Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study

Carlos Martinez, Stephan Rietbrock, Lesley Wise, Deborah Ashby, Jonathan Chick, Jane Moseley, Stephen Evans, David Gunnell

Abstract

Objective To compare the risk of non-fatal self harm and suicide in patients taking selective serotonin reuptake inhibitors (SSRIs) with that of patients taking tricyclic antidepressants, as well as between different SSRIs and different tricyclic antidepressants.
Design Nested case-control study.
Setting Primary care in the United Kingdom.
Participants 146 095 individuals with a first prescription of an antidepressant for depression.
Main outcome measures Suicide and non-fatal self harm.
Results 1968 cases of non-fatal self harm and 69 suicides occurred. The overall adjusted odds ratio of non-fatal self harm was 0.99 (95% confidence interval 0.86 to 1.14) and that of suicide 0.57 (0.26 to 1.25) in people prescribed SSRIs compared with those prescribed tricyclic antidepressants. We found little evidence that associations differed over time since starting or stopping treatment. We found some evidence that risks of non-fatal self harm in people prescribed SSRIs compared with those prescribed tricyclic antidepressants differed by age group (interaction P = 0.02). The adjusted odds ratio of non-fatal self harm for people prescribed SSRIs compared with users of tricylic antidepressants for those aged 18 or younger was 1.59 (1.01 to 2.50), but no association was apparent in other age groups. No suicides occurred in those aged 18 or younger currently or recently prescribed tricyclic antidepressants or SSRIs.
Conclusion We found no evidence that the risk of suicide or non-fatal self harm in adults prescribed SSRIs was greater than in those prescribed tricyclic antidepressants. We found some weak evidence of an increased risk of non-fatal self harm for current SSRI use among those aged 18 or younger. However, preferential prescribing of SSRIs to patients at higher risk of suicidal behaviour cannot be ruled out.

Introduction

Data in adults have not consistently shown any influence on suicide or self harm from use of selective serotonin reuptake inhibitor (SSRI) antidepressants.[1] Randomised controlled trials in young people, however, indicate that they may increase the risk of suicidal thoughts and self harm in those aged under 19.[2 3]

The most comprehensive studies of suicidal behaviour are based on data from the General Practice Research Database.[4 5] The first found some evidence of an increased risk of suicide among people prescribed fluoxetine,[4] but the drug's safety in overdose may have led to selective prescription to people at risk of self harm. The other study found no notable differences between a range of antidepressants and risk of fatal or non-fatal suicidal behaviour.[5] However, the study was not restricted to patients treated for depression and examined only four antidepressants.

We report a nested case-control study, based on the General Practice Research Database, of patients with a new diagnosis of depression who were prescribed antidepressants for the first time between 1995 and 2001. We compared the risk of non-fatal self harm and suicide in association with the use of SSRIs and tricyclic antidepressants.

Methods

Materials

Our cohort comprised patients aged 10 to 90 years with a first recorded prescription for antidepressants between 1 January 1995 and 31 December 2001. Members of the cohort were required to have contributed a minimum of 365 days to the database before their first recorded prescription for antidepressants and to have received a diagnosis of depression in the 180 days before or 90 days after entry to the cohort. The date of the first prescription of antidepressants defined entry to the cohort. Follow up ended with the earliest of either an episode of suicidal behaviour, the end of the first treatment episode, the end date of the study, or when the patient left the practice.

We identified depression by a set of Read and Oxford Medical Information System (OXMIS) medical terms indicative of depression, bipolar disorder, or dysthymic disorder. We classed severity of depression as mild, moderate, or severe (see bmj.com). We categorised antidepressants into three classes: tricyclic and related antidepressants, SSRIs, and other antidepressants (see bmj.com).

We studied two outcomes, non-fatal self harm and suicide, using the relevant medical terms, review of the patient's free text notes, and death certificates when available (around 60% of cases).

We selected a random sample of up to 20 controls for each case from the cohort, matching for sex, year of birth within one year, and duration of cohort membership. We derived the duration of prescriptions from the quantity of drug prescribed and the daily dose plus an additional seven day washout period (see bmj.com).

