PAPERS

Antidepressants and suicide

Susan S Jick, Alan D Dean, Hershel Jick

Abstract

Objective—To estimate the rate and means of suicide among people taking 10 commonly prescribed antidepressant drugs: dothiepin, amitriptyline, clomipramine, imipramine, flupenthixol, lofepramine, mianserin, fluoxetine, doxepin, and trazodone.

Design—Open cohort study with a nested case-control analysis.

Setting—General practices in the United Kingdom that used VAMP computers to maintain their patient records from January 1988 to February 1993.

Subjects—172 598 people who had at least one prescription for one of the 10 antidepresssants during the study period.

Main outcome measure—Suicide confirmed by general practitioner or on death certificate, or both.

Results—143 people committed suicide. The overall rate of suicide was estimated to be 8·5 per 10 000 person years (95% confidence interval 7·2 to 10·0). Rates of suicide were higher in men than women (relative risk 2·8 (95% confidence interval 1·9 to 4·0)), people with a history of feeling suicidal (19·2 (9·5 to 38·7)), and people who had taken several different antidepressants (2·8 (1·8 to 4·3)). People who received high doses of antidepressants and those who had had a prescription in the 30 days before they committed suicide were also at higher risk than those who had received low doses and had had their prescriptions 30 or more days previously (2·3 (1·4 to 3·7) and 2·3 (1·6 to 3·4)) respectively. Rates of suicide were higher in patients who received fluoxetine, but this may be explained by selection biases which were present for those drug users.

Conclusion—Several factors correlate with the risk of suicide in people taking antidepressants. After controlling for these factors, the risk of suicide was similar among the 10 study antidepressants. Overdose with antidepressants accounted for only 14% of the suicides.

Introduction

Published rates of suicide in the United Kingdom among people taking antidepressants have been based on mortality statistics from the Office of Population Censuses and Surveys (accidents and violence) and on sales figures for individual antidepressants.[1-3] Such estimated rates given in deaths per million prescriptions are necessarily crude and do not provide relevant details of the demographics of the population at risk or of other risk factors such as history of suicidal behaviour or details of antidepressant use.

We measured drug specific rates of suicide over five years in patients from 495 general practices supplied with VAMP computers. In addition, we performed a nested case-control analysis to evaluate the effects of several risk factors for suicide.

Subjects and methods

The VAMP health resource (now known as the General Practice Research Database) encompasses over 4 million residents in the United Kingdom who are on the lists of selected general practitioners who use office computers provided by VAMP and have agreed to provide data for research purposes in return for compensation.[4-6] The general practices were selected to represent the age and sex distributions of the population and the geographical and size distribution of general practices in the United Kingdom. General practitioners were trained to record medical information in a standard manner and supply it anonymously to VAMP Research on an ongoing basis. The recorded information includes the patient's demographic details, medical dignoses, referral letters, and a record of all prescriptions issued by the general practitioner. The general practitioners generate prescriptions directly with the computer, and these are automatically transcribed to the computer record. A modification of the classification of the Oxford medical information system[7] is used to enter diagnoses, and a coded drug dictionary based on the dictionary of the Prescription Pricing Authority is used to record drugs.

The results of two recent validation studies determined that the information from the manual medical records was recorded on the computer over 90% of the time[4 5] and that the indication for prescribed drugs was present in the computer file in over 95% of instances.[4 5]

From January 1988 to February 1993 we identified all patients who had received at least one prescription for one or more antidepressants (table I) (the study cohort); we recorded all such patients who committed suicide. The antidepressants included were those in the database that were most commonly used. We did not include people who had been part of a previous study.[8] Cases of suicide were identified from the computer record from among all the study subjects who died. When the cause of death was recorded as suicide or was considered to be uncertain, we obtained further information from the general practitioner and the death certificate to determine the final diagnosis and means of committing suicide.

