

Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998–2000

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Background Deaths from antidepressants continue to account for a substantial proportion of drug-related deaths.

Aims To investigate the relative toxicity of the major classes of antidepressant drugs, with the specific objective of assessing this in relation to the cause of death; and to analyse the deaths where there were multiple mentions of antidepressant drugs or other psychoactive drugs with antidepressants.

Method Mortality data were collected from the National Programme of Substance Abuse Deaths, and antidepressant prescription data were collected.

Results Most deaths from antidepressant drugs were suicides (80%). Tricyclic antidepressants (TCAs) accounted for more drug mentions than did other antidepressant drugs (12 per million prescriptions). Selective serotonin reuptake inhibitors (SSRIs) were associated with a significantly lower risk of toxicity, but 93% of deaths from SSRIs occurred in combination with other drugs, especially TCAs (24.5%). In 'combination' deaths patients were significantly more likely to have had a history of drug misuse.

Conclusions The efficacy and safety of augmentation therapy with TCAs in SSRI-resistant patients should be monitored carefully, and patients prescribed antidepressants should be screened for drug use/misuse.

Declaration of interest None.

Studies reporting on the toxicity of different antidepressants in overdose indicate that, compared with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, particularly amitriptyline and dothiepin, are associated with an increased risk from overdose (Henry *et al*, 1995; Shah *et al*, 2001). Although this information has aided in the choice of antidepressants prescribed, several questions remain about the profile of toxicity of different antidepressants. First, studies on antidepressant-related deaths have failed to distinguish between accidental deaths and deaths with suicidal intent. Furthermore, no studies have examined whether certain antidepressant drugs are more likely to be used in multiple drug overdoses, particularly in combination with other antidepressants or other psychoactive drugs. With this in mind, the aims of this paper were: to investigate the relative toxicity of the major classes of antidepressant drugs, with the specific objective of assessing the cause of death as either accidental or intentional; and to analyse deaths where other drugs were present in combination with antidepressants.

METHOD

Sources of data

The np-SAD database on drug-related deaths
In July 1997 the National Programme of Substance Abuse Deaths (np-SAD; Ghodse *et al*, 2002) was established after the Home Office's index of addicts closed. Data are collected from coroners in England and Wales where licit or illicit psychoactive drugs are implicated in death. Coroners supply demographic data and information regarding the drugs implicated in these fatalities.

Prescription cost analysis

Prescription cost analysis provides details on the total quantity, number of prescription items and net ingredient cost of all

antidepressant prescriptions dispensed in the community by doctors in England (Department of Health, Statistics Division 1E, Prescription Cost Analysis system) and Wales (Prescribing Services Unit, Health Solutions, Wales) during 1998–2000. Prescriptions written by hospital doctors are also included provided that they were dispensed in the community. Prescription cost analysis uses the concept of the 'defined daily dose', which is an international system developed by the World Health Organization, and is defined as 'the assumed average maintenance dose per day for a drug used on its main indication in adults'. It also collects information on 'average daily quantity' for antidepressants, a concept developed by an expert group convened by the Prescribing Support Unit and used to reflect more adequately general practitioner prescribing in England, based on several measures, including defined daily doses and *British National Formulary* information. Prescription cost analysis does not cover items dispensed in hospitals or on private prescriptions. However, because 90–98% of patients with depression are seen by general practitioners rather than psychiatrists (Thompson & Thompson, 1989; McCarthy, 1993; Donoghue & Tylee, 1996; Dunn *et al*, 1999; Middleton *et al*, 2001), the exclusion of private prescriptions and hospital-dispensed prescriptions from our analysis should not appreciably affect the outcome of this study.

Study population

The study population consisted of cases reported by coroners in England and Wales to the np-SAD for deaths occurring during the 3-year period 1998–2000. Cases for the study were those who had a current prescription for antidepressant drugs at the time of the fatality and where antidepressant drugs were implicated in the cause of death. Contribution to fatalities is defined by the np-SAD as being when substances are specifically mentioned in the cause of death by the coroner, or when the drug type in the cause of death is not specified (e.g. 'polydrug toxicity') but the coroner reports that drugs were present post-mortem. Cases are classified as intentional in the np-SAD database according to the coroner's verdict of 'suicide' or 'open' where suicide is likely. For the purposes of this study, 'accidental' includes deaths by accidental overdose, traumatic accident or

acute medical conditions. Cases are also classified as those with or without a drug misuse history.