Data analysis

We classified the cases and controls as currently or previously exposed to an SSRI, tricyclic antidepressant, or

P+ *A classification system for the severity of depression, the method used to measure exposure to antidepressants, and supplemental tables are on bmj.com*

ELPS *This is the abridged version; the full version is on bmj.com*

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General Practice Research Database Division, Medicines and Healthcare products Regulatory Agency, London SW8 5NQ
Carlos Martinez *epidemiologist*
Stephan Rietbrock *epidemiologist*

Post-Licensing Division, Medicine and Healthcare products Regulatory Agency
Lesley Wise *epidemiologist*
Jane Moseley *epidemiologist*

Wolfson Institute of Preventive Medicine, Queen Mary, University of London
Deborah Ashby *professor of medical statistics*

Department of Psychiatry, University of Edinburgh, Edinburgh
Jonathan Chick *consultant psychiatrist*

Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London
Stephen Evans *professor of pharmacoepidemiology*

Department of Social Medicine, University of Bristol, Bristol BS8 2PR
David Gunnell *professor of epidemiology*

Correspondence to: C Martinez carlos.martinez@gprd.de

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Table 1 Characteristics of study cohort according to first antidepressant class prescribed. Values are numbers (percentages) unless otherwise indicated

Characteristic	SSRIs (n=90 403)	Tricyclic antidepressants (n=50 829)	Other antidepressants (n=4863)	Total (n=146 095)
Age in years:				
10-18	3830 (4)	1316 (3)	141 (3)	5287 (4)
19-30	23 561 (26)	10 145 (20)	1086 (22)	34 792 (24)
31-45	31 541 (35)	15 431 (30)	1548 (32)	48 520 (33)
46-60	18 310 (20)	11 506 (23)	989 (20)	30 805 (21)
61-75	7949 (9)	7538 (15)	605 (12)	16 092 (11)
76-89	5212 (6)	4893 (10)	494 (10)	10 599 (7)
Women	58 444 (65)	33 399 (66)	2924 (60)	94 767 (65)
Men	31 959 (35)	17 430 (34)	1939 (40)	51 328 (35)
Median (interquartile range) duration of observation (years)	0.67 (0.57-1.03)	0.65 (0.57-1.02)	0.65 (0.57-1.02)	0.66 (0.57-1.03)
Severity of depression:				
Mild	60 537 (67)	36 893 (72)	3306 (68)	100 736 (69)
Moderate	26 710 (30)	12 116 (24)	1329 (27)	40 155 (27)
Severe	3156 (3)	1820 (4)	228 (5)	5204 (4)
Referral to psychiatrist or psychologist*	721 (1)	211 (0)	75 (2)	1007 (1)
History of self harm†	479 (1)	201 (0)	33 (1)	713 (<1)
Concomitant conditions:				
Diagnosis of, or therapy for, anxiety and panic disorders	21 501 (24)	11 209 (22)	1476 (30)	34 186 (23)
Schizophrenia	101 (0)	97 (0)	10 (0)	208 (0)
Antipsychotic therapy	2947 (3)	1916 (4)	252 (5)	5115 (4)
Drug misuse	61 (0)	45 (0)	3 (0)	109 (0)
Alcohol misuse	2408 (3)	1269 (2)	184 (4)	3861 (3)

*In year previous to index day.
†Includes drug overdose, poisoning, self laceration, and other non-fatal suicidal attempts before entry to cohort.

other antidepressant, or co-exposed to more than one antidepressant, according to the exposure status on the index day (day of self harm or suicide or equivalent control day). We standardised the incidence rates to the UK population in 2001.

We assessed risks associated with "current exposure" by using multivariable conditional logistic regression controlling for a range of possible confounding factors (see bmj.com). We investigated whether risk varied in relation to duration of current use of antidepressants, time since stopping treatment, and age at entry to the cohort (10-18, 19-30, and >30). We stratified by the duration of exposure (days) to antidepressants and time since discontinuation. In all comparisons, we compared SSRI monotherapy with tricylic antidepressant monotherapy for the same duration of exposure.

