Fatal toxicity of antidepressants in England and Wales, 1993–2002

Oliver Morgan, Clare Griffiths, Allan Baker
Office for National Statistics
Azeem Majeed
Imperial College, London

This article examines trends in drug poisoning deaths involving antidepressant drugs between 1993 and 2002 in England and Wales as a whole and focuses particularly on the relationship between antidepressant prescribing and deaths in England. Between 1993 and 2002, age-standardised mortality rates in England and Wales decreased from about 9 to 7 per million population for both males and females. However, unlike females, rates in males rose to a peak of 12 per million in 1997 before declining. During the study period, the number of prescription items for antidepressants increased two and a half fold, largely due to increased use of selective serotonin re-uptake inhibitors and other antidepressants. Overall, death rates in England, per million prescription items, declined over the study period, with reductions in the rates for Dothiepin, Amitriptyline and all tricyclic antidepressants. There was no change in the rate for selective serotonin re-uptake inhibitors while rates for other antidepressants increased. Despite these trends, through all the study period rates were highest for tricyclic antidepressants and lowest for selective serotonin re-uptake inhibitors.

Introduction

Depression is an important public health problem affecting 5–10 per cent of the population.[1] Management and treatment of depressive illness is predominantly provided in primary care using antidepressant drugs.[2] There are several different classes of antidepressant that work in different ways to affect transmitter systems in the brain. While their effectiveness at treating depression is broadly similar,[2] they have a number of side effects and can be highly toxic in overdose.[2-4] This is of particular concern as patients who are depressed are at higher risk of suicide or self harm.[5]

Antidepressant drugs are involved in about 20 per cent of all drug poisoning deaths in England and Wales.[6] Previous studies have shown that tricyclic antidepressant drugs (TCAs) are more toxic in overdose, with just two TCAs (Dothiepin and Amitriptyline) accounting for over 75 per cent of antidepressant-related poisoning deaths.[7,8] While selective serotonin re-uptake inhibitors (SSRIs) and other 'atypical' antidepressants are considered to be safer in overdose,[4] Fluoxetine (Prozac) has also been implicated in a number of deaths.[8] Until 1998, TCAs were the most commonly prescribed antidepressant in general practice.[9] However, newer antidepressants such as SSRIs and others have become increasingly popular because they have fewer adverse effects and lower toxicity.[10]

Previous studies in Finland,[11] Norway,[12] Australia[13] and England[8] suggest that increased prescribing of antidepressants is associated with higher death rates from antidepressant overdose. In this study we examine trends in antidepressant prescribing and antidepressant-related poisoning mortality between 1993 and 2002 in England and Wales.

Methods

Mortality data

In England and Wales, deaths that are sudden, unexpected, not due to natural causes or with no known cause are referred to the coroner for investigation.[14] Following most drug poisoning deaths there is an investigation, which may include a post-mortem and toxicological examination. Following the investigation, the coroner holds an inquest and pronounces a verdict on the cause of death. The death is then registered using Form 99 (Rev), which includes the cause of death. Additional details about the circumstances of the death, including any drugs identified during the investigation, may be included on Part V of Form 99 (Rev). This information is provided voluntarily by coroners to ONS for use in statistics and is not recorded on the public record of the death. Over 99 per cent of all drug-related deaths between 1993 and 1996 had both a post-mortem and an inquest.[15] Until 2000, cause of death was coded using the International Classification of Diseases Ninth Revision (ICD-9) and from 2001 using the Tenth Revision (ICD-10).

The Office for National Statistics has stored drug poisoning mortality data for England and Wales from 1993 onwards in a dedicated database.[15] The database contains data on cause of death, individual characteristics (including age and sex) as well as textual information from Part V of Form 99 (Rev) where provided. This textual information has been examined to identify and code the substances involved in the death. The range of substances contained in the database is wide. It includes legal and illegal drugs, prescription drugs and over-the-counter medications. All drugs mentioned are also coded to British National Formulary (BNF) categories where appropriate.