Boston Collaborative Drug Surveillance Program, Boston University Medical Center, 11 Muzzey Street, Lexington, MA 02173, USA
Susan S Jick, *assistant professor of public health*
Hershel Jick, *associate professor of medicine*

Orsett, Essex
Alan D Dean, *consultant*

TABLE I—*Antidepressants included in study with numbers of patients prescribed them and numbers of person years at risk*

Antidepressant	No of patients*	Person years at risk
Dothiepin	74 340	59 851
Amitriptyline	48 580	43 523
Clomipramine	11 239	11 826
Imipramine	15 009	12 597
Flupenthixol	16 599	10 822
Lofepramine	15 177	8 579
Mianserin	6 609	6 814
Fluoxetine	11 860	5 804
Doxepin	4 329	4 092
Trazodone	4 049	2 709
Maprotiline†	906	1 037
Desipramine†	202	165

*Some people received more than one antidepressant.
†Not included in any further analyses because of limited information.

We included all suicides that had occurred within six months of an antidepressant having been prescribed. Rates of suicide were based on the last antidepressant prescribed.

COHORT ANALYSIS

Person time of exposure was calculated from the cohort of 172 598 people prescribed antidepressants by considering 10 mutually exclusive categories of antidepressants. For each antidepressant, time was accumulated for each subject from the date of prescription for 180 days or until the next antidepressant prescription, whichever was the sooner, unless one of the following occurred: a different antidepressant was prescribed (at which time person time was accumulated for the new drug), the subject committed suicide, the subject died (from other causes) or left the practice, or the study ended. Drug specific rates were derived by dividing the number of suicides by the person time at risk.

CASE-CONTROL ANALYSIS

A nested case-control study was performed to evaluate possible confounding and modification of effects by age, sex, dose of antidepressant, how long the antidepressant had been prescribed, history of suicidal behaviour, the number of antidepressants prescribed before the suicide, and the indication for the antidepressant. All of the patients who committed suicide identified in the cohort evaluation were included as cases, the date of suicide being the index date. For controls we randomly chose 1000 subjects who had not committed suicide from among the cohort of patients taking antidepressants. They were assigned a random date during the study as the index date. Controls were included only if they had been prescribed an antidepressant within the six months before the index date.

Age was divided into three categories: <40 years, 40-59 years, and ≥60 years. For each drug the daily dose was arbitrarily divided into high or low dose according to the recommended doses in the *Monthly Index of Medical Specialties (MIMS)*. A history of suicidal behaviour was determined from each subject's computer record by using codes of the Oxford medical information system for suicidal ideation (3009BN), suicidal thoughts (3009BT), suicide plan (3009BD), suicidal threat (3009CT), suicide attempt (3009C), or suicidal drug overdose (9779L, 9779NA).

The evaluation of the effect of time since the first antidepressant was prescribed was restricted to subjects who had at least six months of recorded computer data before they were first prescribed an antidepressant.

Analyses were carried out by logistic regression controlling for age, sex, and calendar year in the model using the EPILOG statistical package.[9] A multivariate Poisson model was used for the cohort analysis using generalised linear interactive modelling.[10]

Results

We identified 172 598 subjects who had 1 198 303 prescriptions for an antidepressant during the study. Table I shows the antidepressants included in the study, the number of people taking them, and the estimated person time at risk.

One hundred and forty three people committed suicide within six months of using antidepressants. Of these, 67 had a history of suicidal behaviour or had been prescribed more than one antidepressant, or both.

Table II shows how the 143 people committed suicide according to the antidepressant they had been prescribed. Fifty subjects committed suicide by drug or substance overdose. The remainder committed suicide by other means, primarily carbon monoxide poisoning and self inflicted violence. In eight of the 50 people who died from drug or substance overdose death was caused exclusively or primarily by the antidepressant that they were taking at the time; all were taking tricyclic antidepressants.