Data analysis

Antidepressants were assigned to four therapeutic classes according to the *British National Formulary*: tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and other antidepressant drugs. The antidepressants included in each therapeutic class can be seen in Table 2. For each of the above classes of antidepressant, the following variables were analysed:

- frequencies of drug mentions per million prescriptions; the observed number of mentions was compared with the expected number of mentions, which was calculated by standardising for the number of prescriptions;
- frequencies of mentions in deaths by single drug or in combination with other drugs;
- other drugs most likely to be implicated in deaths in combination with antidepressants;
- history of drug misuse or dependence;
- the incidence of antidepressants by class in accidental and intentional deaths.

Statistical analysis

We used prevalence ratios and their 95% confidence intervals (CIs) to compare differences in proportions. Standardised mortality ratios and their 95% CIs were used to compare observed and expected number of deaths when standardised for the number of prescriptions for antidepressant drugs. The χ^2 statistical test was used to test for differences between the antidepressant therapies. All analyses were undertaken using the Statistical Package

for the Social Sciences for Windows version 1.0 and CLINISTAT (Bland, 1990).

RESULTS

Antidepressant classes implicated in death compared with the number of prescriptions

During the study period there were 4167 drug-related deaths, of which 468 had an antidepressant implicated in the deaths. Therefore, 11.2% of all drug-related deaths involved antidepressant drugs. Among the 468 fatalities there were 473 mentions of antidepressants by class implicated in the deaths. A total of 285 cases had a single antidepressant class implicated in the deaths and there were 186 cases where two or more specific drug types were implicated: an antidepressant class and another drug or multiple mentions of antidepressants with or without other drugs. There were 498 mentions of specific antidepressants and there were 10 cases that had a mention of both nortriptyline and amitriptyline. Because nortriptyline is a metabolite of amitriptyline (Sanchez & Hyttel, 1999) these cases were included in fatalities associated with amitriptyline only.

There was a substantial variation in the risk of death from the different antidepressant classes when compared with the number of prescriptions. As can be seen from Table 1, the tricyclics (12 mentions per million prescriptions) and the MAOIs (14 mentions per million prescriptions) had a higher number of mentions per million prescriptions compared with the SSRIs (2 mentions per million prescriptions). The tricyclics prescribed most frequently were dothiepin, amitriptyline and lofepramine. Both dothiepin and amitriptyline were associated with significantly more deaths than would be expected when standardised for the number of prescriptions but

lofepramine was associated with significantly fewer mentions. In contrast to amitriptyline and dothiepin, the SSRIs were associated with significantly fewer mentions than would be expected ($P < 0.0001$) when standardised for the number of prescriptions, and this was the case for the four most widely prescribed SSRIs: fluoxetine, paroxetine, citalopram and sertraline (Table 2). For the class of other antidepressant drugs, 88% of fatalities were due to venlafaxine and the remainder were due to trazodone, which was associated with significantly fewer mentions than would be expected ($P < 0.05$) when standardised for the number of prescriptions. Venlafaxine, however, had a mortality rate not dissimilar to that seen with the tricyclics, and there were 13 mentions per million prescriptions of this drug (see Table 2).

Antidepressants in combination with other drugs implicated in mortality

Of 468 deaths in which antidepressant drugs were implicated, 60% had antidepressants solely implicated in death, whereas antidepressants in combination with other drugs were implicated in 40% of cases. There was a significant relationship between whether antidepressants were implicated alone or in combination with other drugs and the type of antidepressant ($\chi^2 = 55.39$, $P < 0.0001$), and antidepressant-related fatalities involving multiple drug mentions were almost three times more likely to occur in SSRI-related cases than in tricyclic-related cases (percentage ratio = 2.7, 95% CI 2.3–3.2; see Table 3). As can be seen from Table 4, the most frequently mentioned drugs in combination with SSRIs were alcohol (26%), tricyclic antidepressants (24%)