Definition of antidepressant-related deaths

Drug poisoning deaths were defined using the International Classification of Diseases codes shown in Box 1. Antidepressant-related deaths were defined as any drug poisoning death where an antidepressant drug was mentioned on the death certificate, with or without mentions of alcohol or other drugs. Antidepressant drugs were further classified according to their BNF categories (Box 2).

Box one

ICD-9 and ICD-10 codes for drug poisoning deaths

Description	ICD-9	ICD-10
Mental and behavioural disorders due to drug use (excluding alcohol and tobacco)	292, 304, 305.2–9	F11–F16, F18–F19
Accidental poisoning by drugs, medicaments and biological substances	E850–E858	X40–X44
Intentional self-poisoning by drugs, medicaments and biological substances	E950.0–E950.5	X60–X64
Poisoning by drugs, medicaments and biological substances, undetermined intent	E980.0–E980.5	Y10–Y14
Assault by drugs, medicaments and biological substances	E962.0	X85

Box two

British National Formulary Categories for Antidepressant Drugs

BNF Category	Description
4.3.1	Tricyclics and related antidepressants (TCA)
4.3.2	Monoamine oxidase inhibitors (MAOI)
4.3.3	Selective serotonin re-uptake inhibitors (SSRI)
4.3.4	Other antidepressants

Prescription data

The Department of Health supplied data on prescription items for all antidepressants dispensed in England between 1993 and 2002. Prescription information is derived from the Prescription Cost Analysis (PCA) system, which collects data from all prescriptions dispensed in the community.[16] This includes community pharmacists, dispensing doctors and prescriptions submitted by prescribing doctors for items personally administered (i.e. given by the doctor during a consultation). PCA data also includes prescriptions written in Wales, Scotland, Northern Ireland and the Isle of Man but dispensed in England. Drugs dispensed in hospital or private prescriptions are not included.

Population estimates

Mid-year population estimates revised on the basis of the 2001 Census were used to calculate death rates. National population estimates for 1993 to 2000 were interim revised estimates published in September 2003. National population estimates for 2001 and 2002 were published in September 2003 but did not include revisions to the population of Manchester published in November 2003.

Analysis

Directly age-standardised mortality rates for England and Wales were calculated using the European Standard Population. For antidepressant-related poisoning deaths, these were compared to overall suicide rates in England and Wales. To assess the relative toxicity of individual antidepressants it is necessary to include a measure of drug usage. As prescribing information was only obtained for England, we calculated death rates in England (and Poisson confidence intervals) per million prescriptions items for drugs mentioned in at least fifty deaths during the study period. Statistical analysis was done using Stata 8.2.[17]

Results

England and Wales

Mortality

Between 1993 and 2002, there were 4,767 deaths in England and Wales involving antidepressant drugs, accounting for 18 per cent of all drug poisoning deaths. The number of deaths was similar for males and females. Tricyclic antidepressants (TCAs) were involved in the largest proportion of deaths involving antidepressants (89 per cent) (Table 1). Between 1997 and 2002 the number of deaths involving TCAs declined. Over six per cent of deaths involved selective serotonin re-uptake inhibitors (SSRIs) and about three per cent involved other antidepressant drugs. These increased considerably during the study period. Deaths involving monoamine oxidase inhibitors (MAOIs) were mentioned on the death certificate for 52 deaths during the study period.

Table 1 **Frequency of antidepressant drugs mentioned on the death certificate for drug poisoning deaths, 1993–2002**

England and Wales

	Tricyclic and related antidepressants	Monoamine oxidase inhibitors	Selective serotonin re-uptake inhibitors	Other antidepressants	Total
1993	437	10	11	0	461
1994	460	11	5	1	478
1995	462	4	23	0	489
1996	506	2	18	6	540
1997	497	9	23	11	539
1998	469	5	28	6	510
1999	425	4	38	20	493
2000	381	2	55	18	449
2001	323	1	60	35	416
2002	295	4	49	51	392
Total	**4,255**	**52**	**310**	**148**	**4,767**

Note: Mentions of individual antidepressants do not sum to the total as 90 deaths had no specific antidepressant drug mentioned on the death certificate and 88 deaths mention antidepressants from more than one class.
See Box 2 for British National Formulary codes.

