062.86

ED, subject to extended dominance; LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (–) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

TABLE 159 Differences in incremental cost, incremental number of averted hyponatraemia cases and incremental cost per averted hyponatraemia case

Antidepressant drug	Incremental mean cost (£)	Incremental no. of hyponatraemia cases	Difference in incremental mean cost (£)	Difference in incremental no. of hyponatraemia cases	ICER (£)
Amitriptyline hydrochloride (TCA)	498.75	0.0034			
Dosulepin hydrochloride (TCA)	248.61	–0.0005	12.73	0.0012	10,914.37
Lofepamine (TCA)	536.83	0.0001			
Trazodone hydrochloride (TCA)	541.30	0.0056			
Citalopram hydrobromide (SSRI)	280.95	0.0072			
Escitalopram (SSRI)	345.79	0.0107			
Fluoxetine hydrochloride (SSRI)	217.30	0.0080	LC		LC
Paroxetine hydrochloride (SSRI)	370.12	0.0015			
Sertraline hydrochloride (SSRI)	235.88	0.0006	18.58	0.0073	2532.67
Mirtazapine (other)	330.97	0.0007			
Venlafaxine hydrochloride (other)	851.55	0.0061			
TCAs	425.51	0.0020	152.81	0.0042	36,028.14
SSRIs	272.70	0.0062	LC		LC
Other antidepressants	526.56	0.0036			

LC, lowest cost.

No values are reported when the drug in question is dominated by at least one other option; a negative (–) value indicates that fewer events were predicted for those taking a particular antidepressant than for those who were prescribed no antidepressants.

Appendix 3

Final protocol

Protocol

A study of the safety and harms of antidepressant drugs for older people: an analysis using a large primary care database.

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Detailed project description

Project title

Safety and harms of antidepressant drugs for older people: an analysis using a large primary care database.

HTA project number: 06/42/01.

Summary

Depression is a common and debilitating condition in older people. Adverse drug events may be more common in the treatment of depression in older people compared with younger age groups owing to higher levels of comorbidity, age-related physiological changes and polypharmacy. The under-representation of older people in clinical trials of antidepressants makes it difficult to make reliable or precise estimates of the incidence of adverse events. This problem is further compounded when trial exclusion criteria exclude older people with comorbid conditions.

The overall aim of this study is to establish the relative safety and balance of risks for individual antidepressant drugs in older people. The study is a cohort study of people aged 65 years and

over who have been diagnosed with a major depressive disorder or with unipolar depression identified from a large primary care database (QResearch). Prescribing data for these patients will be used to ascertain their use of antidepressant drugs following diagnosis of depression including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other antidepressants. Prospectively recorded data on these patients will be used to ascertain harms and adverse events that occurred in these patients over a minimum of 12 months' follow-up after their diagnosis. Primary outcomes will include the following events: all-cause mortality, suicide, sudden cardiac death, overdose/poisoning, attempted suicide, myocardial infarction (MI), stroke, seizures, gastrointestinal (GI) bleeding, falls and fractures, road traffic accidents (RTAs), adverse drug reactions (ADRs) and hyponatraemia. The analysis will examine the associations between exposure to the different classes of antidepressant and risk of the adverse events. Annual costs of antidepressant medication and costs of adverse events will be calculated and compared. A further analysis will use the self-controlled case-series approach to reduce effects of residual confounding and indication biases.

Background

Depression is a common and debilitating condition in older people. A pooled estimate of prevalence of depression from community-based studies of older people is 13.5%.¹ Across all ages, 29 million prescriptions for antidepressant drugs were issued in 2004.² Adverse drug events may be more common in the treatment of depression in older people compared with younger age groups owing to higher levels of comorbidity, age-related physiological changes and polypharmacy.³ The under-representation of older people in clinical trials of antidepressants makes it difficult to make reliable or precise estimates of the incidence of adverse events.^{4,5} This problem is further compounded when trial exclusion criteria exclude older people with comorbid conditions.⁶ Even though older people with depression are more likely to be treated since the introduction of the newer generation of antidepressants,^{7,8} under treatment of depression among older people is a global problem.⁹ Evidence from a systematic review suggests that TCAs and SSRIs are equivalent in terms of efficacy, but classical TCAs are associated with a higher discontinuation rate owing to the side effect profile.¹⁰

Antidepressants, and particularly TCAs are an important cause of deaths by overdose and poisoning.¹¹ There appears to be some evidence from a meta-analysis of placebo-controlled trials that SSRIs are associated with a small increase in risk of fatal and non-fatal suicide attempts.¹² Lack of sufficient trial data meant that it was not possible to see whether this finding held within those aged 60 years and over. Observational studies across all age groups have found associations between antidepressant use and suicide, but have been unable to rule out confounding by indication.¹³ There is little evidence to support any difference in terms of class of antidepressant and risk of suicide,¹⁴ but studies have tended to look at risks across all ages or among adolescents and young adults.¹⁵

There may be an increased risk of subsequent ischaemic heart disease associated with dosulepin (formerly known as dothiepin) use, but not other TCAs or SSRIs.¹⁶ Some studies have found no evidence of an increased risk of MI among users of antidepressants¹⁷ or have suggested that an increased risk of MI may be explained by confounding factors relating to depression itself rather than specific adverse drug effects.¹⁸

Findings from both case-control,¹⁹ and case-series analysis studies,²⁰ indicate that risk of hip fracture is elevated with the use of TCAs and SSRIs among older people, although the magnitude of the increased risk did not differ between the two classes of antidepressant.¹⁹ The likely mechanism underlying this increased risk appearing to be changes in orthostatic blood pressure,²¹ rather than altered bone mineral density.²²

Older people who use lithium may be at increased risk of being involved in an injurious motor vehicle accident.²³ In studies that have formally tested the effects of antidepressants on driving performance, sedating antidepressants have a similar effect to alcohol.²⁴

Hyponatraemia associated with antidepressant use is rare, but it is an adverse event that disproportionately affects older people.^{25,26} Similarly, GI bleeding is more common among those taking SSRIs who are aged 80 years or over,²⁷ although there is a lack of consensus as to whether the risk of GI bleeding associated with SSRI use is further increased with concurrent use of non-steroidal anti-inflammatory drugs^{28,29} or not.³⁰

The gaps in the research into adverse effects for these drugs specifically in older people and the lack of consistent findings pose problems for clinicians prescribing these drugs and making choices as to the most appropriate drug for individual older patients. In this study we will use a large primary care database containing information on virtually all prescriptions for antidepressants and a range of potential adverse effects to derive a unified picture of the balance of risks for antidepressant drugs in older people with depression.

Specific aims and objectives

The overall aim of this study is to establish the relative safety and balance of risks for individual antidepressant drugs in older people, in order to provide a robust evidence base to support decision making for clinicians prescribing these medications to individual patients.

The project has five key objectives, which are:

1. to determine the relative and absolute risks of predefined adverse events in older people diagnosed with depression. Comparisons will be made between classes of antidepressant drugs: TCAs; SSRIs; monoamine oxidase inhibitors (MAOIs); other antidepressants; and non-use of antidepressant drugs
2. to directly compare the risk of adverse events in patients prescribed SSRIs compared with TCAs in older people diagnosed with depression
3. to determine how the dose and duration of prescribed antidepressant medication is associated with the risk of an adverse event
4. to describe patterns of antidepressant use in older people diagnosed with depression, in particular the types and doses prescribed, the durations and the proportions switched between different antidepressants (TCAs, SSRIs and other antidepressant drugs)
5. to determine the annual costs of antidepressant medication, the costs of the adverse events, and the costs of health-care resource use in older people diagnosed with depression, comparing patients by type of antidepressant drugs (TCAs, SSRIs, MAOIs and other antidepressants).

