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Relative mortality from overdose of antidepressants

John A Henry, Carol A Alexander, Ersin K Sener

See pp 215, 219, and editorial by Edwards

Abstract

***Objective*—To compare the fatal toxicities of antidepressant drugs in 1987-92.**

***Design*—Retrospective epidemiological review of prescription data of the Department of Health, Scottish Office Home and Health Department, and Welsh Health Common Services Authority (excluding data from most private general practices and most hospitals), and mortality data from the Office of Population Censuses and Surveys and General Register Office in Scotland.**

***Setting*—General practice, England, Scotland, and Wales.**

***Main outcome measures*—Deaths per million prescriptions and deaths per defined daily dose.**

***Results*—81·6% (1310/1606) of deaths from antidepressant overdose were due to two drugs, amitriptyline and dothiepin. The overall average of deaths per million prescriptions was 30·1. The overall rate for tricyclic drugs was 34·14 (95% confidence interval 32·47 to 38·86; $P<0·001$), monoamine oxidase inhibitors 13·48 (6·93 to 22·19; $P<0·001$), atypical drugs 6·19 (4·04 to 8·80; $P<0·001$), and selective serotonin reuptake inhibitors 2·02 (0·64 to 4·17; $P<0·001$). The numbers of deaths per million prescriptions of amoxapine, dothiepin, and amitriptyline were significantly higher than expected, while nine drugs had a significantly lower number of deaths per million prescriptions than expected. Analysis of deaths per defined daily dose showed a similar pattern.**

***Conclusions*—Safety in overdose should be considered in risk-benefit and cost-benefit considerations of antidepressants. A switch in prescribing, from drugs with a high number of deaths per million prescriptions to drugs with a low number, could reduce the numbers of deaths from overdose. Although this form of suicide prevention can be implemented easily and immediately, its introduction needs to be considered against the higher costs of some of the newer drugs.**

Introduction

While little demonstrable difference exists between antidepressants in terms of efficacy,[1] toxicity in overdose varies widely.[2] We compared the fatal toxicities of antidepressants currently available in Britain individually and by group during 1987-92, during which time the selective serotonin reuptake inhibitors were introduced.

Methods

Antidepressants were assigned to four classes: monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, and the so called "atypical"[3] antidepressants. We obtained numbers of deaths in England, Wales, and Scotland due to acute poisoning by a single antidepressant.[4,5] The statistics and research division of the Department of Health supplied data on the number of antidepressant prescriptions for general medical practices within the NHS for England, Wales, and Scotland for 1987-9 and for England for 1990-2; for 1990-2 the Scottish data were provided by the Scottish Office Home and Health Department and the Welsh data by the Welsh Health Common Services Authority. Private general practice and most hospitals were excluded; figures for 1991 and 1992 include dispensing practices. About three quarters of all drug prescriptions are written by general practitioners.[6,7] Most patients with psychiatric disorders, however, are treated by general practitioners rather than by psychiatrists[8-10] (90% to 98% of depressed patients[8-11]). The exclusion of hospital prescriptions from our analysis should not, therefore, appreciably affect the outcome of this study.

We calculated the number of deaths per million prescriptions during the six years for all the drugs taken together; for each of the four groups of antidepressants; and for each drug individually. The χ^2 test was applied to the groups of antidepressants. The expected numbers of deaths are given for the individual drugs, with Fisher's exact test (one tailed) applied to the data. Confidence limits are calculated as $x \pm 1·96$ SD(x).

Using the prescribed data, we considered each preparation of each drug analysed, multiplied the strength of the preparation by the quantity prescribed, and divided this by the defined daily dose values (obtained from the World Health Organisation).[12,13] We calculated the number of defined daily doses per prescription for each drug and the number of deaths per million defined daily doses prescribed.