A third of all antidepressant-related poisoning deaths had other drugs or alcohol mentioned on the death certificate. Twenty per cent of death certificates mentioned alcohol, 12 per cent opiates, 8 per cent paracetamol and 6 per cent benzodiazepines. There were 82 deaths involving antidepressants from more than one class. Twenty-six per cent of deaths involving TCAs also had other substances mentioned on the death certificate. This was lower than for MAOIs (50 per cent) SSRIs (77 per cent) and other antidepressants (55 per cent).

Between 1993 and 2002, age-standardised mortality rates decreased from about 9 to 7 per million population for both males and females (Figure 1). However, unlike females, rates in males rose to a peak of 12 per million in 1997 before declining. For females, trends in antidepressant-related mortality were similar to those for all suicides (including non-drug-poisoning suicides) (Figure 1). For males, the decline in rates of antidepressant-related mortality appeared be greater than for all suicides. The decline in mortality rates for all antidepressant-related poisoning was similar across age groups throughout the study period. Rates were highest in males aged 30–44 (Figure 2). Mortality rates were also high in both males and females aged 45–59 years. At older ages antidepressant-related death rates were higher in females than males. Amongst children aged 14 years and under there were too few deaths (n=11) during the study period to calculate rates reliably.

Figure 1 **Age-standardised mortality rates per million population from antidepressant-related poisoning and suicide, 1993–2002**

England and Wales

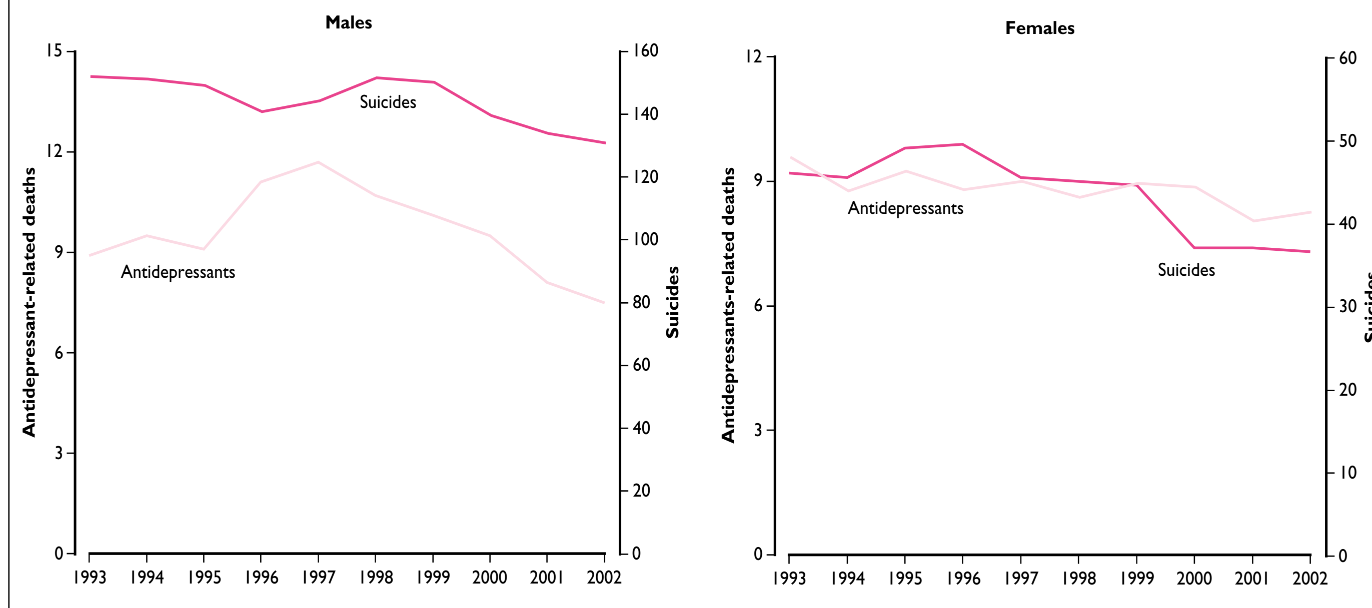
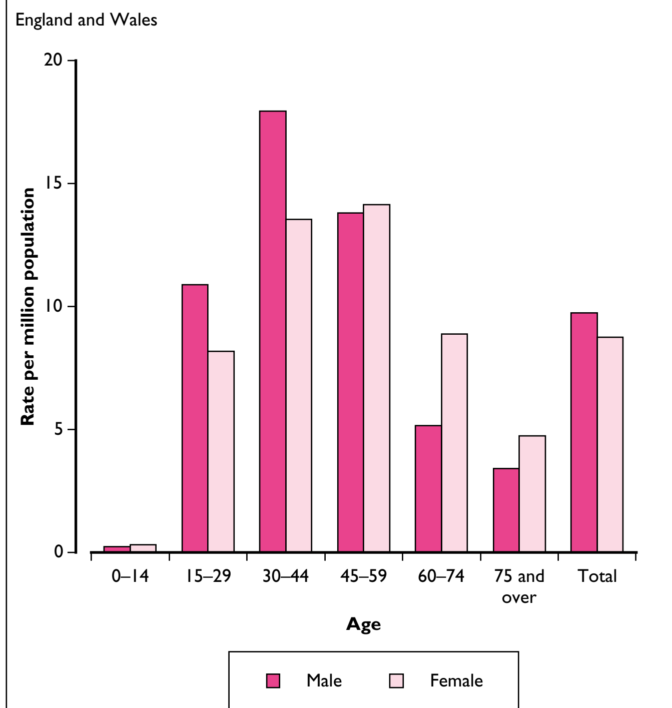