COHORT ANALYSIS

Among the 172 598 patients taking antidepressants, the accumulated time was 167 819 person years at risk. The overall crude rate of suicide for all antidepressant users was 8·5 per 10 000 person years (95% confidence interval 7·2 to 10·0). Table III shows drug specific crude rates of suicide with relative risk estimates adjusted for age, sex, and calendar year. Dothiepin

TABLE III—*Crude rates and adjusted relative risk estimates of suicide for prescribed antidepressants in cohort of 172 598 patients*

Antidepressant	Rate per 10 000 person years	Adjusted relative risk (95% confidence interval)*
Dothiepin†	8·7	1·0
Amitriptyline	6·7	0·8 (0·5 to 1·2)
Clomipramine	7·6	0·8 (0·4 to 1·7)
Imipramine	5·6	0·6 (0·3 to 1·3)
Flupenthixol	12·0	1·3 (0·7 to 2·4)
Lofepramine	4·7	0·5 (0·2 to 1·5)
Mianserin	16·1	1·8 (1·0 to 3·6)
Fluoxetine	19·0	2·1 (1·1 to 4·1)
Doxepin	7·3	0·9 (0·3 to 2·8)
Trazodone	14·8	1·7 (0·6 to 4·6)

*Adjusted for age, sex, and calendar year. †Reference group.

(the most commonly used antidepressant) was arbitrarily taken as the reference for each of the antidepressants. Compared with dothiepin, only fluoxetine and mianserin yielded relative risks that were significantly raised. The adjusted risk estimates of suicide ranged from 0·5 (0·2 to 1·5) in those taking lofepramine to 2·1 (1·1 to 4·1) in those taking fluoxetine.

CASE-CONTROL ANALYSIS

Table IV provides the adjusted relative risk estimates for suicide from the case-control analysis, comparing users of each antidepressant drug with those who used dothiepin. When age, sex, and calendar year were included in the model, only fluoxetine had a significantly higher rate. The relative risk estimates obtained from the case-control analysis were similar to those obtained in the cohort analysis (table III).

Characteristics of the 143 cases and the 1000

TABLE II—*Means of committing suicide according to last prescription of antidepressant received. Values are numbers of patients*

Last antidepressant received	Method of suicide					Person years at risk
	Overdose	Violence*	Carbon monoxide poisoning	Unknown	Total	
Dothiepin	19	27	4	2	52	59 851
Amitriptyline	11	13	5		29	43 523
Clomipramine	3	4	1	1	9	11 826
Imipramine	6	1			7	12 597
Flupenthixol	5	5	3		13	10 822
Lofepramine	1	2	1		4	8 579
Mianserin		5	6		11	6 814
Fluoxetine	1	5	5		11	5 804
Doxepin	2		1		3	4 092
Trazodone	2	2			4	2 709
Maprotiline†						1 037
Desipramine†						165
Total	50	64	26	3	143	167 819

*Includes hanging, drowning, shooting, jumping, stabbing or cutting, dying on a railway, burning, suffocation, electrocution, or road accident.
†Not included in any further analysis because of limited information.

controls, as well as estimates of relative risk for suicide after age, sex, and calendar year were controlled for are shown in table V. Men were substantially more likely than women to commit suicide (relative risk 2·8 (1·9 to 4·0). Age had little effect on the risk of suicide. Subjects taking antidepressants who had a history of being suicidal—that is, they had attempted suicide or had had suicidal thoughts, etc—had a substantially higher risk of committing suicide (relative risk 19·2 (9·5 to 38·7)) than those who did not, as did subjects who had been prescribed more than one antidepressant before the index date (2·8 (1·8 to 4·3)) and those who received a high dose of antidepressant (2·3 (1·4 to 3·7)).

EFFECT OF SUICIDAL HISTORY AND USE OF ANTIDEPRESSANTS

Further analyses were carried out to evaluate the risks among the 76 cases and 823 controls who had no history of being suicidal and had been prescribed only one antidepressant in order to compare the rates of suicide in the absence of confounding by a history of these risk factors. The risk estimates adjusting for age, sex, and calendar year for fluoxetine and mianserin in this group of subjects compared with those taking dothiepin fell to 2·1 (0·6 to 7·9) and 1·1 (0·4 to 3·2), respectively (table VI).