Results

The mean annual number of deaths due to overdose with a single antidepressant over the six years was 268 (range 238 to 288). The tricyclic drugs were implicated in most deaths (table I), with two drugs—amitriptyline and dothiepin—accounting for 81·6% of all deaths. Tables II and III show the figures for mortality and data for prescriptions for deaths per million prescriptions for the four groups of drugs for the six years. The tricyclic antidepressants as a group

TABLE I—*Mean yearly numbers of deaths from tricyclic and other antidepressants, 1987-92*

Cause of death	Death from tricyclic drugs	Death from non-tricyclic drugs
Suicide with single antidepressant	150	4
Suicide with more than one substance, including antidepressants	240	10
Overdose with single antidepressant	260	12
Overdose with more than one substance, including antidepressants	424	24

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had a significantly higher number of deaths per million prescriptions than expected compared with all the antidepressants taken together ($P<0.001$). The monoamine oxidase inhibitors as a group had a lower than expected number of deaths per million prescriptions ($P<0.001$). The groups of atypical antidepressants and selective serotonin reuptake inhibitors each had the lowest number of deaths per million prescriptions ($P<0.001$). Tables IV and V list each drug in each group with its number of deaths per million prescriptions, which is used to rank them within groups, and shows that three of the tricyclic agents (dothiepin, amitriptyline, and amoxapine) had a significantly higher number of deaths per million prescriptions than expected. A further three drugs from this group (lofepramine, clomipramine and trimipramine) had a significantly lower number of deaths per million prescriptions than expected when compared with all antidepressants. One monoamine oxidase inhibitor (phenelzine) had a significantly lower number of deaths per million prescriptions. Two of the atypical drugs (mianserin and trazodone) had a significantly lower number of deaths per million prescriptions. Three of the selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, and paroxetine) had a lower number of deaths per million prescriptions. No deaths were recorded for five drugs, all of which had low prescription figures (table III). Calculation of data with defined daily doses showed a pattern that was broadly similar to the data derived from deaths per million prescriptions.

TABLE II—*Fatal poisonings and deaths per million prescriptions for deaths from single antidepressant, by groups of drug. Values in parentheses are 95% confidence intervals*

Antidepressant	Observed deaths 1987-92	Expected deaths 1987-92	No of prescriptions (millions) 1987-92	χ^2 value	Deaths per million prescriptions 1987-92
Tricyclic drugs	1563	1378	45·78	24·80	4·14 (34·47 to 35·86)*
Monoamine oxidase inhibitors	12	27	0·89	8·17	13·48 (6·93 to 22·19)*
Atypical drugs	26	126	4·20	79·78	6·19 (4·04 to 8·80)*
Selective serotonin reuptake inhibitors	5	75	2·48	64·99	2·02 (0·64 to 4·17)
All antidepressants	1606	1606	53·35		30·10

*$P<0.05$ $P<0.001$ (difference from all by χ^2 test).

TABLE III—*Fatal poisonings and deaths per million defined daily doses for deaths from single antidepressants, by groups of drug. Values in parentheses are 95% confidence intervals*

Antidepressant	Observed deaths 1987-92	Expected deaths 1987-92	Mean defined daily dose (mg) 1987-92	χ^2 value	Deaths per million defined daily doses 1987-92
Tricyclic drugs	1563	1346	94	34·98	16·63 (1·36 to 1·50)*
Monoamine oxidase inhibitors	12	41	28	20·51	0·43 (0·19 to 0·60)*
Atypical drugs	26	62	165	20·90	0·16 (0·34 to 0·74)*
Selective serotonin reuptake inhibitors	5	56	66	46·45	0·08 (0·03 to 0·23)
All antidepressants	1606	1606	89		1·26

*$P<0.001$ (difference from all by χ^2 test).

TABLE IV—*Fatal poisonings and deaths per million prescriptions for deaths from single antidepressants, by individual antidepressant. Values in parentheses are 95% confidence intervals*