Figure 2 Age-specific mortality rates from antidepressant-related poisoning, 1993–2002



Verdict

The most common verdicts recorded on the death certificate of antidepressant-related drug poisonings were intentional self poisoning (45 per cent) and poisoning due to undetermined intent (33 per cent) (Table 2). Poisonings due to undetermined intent are thought to be mostly suicides for which there was insufficient evidence that the deceased deliberately intended to kill themselves.[18] Therefore, these two verdicts are usually combined to estimate deaths due to suicide (78 per cent of all antidepressant-related deaths - top line of Table 2). The proportion of deaths due to suicide was less for deaths involving SSRIs and others compared to TCAs, while a greater proportion of SSRI and other deaths were recorded as accidental.

England

Prescriptions

The number of prescription items for all antidepressants in England increased two and a half fold between 1993 and 2002 from about 10 to 26 million prescription items per year (Figure 3). The increase for TCAs was modest compared to SSRIs, and was entirely due to increased prescriptions for Amitriptyline and Trazodone. Prescription items for all other TCAs decreased during the study period. The number of prescription items for MAOIs declined to about half of 1993 levels.

Figure 3 Prescription items (millions) for selected antidepressants, 1993–2002

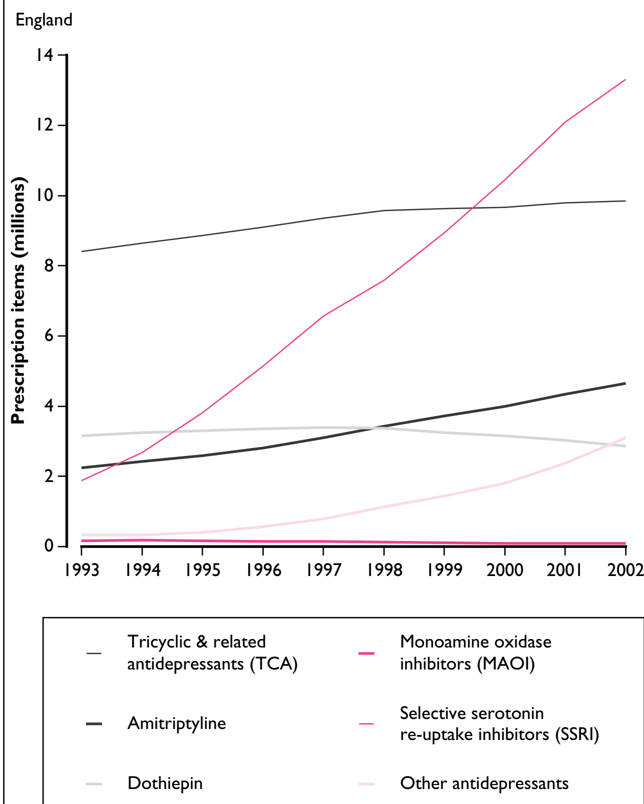


Table 2 Frequency of antidepressant drugs mentioned on the death certificate by verdict in England and Wales, 1993–2002

	Tricyclic and related antidepressants		Monoamine oxidase inhibitors		Selective serotonin re-uptake inhibitors and others		All	
	n	(%)	n	(%)	n	(%)	n	(%)
Suicide (Intentional self-poisoning and undetermined intent combined)	3,368	79.2	41	78.8	320	70.8	3,722	78.1
Intentional self-poisoning by drugs, medicaments and biological substances	1,938	45.5	20	38.5	182	40.3	2,134	44.8
Poisoning by drugs, medicaments and biological substances, undetermined intent	1,430	33.6	21	40.4	138	30.5	1,588	33.3
Accidental poisoning by drugs, medicaments and biological substances	773	18.2	9	17.3	115	25.4	909	19.1
Mental and behavioural disorders due to drug use (excluding alcohol and tobacco)	108	2.5	2	3.8	17	3.8	130	2.7