Table 1 Number of mentions of antidepressants by class per million prescriptions in England and Wales, 1998–2000

Class of antidepressant drug	Number of observed deaths	Number of expected deaths	Prescriptions (thousands)	Deaths per million prescriptions	Standardised proportionate mortality ratio (95% CI)
Tricyclic and related antidepressants	403	258	33 088.9	12	1.5 (1.4–1.7)***
Monoamine oxidase inhibitors	5	3	357.7	14	1.6 (0.5–3.8)
Selective serotonin reuptake inhibitors	41	176	22 537.2	2	0.2 (0.1–0.3)****
Other antidepressant drugs	24	34	4356.9	6	0.7 (0.4–1.0)
Total	473		60 340.7		

*** $P < 0.001$, **** $P < 0.0001$ for total expected deaths in comparison with total observed deaths.

Table 2 Number of drug mentions by specific drug and per million prescriptions in England and Wales, 1998–2000

Antidepressant drug	Number of observed mentions	Number of expected mentions	Prescriptions (thousands)	Mentions per million prescriptions	Standardised proportionate mortality ratio (95% CI)
Tricyclic and related antidepressants					
Amitriptyline	168	92	11 557.7	15	1.8 (1.5–2.1)****
Amoxapine	2	0.2	20.6	97	10 (1.2–36)*
Clomipramine	16	12	1518.3	11	1.3 (0.7–2.1)
Desipramine	0	0	0.3	0	–
Dothiepin	203	114	14 257.2	14	1.7 (1.5–2.0)****
Doxepin	2	6	720.5	3	0.3 (0.0–1.2)
Imipramine	13	9	1141.9	11	1.4 (0.7–2.4)
Lofepramine	3	21	2533.9	1	0.1 (0.0–0.4)****
Nortriptyline	4 ¹	4	460.1	9	1 (0.2–2.5)
Protriptyline	1	0.2	23.6	42	5 (0.1–27.8)
Trimipramine	5	7	854.8	6	0.7 (0.2–1.6)
Subtotal	417		33 088.9		
Monoamine oxidase inhibitors					
Isocarboxazid	0	0.2	19.9	0	–
Moclobemide	2	0.9	116.8	17	2.2 (0.2–8.0)
Phenelzine	1	0.9	115.9	9	1.1 (0.0–6.1)
Tranlycypromine	2	0.8	105.1	19	2.5 (0.3–9.0)
Subtotal	5		357.7		
Selective serotonin reuptake inhibitors					
Citalopram	10	33	4064.2	2	0.3 (0.1–0.5)****
Fluoxetine	20	60	7458.3	3	0.3 (0.2–0.5)****
Fluvoxamine	0	1	150.2	0	–
Paroxetine	8	57	7153.9	1	0.1 (0.0–0.2)****
Sertraline	4	30	3710.6	1	0.1 (0.0–0.3)****
Subtotal	42		22 537.2		
Other antidepressant drugs					
Maprotiline	0	0.4	55.4	0	–
Mianserin	0	2	202.5	0	–
Mirtazapine	0	5	574.9	0	–
Nefazodone	0	3	342.6	0	–
Reboxetine	0	2	225.3	0	–
Trazodone	3	10	1287.6	2	0.3 (0.0–0.8)*
Tryptophan	0	0.1	13.9	0	–
Venlafaxine	21	13	1651.5	13	1.6 (1–2.4)*
Viloxazine	0	0	3.2	0	–
Subtotal	24		4356.9		
Total	488		60 340.7		

1. Excludes ten mentions probably recorded as a metabolite of amitriptyline.

* $P < 0.05$, **** $P < 0.0001$ for total expected deaths in comparison with total observed deaths.

and other opiates (24%). Antipsychotics (12%) were also implicated. When tricyclics were found in combination with other drugs in antidepressant-related deaths, the other

drugs most likely to be implicated were alcohol (41.4%), other opiates (20.7%), SSRIs (8.6%), heroin (8.6%) and methadone (7.1%). A different profile emerged

for the class of other antidepressants, where antipsychotics (38.9%), alcohol (27.8%) and other opiates (16.7%) were most likely to be found in combination.