Antidepressant	Year introduced to Britain	Observed deaths 1987-92	Expected deaths 1987-92 from mean of all	Deaths per million prescriptions 1987-92
Tricyclic drugs:				
Amoxapine	1989	13	2	157·18 (83·35 to 254·23)***
Desipramine	1963	3	1	75·76 (14·28 to 185·74)
Nortriptyline	1963	19	11	51·77 (31·11 to 77·67)
Dothiepin	1969	801	504	47·86 (44·60 to 51·23)***
Amitriptyline	1961	509	394	38·94 (35·63 to 42·39)*
Imipramine	1959	111	106	31·54 (25·95 to 37·68)
Doxepin	1969	37	46	23·99 (16·89 to 32·35)
Trimipramine	1966	34	73	13·93 (9·64 to 19·01)***
Clopramine	1970	26	108	7·26 (4·74 to 10·32)***
Lofepramine	1983	10	125	2·42 (1·15 to 4·14)***
Protriptyline	1966	0	4	0·00
Iprindole	1968	0	1	0·00
Butriptyline	1975	0	0	0·00
Monoamine oxidase inhibitors:				
Tranylcypromine	1960	8	9	27·87 (11·90 to 50·54)
Phenelzine	1959	4	15	7·86 (2·04 to 17·45)
Iproniazid	1958	0	0	0·00
Isocarboxazid	1960	0	3	0·00
Atypical drugs:				
Viloxazine	1974	1	0	63·17 (0·03 to 247·66)
Maprotiline	1974	6	11	16·22 (5·84 to 31·80)***
Trazodone	1980	7	27	7·83 (3·10 to 14·70)***
Mianserin	1976	12	88	4·11 (2·11 to 6·76)***
Selective serotonin reuptake inhibitors:				
Sertraline	1990	1	5	6·23 (0·00 to 24·43)
Paroxetine	1991	1	12	2·60 (0·00 to 10·18)**
Fluvoxamine	1987	2	13	4·78 (0·45 to 13·71)**
Fluoxetine	1989	1	46	0·66 (0·00 to 2·58)***
All antidepressants		1606		30·10

*$P<0.05$, **$P<0.01$, ***$P<0.001$ (difference from all by Fisher's exact test).
Total expected deaths differ from total observed owing to rounding.

Discussion

The atypical antidepressants form a heterogeneous group of drugs, while the other antidepressants fall into three pharmacologically homogeneous groups. The selective serotonin reuptake inhibitors share a common mechanism of action, despite their remarkably differing chemical structures (fluvoxamine is a monocyclic agent, fluoxetine a bicyclic agent, sertraline a naphthylamine derivative, and paroxetine a phenyl piperidine derivative). They also had the lowest toxicity in overdose of the groups of drugs studied here. This accords with clinical experience.[14-17] The numbers of deaths per million prescriptions of antidepressants have been shown to be inversely related to their serotonin reuptake inhibition activity,[18] but this relation may be coincidental with their structural properties.

Shortcomings of a study of this nature include systematic error in prescription or mortality data, or both; confounding by prescriber biases or patient biases—such as, an inability to distinguish between the use of "first line" and "second line" drugs—or both biases; and the fact that no allowance was made for prescribing for indications other than those of concern to the study. These factors, however, are unlikely to affect the conclusions of our study as most biases run in favour of the tricyclic drugs, which are more widely used as first line drugs.[19] It is also possible that selective serotonin reuptake inhibitors are being prescribed to patients at greater risk of overdose.[20] These drugs may also have a different role from tricyclic drugs in patients with depression resistant to treatment—for example, paroxetine[3]—or with suicidal thoughts—for example, fluoxetine[21] and fluvoxamine.[22] Our data thus provide a useful guide to the relative toxicities of drugs and an indication of the needs of prescribing policy and correlate with the results of median lethal dose in animals.[23] Our data also agree with alternative indices based on deaths per million standard quantity units or deaths per thousand kilograms of drug prescribed.[24]

The use of data on defined daily dose is gaining popularity internationally, mainly because defined daily doses provide a standardised technical measure of drug use that is not influenced by strength of dosage form. The dose is an assumed average daily dose for the main indication of a drug as determined by the Nordic Council on Medicines,[13] and this causes problems in its use in a study like ours. Problems include variation in the number of prescriptions that depressed patients have each year; discontinuation or non-compliance, especially for tricyclic drugs,[25] which increases the apparent market share of other antidepressants; and prescription of drugs at doses below or above the defined daily dose. These factors might be expected to bias toxicity data in favour of the tricyclic drugs,[26] but our analysis shows a strong correlation in the ranking of the two indices.