Assault by drugs, medicaments and biological substances	6	0.1	0	0	0	0	6	0.1
Total	**4,255**	**100**	**52**	**100**	**452**	**100**	**4,767**	**100**

Note: Mentions of individual antidepressants do not sum to the total as 90 deaths had no specific antidepressant drug mentioned on the death certificate. 82 deaths mentioned antidepressants from more than one class.
See Box 2 for British National Formulary codes.

Overall, prescription items for SSRIs increased seven-fold, with increases for all SSRIs except Fluvoxamine, which decreased from 106,000 to 33,000 prescription items between 1993 and 2002. The other antidepressants (BNF 4.3.4) also increased noticeably from 0.3 to 3.1 million prescription items per year.

Individual antidepressants

Table 3 shows the number of deaths and prescription items for individual antidepressants in England between 1993 and 2002, where there were more than 50 deaths during this period. The most commonly prescribed antidepressants were the TCAs – Dothiepin and Amitriptyline – and SSRIs – Fluoxetine and Paroxetine. Forty-four per cent (2,088/4,767) of all antidepressant-related deaths involved Dothiepin and 30 per cent (1,437/4,767) involved Amitriptyline. Death rates per million prescription items were ten times higher for TCAs than SSRIs, the highest being for Dothiepin. The rate for other antidepressants was three time greater than for SSRIs. Of the non-TCA drugs, the rate was highest for Venlafaxine, a serotonin and noradrenaline re-uptake inhibitor. The SSRI with the highest death rate per million prescriptions was Citalopram. Considering deaths where only a single antidepressant was mentioned on the death certificate (with or without alcohol), there was almost no change in rank order (Table 4).

Despite high period mortality rates between 1993 and 2002, death rates per million prescription items for the most commonly mentioned antidepressants, Dothiepin and Amitriptyline, have decreased since 1996 (Figure 4). There was little change for all SSRIs while for the other antidepressants rates increased. For all antidepressants combined, death rates per million prescription items decreased year on year from 41 to 14 deaths per million prescription items between 1993 and 2002.