Study design

Design

The planned investigation will use a large primary care database (QResearch) to investigate the relative safety and costs of antidepressant drugs in older people.

Two main approaches will be used to achieve the study objectives:

1. a cohort study
2. a self-controlled case-series study.

The cohort study is a well-established powerful method for determining absolute and relative risks associated with exposures. The self-controlled case-series method is a newer approach

that estimates relative incidence of an outcome in high-risk compared with low-risk periods of time, based only on data from cases. It is useful for investigating the short-term effect of drug exposures on the risk of acute outcomes, as it eliminates problems of confounding from unmeasured variables, such as severity of disease. Both of these studies will derive data from a large primary-care research database (QResearch).

Cohort study

Our target population for the cohort study will be all patients aged 65 years and over with a recorded diagnosis of depression (major depressive disorder or unipolar depression) between 1 January 1996 and 31 December 2007. Patients with previous diagnoses of depression before the age of 65 years will be included. We will use Read codes to identify a major depressive disorder or unipolar depression, using case definitions that have been used in previous studies. The cohort will be followed up until 1 January 2009. Information on all prescriptions for antidepressants will be extracted, along with information on potential confounding variables and adverse events during follow-up.

Self-controlled case-series study

The self-controlled case-series study only uses the patients in the cohort who have the outcomes of interest. Cases with each type of adverse event will be identified; these will be cases with a diagnosis of the adverse event between 1 January 1996 to 31 December 2006, who had a previous diagnosis of depression between 1 January 1996 to 31 December 2005. Information on prescriptions for antidepressants in these cases will be extracted and the analysis will compare rates of the adverse events in periods following a first prescription for an antidepressant compared with a baseline period.

Setting: QResearch database

We will undertake the study using data from the QResearch primary-care research database (www.qresearch.org). This validated database is the largest general practice research database in the UK and it contains the anonymised electronic health-care records of over 10 million patients ever registered with 525 general practices throughout England, Wales, Scotland and Northern Ireland. Consent to provide data for QResearch was sought from all UK practices using 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 two-thirds of all UK general practices. The consenting practices form a representative sample of 6–7% of all UK general practices, and there are practices in every strategic health authority and each health board in England, Wales and Scotland.

The information recorded on the QResearch database includes patient demographic data (year of birth, gender, socioeconomic data derived from the UK 2001 census), characteristics (height, weight, smoking status), symptoms, clinical diagnoses, consultations, referrals, prescribed medications and results of investigations. The latest version of the QResearch database, which is updated quarterly, will be used for the analysis.

Detailed analyses have compared QResearch practices with all UK practices and found that practices contributing to QResearch are somewhat larger than UK practices overall, but are very similar in other respects.³¹ The database has been validated by comparing birth rates, death rates, consultation rates, prevalence and mortality rates with other data sources including the General Household Survey and the General Practice Research Database (<http://secure.qresearch.org/SiteSections/DataValidation/DataValidationMain.aspx>). The age–gender structure of the population has been compared with that reported in the 2001 census. There was good correspondence for all of these measures, although the QResearch population is slightly older and has marginally higher prevalence figures for some diagnoses compared with less recent data,³²

but they are almost identical to current prevalence data from the new General Medical Services Contract for General Practitioners.

Compared with other primary care databases QResearch is the largest [currently 525 practices compared with around 200–400 [depending on selection criteria] in the General Practice Research Database (GPRD) and 100 in The Health Improvement Network (THIN)³³], and it has information on deprivation derived from postcode data, which is not currently available in the other databases. The database is completely independent from commercial organisations and QResearch receives no funding from pharmaceutical companies. The database contains only anonymised data, which are encrypted and kept in secure conditions. One of the coapplicants (Professor Julia Hippisley-Cox) is the chief custodian of the database and QResearch has been used to examine the risks and benefits associated with a number of commonly prescribed drugs including statins^{34,35} and non-steroidal anti-inflammatory drugs (NSAIDs).³⁶ The applicants have also published studies examining antidepressants as risk factors for ischaemic heart disease.¹⁶

Outcome measures

The outcomes to be assessed will be extracted from the routine primary-care computer records of patients in the cohort. Outcomes will only be included if they occurred after the initial diagnosis of depression and up until 31 December 2008. The relevant computer recorded Read codes and ICD-9/ICD-10 codes, where appropriate, will be used to identify patients with the outcomes.

The outcomes that will be assessed will include:

- all-cause mortality
- suicide (including open verdicts)
- attempted suicide/self-harm
- sudden cardiac death
- overdose/poisoning from antidepressants
- myocardial infarction
- stroke/TIA
- epilepsy/seizures
- upper GI bleeding
- falls
- fractures (upper limb, lower limb, ribs, skull, vertebrae and pelvis)
- road traffic accidents
- adverse drug reactions (including bullous eruption)
- hyponatraemia.

QResearch is undertaking a national audit on care for patients with osteoporosis and falls in primary care. As part of this project, funded by the Information Centre, we will be examining the clinical coding of falls and fractures in some detail, and will be able to utilise the definitions for the proposed project. We have consulted professional groupings regarding the diagnostic codes (Read codes) which are likely to be used in clinical practice. Other outcomes are likely to be well recorded, although sudden cardiac deaths may be difficult to identify.

Exposures

Our exposure of interest is antidepressant medication. We will extract details of all prescriptions for antidepressants in patients in our cohort, following their diagnosis of depression; this will include the date of prescription, the type of drug, the dose and the duration.

The antidepressant drugs will be grouped for analysis according to the major classes as described in the *British National Formulary* (BNF), namely tricyclic and related antidepressants

(TCAs: section 4.3.1), selective serotonin reuptake inhibitors (SSRIs: section 4.3.3), monoamine oxidase inhibitors (MAOIs: section 4.3.2) and other antidepressants (section 4.3.4). Effects of individual antidepressant drugs will also be assessed where numbers are sufficient. The number of prescriptions, duration and dose of the antidepressant drugs will be examined in the analyses.

We will determine the proportions of patients who switch between antidepressants, including switches between classes of drugs and between different drugs within a class. We will examine the proportions for patients who discontinue a drug before the recommended time by examining the proportions who have only one prescription, have two to three and have four to six prescriptions for a particular drug.

Confounding variables

Data will be extracted on the following variables, and these will be considered as confounding variables in the analysis of the cohort study:

- age, gender, year of diagnosis of depression, previous recorded diagnosis of depression before age 65 years, severity of index diagnosis of depression, deprivation, smoking status, comorbidities (ischaemic heart disease, diabetes, hypertension, stroke/TIA, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder), and use of other drugs (including statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics).

In addition for the analysis of suicide as an outcome, previous attempted suicide at baseline was considered as a confounding variable, and, for the analysis of fracture, previous falls at baseline was considered as a confounding variable.

Inclusion/exclusion criteria

Patients will be eligible for inclusion in the cohort study if:

- they have a recorded diagnosis of depression (a major depressive disorder or unipolar depression including depression mixed with anxiety)
- they are aged between 65 and 100 years
- the diagnosis of depression was made at the age of 65 years or over (but does not need to be their first recorded diagnosis of depression)
- the diagnosis was recorded between 1 January 1996 and 31 December 2007
- the diagnosis occurred at least 12 months after registration with a study practice and after the date of the installation of the practice EMIS computer system.

Patients will be excluded from the cohort study if:

- they are temporary residents
- they have a previous diagnosis of depression in the 12-month period prior to their index recorded diagnosis of depression
- they have been prescribed antidepressants in the 12-month period prior to their recorded diagnosis of depression
- they have a diagnosis of schizophrenia or bipolar disorder
- they have a diagnosis of other types of psychoses.