EFFECT OF TIME FROM FIRST PRESCRIPTION TO SUICIDE

To evaluate the time from the first antidepressant prescription to suicide we had to restrict the analysis to the 46 subjects who had at least six months of recorded computer data before the first prescription for an antidepressant. (The remaining 97 people had been using an antidepressant when computer recording was begun.) In this group the time from first use did not seem to have a measurable effect. When subjects with an interval of less than 30 days between their first use and the index date were compared with those with intervals of 30 to 59 days, 60 to 89 days, 90 to 179 days,

TABLE IV—Adjusted relative risk estimates of suicide for prescribed antidepressants in cases and controls

Antidepressant prescribed	No (%) of cases (n=143)	No (%) of controls (n=1000)	Adjusted relative risk (95% confidence interval)*
Dothiepin†	52 (36)	358 (36)	1·0
Amitriptyline	29 (20)	275 (28)	0·7 (0·4 to 1·2)
Clomipramine	9 (6)	71 (7)	0·8 (0·4 to 1·8)
Imipramine	7 (5)	63 (6)	0·7 (0·3 to 1·7)
Flupenthixol	13 (9)	60 (6)	1·5 (0·7 to 3·0)
Lofepramine	4 (3)	55 (6)	0·5 (0·2 to 1·6)
Mianserin	11 (8)	51 (5)	1·6 (0·7 to 3·3)
Fluoxetine	11 (8)	28 (3)	3·8 (1·7 to 8·6)
Doxepin	3 (2)	21 (2)	1·0 (0·3 to 3·7)
Trazodone	4 (3)	18 (2)	1·2 (0·4 to 4·0)

*Adjusted for age, sex, and calendar year. †Reference group.

TABLE V—Adjusted relative risk estimates of suicide according to characteristics of cases and controls

	No (%) of cases (n=143)	No (%) of controls (n=1000)	Adjusted relative risk (95% confidence interval)*
Age (years):			
<40†	31 (22)	221 (22)	1·0
40-59	62 (43)	349 (35)	1·2 (0·7 to 1·9)
≥60	50 (35)	430 (43)	0·8 (0·5 to 1·3)
Sex:			
Female†	71 (50)	728 (73)	1·0
Male	72 (50)	272 (27)	2·8 (1·9 to 4·0)
Dose:			
Low†	106 (74)	824 (82)	1·0
High	32 (22)	100 (10)	2·3 (1·4 to 3·7)
Unknown	5 (3)	76 (8)	0·5 (0·2 to 1·3)
History of suicidal behaviour:			
No†	115 (80)	980 (98)	1·0
Yes	28 (20)	20 (2)	19·2 (9·5 to 38·7)
Previous prescription of antidepressants:			
No†	96 (67)	838 (84)	1·0
Yes	47 (33)	162 (16)	2·8 (1·8 to 4·3)

*Adjusted for age, sex and calendar year. †Reference group.

TABLE VI—Adjusted relative risk estimates of suicide in patients prescribed antidepressants for first time who had no history of suicidal behaviour

Antidepressant prescribed	No (%) of cases (n=76)	No (%) of controls (n=823)	Adjusted relative risk (95% confidence interval)*
Dothiepin†	37	308	1·0
Amitriptyline	15	233	0·5 (0·3 to 1·0)
Clomipramine	4	51	0·7 (0·2 to 2·0)
Imipramine	4	56	0·5 (0·2 to 1·5)
Flupenthixol	6	49	0·9 (0·4 to 2·4)
Lofepramine	1	36	0·2 (<0·1 to 1·7)
Mianserin	5	41	1·1 (0·4 to 3·2)
Fluoxetine	3	18	2·1 (0·6 to 7·9)
Doxepin	1	19	0·5 (0·1 to 3·7)
Trazodone	0	12	

*Controlling for age, sex, and calendar year. †Reference group.