Table 3 Deaths per million prescriptions associated with selected antidepressants, 1993 to 2002

England

	Number of deaths	Prescriptions (thousands)	Deaths per million prescriptions	95% Confidence Interval
Tricyclic and related antidepressants				
All TCAs	3,987	92,552	43.1	41.8 – 44.4
Dothiepin	2,088	32,107	65.0	62.2 – 67.9
Amitriptyline	1,437	33,273	43.2	41.0 – 45.4
Imipramine	165	3,887	42.4	36.2 – 49.4
Clomipramine	117	4,930	23.7	20.6 – 28.4
Nortriptyline*	15	1,545	9.7	5.4 – 16.0
Trimipramine	72	2,734	26.3	20.6 – 33.2
Doxepin	55	1,639	33.6	25.3 – 43.7
Selective serotonin re-uptake inhibitors				
All SSRIs	310	72,408	4.3	3.8 – 4.8
Fluoxetine	115	28,585	4.0	3.3 – 4.8
Citalopram	74	10,612	7.0	5.5 – 8.8
Paroxetine	67	23,248	2.9	2.2 – 3.7
Other antidepressants				
All other	148	12,263	12.1	10.2 – 14.2
Venlafaxine	118	6,691	17.6	14.5 – 21.1

* There were 85 deaths where nortriptyline was mentioned on the death certificate. However, as nortriptyline is a metabolite of amitriptyline, we excluded all deaths where both were mentioned together.
See Box 2 for British National Formulary codes.

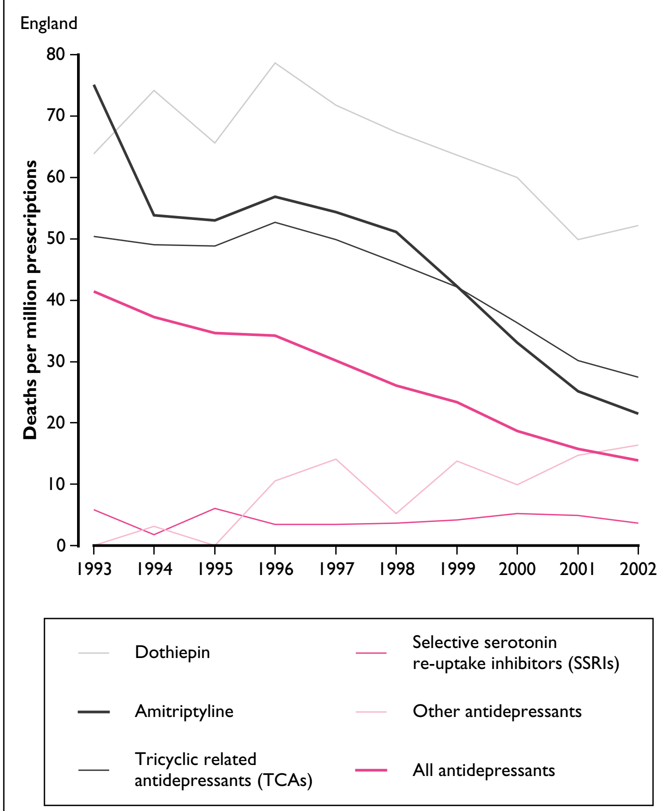
Table 4 Deaths per million prescriptions associated with selected antidepressants without mention of other drugs, 1993 – 2002

England

	Number of deaths	Prescriptions (thousands)	Deaths per million prescriptions	95% Confidence Interval
Tricyclic and related antidepressants				
All TCAs	2,787	92,552	30.1	29.0 – 31.3
Dothiepin	1,558	32,107	48.5	46.1 – 51.0
Amitriptyline	932	33,273	28.0	26.2 – 30.0
Imipramine	110	3,887	28.3	23.3 – 32.1
Clomipramine	65	4,930	13.2	10.2 – 16.8
Nortriptyline	10	1,545	0.6	0.3 – Pe1.2
Trimipramine	36	2,734	13.1	10.0 – 18.2
Doxepin	35	1,639	21.3	14.9 – 29.7
Selective serotonin re-uptake inhibitors and others				
All SSRIs	71	72,408	1.0	0.7 – 1.2
Fluoxetine	22	28,585	0.8	0.5 – 1.2
Citalopram	20	10,612	1.9	1.2 – 2.9
Paroxetine	13	23,248	0.6	0.3 – 1.0
Other antidepressants				
All other	66	12,263	5.2	4.2 – 6.8
Venlafaxine	57	6,691	8.5	6.6 – 11.0

Note: Deaths where a single antidepressant was mentioned may be with or without alcohol.
See Box 2 for British National Formulary codes.