Quality of life

Quality of life is not recorded in primary-care consultations, so we are unable to examine this outcome in our database; however, as part of our review of the literature we will search for literature on quality of life and antidepressant medication in older people with depression to see

if some estimations can be made about the likely effectiveness and cost-effectiveness of different antidepressants in older people. However, a basic literature search undertaken to support the development of this proposal found very few cost-utility studies³⁷ comparing different types of antidepressants in a population aged 18 years or over and therefore, there may well be limited published economic evidence specific to a more elderly population.

Strengths and limitations of study design

The strengths of using a cohort study design for this project are that it will include a large and representative number of older people with depression, it can calculate absolute as well as relative risks, it can take account of exposures changing over time and it is able to adjust for a number of potential confounding variables. The recording of prescriptions in primary-care records is high, and the exposures under consideration are available only on prescription. The outcomes we have included are likely to be well recorded, and we will compare their rates in this study against other published data where possible.

The limitations of the cohort design approach are that it can be vulnerable to indication bias and residual confounding whereby relevant confounding variables may be imprecisely recorded or not recorded at all in primary-care records (for example diet, physical activity). Indication bias can cause difficulties in the interpretation of results on effects of drugs in observational studies; in this instance whether or not an antidepressant is prescribed or the type of antidepressant prescribed may be related to important prognostic factors for the outcome in question, such as the severity of depression or the attitude of the patient towards taking medication. These characteristics could influence the outcome but are unlikely to be recorded well in a patient's medical records. The self-controlled case-series method has been proposed as a means of addressing this problem.^{38,39} This is an internally controlled method whereby analyses are carried out only in patients with the outcome of interest, thereby eliminating the effect of indication bias and unmeasured confounding variables that do not vary over time. This method has previously been used to examine the relationship between antidepressants and hip fracture,²⁰ and is of most relevance for acute events occurring within a short period after exposure. A limitation of the case-series design is that it requires that probability of exposure is not affected by occurrence of an outcome event, which is a particular problem for fatal outcomes, but this can be resolved by using only time from first prescription in the observation period for analysis.

Sample size

Cohort study

All eligible patients aged 65 years and over diagnosed with incident depression between 1 January 1996 and 31 December 2007 in the QResearch database will be included in the cohort study.

A feasibility study shows there are approximately 5.0 million years of observation and 18,000 incident cases of depression arising from patients aged 65 and older between 1996 and 2005 on the database.

Assuming 88% of patients aged 65 years and over, diagnosed with depression, are prescribed an antidepressant drug as we found in our feasibility study, and for a rare outcome with an incidence of 5 per 1000 per year (e.g. upper GI event⁴⁰ or lower limb fracture⁴¹), and an average follow-up of 5 years, we will be able to detect a relative risk of 1.5 with 88% power and a 5% significance level comparing those on antidepressants with those not on antidepressants. For all-cause mortality with a mortality rate of 47 per 1000 per year (Office for National Statistics for 2001) we will be able to detect a relative risk of 1.15 with 95% power. In comparisons between TCAs and SSRIs, assuming 39% of patients on antidepressants take TCAs and 50% take SSRIs we will be able to detect a relative risk of 1.4 with 86% power for rare outcomes and 1.12 with 92% power for all-cause mortality.

Self-controlled case-series study

The exposed cases contribute to the statistical power in the case-series method, under certain conditions the power of the analysis can be similar to that of the cohort study from which the cases are derived. To detect a rate ratio of 2.0 in a risk period of 1–14 days after the first prescription for an antidepressant with 80% power and 5% significance, then with a proportion of 0.0077 in the risk period of 14 days compared with an average observation period of 5 years (3/1825) then 1435 exposed cases would be required for each outcome.⁴² We would anticipate having at least this number for all-cause mortality and falls/fracture. To detect a rate ratio of 3.0 in a risk period of 1–14 days then 448 exposed cases would be required. We would anticipate having around this number for rare outcomes such as GI events (incidence rate 5/1000/year).

Statistical analysis

Descriptive statistics

Descriptive statistics will be derived primarily using the data from the cohort study.

1. We will calculate incidence rates of diagnosed depression in people aged 65 years and over, and examine these rates by gender, age group (65–74, 75–84, 85+ years) and study year. We will compare these rates with other published rates of depression.
2. In patients with a diagnosis of depression in the study cohort we will describe patterns of antidepressant use according to type of antidepressant prescribed, duration of use and dose, and will examine these patterns by gender, age group, use of other medications, comorbidities and study year. We will also examine variations between practices in patterns of antidepressant prescribing.
3. We will calculate the proportions of people switched between different antidepressants (TCAs, SSRIs and other antidepressant drugs) by gender, age group and study year, and examine duration of use before switching.
4. Discontinuation rates for each drug will also be determined by examining the proportion of those with at least one prescription for a drug who only have one prescription, have two to three and have four to six prescriptions.
5. We will describe the severity of depression (classified as mild, moderate or severe) in the study cohort, overall and by age group and gender. We will describe patterns of antidepressant use according to severity of depression.

Analysis of cohort study

The analysis of the cohort study will determine absolute and relative risks of adverse events in older people with depression according to type of antidepressant prescribed, and will also examine risks according to dose and duration of treatment.

Incidence rates of the adverse events will be calculated in the study cohort. The statistical analysis will comprise a series of survival analyses to assess the relationship between exposure to antidepressant drugs and a number of potential adverse effects. These analyses will be restricted to the cohort of older people with a diagnosis of depression. The exposure variables will be use of antidepressant drugs, including SSRIs, TCAs and other antidepressants. The number of prescriptions, duration and dose of the antidepressant drugs will be examined in the analyses. The date of entry into the survival analyses will be the date of diagnosis of depression (their earliest date at the age of 65 years or over or the date of the first prescription for an antidepressant after the age of 65 years in patients if that occurred before the recorded date of depression), and the right censor date will be the earliest of the following: date of diagnosis of the outcome of interest, date of death, date of leaving the practice, date of the latest download of data or the study end date.

Cox's proportion hazards models will be used with antidepressant exposure treated as a time-varying exposure. The analysis will calculate HRs and 95% CIs comparing:

1. The risk of each adverse effect in patients on any type of antidepressant compared with patients with no antidepressant treatment.
2. Each separate class of antidepressants (SSRIs, TCAs and other antidepressants) compared with no treatment.
3. The risk of each adverse effect for each class of antidepressant will be directly compared with each other class (in particular SSRIs will be directly compared with TCAs).
4. Analyses will also calculate HRs according to duration of use and prescribed dose of antidepressant. Where numbers are sufficient, subcategories and individual antidepressants within each class will be examined.
5. Analyses will calculate HRs according to time since stopping antidepressant medication.
6. Analyses of interaction will be carried out to examine the extent to which patient's characteristics (age, gender), use of other medications and comorbidities modify the relationship between antidepressant use and adverse outcomes.

Adjustment will be made for potential confounders including:

1. age, gender, year of diagnosis of depression, previous recorded diagnosis of depression before age 65 years, severity of index diagnosis of depression, deprivation, smoking status, comorbidities (ischaemic heart disease, diabetes, hypertension, stroke/TIA, cancer, dementia, epilepsy/seizures, Parkinson's disease, hypothyroidism, obsessive-compulsive disorder) and use of other drugs (including statins, NSAIDs, antipsychotics, lithium, aspirin, antihypertensive drugs, anticonvulsants, hypnotics/anxiolytics).

The analysis will also compare these patient characteristics according to the type of antidepressant prescribed. The assumptions of the Cox proportional hazards model will be checked. Absolute risks of the adverse events will also be estimated and presented.