TABLE VII—Rates of suicide by last antidepressant prescribed and by time since last prescription

	0 to 30 Days		31 to 180 Days	
Antidepressant	No of cases (n=91)	Rate per 10 000 person years	No of cases (n=52)	Rate per 10 000 person years
Dothiepin	34	11·9	18	5·8
Amitriptyline	19	8·6	10	4·7
Clomipramine	7	11·1	2	3·6
Imipramine	6	9·7	1	1·6
Flupenthixol	6	13·3	7	11·1
Lofepramine	3	7·9	1	2·1
Mianserin	4	10·3	7	2·4
Fluoxetine	7	27·4	4	12·3
Doxepin	2	9·2	1	5·2
Trazodone	3	21·5	1	7·6

180 to 364 days, and 365 days or more, the adjusted risk estimates were 1·4, 1·3, 0·9, 1·0, and 0·7, respectively. The risk estimate comparing taking an antidepressant for less than 30 days before the index date with taking it for 30 days or more before then was 1·0 (0·4 to 2·3).

EFFECT OF TIME FROM LAST PRESCRIPTION TO SUICIDE

Subjects who had received their last prescription 30 days or less before the index date were more likely to commit suicide than those who had received a prescription more than 30 days before the index date; the relative risk estimate controlling for antidepressant, age, sex, and calendar year was 2·3 (1·6 to 3·4). Table VII shows drug specific rates of suicide for subjects in each of the two time intervals. For each drug the rate of suicide was higher in the 0 to 30 days than in the 31 to 180 days after the last antidepressant prescription.

EFFECT OF DEPRESSIVE ILLNESS

Of the 143 cases, 112 had an indication of depression recorded on the computer. When we restricted the analysis to people with a diagnosis of depression, the results were not materially different from those in the full study population.

Discussion

SUMMARY OF RESULTS

Our population based observational study estimates the risk of suicide in a population of people who had taken antidepressant drugs in the six months before they died and who were enrolled in a large number of general practices in the United Kingdom. We estimate the risk to be 8·5 per 10 000 person years. The most common means of committing suicide were by violence (45%) and overdose (35%). As has been found previously, men were more likely to commit suicide than women (relative risk 2·8).[8]

People with a history of feeling suicidal (relative risk 19·2) or who had been prescribed multiple antidepressants (relative risk 2·8) were more likely to commit

<table>
<tr><td>

Key messages

● In this population-based study the risk of suicide among patients taking antidepressants was estimated to be 8·5 per 10 000 person years

● As in previous studies, more men than women committed suicide

● People with a history of suicidal behaviour were at a greatly increased risk of committing suicide

● People who had received their last anti-depressant prescription in the previous 30 days were more likely to commit suicide than those who had received their last antidepressant 30 or more days previously

● The risk of suicide was not determined by the antidepressant prescribed

</td></tr>
</table>

suicide than those with no such history. People were also more likely to commit suicide if they had received their last prescription within 30 days (relative risk 2·3), but the risk was not higher during this time if the prescription was their first for antidepressants (relative risk 1·0).

In comparing rates of suicide for individual anti-depressants, it is necessary to consider that patients are preselected to receive particular antidepressants. In the absence of random assignment of drugs, recipients of different antidepressants will probably have different pre-existing risks for committing suicide. Therefore, interpretation of the results of such comparisons must be made with caution. We controlled for several factors which reflect usage patterns including age, sex, calendar year, history of suicidal behaviour, and the number of antidepressants prescribed before the suicide. The last two factors correlated strongly with the risk of suicide.

Among the 1000 controls, 162 had used more than one antidepressant drug before the index date. Controls who used clomipramine (44), trazodone (45), lofepramine (50), and fluoxetine (58) had a substantially higher proportion of previous antidepressant use. This suggests that people who received these drugs were at a higher risk of suicide. This pattern has been noted for fluoxetine.[11]

The results indicate that only fluoxetine has a rate that seems to be substantially higher than that of the other antidepressants. However, when the analysis was restricted to those without a history of having felt suicidal or who had taken only one antidepressant, the increased risk for those who took fluoxetine was reduced. We conclude that the increased risk associated with fluoxetine in the current studies may be explained by selection bias. Even after removing from the analysis subjects with a history of being suicidal or taking multiple antidepressants, there may have been residual factors which reflected a higher risk of suicide for subjects taking fluoxetine.