Figure 4 Antidepressant-related deaths per million prescriptions for selected antidepressants, 1993–2002



Discussion

The age-standardised mortality rate for antidepressant-related poisoning in men increased from 9 to 12 per million between 1993 and 1997 and then decreased to 7 per million population in 2002. The age-standardised mortality rate for women decreased from 9 to 7 per million during the study period. During the study period, the number of prescription items for antidepressants increased two and a half fold, largely due to increased use of SSRIs. For all antidepressants combined, rates per million prescription items have decreased since 1996. The TCAs Dothiepin and Amitriptyline were associated with 74 per cent of all antidepressant-related deaths. TCA-related deaths were less likely to have other substances mentioned on the death certificate than deaths involving SSRIs or others, for which 77 per cent and 55 per cent respectively had mentions of other substances. Mortality rates per million prescription items were highest for the TCAs. Other antidepressants had a higher rate than SSRIs. In particular the rate for Venlafaxine was the highest of any non-TCA and increased during the study period.

Strengths and weaknesses

Routinely-collected mortality data provides the most complete dataset on antidepressant-related deaths in England and Wales. However, it must be interpreted with caution: information on the death certificate is not recorded for epidemiological purposes.[15] For example, where an antidepressant is taken with other substances, there is no indication that the death was caused by the antidepressant rather than the other substances. The implication is that some deaths may be incorrectly attributed to antidepressant poisoning. This may be particularly important for SSRI-related deaths, which were more likely to involve other substances, possibly leading to an overestimation of SSRI mortality. Additionally, antidepressant drugs may not be mentioned on the death certificate if the coroner does not consider them to be relevant.[15] About 10 per cent of drug poisoning deaths have no specific information about the drug(s) taken.[6] Inconsistency in the application and scope of toxicological examinations undertaken by coroners can also mean that some deaths involving antidepressants may not be identified.[15]

We considered antidepressant-related deaths by coroner's verdict and found that deaths involving SSRIs and others were less likely to be recorded as due to suicide (intentional self harm and undetermined intent combined). A correspondingly higher proportion of SSRI-related deaths were recorded as due to accidental poisoning. This was surprising as we expected that accidental poisoning would be greater for the potentially more toxic TCAs. This may have been due to the involvement of opiates (often taken in overdose accidentally), or other substances, in a large proportion of SSRI-related deaths. Of the 115 SSRI deaths recorded as accidental, only 29 (25 per cent) did not involve other substances. This was compared to 64 per cent of TCAs that were recorded as an accidental death. Furthermore, choice of verdict has been shown to vary considerably between coroners[19] and therefore some of the differences in verdict may be artefactual.

We assessed the relative toxicity of individual antidepressants by calculating mortality rates per million prescription items. This method has been used in several previous studies of antidepressant mortality.[7,8] Although prescription data for England do not include prescriptions dispensed in hospitals, 90–98 per cent of patients with depression are treated in a primary care setting and so this is unlikely to influence the results substantially.[7] The prescription data include prescriptions of antidepressant drugs used to treat conditions other than depression. Some TCAs may be prescribed for insomnia, migraine prophylaxis, neuralgia and nocturnal enuresis and some SSRIs are prescribed for panic disorders or obsessive-compulsive disorders.[20] Not being able to exclude these prescriptions may have inflated the denominator and hence underestimated the toxicity for some antidepressants. Prescription data do not take into account prescription length. Prescriptions for TCAs are likely to be for shorter periods as clinicians may be wary of prescribing large amounts of drugs that are toxic in overdose. In contrast, longer (and hence fewer) prescriptions may be written for SSRIs which are less toxic in overdose. This might inflate the denominator for TCAs, underestimating the mortality rate per million prescriptions. An alternative method, used to avoid this potential bias, estimates defined daily doses from the prescribing data. However, a previous study showed that the ranking of defined daily dose and prescription items is highly correlated, suggesting that it will have a limited effect on our results.[7]

