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# Use of antidepressants among people committing suicide in Sweden

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### **Abstract**

Objective—To analyse the outcome of depression in the Swedish population as reflected by the detection of antidepressants in a national forensic toxicological screening programme of unnatural deaths.

Design—Antidepressants detected by the National Laboratory of Forensic Chemistry were related to data on use expressed in person years of exposure.

Subjects-All 7000 cases of unnatural death with results from forensic toxicological screening in 1990-1; this included 3400 (85%) of the 4000 cases of suicide in Sweden.

Main outcome measures—Number of findings of antidepressants in the screening programme and number of findings of different antidepressants in relation to their use.

Results—Antidepressants were found in 585 screening tests, corresponding to 542 subjects or less than 16% of the 3400 cases of suicide. Newer, less toxic antidepressants were found more often than the older compounds. Toxic concentrations of antidepressants were found in only 190 cases (5.6%).

Conclusion-A consistent finding in surveys of suicide is that about half of the patients who commit suicide are depressed. The current data suggest that most depressed patients who commit suicide are not taking antidepressants immediately before death. Therapeutic failure may be a greater problem with antidepressants than toxicity as the results did not indicate any advantage of the newer, less toxic antidepressants. All causes of death should be included in risk analyses, thereby providing an estimate of effectiveness as well as toxicity of antidepressants.

## Introduction

There is a strong relation between suicide and depression, but the availability of effective antidepressants has not substantially lowered the incidence of suicide.14 Several factors may contribute to this. Firstly, depression is often wrongly diagnosed or inadequately treated156; secondly, traditional antidepressants often have side effects, and compliance with the treatment is therefore low7; and, thirdly, antidepressants are toxic drugs and may be used to commit suicide.8-10

The toxicity of the classic tricyclic antidepressants in

overdose has been referred to as a marketing argument for newer and less toxic antidepressants. The efficacy of these new drugs relative to tricyclics, however, is debatable.11 With a national health insurance scheme covering all 8.6 million inhabitants and with all pharmacies run by the National Corporation of Pharmacies, Sweden provides a good opportunity for pharmacoepidemiological studies. As the Swedish screening programme for forensic toxicology covers practically all suicides we decided to analyse the outcome of depression in the population as reflected by the detection of different antidepressants in this screening programme.

## Subjects and methods

Unnatural deaths are handled by the National Board of Forensic Medicine in any of six regional units in Sweden. Cases of suspected or obvious suicide are routinely screened for about 200 substances including medicines, illegal drugs, and alcohol at one laboratory, the National Laboratory of Forensic Chemistry in Linköping. This is routinely done from the three major regional units covering 62% of all cases of suicide, but in one region only about two thirds of cases were subject to forensic toxicological screening. Thus of all suicides in 1990-1, 85% were subject to such screening. Blood samples, usually taken from the femoral vein at necropsy, are analysed by using headspace gas chromatography and capillary gas chromatography with nitrogen specific detector.12 The screening procedure is primarily focused on finding drugs in toxic concentrations. Antidepressants, however, will be detected at blood concentrations in the therapeutic range (above 0.2-0.4 µmol/l). The results are stored on a computerised database from which we obtained the number of screenings (and concentrations) at which each antidepressant had been detected. All antidepressants available in Sweden were covered by these toxicological screenings and thus included in the study (except selective serotonin reuptake inhibitors, which were introduced during 1990-1 and then had a minimal share of the market). Results are, however, given for only the nine major antidepressants, covering 98% of the sales (table I).

Nortriptyline was considered to be a metabolite and not counted when the parent drug amitriptyline was found in the same blood sample. Desipramine was

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counted as the parent drug lofepramine except when imipramine, which is also metabolised to desipramine was also detected. Desipramine as such was hardly used and was withdrawn from the market in 1992.

In 1990-1, 7000 fatalities were screened for drugs at the National Laboratory of Forensic Chemistry. During the same years there were 4005 suicides in Sweden (including 532 uncertain cases), of which 3779 (94%) were investigated forensically; 3400 (85%) were subject to toxicological screening and thus included in our data.