Results

Our cohort included 146 095 patients with a first prescription for an antidepressant for depression, contributing 62 224 person years of follow (see bmj.com). Almost twice as many women as men received antidepressants. SSRIs were the most commonly prescribed antidepressants. People prescribed SSRIs tended to be younger, with a more frequent history of self harm and referral to psychiatrists than those prescribed tricyclic antidepressants (table 1).

The strongest predictors of non-fatal self harm were a history of self harm, referral to a psychiatrist, alcohol misuse, and drug misuse. The strongest predictors for suicide were a history of non-fatal self harm, antipsychotic therapy, number of antidepressants prescribed in the previous year, alcohol misuse, and referral to a psychiatrist.

Over the study period, 1968 people had a recorded episode of non-fatal self harm: 1344 were exposed to antidepressant medication at the time, and 624 had stopped treatment before the episode. Drug overdose accounted for most episodes of non-fatal self harm (81%). The incidence rate of non-fatal self harm, standardised by age and sex, per 100 000 person years of follow up among people prescribed antidepressants was 2894 (95% confidence interval 2618 to 3170). The rate per 100 000 person years for men was 2834 (2579 to 3089) and for women was 2952 (2471 to 3432).

Overall, 69 suicides took place (56 men, 13 women); 36 of those people were taking antidepressants at the time of death. The overall standardised incidence rate for suicide was 62 (40 to 85) per 100 000 person years; in men this was 117 (72 to 163) and in women 9 (1 to 18).

The adjusted odds ratio for non-fatal self harm among SSRI users compared with users of tricyclic antidepressants was 0.99 (0.86 to 1.14). We found no evidence that the risk of non-fatal self harm varied among the different individual SSRIs or tricyclic antidepressants ($P=0.35$ and $P=0.69$, respectively) and no evidence of an increased risk of suicide associated with use of SSRIs compared with tricyclic antidepressants (odds ratio 0.57, 0.26 to 1.25; table 2).

We found borderline evidence that the risk of non-fatal self harm (P for interaction = 0.05), but not suicide (P for interaction = 0.73), differed between the different antidepressant categories in relation to time since starting therapy. This association showed no clear pattern.

We found evidence of a difference in risk of non-fatal self harm for current SSRI users compared with current users of tricyclic antidepressants in

Table 2 Risk of non-fatal self harm and completed suicide in people prescribed SSRIs, other antidepressants, or exposed to more than one antidepressant compared with people prescribed tricylic antidepressants and among specific SSRIs compared with paroxetine and specific tricyclic antidepressants compared with dothiepin (all ages)

	Non-fatal self harm				Completed suicides			
Exposure	Cases (n=1344)	Controls (n=19 953)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	Cases (n=36)	Controls (n=664)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Any current use of tricylic antidepressant	319	4901	1	1	15	201	1	1
Any current use of SSRIs	854	13 636	0.97 (0.85 to 1.12)	0.99 (0.86 to 1.14)	17	406	0.59 (0.28 to 1.27)	0.57 (0.26 to 1.25)
Other antidepressants	86	894	1.30 (1.01 to 1.68)	0.99 (0.76 to 1.29)	3	28	1.51 (0.39 to 5.85)	0.80 (0.16 to 4.06)
Co-exposure†	85	522	2.55 (1.96 to 3.31)	1.53 (1.15 to 2.04)	1	29	-	-
Specific SSRIs:								
Paroxetine	289	4209	1	1	8	135	1	1
Citalopram	128	1915	1.03 (0.83 to 1.29)	1.01 (0.80 to 1.26)	2	5	-	-
Fluoxetine	304	5239	0.88 (0.74 to 1.04)	0.94 (0.79 to 1.11)	6	159	0.60 (0.20 to 1.81)	0.42 (0.13 to 1.39)
Fluvoxamine	42	810	0.74 (0.52 to 1.03)	0.73 (0.52 to 1.04)	0	29	-	-
Sertraline	91	1463	0.92 (0.72 to 1.17)	0.86 (0.67 to 1.10)	1	33	-	-
Specific tricyclic antidepressants:								
Dothiepin	136	2334	1	1	7	102	1	1
Amitriptyline	66	926	1.21 (0.89 to 1.65)	1.18 (0.86 to 1.61)	2	31	-	-
Lofepramine	68	1096	1.11 (0.82 to 1.50)	1.08 (0.79 to 1.47)	4	47	1.12 (0.30 to 4.20)	0.94 (0.24 to 3.61)
Other tricylic antidepressant	49	545	1.43 (1.01 to 2.02)	1.19 (0.83 to 1.69)	2	21	-	-