Self-controlled case-series analysis

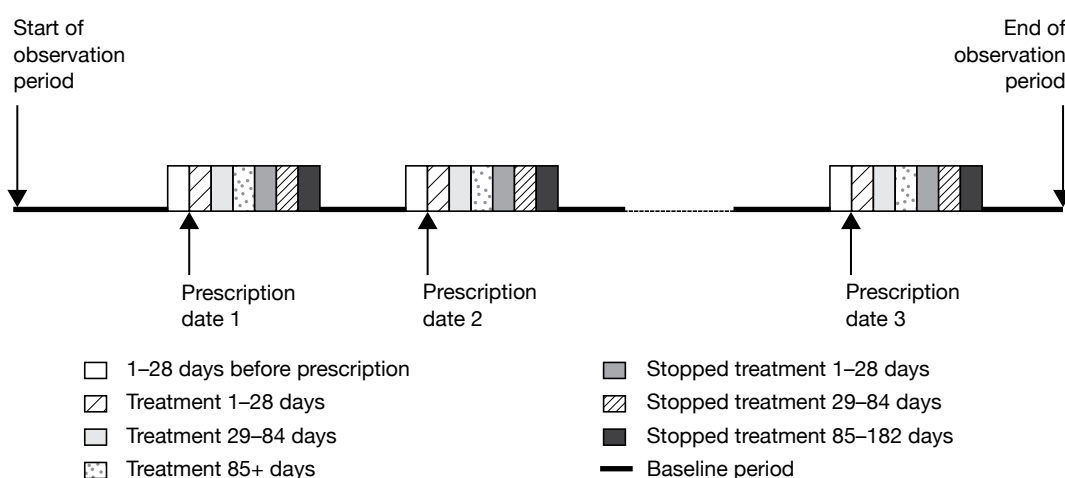
We will perform self-controlled case-series analyses using data only on patients who have had an adverse event. We will carry out a separate analysis for each type of outcome. The case-series method will enable us to determine the relative incidence of the outcomes of interest for high-risk versus low-risk time periods relative to commencing use of antidepressants in individuals who have the outcome of interest.

In the case-series analyses we will include cases who have the outcomes of interest as in the cohort study. We will use only the first recorded diagnosis of the outcome of interest rather than recurrent events. Patients who have the outcome of interest occurring on the same day as their first prescription for antidepressants will be distinguished in the analysis. Cases without any prescriptions for antidepressants will be included in the analyses to improve adjustment for age.

We will use conditional Poisson regression to estimate the relative incidence of the outcomes of interest for defined time periods of risk after the first prescription for antidepressants in a treatment episode. We will account for multiple periods of exposure in the analysis, defining a period of antidepressant treatment as one without gaps of more than 90 days between the end of a prescription and the start of the next prescription. A prescription after more than 90 days will count as a new treatment episode. The time periods for assessing potential short term effects of antidepressants will be defined as follows as shown in the figure below: 0 days (day of first prescription in each treatment episode); 1–28 days after the first prescription; 29–84 days

and 85+ days (remaining treatment period); and periods after stopping treatment (1–28 days, 29–84 days and 85 to 182 days after stopping). The 28 days before the first prescription will be considered as a separate category, as occurrence of the outcome of interest in this period could affect the probability of an antidepressant prescription. All other time periods outside these specified risk periods will contribute to the baseline person time, i.e. the unexposed periods. These periods will enable us to examine short- and longer-term effects of antidepressants on the risks of adverse events and are similar to those used in other studies of antidepressants.^{18,20} Where the outcome is a fatal one we will only use time from the first prescription in the observation period for analysis, as otherwise the method is invalid. We will adjust for age in the analyses and also take account of repeated prescriptions over time.

Figure showing risk periods in case-series design:



Measurement and analysis of costs

The cost analysis will be undertaken from an NHS health-care perspective with the aim of detecting whether there are any significant differences in health-care costs for patients on different types of antidepressants. Patient-specific resource use data (identified using the QResearch database), including data on antidepressant medication and primary-care consultations will be captured. The unit costs of these resources will be estimated using published data for a common price year from, for example the *British National Formulary* (BNF) and Curtis and Netten.⁴³ This will enable the overall aggregate cost per patient to be calculated over 1 year and 5 years following diagnosis of depression. In turn, the incremental mean cost associated with each type of antidepressant (SSRIs, TCAs, MAOIs and others) will be estimated, controlling for patient characteristics (age, gender), and other factors (comorbidities, whether they switched treatment, and severity of depression, for instance), which may be associated with differences in mean costs between the antidepressant groups that are not a result of the antidepressant they are taking. Sensitivity analyses will be undertaken to assess the robustness of results. Accepted methods will be used.⁴⁴ The cost of adverse events cannot be estimated using patient-specific resource use data as secondary care resource use data within the QResearch database is not routinely recorded by all GP practices within the database.

We will measure and analyse costs based on the cohort analysis to ensure representative costs are estimated for the population as a whole rather than just for those who experience the outcome of interest as would be the case using the self-controlled case-series study. We will estimate

and compare, for instance, the incremental cost per adverse event avoided across the different antidepressants and those not taking antidepressants.

However, we recognise that cost-effectiveness ratios, such as cost per adverse event avoided, may capture only intermediate as opposed to final outcomes. In order to capture final outcomes it is usual to estimate quality-adjusted life-years (QALYs). As stated on p. 10, health-related quality of life, is not recorded in primary care databases, and whilst we shall search for literature on quality of life of older people with depression and for different antidepressants, initial searches do not reveal a vast literature on this and our ability to extrapolate from published studies therefore, is likely to be limited. However, we will explore this possibility in order to try and estimate the incremental cost per QALY between different types of antidepressants and those not on antidepressants but diagnosed with depression. Our primary focus, however, will relate to adverse events that may be associated with antidepressant use in older people, and we will be able to determine the cost per adverse event avoided based on data recorded in the database.

Research governance

All projects using QResearch are independently reviewed by the QResearch scientific committee and reported both to Trent Research Ethics Committee (REC) and also the national QResearch advisory board.

R&D governance of QResearch projects undertaken by the applicants is undertaken by Nottinghamshire County Teaching Primary Care Trust.

Ethical arrangements

The project will be independently peer reviewed by the QResearch scientific board and has been reported to Trent REC in accordance with the agreed procedure with the Committee.

Funding

This study is funded by the NIHR Coordinating Centre for Health Technology Assessment.

Project timetable and milestones

Duration

- 15 months.

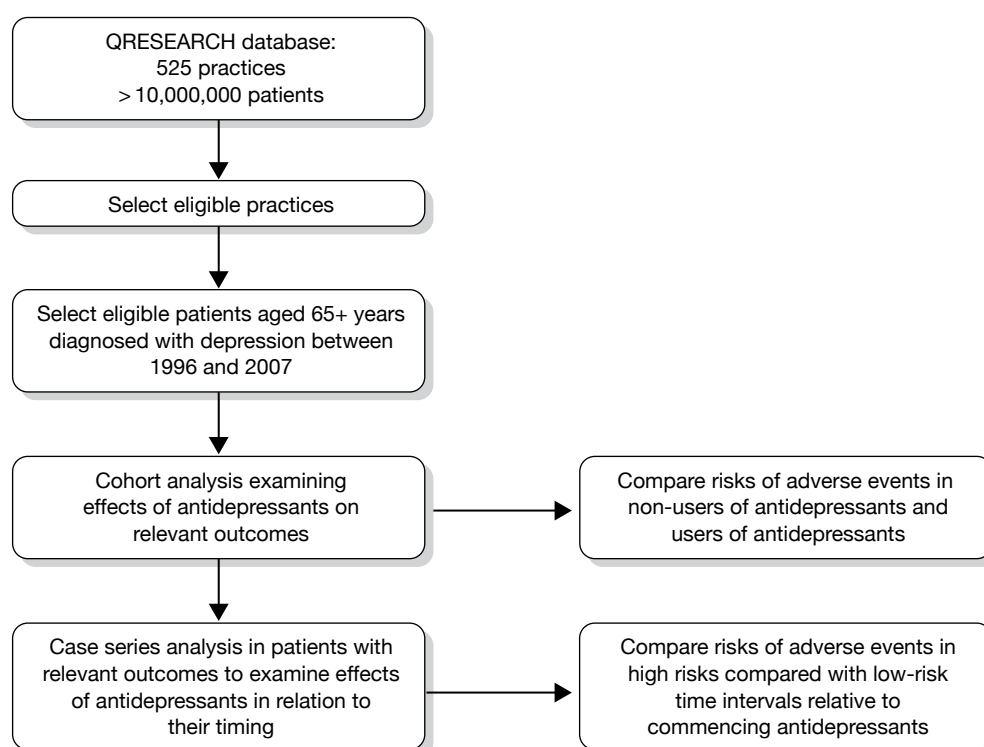
Project timetable

Months 1–3	Finalise protocol Specify detailed data definitions for data extraction Commence data extraction
Months 4–7	Refresh literature review Complete data extraction Carry out data validation and manipulation
Month 8	Produce full statistical analysis plan
Months 9–10	Undertake descriptive statistical analyses
Months 11–12	Analyse cohort study data Analyse case-series study data
Months 13–15	Undertake analyses of cost data Prepare reports and papers for publication