Table 3 Classes of antidepressant drugs implicated in deaths between 1998 and 2000 either alone or in combination with other drugs

Antidepressant category	Single drug class implicated	Single drug class in combination with other class or type	More than one drug of class in combination with other class or type	Total drugs of class implicated
Tricyclic and related antidepressants	266 (66%)	126 (31%)	11 (3%)	403
Monoamine oxidase inhibitors	5 (100%)	–	–	5
Selective serotonin reuptake inhibitors	3 (7%)	37 (90%)	1 (3%)	41
Other antidepressant drugs	11 (46%)	13 (54%)	–	24
Total	285	176	12	473

Table 4 Frequencies of antidepressants by class associated with other common psychoactive drugs and other antidepressants¹

Drug category	TCA's	SSRIs	Other antidepressant
Alcohol	58 (41.4%)	13 (26.0%)	5 (27.8%)
Amphetamines	1 (0.7%)	2 (4.0%)	–
Anti-epileptics	4 (2.6%)	–	1 (5.6%)
Anti-Parkinsonian	3 (2.1%)	–	–
Antipsychotics	9 (6.4%)	6 (12.0%)	7 (38.9%)
Cannabis	–	1 (2.0%)	–
Cocaine	1 (0.7%)	1 (2.0%)	–
Ecstasy	1 (0.7%)	–	–
Heroin	12 (8.6%)	–	1 (5.6%)
Methadone	10 (7.1%)	2 (4.0%)	–
Other opiates	29 (20.7%)	12 (24.0%)	3 (16.7%)
Antidepressants			
TCA's	–	12 (24.0%)	–
MAOIs	–	–	–
SSRIs	12 (8.6%)	–	1 (5.6%)
Other antidepressants	–	1 (2.2%)	–
Volatile substances	–	–	–
Total	140	50	18

TCA's, tricyclic antidepressants; SSRIs, selective serotonin reuptake inhibitors; MAOIs, monoamine oxidase inhibitors. 1. Values exclude numbers of antidepressant mentions in combination with uncommon psychoactive and non-psychoactive drugs.

Drug misuse status of antidepressant-implicated deaths

Deaths related to antidepressant use in combination with other drugs were more likely to occur among drug misuse cases than non-drug misuse cases ($\chi^2=20.87$, $P<0.0001$). However, among these 'combination' deaths there was no evidence that being a drug misuser was related to a particular class of antidepressant ($\chi^2=1.55$, $P=0.4$).

Accidental and intentional antidepressant deaths

As can be seen from Table 5, 20% of mentions were associated with accidental

deaths whereas 80% of mentions were associated with intentional deaths, suggesting that most deaths from antidepressant drugs are due to suicide. Tricyclic antidepressants are associated with a higher number of accidental and intentional deaths, and significantly more accidental ($P<0.0001$) and intentional ($P<0.001$) deaths were observed with the tricyclics than would be expected when standardised for the number of prescriptions. The SSRIs were associated with significantly fewer accidental ($P<0.0001$) and intentional ($P<0.0001$) deaths than would be expected when standardised for the number of prescriptions. For the other antidepressant drugs there was no significant difference

between the number of observed and expected mentions when standardised for the number of prescriptions. Finally, there was no evidence of a relationship between type of antidepressant and the occurrence of an intentional or accidental death.

DISCUSSION

Fatalities related to tricyclic antidepressants

The present study suggests that up to 80% of deaths from antidepressants are suicides, and confirms previous findings that the tricyclics most likely to be implicated in antidepressant-related deaths are amitriptyline and dothiepin. Although the antidepressant properties of tricyclics are attributed to their ability to inhibit both noradrenalin and serotonin reuptake, it has been suggested that the increased toxicity of these drugs in overdose may be due to modulation of ion channel function within the myocardium. Indeed the tricyclics, particularly amitriptyline, have been associated with the inhibition of both cardiac sodium (Na^+) channels and potassium (K^+) channels, which is associated with an increased risk of cardiac arrhythmias and sudden death (Freeman *et al*, 1969; Marshall & Forker, 1982; Ma & Henry, 2001; Witchel *et al*, 2003). Lofepamine was the only tricyclic associated with a lower incidence of mortality. Although the mechanism of the lower toxicity of this drug has yet to be clarified, its membrane-stabilising activities (which may increase the risk of cardiac arrhythmias) are much lower than those of amitriptyline and desipramine (Darcy *et al*, 2002).