*Adjusted for severity of depression; time depression was diagnosed in relation to start of therapy; referral to psychiatrist or psychologist before index day; history of self harm; diagnosis of, or treatment for, anxiety or panic disorder; schizophrenia; antipsychotic drugs; drug misuse; and alcohol misuse.
†Any exposure to more than one antidepressant of same class or different classes.

relation to age (P for interaction = 0.02), with an increased risk associated with SSRI use among those aged 18 or younger, but not in 19 to 30 year olds or those older than 30 (table 3).

In people aged 18 or younger, we found no evidence of any difference in risk of non-fatal self harm between individual tricyclic antidepressants, but among SSRIs (figure), the greatest risk was in relation to paroxetine use.

The risk of non-fatal self harm or suicide did not seem to differ between or within antidepressant classes according to the time since stopping treatment (see bmj.com).

Discussion

In patients with newly diagnosed depression treated with antidepressants for the first time, we have found no evidence that the risk of suicide or non-fatal self harm in people currently prescribed SSRIs is higher than in those prescribed tricyclic antidepressants.

We found no strong evidence of variability in the risk of non-fatal self harm between substances or between drug classes associated with time since starting or stopping antidepressant therapy. However, in patients aged 18 or younger, we found the risk of non-fatal self harm was higher in people prescribed SSRIs than with tricyclic antidepressants. In this age group, we found a weak indication that the risk of non-fatal self harm among users of the SSRIs studied is highest in those who used paroxetine. These findings are in keeping with those of Jick et al.[5]

Limitations

SSRIs are relatively non-toxic in overdose; it is possible that they were selectively given to individuals at higher risk of overdose and that SSRI overdose did not result in presentation to hospital or general practice.

Table 3 Risk of non-fatal self harm in people prescribed SSRIs compared with tricyclic antidepressants in relation to age

	Non-fatal self harm			
Exposure	Cases (n=1344)	Controls (n=19 953)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
10-18 years†:				
Any current use of tricyclic antidepressants	24	493	1	1
Any current use of SSRIs	168	2148	1.73 (1.10 to 2.72)	1.59 (1.01 to 2.50)
19-30 years:				
Any current use of tricyclic antidepressants	106	1687	1	1
Any current use of SSRIs	312	5013	1.00 (0.79 to 1.27)	1.04 (0.82 to 1.32)
>30 years:				
Any current use of tricyclic antidepressants	189	2721	1	1
Any current use of SSRIs	374	6475	0.83 (0.69 to 1.01)	0.86 (0.71 to 1.04)

Participants exposed to more than one antidepressant or prescribed non-SSRI, non-tricyclic antidepressants (see table 2) were included in models but, for presentational purposes, data are not given in table.
*Adjusted for severity of depression; time depression was diagnosed in relation to start of therapy; referral to psychiatrist or psychologist before index day; history of self harm; diagnosis of, or treatment for, anxiety or panic disorder; schizophrenia; antipsychotic drugs; drug misuse, and alcohol misuse.
†Includes nine cases of non-fatal self harm and 86 controls exposed to SSRIs, and no cases and 18 controls exposed to tricyclic antidepressants among patients aged 10 to 14 years.