The differing toxicities of antidepressants in overdose should be considered against the wider issue of costs. The selective serotonin reuptake inhibitors are relatively expensive and are generally prescribed at effective daily doses, which can hardly be reduced to save on costs. Ironically, it is the cheaper, tricyclic

TABLE V—*Fatal poisonings and deaths per million defined daily doses for deaths from single antidepressants, by individual antidepressant. Values in parentheses are 95% confidence intervals*

Antidepressant	Defined daily dose	Observed deaths 1987-92	Expected deaths 1987-92 for mean of all	Deaths per million defined daily doses 1987-92
Tricyclic drugs:				
Amoxapine	150	13	2	6·22 (4·13 to 12·6)***
Desipramine	100	3	1	2·79 (0·55 to 7·15)
Nortriptyline	75	19	10	2·28 (1·38 to 3·44)**
Amitriptyline	75	509	394	1·64 (1·46 to 1·74)*
Dothiepin	75	801	648	1·54 (1·42 to 1·63)***
Imipramine	100	111	94	1·47 (1·2 to 1·74)
Doxepin	100	37	33	1·4 (0·98 to 1·88)
Trimipramine	150	34	38	1·1 (0·76 to 1·49)
Clomipramine	100	26	84	0·38 (0·25 to 0·54)***
Lofepramine	105	10	196	0·08 (0·03 to 0·11)***
Protriptyline	30	0	3	0
Iprindole	90	0	0	0
Butriptyline	75	0	0	0
Monoamine oxidase inhibitors:				
Tranylcypromine	10	8	22	0·54 (0·19 to 0·8)**
Phenelzine	60	4	14	0·38 (0·09 to 0·79)*
Iproniazid		0	0	0
Isocarboxazid	15	0	6	0
Atypical drugs:				
Viloxazine	200	1	0	3·03 (0 to 12·27)
Maprotiline	100	6	11	0·77 (0·25 to 1·39)
Trazodone	300	7	16	0·6 (0·21 to 0·99)
Mianserin	60	12	70	0·2 (0·11 to 0·35)***
Selective serotonin reuptake inhibitors:				
Fluvoxamine	150	2	11	0·19 (0·02 to 0·66)*
Sertraline	75	1	6	0·13 (0 to 0·81)
Paroxetine	20	1	19	0·04 (0 to 0·26)***
Fluoxetine	20	1	66	0·02 (0 to 0·07)***
All antidepressants	89	1606		

*P<0·05, **P<0·01, ***P<0·001 (difference from all by Fisher's exact test).
Total expected deaths differ from total observed owing to rounding.

antidepressants that are more likely to be prescribed in subtherapeutic doses[10 27] to avoid adverse effects.[10 27 28] The widely perceived cost advantage of tricyclic drugs is based almost entirely on market price alone[29]; many other factors influence the cost to the NHS, and virtually all models of clinical practice give the selective serotonin reuptake inhibitors a cost advantage.[29-31] One cost effectiveness study estimated that £19 000-173 000 per life year was gained from deaths from overdose prevented by a switch in routine first line use from tricyclic drugs to selective serotonin reuptake inhibitors.[32] This finding rested, however, on the assumption that the only differences between the different groups of antidepressant drugs lay in the market prices of the drugs and the numbers of deaths from overdose. Many other factors would need to be considered for a valid comparison. Overdose itself has cost implications, regardless of whether death results. The tricyclic drugs are more likely to lead to medical complications and admissions to intensive therapy units.[33]

The British Association for Psychopharmacology concluded that the newer antidepressants have real advantages over the older ones in terms of safety and tolerability when given in an effective dose.[34] Low toxicity in overdose is an important consideration in the drug treatment of depressed patients. Although it can be argued that a failed suicide attempt may only delay the ultimate outcome, it is widely accepted that a suicide attempt is a poor predictor of further attempts[35]; about 10% of those who fail to kill themselves with acute overdose go on to successful suicide.[36] Furthermore, a drug overdose might bring the patient under closer medical supervision and lead to a better outcome to the depressive episode. While the present study shows that fatal overdose is an important problem, untreated depression may be even more important.[26]

As a result of the "Defeat Depression" campaign by the Royal Colleges of Psychiatrists and General Practitioners the diagnosis of depression may increase over the next few years. Wider use of drugs with a high number of deaths per million prescriptions could lead to an increase in the number of successful suicides from antidepressant overdose. Conversely, wider use of drugs with a low number of deaths per million prescriptions would make a contribution towards the government's targets for the year 2000 of reducing the number of suicides.