Fatalities related to selective serotonin reuptake inhibitors

In contrast to amitriptyline and dothiepin, this study clearly suggests that the SSRIs when taken on their own are safer in

Table 5 Frequencies of drug mentions by class in accidental and intentional deaths

	No. of observed deaths	No. of expected deaths	Prescriptions (thousands)	Deaths per million prescriptions	Standardised proportionate mortality ratio (95% CI)
Accidental deaths					
TCA's	80	50	33 088.9	2	1.6 (1.2–1.9)****
MAOIs	1	0.5	357.7	3	2 (0.0–11.1)
SSRIs	10	34	22 537.2	0.4	0.2 (0.1–0.5)***
Others	3	7	4356.9	0.6	0.4 (0.0–1.2)
Intentional deaths					
TCA's	323	205	33 088.9	10	1.5 (1.4–1.7)***
MAOIs	4	2	357.7	11	2 (0.5–5.1)
SSRIs	31	140	22 537.2	1	0.2 (0.1–0.3)****
Others	21	27	4356.9	5	0.7 (0.4–1.0)
Total	473				

TCA's, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors. *** $P < 0.001$, **** $P < 0.00001$ for total expected deaths in comparison with total observed deaths.

overdose and are less likely to be implicated in both intentional and accidental deaths. In addition to the treatment of depression, antidepressant drugs have been used for many other indications. In particular, SSRIs have been used in the treatment of generalised anxiety disorders, obsessive-compulsive disorders, social phobia, premenstrual dysphoric disorder and post-traumatic stress disorder (Ables & Baughman, 2003). Because these disorders are likely to carry a lower risk of suicide than depressive illnesses, this could also account for the reduced toxicity of these drugs in overdose. The present study suggests that when SSRIs are implicated in death they are mostly found in combination with other drugs, especially with tricyclics. In clinical practice, augmentation therapy involving the prescription of an antidepressant alongside another antidepressant drug of the same or different pharmacological class has largely been used in patients with treatment-resistant depression or in patients who only partially respond to antidepressants (Fava, 2001). Therefore, a possible explanation for the increased number of combination deaths with SSRIs is that these individuals were suffering from a treatment-resistant depression and tricyclics may have been prescribed concurrently, accounting for the fatal outcome. The SSRIs have been shown also to differ in the extent of their inhibition of the cytochrome P-450 enzymes of the liver, which are crucial in the metabolism of numerous drugs (Richelson, 1997), raising the possibility of drug-drug interactions in patients taking

multiple medications. Enzyme CYP2D6 is considered the principal P-450 cytochrome enzyme in the clearance of tricyclics, and data from *in vitro* studies suggest that the rank order of potency for inhibition of CYP2D6 by antidepressants is paroxetine \geq fluoxetine > sertraline > fluvoxamine > venlafaxine > mirtazapine (Vaughan, 1988; Crewe *et al*, 1992). Therefore, it is possible that by inhibiting CYP2D6 the SSRIs may increase plasma levels of tricyclics, thereby increasing the toxic effects associated with these drugs. This could be an explanation for the present findings of increased risk of death from SSRIs in combination with tricyclics, although the data at present do not seem to support this hypothesis because higher rates of deaths involving SSRIs such as fluoxetine and paroxetine were not found. Although we do not know what percentage of the combination deaths from SSRIs and tricyclics occurred as a result of prescription within the normal clinical guidelines, the present findings do suggest that the clinical efficacy of augmentation therapy in SSRI-resistant patients should be monitored carefully because of the risk of suicide.