Previous self harm is an important predictor of further self harm and suicide. The prevalence of recorded past self harm among study members who harmed themselves (<5%) is considerably lower than reported among case series of people who harmed themselves (50%)[6] and completed suicides (30% to 47%),[7] which indicates the possibility of residual confounding if non-fatal self harm is recorded differentially for SSRIs compared with tricyclic antidepressants. Three other limitations are worth noting. Firstly, we assumed prescribing to be a marker for exposure, but not all prescriptions are dispensed, and some of those dispensed are not taken. Secondly, it is possible that some associations may be chance findings. Thirdly, we did not deal with the question of whether people treated with SSRIs are at greater risk of self harm than those with equivalent morbidity who do not receive treatment. We have assessed risk only relative to people receiving tricyclic antidepressants.

Representativeness of the study

The suicide rate in our study (62 per 100 000 patient years) was higher than in the general population (9 per 100 000 people). The incidence of non-fatal self harm was seven times higher than that of around 400/100 000 in 1995 reported in Oxford.[8] The ratio of cases of non-fatal to fatal self harm (approximately 30:1) in our study approximates to the ratio of the estimated number of hospital presenting episodes of self harm (n=142 000)[8] and suicides in the general population of England and Wales (n=5000).[9]

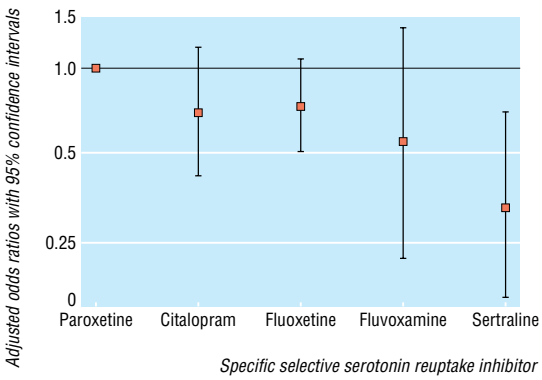
Potential biases

Our findings for people younger than 19 are consistent with the results from randomised controlled trials,[2 3] but they may have resulted from confounding by indication. For example, patients with personality disorders and adjustment disorders may be given a diagnosis of depression in primary care and be prescribed SSRIs.

Strengths of the study

The main strengths are the large sample size, detailed exposure data, and confounder information. Our study covered 1995 to 2001 and patients with a first prescription of antidepressants in this period. Furthermore, our approach to the ascertainment of cases of non-fatal self harm and suicides gives us considerably more power than previous studies.

We have endeavoured to control as closely as possible for factors that may be associated both with the risk of suicidal behaviour and the choice of antidepressant.



Risk of non-fatal self harm in patients aged 10-18 currently exposed to citalopram, fluoxetine, fluvoxamine, and sertraline compared with paroxetine

What is already known on this topic

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of antidepressant.

Evidence from recent clinical trials shows that SSRIs may increase the risk of self harm and suicidal thoughts in children and adolescents

Previous studies of the risk of suicide in adults have been restricted to the four most frequently prescribed antidepressants and have lacked statistical power to identify whether risks differ in children compared to adults

What this study adds

Risks of self harm and suicide were no different in adults prescribed SSRIs compared with those prescribed tricyclic antidepressants.

Children and adolescents prescribed SSRIs seemed possibly to be at increased risk of self harm compared with those prescribed tricyclic antidepressants

No children taking antidepressants in this study committed suicide

The absence of excess risk of self harm in adult users of SSRIs may be interpreted as reassuring evidence of their safety or that any adverse or protective effects of SSRIs are no different from those seen with other antidepressants.

Conclusion

As prescribing to adults accounts for over 95% of antidepressant use in the United Kingdom, our finding that SSRIs and tricyclic antidepressants have a similar risk profile with respect to suicide and non-fatal self harm is reassuring. It is possible, however, that any adverse or protective effects are common to all classes of antidepressants. Further research, based on large randomised trials, should assess the long term and short term risk and benefits of antidepressants and compare these with non-pharmacological therapies for depression in adults.