Service users

As part of this project we will arrange meetings with the 'Consumer Involvement in Research' group at the Nottingham Primary Care Research Partnership. Members of this group have undertaken introductory-level research training. The Partnership also has strong links with a local mental health service users' group. At these meetings the consumers will consider with us the implications of the study findings, and help us to identify means for dissemination of our findings to service users. We will not include consumers in those meetings that are focused on the technical and statistical aspects of the study.

Flow diagram



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Appendix 4

Original protocol

Protocol

A study of the safety and harms of antidepressant drugs for older people: an analysis using a large primary care database.

Investigators

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Funding

- NCCHTA.

Protocol details

- Version 1.1.

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Detailed project description

Project title

Safety and harms of antidepressant drugs for older people: an analysis using a large primary care database.

HTA project number: 06/42/01.

Summary

Depression is a common and debilitating condition in older people. Adverse drug events may be more common in the treatment of depression in older people compared with younger age groups owing to higher levels of comorbidity, age-related physiological changes and polypharmacy. The under-representation of older people in clinical trials of antidepressants makes it difficult to make reliable or precise estimates of the incidence of adverse events. This problem is further compounded when trial exclusion criteria exclude older people with comorbid conditions.

The overall aim of this study is to establish the relative safety and balance of risks for individual antidepressant drugs in older people. The study is a cohort study of people aged 65 years and over who have been diagnosed with a major depressive disorder or with unipolar depression identified from a large primary care database (QResearch). Prescribing data for these patients will be used to ascertain their use of antidepressant drugs following diagnosis of depression, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other antidepressants. Prospectively recorded data on these patients will be used to ascertain harms and adverse events that occurred in these patients over a minimum of 12 months' follow-up after their diagnosis. Primary outcomes will include the following events: all-cause mortality, suicide, sudden cardiac death, overdose/poisoning, attempted suicide, myocardial infarction (MI), stroke, seizures, gastrointestinal (GI) bleeding, falls and fractures, road traffic accidents (RTAs), adverse drug reactions (ADRs) and hyponatraemia. The analysis will examine the associations between exposure to the different classes of antidepressant and risk of the adverse events. Annual costs of antidepressant medication and costs of adverse events will be calculated and compared. A further analysis will use the self-controlled case-series approach to reduce effects of residual confounding and indication biases.

Background

Depression is a common and debilitating condition in older people. A pooled estimate of prevalence of depression from community-based studies of older people is 13.5%.¹ Across

all ages 29 million prescriptions for antidepressant drugs were issued in 2004.² Adverse drug events may be more common in the treatment of depression in older people compared with younger age groups owing to higher levels of comorbidity, age-related physiological changes, and polypharmacy.³ The under-representation of older people in clinical trials of antidepressants makes it difficult to make reliable or precise estimates of the incidence of adverse events.^{4,5} This problem is further compounded when trial exclusion criteria exclude older people with comorbid conditions.⁶ Even though older people with depression are more likely to be treated since the introduction of the newer generation of antidepressants,^{7,8} under treatment of depression among older people is a global problem.⁹ Evidence from a systematic review suggests that TCAs and SSRIs are equivalent in terms of efficacy but classical TCAs are associated with a higher discontinuation rate due to the side effect profile.¹⁰

Antidepressants, and particularly TCAs are an important cause of deaths by overdose and poisoning.¹¹ There appears to be some evidence from a meta-analysis of placebo-controlled trials that SSRIs are associated with a small increase in risk of fatal and non-fatal suicide attempts.¹² Lack of sufficient trial data meant it was not possible to see whether this finding held within those aged 60 years and over. Observational studies across all age groups have found associations between antidepressant use and suicide but have been unable to rule out confounding by indication.¹³ There is little evidence to support any difference in terms of class of antidepressant and risk of suicide,¹⁴ but studies have tended to look at risks across all ages or among adolescents and young adults.¹⁵

There appears to be an increased risk of subsequent ischaemic heart disease associated with dosulepin (formerly known as dothiepin) use but not other TCAs or SSRIs.¹⁶ Some studies have found no evidence of an increased risk of MI among users of antidepressants,¹⁷ or have suggested that an increased risk of MI may be explained by confounding factors relating to depression itself rather than specific adverse drug effects.¹⁸

Findings from both case-control,¹⁹ and case-series analysis studies,²⁰ indicate that risk of hip fracture is elevated with the use of TCAs and SSRIs among older people although the magnitude of the increased risk did not differ between the two classes of antidepressant.¹⁹ The likely mechanism underlying this increased risk appearing to be changes in orthostatic blood pressure,²¹ rather than altered bone mineral density.²²

Older people who use lithium may be at increased risk of being involved in an injurious motor vehicle accident.²³ In studies that have formally tested the effects of antidepressants on driving performance, sedating antidepressants have a similar effect to alcohol.²⁴

Hyponatraemia associated with antidepressant use is rare but is an adverse event that disproportionately affects older people.^{25,26} Similarly, GI bleeding is more common among those taking SSRIs who are aged 80 years or over,²⁷ although there is a lack of consensus as to whether the risk of GI bleeding associated with SSRI use is further increased with concurrent use of non-steroidal anti-inflammatory drugs,^{28,29} or not.³⁰

The gaps in the research into adverse effects for these drugs specifically in older people and the lack of consistent findings pose problems for clinicians prescribing these drugs and making choices as to the most appropriate drug for individual older patients. In this study we will use a large primary care database containing information on virtually all prescriptions for antidepressants and a range of potential adverse effects to derive a unified picture of the balance of risks for antidepressant drugs in older people with depression.

Specific aims and objectives

The overall aim of this study is to establish the relative safety and balance of risks for individual antidepressant drugs in older people, in order to provide a robust evidence base to support decision making for clinicians prescribing these medications to individual patients.

The project has five key objectives which are:

1. to determine the relative and absolute risks of predefined adverse events in older people diagnosed with depression. Comparisons will be made between classes of antidepressant drugs (tricyclic and related antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and other antidepressants) and non-use of antidepressant drugs
2. to directly compare the risk of adverse events in patients prescribed SSRIs compared with TCAs in older people diagnosed with depression
3. to determine how the dose and duration of prescribed antidepressant medication is associated with the risk of an adverse event
4. to describe patterns of antidepressant use in older people diagnosed with depression, in particular the types and doses prescribed, the durations and the proportions switched between different antidepressants (TCAs, SSRIs and other antidepressant drugs)
5. to determine the annual costs of antidepressant medication, the costs of the adverse events, and the costs of health-care resource use in older people diagnosed with depression, comparing patients by type of antidepressant drugs (TCAs, SSRIs, MAOIs, and other antidepressants).