Antidepressant-related deaths and drug misuse

The present study is the first to demonstrate that cases involving antidepressants with other drugs are significantly more likely to involve drug addicts. The other drugs that are most likely to be implicated in

combination with the antidepressants were alcohol and opiate-based drugs. These findings suggest that general practitioners and psychiatrists should screen for drug use/misuse patterns in patients being prescribed antidepressants and should prescribe cautiously for these individuals.

Venlafaxine-related fatalities

This study suggests that, of the miscellaneous group of antidepressants, venlafaxine may be more toxic in overdose than other drugs in this class. This finding supports evidence from a recent study published by Buckley & McManus (2002). Venlafaxine is a serotonin and noradrenalin reuptake inhibitor and at low doses is very similar to SSRIs in that it predominantly inhibits the reuptake of serotonin, although at higher doses noradrenalin reuptake inhibition is predominant. Furthermore, recent case studies have suggested a link between cardiac illness/failure and venlafaxine, and there is evidence that this drug blocks Na⁺ channels (Blythe & Hackett, 1999; Khalifa *et al*, 1999; Reznik *et al*, 1999; Drent *et al*, 2003). However, the other drugs most likely to be found in combination with venlafaxine were antipsychotics, which were implicated in 38.9% of cases in this group. The higher rate of antipsychotic prescribing with venlafaxine suggests that a different patient group may have been involved, possibly the seriously depressed or dual-diagnosis patients who are difficult to treat and possibly at a greater risk from suicide.

Limitations and summary

It is important to note that there are several reasons apart from the toxicity of antidepressant medication that can lead to a fatal overdose. These include treatment-resistant depression, non-response to the antidepressant therapy, medication non-compliance, duration of illness, history of antidepressant treatments and undertreatment of depression. Previously it has been suggested that in primary care practice tricyclic antidepressants are frequently prescribed at doses below those that are shown to be efficacious in randomised controlled clinical trials (Donoghue & Taylor, 2000), with studies showing that up to 88% of patients receiving tricyclics were on doses below those recommended in the national guidelines (Donoghue & Tylee, 1996). However, a recent meta-analysis of randomised controlled clinical trials comparing the effects of low-dose and standard-dose tricyclics suggests that low dosage regimes are more effective than placebo in the treatment of depression, and may or may not be as effective as standard dosage regimes but that the drop-out rate is lower because they produce fewer side-effects (Furukawa *et al*, 2002). This is in contrast to the SSRIs, which are associated with the lowest level of mortality and are almost always prescribed at efficacious doses in primary care settings (Donoghue & Tylee, 1996; Dunn *et al*, 1999). Furthermore, not all coroners report to the np-SAD database, although the response rate from the coroners in England and Wales has been estimated to be as high as about 95% (Oyefeso *et al*, 1999). Despite these limitations, the present study clearly suggests that, although tricyclic antidepressants are more toxic in overdose, the SSRIs are largely implicated in death in combination with other drugs, especially tricyclics, suggesting either a treatment-resistant depression or non-response to pharmacotherapy. Therefore, suicide risk should be monitored carefully when augmentation therapy is used in SSRI-resistant patients. Furthermore, all patients prescribed antidepressants should be screened routinely for a history of drug use/misuse.

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CLINICAL IMPLICATIONS

- Because 80% of deaths from antidepressants are intentional, suicide risk needs to be monitored carefully in all patients prescribed antidepressant drugs.
- Although selective serotonin reuptake inhibitors (SSRIs) are safer in overdose than the tricyclic antidepressants, deaths in which SSRIs are implicated are most likely to be in combination with other drugs, particularly tricyclics. Therefore, the efficacy and safety of augmentation therapy in SSRI-resistant patients should be monitored carefully.
- Deaths in which antidepressants are implicated in combination with other drugs are more likely to happen in drug misusers. Therefore, all patients prescribed antidepressants should be screened routinely for a history of drug use/misuse.

LIMITATIONS

- Because not all coroners report to the National Programme of Substance Abuse Deaths database, the number of deaths in which antidepressant drugs are implicated is likely to be underestimated.
- Factors other than the antidepressant medication, such as medication non-compliance, undertreatment of depression and non-response to antidepressant therapy, may have led to the fatal outcome.
- Toxicology reports on the quantity of drug detected at post-mortem examination were not available.

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