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Contributors: See bmj.com

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Competing interests: The UK Committee on Safety of Medicines established an expert working group to conduct a

review of the safety of SSRIs. No members of the expert working group have financial interests in any of the companies that hold marketing authorisations for SSRIs. The MHRA funded the study and professional staff at the MHRA, including JM and LW, have been acting as secretariat to or observers on the expert working group's review. Neither JM nor LW have any personal financial interests in any drug product. DG, JC, and DA are members of the MHRA's expert working group on the safety of SSRIs, and DA is a member of the Committee on Safety of Medicines. They act as independent advisers, receiving travel expenses and a small fee for meeting attendance and reading materials in preparation for the meeting. DA has spoken on the methodology of adverse drugs reactions in HIV at a scientific meeting attended by several pharmaceutical companies and sponsored by GlaxoSmithKline (GSK). A honorarium was paid to her department. SE has no personal interests to declare. His department receives funding from many pharmaceutical companies, including GSK, but mainly for methodological research. SE has no direct involvement in any of this. The General Practice Research Database Division receives funding for services, including the conduct of commissioned research, from a wide range of public sector bodies and the pharmaceutical industry. CM and SR have no competing interests to declare.

Ethical approval: General Practice Research Database Scientific and Ethical Advisory Group.

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Subfecundity and neonatal mortality: longitudinal study within the Danish national birth cohort

Olga Basso, Jørn Olsen

Treatment for infertility correlates with adverse outcomes in pregnancy, especially in singleton deliveries.[1] A long time to pregnancy (subfecundity) also correlates with adverse outcomes,[2–4] but few studies evaluating treatment take subfecundity into consideration. We explored the association between time to pregnancy and neonatal death in the Danish national birth cohort.

Participants, methods, and results

We identified 27 624 firstborn singleton babies, born alive from the 24th week of gestation between March 1998 and December 2001, whose mothers were enrolled in the Danish national birth cohort.[4 5] Mothers had been interviewed during pregnancy (50% by the 16th completed week and 95% by the 25th) and asked about pregnancy planning and other factors.

Women who reported having planned or partly planned their pregnancy were asked how long it had taken them to conceive. If the answer was six months or longer, they were further asked whether they had received infertility treatment. We excluded 402 women reporting infertility treatment after less than one year of trying and 11 women with missing data on smoking. We analysed 27 329 births (with 66 deaths within 28 days of life (0.24%)). Age at death was recorded in the Danish birth registry.

We grouped women into five categories: up to two months of waiting time (reference); 3-12 months; >12 months, no infertility treatment; >12 months, treatment reported; and non-planners (including part planners). We examined the association between these categories and neonatal death through logistic regression, adjusting for mother's age, body mass index, smoking, and social class, the latter derived from the mother's job title.[4]

The risk of neonatal death increased with increasing time to pregnancy (table). Death between the 29th and the 365th day of life was not related to time to pregnancy (data not shown).

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Danish Epidemiology Science Centre, Department of Epidemiology and Social Medicine, University of Århus, Århus, Denmark (DK8000)
Olga Basso *research associate professor*
Jørn Olsen *professor*
Correspondence to: O Basso bassoo2@niehs.nih.gov

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Neonatal deaths (per 1000 births) as a function of time to pregnancy and treatment and crude and adjusted logistic regressions

Time to pregnancy or treatment	Deaths/births (per 1000)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
<3 months	13/8361 (1.55)	1.00	1.00
3-12 months	22/7944 (2.77)	1.78 (0.90 to 3.54)	1.76 (0.89 to 3.50)
>12 months	18/4142 (4.35)	2.80 (1.37 to 5.73)	2.82 (1.35 to 5.90)
No treatment reported	11/2104 (5.23)	3.38 (1.51 to 7.54)	3.32 (1.47 to 7.53)
Treatment reported	7/2038 (3.03)	2.21 (0.88 to 5.55)	2.32 (0.86 to 5.80)
Unplanned or partly planned	13/6882 (1.89)	1.22 (0.56 to 2.62)	1.14 (0.52 to 2.49)

*Adjusted for mother's age at delivery (<26 years, 26-30, 31-35, ≥36), smoking from conception to time of interview (no/yes), pre-pregnancy body mass index (<20, 20-24.9, 25-29.9, ≥30, missing), and social class (low, middle, high, missing). All covariates except age were self reported. When social class or body mass index were missing (4.8%), we included a separate category in the variable.