The ability of our analysis to discriminate between the relative toxicities of different antidepressants is limited. This is for a number of reasons, involving both the prescriber and the patient.[2] SSRIs and others may have clinical advantages over the TCAs, possibly leading to different prescribing patterns by doctors. For example, because SSRIs and others have fewer side effects, treatment can be started at therapeutic doses, making them popular for treatment of newly diagnosed depression.[21] In addition, their low toxicity in overdose may lead them to be prescribed in preference to TCAs for individuals who are at greater risk of overdose.[5] In contrast, TCAs are often prescribed at sub-therapeutic doses or taken at lower doses by patients themselves to avoid side effects.[2,21] In a study in Tayside, as many as 72 per cent of patients prescribed TCAs for depression in general practice received sub-therapeutic doses compared to only 8 per cent of patients receiving an SSRI.[22] Depressed patients prescribed TCAs but treated at sub-therapeutic doses may have increased suicide risk,[23,24] possibly leading to an apparent higher rate of TCA mortality. Adequate duration of treatment is just as important as dosage.[2] As many as 21–33 per cent of patients do not complete their course of treatment with antidepressant drugs.[25] Within this group of patients, discontinuation rates may be about 10 per cent lower for SSRIs than TCAs.[26] However, in absolute terms, the difference between SSRIs and TCAs is probably too small to have a strong confounding effect.

Interpretation of results

Previous studies have suggested that increased antidepressant prescribing is associated with higher death rates from antidepressant overdose.[8,11-13] In this study, the decrease in both age-standardised mortality rates and death rates per million prescriptions for all antidepressants combined appears to contradict this hypothesis.

The fall in death rates per million prescription items for Dothiepin, Amitriptyline and all TCAs combined might suggest that TCAs are either being prescribed more effectively, or are being prescribed for individuals at lower risk. Encouragingly, for SSRIs there has been little change in mortality per million prescription items, despite the very large increase in their usage. In contrast, mortality per million prescription items for the other antidepressant drugs has been increasing. This is largely due to Venlafaxine, a serotonin and noradrenaline re-uptake inhibitor, whose toxicity has previously been noted.[27] The ranking of antidepressant-related deaths per million prescription items was relatively insensitive to mentions of other drugs, which for SSRIs especially was a substantial proportion of poisoning deaths.

Increased prescribing of antidepressants may reflect improvements in the recognition and treatment of depression in general practice,[28] which may in turn have contributed to reduced fatal poisoning. TCAs remain more toxic than SSRIs, although death rates per million prescription items have fallen since 1996. The increase in death rates for the other antidepressants suggests that they might be more toxic than the SSRIs. In 2002, deaths involving these drugs were greater than for SSRIs. It is important therefore to monitor the safety of these drugs in the future. Despite changes in overall patterns of antidepressant use, poisoning deaths involving antidepressants remain an important public health problem accounting for about 400 deaths each year.

Key findings

- Between 1993 and 2002, there were 4,767 deaths in England and Wales involving antidepressant drugs, accounting for 18 per cent of all drug poisoning deaths.
- A third of all antidepressant-related deaths had other drugs mentioned on the death certificate. This was greater for deaths involving selective serotonin re-uptake inhibitors (77 per cent) than tricyclic antidepressants (26 per cent).
- Between 1993 and 2002, age-standardised mortality rates decreased from about 9 to 7 per million population for both males and females. However, unlike females, rates in males rose to a peak of 12 per million in 1997 before subsequently declining to a rate similar to that for females in 2002.
- Death rates per million prescription items were about 10 times higher for tricyclic antidepressants than for selective serotonin re-uptake inhibitors.
- For other antidepressants, death rates per million prescriptions increased during the study period and in 2002 the number of deaths involving these drugs exceeded that for SSRIs.

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