Study design

Design

The planned investigation will use a large primary care database (QResearch) to investigate the relative safety and costs of antidepressant drugs in older people.

Two main approaches will be used to achieve the study objectives:

1. a cohort study
2. a self-controlled case-series study.

The cohort study is a well-established powerful method for determining absolute and relative risks associated with exposures. The self-controlled case-series method is a newer approach that estimates relative incidence of an outcome in high-risk compared with low-risk periods of time based only on data from cases. It is useful for investigating the short term effect of drug exposures on the risk of acute outcomes, since it eliminates problems of confounding from unmeasured variables, such as severity of disease. Both of these studies will derive data from a large primary-care research database (QResearch).

Cohort study

Our target population for the cohort study will be all patients aged 65 years and over with a first recorded diagnosis of depression (major depressive disorder or unipolar depression) between 1 January 1996 and 31 December 2005. We will use Read codes to identify a major depressive disorder or unipolar depression, using case definitions that have been used in previous studies. The cohort will be followed up until 31 December 2006. Information on all prescriptions for antidepressants will be extracted, along with information on potential confounding variables and adverse events during follow-up.

Self-controlled case-series study

The self-controlled case-series study only uses the patients in the cohort who have the outcomes of interest. Cases with each type of adverse event will be identified; these will be cases with a diagnosis of the adverse event between 1 January 1996 and 31 December 2006, who had a previous diagnosis of depression between 1 January 1996 and 31 December 2005. Information on prescriptions for antidepressants in these cases will be extracted and the analysis will compare rates of the adverse events in periods following a first prescription for an antidepressant compared with a baseline period.

Setting: QResearch database

We will undertake the study using data from the QResearch primary-care research database (www.qresearch.org). This validated database is the largest general practice research database in the UK and it contains the anonymised electronic health-care records of over 10 million patients ever registered with 525 general practices throughout England, Wales, Scotland and Northern Ireland. Consent to provide data for QResearch was sought from all UK practices using 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 two-thirds of all UK general practices. The consenting practices form a representative sample of 6–7% of all UK general practices, and there are practices in every strategic health authority and each health board in England, Wales and Scotland.

The information recorded on the QResearch database includes patient demographic data (year of birth, gender, socio-economic data derived from the UK 2001 census), characteristics (height, weight, smoking status), symptoms, clinical diagnoses, consultations, referrals, prescribed medications and results of investigations. The latest version of the QResearch database, which is updated quarterly, will be used for the analysis.

Detailed analyses have compared QResearch practices with all UK practices and found that practices contributing to QResearch are somewhat larger than UK practices overall but are very similar in other respects.³¹ The database has been validated by comparing birth rates, death rates, consultation rates, prevalence and mortality rates with other data sources including the General Household Survey and the General Practice Research Database <http://secure.qresearch.org/SiteSections/DataValidation/DataValidationMain.aspx>. The age–gender structure of the population has been compared with that reported in the 2001 census. There was good correspondence for all of these measures, although the QResearch population is slightly older and has marginally higher prevalence figures for some diagnoses compared with less recent data.³² but they are almost identical to current prevalence data from the new General Medical Services (GMS) contract for General Practitioners.

Compared with other primary care databases QResearch is the largest (currently 525 practices compared with around 200–400 (depending on selection criteria) in GPRD and 100 in The Health Improvement Network (THIN³³), and it has information on deprivation derived from postcode data which is not currently available in the other databases. The database is completely independent from commercial organisations and QResearch receives no funding from pharmaceutical companies. The database contains only anonymised data, which are encrypted and kept in secure conditions. One of the co-applicants (Professor Julia Hippisley-Cox) is the chief custodian of the database and QResearch has been used to examine the risks and benefits associated with a number of commonly prescribed drugs including statins^{34,35} and non-steroidal anti-inflammatory drugs (NSAIDs).³⁶ The applicants have also published studies examining antidepressants as risk factors for ischaemic heart disease.¹⁶

Outcome measures

The outcomes to be assessed will be extracted from the routine primary-care computer records of patients in the cohort. Outcomes will only be included if they occurred after the initial diagnosis of depression. The relevant computer recorded Read codes will be used to identify patients with the outcomes.

The outcomes that will be assessed will include:

- all-cause mortality
- suicide
- sudden cardiac death
- overdose/poisoning
- attempted suicide
- myocardial infarction
- stroke
- seizures
- gastrointestinal bleeding
- falls and fractures
- road traffic accidents
- adverse drug reactions.

We will examine hyponatraemia in a subset of practices with electronic links for pathology results.

QResearch is undertaking a national audit on care for patients with osteoporosis and falls in primary care. As part of this project, funded by the Information Centre, we will be examining the clinical coding of falls and fractures in some detail and will be able to utilise the definitions for the proposed project. We have consulted professional groupings regarding the diagnostic codes (Read codes) which are likely to be used in clinical practice. Other outcomes are likely to be well recorded, although sudden cardiac deaths may be difficult to identify.

Exposures

Our exposure of interest is antidepressant medication. We will extract details of all prescriptions for antidepressants in patients in our cohort, following their diagnosis of depression; this will include the date of prescription, the type of drug, the dose and the duration. The antidepressant drugs will be grouped for analysis according to the major classes as described in the *British National Formulary* (BNF), namely: tricyclic and related antidepressants (TCAs: section 4.3.1), selective serotonin reuptake inhibitors (SSRIs: section 4.3.3), monoamine oxidase inhibitors (MAOIs: section 4.3.2) and other antidepressants (section 4.3.4). Effects of individual antidepressant drugs will also be assessed where numbers are sufficient. The number of prescriptions, duration and dose of the antidepressant drugs will be examined in the analyses.

We will determine the proportions of patients who switch between antidepressants, including switches between classes of drugs and between different drugs within a class. We will examine the proportions for patients who discontinue a drug before the recommended time by examining the proportions who have only one prescription, have two to three and four to six prescriptions for a particular drug.

Confounding variables

Data will be extracted on the following variables, and these will be considered as confounding variables in the analysis of the cohort study:

- age, gender, deprivation, government office region, comorbidities (e.g. ischaemic heart disease, diabetes, hypertension, cancer, dementia, epilepsy, Parkinson's), body mass index (BMI), smoking and use of other drugs (including statins, NSAIDs, anti-psychotics, aspirin, antihypertensive drugs, anticonvulsants).

Inclusion/exclusion criteria

Patients will be eligible for inclusion in the cohort study if:

- they have a recorded diagnosis of depression (a major depressive disorder or unipolar depression)
- the diagnosis was made at the age of 65 years or over
- the diagnosis was recorded between 1 January 1996 to 31 December 2005
- the diagnosis occurred at least 12 months after registration with a study practice and after the date of the installation of the practice EMIS computer system.

Patients will be excluded from the cohort study if:

- they are temporary residents
- they have a previous recorded diagnosis of depression
- they have been prescribed antidepressants more than 1 month prior to their recorded diagnosis of depression.

Quality of life

Quality of life is not recorded in primary-care consultations so we are unable to examine this outcome in our database, however, as part of our review of the literature we will search for literature on quality of life and antidepressant medication in older people with depression to see if some estimations can be made about the likely effectiveness and cost-effectiveness of different antidepressants in older people. However, a basic literature search undertaken to support the development of this proposal found very few cost–utility studies³⁷ comparing different types of antidepressants in a population aged 18 years or over and therefore, there may well be limited published economic evidence specific to a more elderly population.

Strengths and limitations of study design

The strengths of using a cohort study design for this project are that it will include a large and representative number of older people with depression, it can calculate absolute as well as relative risks, it can take account of exposures changing over time and it is able to adjust for a number of potential confounding variables. The recording of prescriptions in primary-care records is high, and the exposures under consideration are available only on prescription. The outcomes we have included are likely to be well recorded, and we will compare their rates in this study against other published data where possible.