No one taking maprotiline or desipramine committed suicide, but only a few patients took these two antidepressants (table I).

A recent study from Sweden which described the use of antidepressants among 3400 victims of suicide[12] found that less than 16% of all suicide victims screened had detectable concentrations of antidepressants in their blood and that toxic concentrations were found in only a third of them. We studied only those prescribed antidepressants and around 14% of suicides were reported to have been due wholly or in part to overdose with an antidepressant.

CONCLUSIONS

Deliberate overdose with tricyclic antidepressant drugs is more likely to be fatal than is deliberate overdose of non-tricyclic antidepressants, such as mianserin and fluoxetine.[3 13 14] Indeed, like Isacsson et al[2] we found that suicide by drug overdose was more common among those who took tricyclic antidepressants than among those who took other antidepressants, but suicide by other means was higher among those who took other antidepressants. This is consistent with the proposition that people who are determined to commit suicide will find a way that produces the intended outcome. Though the suggestion has been made that fluoxetine may trigger an emotional state which itself increases the risk of suicide,[15] this suggestion has not been supported by formal evidence.

In summary, our study provides reliable population based estimates of rates of suicide among those who take antidepressants which take into account and describe several risk factors. Such population based estimates have been lacking because estimates of risk have been based primarily on reports to various agencies and on sales data for particular drugs.

1 Leonard BE. Toxicity of antidepressant. Lancet 1986;i:1105.
2 Cassidy S, Henry J. Fatal toxicity of antidepressant drugs in overdose. BMJ 1982;295:1021.
3 Henry JA, Antao CA. Suicide and fatal antidepressant poisoning. European Journal of Medicine 1992;1:343-8.
4 Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ 1991;302:766-8.
5 Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. Pharmacoepidemiology and Drug Safety 1992;1:347-9.
6 García Rodríguez LA, Jick H. The risk of upper gastrointestinal bleeding and/or perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:769-72.
7 Perry J, ed. OXMIS problem codes for primary medical care. Oxford: OXMIS Publications, 1978.
8 Derby LE, Jick H, Dean AD. Antidepressant drugs and fatal suicide. J Clin Psychopharmacol 1992;12:235-40.
9 Epicenter Software. Epilog plus, version 3. Pasadena, CA: Epicenter Software, 1993.
10 Payne CD, ed. Generalised linear interactive modelling system, Release 3.77. Oxford: Royal Statistical Society, 1986.
11 Jick H, Ulcickas M, Dean A. Comparison of frequencies of suicidal tendencies among patients receiving fluoxetine, lofepramine, mianserin or trazodone. Pharmacotherapy 1992;12:451-4.
12 Isacsson G, Holmgren P, Wasserman D, Bergman U. Use of antidepressants among people committing suicide in Sweden. BMJ 1994;308:506-9.
13 Montgomery SA, Bullock T, Baldwin D, Montgomery DB. The provocation and prevention of suicide attempts. Int Clin Psychopharmacol 1992; 95(suppl): 22-34.
14 Kapur S, Mieczkowski T, Mann J. Antidepressant medications and the relative risk of suicide attempt and suicide. JAMA 1992;268:3441-5.
15 Teicher MN, Rosenbaum J. Suicidality and fluoxetine: is there a relationship? J Clin Psychiatry 1991;52:108-11.

(Accepted 4 November 1994)

<table>
<tr><td>

ONE HUNDRED YEARS AGO

DIRTY RAILWAY CARRIAGES.

Mr. Thomas Christy writes complaining of the condition of certain first class carriages on the London, Brighton, and South Coast Railway. He has dealt with dirty carriages as other people do with abusive cabbies, and has taken their number. We fear, however, that the long list of delinquent vehicles which he sends us would not form interesting reading. Nevertheless, he has our every sympathy. To wage war against dirt wherever found is the first duty of sanitary man, and the conditions he describes must be deleterious to the health of those innocents who go by rail in search of pure air. (BMJ 1895;i:350.)

</td></tr>
</table>