Key messages

- Overdose with an antidepressant such as amitriptyline or dothiepin could lead to severe toxicity and could be fatal
- Antidepressant drugs such as the selective serotonin reuptake inhibitors and lofepramine have low toxicity in overdose
- Deaths from overdose can be prevented by switching prescribing from older, tricyclic drugs; such a move may contribute to government targets for reducing suicide
- Choice of a first line antidepressant should be based on several factors, including adverse effect profile, compliance, overdose safety, and cost, and the antidepressant should be appropriate to the patient and his or her clinical condition
- Patients with evidence of suicidal ideation should be given special consideration—admission to hospital may be indicated

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Is the three year breast screening interval too long? Occurrence of interval cancers in NHS breast screening programme's north western region

Ciaran B J Woodman, Anthony G Threlfall, Caroline R M Boggis, Pat Prior

See p 229 and editorial by Mitchell

Abstract

***Objective*—To report the detection rate of interval cancers in women screened by the NHS breast screening programme.**

***Design*—Detection of interval cancers by computer linkage of records held by the screening centres in the North Western Regional Health Authority with breast cancer registrations at the regional cancer registry.**

***Setting*—North Western Regional Health Authority.**

***Subjects*—137 421 women screened between 1 March 1988 and 31 March 1992 who had a negative screening result.**

***Results*—297 invasive interval cancers were detected. The rate of detection of interval cancers expressed as a proportion of the underlying incidence was 31% in the first 12 months after screening, 52% between 12 and 24 months, and 82% between 24 and 36 months.**

***Conclusion*—The incidence of interval cancers in the third year after breast screening approaches that which would have been expected in the absence of screening and suggests that the three year interval between screens is too long.**

Introduction

Trials of mass screening show that there is potential for reducing mortality from breast cancer in women.[1-4] Preliminary results from the NHS breast screening programme have been considered satisfactory[5] but no information has been reported on the incidence of interval cancers. The incidence of these cancers must be kept comparatively low if the screening programme is to be successful.[6] We report the incidence of interval cancers in women screened by the programme in the North Western region.

ORGANISATION OF SCREENING IN NORTH WEST

The NHS breast screening programme began screening women in the North Western region in March 1988. Women on family health services authority registers aged 50-64 are invited to be screened by single view mammography every three years. There are five screening centres in the North Western region; two began screening in March 1988, the third began in June 1988, the fourth in January 1990, and the fifth in June 1991. These centres cover estimated target populations of about 49 200, 49 900, 127 400, 46 600, and 36 800 respectively. The uptake rate in the first screening round estimated from Korner returns form KC62 was 73%, and the cancer detection rate was 5·9 per 1000 women screened.

Subjects and methods

The study population included all women in the North Western Regional Health Authority area aged 50-64 routinely screened for the first time as part of the NHS breast screening programme by the region's first four breast screening centres between 1 April 1988 and 31 March 1992.

Definition of interval cancer—A woman was considered to have an interval cancer if there was histological confirmation of a primary breast cancer within three years of her last negative screening assessment. We included women presenting with symptoms while on early recall but excluded women presenting with in situ disease.

Identification of interval cancers—Interval cancers were identified by linking records held by the screening centres and the North West Regional Cancer Registry. The registry has been population based since 1962 and uses multiple sources of registration to ascertain all cancers occurring in residents of the North Western region. The name, date of birth, and screening history of all women screened after 1 April 1988 were down loaded from the breast screening centres' computer systems. Name and date of birth were used to computer match screened women with registrations of primary breast cancer diagnosed after the start of the screening programme. Positive matches were confirmed by using the woman's address. Women with screen detected cancers were excluded. For the remaining women the date of the last negative screen and the date of the histological diagnosis of cancer were compared and probable interval cancers identified. The screening records of these women were examined to verify that they were interval cancers. In order to minimise delay in cancer registration a policy to "fast track" breast cancer registrations was introduced. However, a few interval cancers that had been reported to the screening centres direct were not registered at the cancer registry but are included in the analysis. In all but three cases this was due to the inevitable delay before a cancer is registered.

Statistical methods—The rate of detection of interval

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