The limitations of the cohort design approach are that it can be vulnerable to indication bias and residual confounding whereby relevant confounding variables may be imprecisely recorded or not recorded at all in primary-care records (for example diet, physical activity). Indication bias can cause difficulties in the interpretation of results on effects of drugs in observational studies; in this instance whether or not an antidepressant is prescribed or the type of antidepressant prescribed may be related to important prognostic factors for the outcome in question such as the severity of depression or the attitude of the patient towards taking medication. These characteristics could influence the outcome but are unlikely to be recorded well in a patient's medical records. The self-controlled case-series method has been proposed as a means of addressing this problem.^{38,39} This is an internally controlled method whereby analyses are carried out only in patients with the outcome of interest, thereby eliminating the effect of indication bias

and unmeasured confounding variables that do not vary over time. This method has previously been used to examine the relationship between antidepressants and hip fracture,²⁰ and is of most relevance for acute events occurring within a short period after exposure. A limitation of the case-series design is that it requires that probability of exposure is not affected by occurrence of an outcome event, which is a particular problem for fatal outcomes, but this can be resolved by using only time from first prescription in the observation period for analysis.

Sample size

Cohort study

All eligible patients aged 65 years and over diagnosed with incident depression between 1 January 1996 to 31 December 2005 in the QResearch database will be included in the cohort study.

A feasibility study shows there are approximately 5.0 million years of observation and 18,000 incident cases of depression arising from patients aged 65 years and older between 1996 and 2005 on the database.

Assuming 88% of patients aged 65 years and over diagnosed with depression are prescribed an antidepressant drug as we found in our feasibility study, and for a rare outcome with an incidence of 5 per 1000 per year (e.g. upper GI event⁴⁰ or lower limb fracture,⁴¹ and an average follow-up of 5 years, we will be able to detect a relative risk of 1.5 with 88% power and a 5% significance level comparing those on antidepressants with those not on antidepressants. For all-cause mortality with a mortality rate of 47 per 1000 per year (Office for National Statistics for 2001) we will be able to detect a relative risk of 1.15 with 95% power. In comparisons between TCAs and SSRIs, assuming 39% of patients on antidepressants take TCAs and 50% take SSRIs we will be able to detect a relative risk of 1.4 with 86% power for rare outcomes and 1.12 with 92% power for all-cause mortality.

Self-controlled case-series study

The exposed cases contribute to the statistical power in the case-series method, under certain conditions the power of the analysis can be similar to that of the cohort study from which the cases are derived. To detect a rate ratio of 2.0 in a risk period of 1–14 days after the first prescription for an antidepressant with 80% power and 5% significance, then with a proportion of 0.0077 in the risk period of 14 days compared with an average observation period of 5 years (3/1825) then 1435 exposed cases would be required for each outcome.⁴² We would anticipate having at least this number for all-cause mortality and falls/fracture. To detect a rate ratio of 3.0 in a risk period of 1–14 days then 448 exposed cases would be required. We would anticipate having around this number for rare outcomes such as GI events (incidence rate 5/1000/year).

Statistical analysis

Descriptive statistics

Descriptive statistics will be derived primarily using the data from the cohort study.

1. We will calculate incidence rates of diagnosed depression in people aged 65 years and over, and examine these rates by gender, age group (65–74, 75–84, 85+ years) and study year. We will compare these rates with other published rates of depression.
2. In patients with a diagnosis of depression in the study cohort we will describe patterns of antidepressant use according to type of antidepressant prescribed, duration of use and dose, and will examine these patterns by gender, age group, use of other medications, comorbidities and study year. We will also examine variations between practices in patterns of antidepressant prescribing.
3. We will calculate the proportions of people switched between different antidepressants (TCAs, SSRIs and other antidepressant drugs) by gender, age group and study year and examine duration of use before switching.

4. Discontinuation rates for each drug will also be determined by examining the proportion of those with at least one prescription for a drug who only have one prescription, have 2–3 and have 4–6 prescriptions.

Analysis of cohort study

The analysis of the cohort study will determine absolute and relative risks of adverse events in older people with depression according to type of antidepressant prescribed, and will also examine risks according to dose and duration of treatment.

Incidence rates of the adverse events will be calculated in the study cohort. The statistical analysis will comprise a series of survival analyses to assess the relationship between exposure to antidepressant drugs and a number of potential adverse effects. These analyses will be restricted to the cohort of older people with a diagnosis of depression. The exposure variables will be use of antidepressant drugs including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other antidepressants. The number of prescriptions, duration and dose of the antidepressant drugs will be examined in the analyses. The date of entry into the survival analyses will be the date of diagnosis of depression, and the right censor date will be the earliest of the following: date of diagnosis of the outcome of interest, date of death, date of leaving the practice, date of the latest download of data or the study end date.

Cox's proportion hazards models will be used with antidepressant exposure treated as a time-varying exposure. The analysis will calculate HRs and 95% confidence intervals (CIs) comparing:

1. The risk of each adverse effect in patients on any type of antidepressant compared with patients with no antidepressant treatment.
2. Each separate class of antidepressants (SSRIs, TCAs and other antidepressants) compared with no treatment.
3. The risk of each adverse effect for each class of antidepressant will be directly compared with each other class (in particular SSRIs will be directly compared with TCAs).
4. Analyses will also calculate HRs according to duration of use and prescribed dose of antidepressant; where numbers are sufficient individual antidepressants within each class will be examined.
5. Analyses of interaction will be carried out to examine the extent to which patient's characteristics (age, gender), use of other medications and comorbidities modify the relationship between antidepressant use and adverse outcomes.

Adjustment will be made for potential confounders including:

1. age, gender, deprivation, government office region, comorbidities (e.g. ischaemic heart disease, diabetes, hypertension, cancer, dementia, epilepsy, Parkinson's), BMI, smoking and use of other drugs (including statins, NSAIDs, anti-psychotics, aspirin, antihypertensive drugs, anticonvulsants). The analysis will also compare these patient characteristics according to the type of antidepressant prescribed. The assumptions of the Cox proportional hazards model will be checked. Absolute risks of the adverse events will also be estimated and presented.

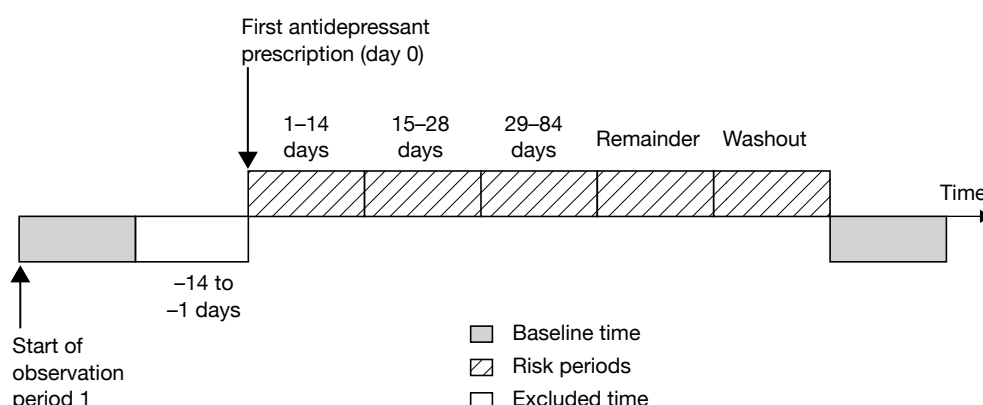
Self-controlled case-series analysis

We will perform self-controlled case-series analyses using data only on patients who have had an adverse event. We will carry out a separate analysis for each type of outcome. The case-series method will enable us to determine the relative incidence of the outcomes of interest for high risk versus low risk time periods relative to commencing use of antidepressants in individuals who have the outcome of interest.

