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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Executive summary

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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.

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Publication

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

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Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 06/42/01. The contractual start date was in September 2008. The draft report began editorial review in July 2010 and was accepted for publication in October 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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