In the case-series analyses we will include cases who have the outcomes of interest as in the cohort study. We will use only the first recorded diagnosis of the outcome of interest rather than recurrent events. Patients who have the outcome of interest occurring on the same day as their first prescription for antidepressants will be distinguished in the analysis. Cases without any prescriptions for antidepressants will be included in the analyses to improve adjustment for age.

We will use conditional Poisson regression to estimate the relative incidence of the outcomes of interest for defined time periods of risk after the first prescription for antidepressants. The time periods for assessing potential short term effects of antidepressants will be defined as follows as shown in the figure below: 0 days (outcome occurs on same day as first prescription); 1–14 days after the first prescription; 15–28 days and 29–84 days; remaining treatment period; washout period (a period of 182 days after stopping treatment). The 14 days before the first prescription will be considered as a separate category, as occurrence of the outcome of interest in this period could affect the probability of an antidepressant prescription. All other time periods outside these specified risk periods will contribute to the baseline person time, i.e. the unexposed periods. These periods will enable us to examine short-term and longer-term effects of antidepressants on the risks of adverse events and are similar to those used in other studies of antidepressants.^{18,20} Where the outcome is a fatal one we will only use time from the first prescription in the observation period for analysis, as otherwise the method is invalid. We will adjust for age in the analyses and also take account of repeated prescriptions over time.

Figure showing risk periods in case-series design:



Measurement and analysis of costs

The cost analysis will be undertaken from an NHS health-care perspective with the aim of detecting whether there are any significant differences in health-care costs for patients on different types of antidepressants. Patient-specific resource use data (identified using the QResearch database), including those specific to depression such as antidepressant medication and resource use as a result of an adverse reaction, will be captured alongside wider health service utilisation in case different medications for depression are associated with distinct impacts on the patients wider health needs. The unit costs of these resources will be estimated using published data for a common price year from, for example, the *British National Formulary* (BNF) and Curtis and Netten.⁴³ This will enable the overall aggregate cost per patient to be calculated over 1 year following diagnosis of depression. In turn, the incremental mean cost associated with each type of antidepressant (SSRIs, TCAs, MAOIs, and others) will be estimated, controlling for patient characteristics (age, gender), and other factors (comorbidities, whether they switched treatment, and severity of depression, for instance), which may be associated with differences in mean costs between the antidepressant groups that are not a result of the antidepressant they

are taking. Sensitivity analyses will be undertaken to assess the robustness of results. Accepted methods will be used.⁴⁴

We will measure and analyse costs based on the cohort analysis to ensure representative costs are estimated for the population as a whole rather than just for those who experience the outcome of interest as would be the case using the self-controlled case-series study. We will estimate and compare, for instance, the incremental cost per adverse event avoided across the different antidepressants and those not taking antidepressants. We will explore the relationship between cost and explanatory factors such as severity, comorbidities, use of other medications and patients' characteristics. In addition, the mean cost of an adverse event, will be estimated using only the sample in the self-controlled case-series study. We will also explore the relationship between time of adverse event relative to time since first antidepressant prescription to see if this has a relationship with the scale of the adverse event cost.

However, we recognise that cost-effectiveness ratios, such as cost per adverse event avoided, may capture only intermediate as opposed to final outcomes. In order to capture final outcomes it is usual to estimate quality-adjusted life years (QALYs). As stated on p. 10, health-related quality of life, is not recorded in primary care databases, and whilst we shall search for literature on quality of life of older people with depression and for different antidepressants, initial searches do not reveal a vast literature on this and our ability to extrapolate from published studies therefore, is likely to be limited. However, we will explore this possibility in order to try and estimate the incremental cost per QALY between different types of antidepressants and those not on antidepressants but diagnosed with depression. Our primary focus however will relate to adverse events that may be associated with antidepressant use in older people, and we will be able to determine the cost per adverse event avoided based on data recorded in the database.

Research governance

All projects using QResearch are independently reviewed by the QResearch scientific committee and reported both to Trent Research Ethics Committee (REC) and also the national QResearch advisory board.

R&D governance of QResearch projects undertaken by the applicants is undertaken by Nottinghamshire County Teaching Primary Care Trust.

Ethical arrangements

The project will be independently peer reviewed by the QResearch Scientific board and has been reported to Trent Research Ethics Committee in accordance with the agreed procedure with the Committee.

Funding

This study is funded by the NCCHTA.

Project timetable and milestones

Proposed start date

- 1 April 2008.

Duration

- 15 months.

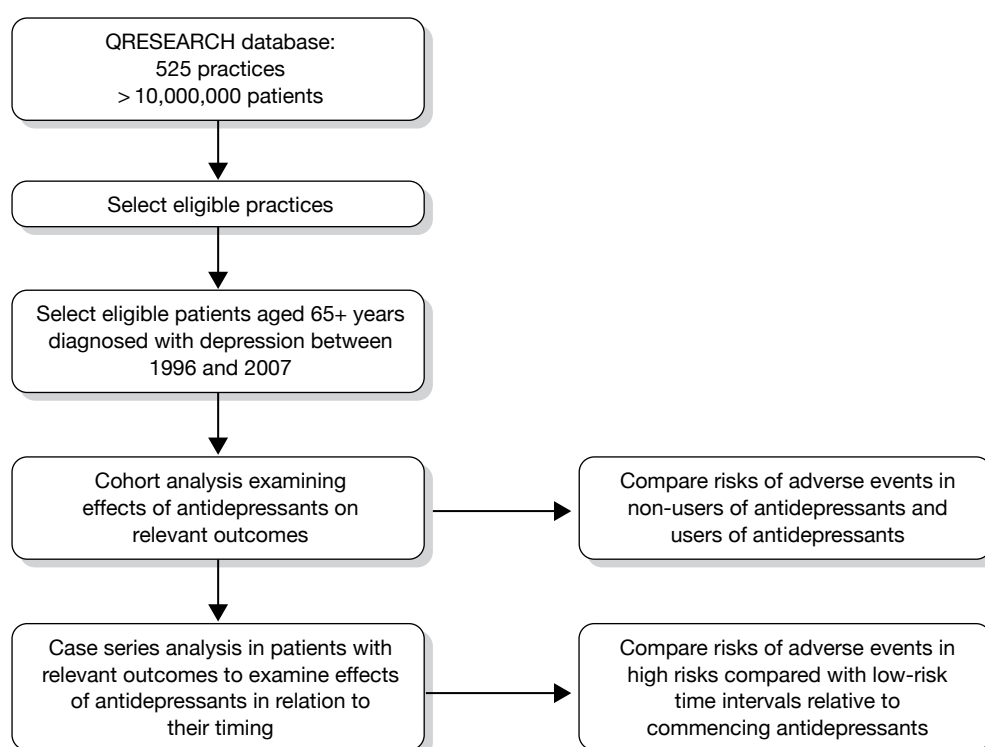
Project timetable

Months 1–3	Finalise protocol
	Specify detailed data definitions for data extraction
	Commence data extraction
Months 4–7	Refresh literature review
	Complete data extraction
	Carry out data validation and manipulation
	Produce full statistical analysis plan
Month 8	Undertake descriptive statistical analyses
Months 9–10	Analyse cohort study data
Months 11–12	Analyse case-series study data
	Undertake analyses of cost data
Months 13–15	Prepare reports and papers for publication

Service users

As part of this project we will arrange meetings with the ‘Consumer Involvement in Research’ group at the Nottingham Primary Care Research Partnership. Members of this group have undertaken introductory-level research training. The Partnership also has strong links with a local mental health service users’ group. At these meetings the consumers will consider with us the implications of the study findings, and help us to identify means for dissemination of our findings to service users. We will not include consumers in those meetings that are focused on the technical and statistical aspects of the study.

Flow diagram



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