All cases in which antidepressants were detected, regardless of blood concentrations and cause of death (for example, accidents, illnesses, suicide by any method), were included in the study. In cases in which we found the two low toxicity antidepressants recently marketed in Sweden, moclobemide (1989) and mianserin (1990), we examined the official death certificates

TABLE I—Use of antidepressants in Sweden in 1990-1 in thousands of purchased defined daily doses as well as factors used for standardisation (age, sex, and county) and for adjustment for average prescribed daily dose

Drug	1000 defined daily doses	Standardisation	Prescribed daily dose adjustment
Imipramine	1217	0.841	1.22
Clomipramine	13010	0.976	1.786
Trimipramine	1601	1.172	1.724
Lofepramine	6339	1.012	0.981
Amitriptyline	17280	1.02	1.442
Nortriptyline	2818	0.934	1.172
Maprotiline	4888	0.998	1.493
Mianserin	1794	1.055	1.364
Moclobemide	3358	0.971	1.017
All*	53370	1	1.407

\*Includes desipramine, opipramol, protriptyline, zimeldine, paroxetine, and fluvoxamine; 1 060 000 defined daily doses (2%), otherwise not considered in this study.

TABLE II—Cause of death from death certificate in all subjects in whom moclobemide and mianserin were detected at necropsy in Sweden, 1990-1

Cause of death	Moclobemide	Mianserin	
Certain suicide:			
Drug intoxication	11	10	
Gas intoxication	-	5	
Hanging	15	6	
Drowning	3	8	
Shooting	2	1	
Cutting	1	-	
Jump from height	2	2	
Railway	3	_	
Uncertain cases:			
Drug intoxication	2	5	
Gas intoxication	_	_	
Hanging	_	-	
Drowning	2	1	
Shooting	_	_	
Cutting	_	_	
Jump from height	_	1	
Railway	_	1	
Not suicide	_	-	
Accidents, illnesses	6	2	
Total	47*	42†	

<sup>\*24</sup> Men and 23 women. †15 Men and 27 women.

TABLE III—Antidepressants detected at necropsy and general use in Sweden, 1990-1. Standardised mortality rate is in comparison with amitriptyline

Drug	Cases	Single cases*	Toxic concentration	Person years	Cases/100 000 person years	Standard mortality rate (95% confidence interval)
Imipramine	12	10	5	3 4 1 9	351	1·192 (0·7 to 2·1)
Clomipramine	145	129	39	62 137	233	0·793 (0·6 to 1·0)
Trimipramine	52	43	15	8 860	587	1.994 (1.5 to 2.7)
Lofepramine	7	5	2	17 236	41	0·138 (0·1 to 0·3)
Amitriptyline	205	179	87	69 644	294	1
Nortriptyline	27	25	12	8 452	319	1.085 (0.7 to 1.6)
Maprotiline	48	41	24	19 953	241	0·817 (0·6 to 1·1)
Mianserin	42	33	2	7 0 7 4	594	2.017 (1.4 to 2.8)
Moclobemide	47	33	4	9 082	518	1·758 (1·3 to 2·4)
Any	542	498	190†	205 730	263	0·890 (0·8 to 1·0)

<sup>\*</sup>Cases in which that drug was the only one detected.

†Any drug found at toxic concentration.

for the cause of death. The numbers of cases in which antidepressants were detected were then related to the use of the respective drug.

We used available sources of information on drug use in Sweden to estimate the use in person years at risk for each drug. 14 Regardless of prescriber (hospital based physicians, general practitioners, etc) all prescriptions are purchased at pharmacies belonging to the National Corporation of Pharmacies. A random sample of one in 25 of all 45 million prescriptions purchased annually at pharmacies in Sweden provides data on age, sex, county, and volume in the technical unit of defined daily dose (ddd). 14 We were thus able to do an indirect standardisation of these prescription data for age, sex, and county with the distribution of cases of suicide in these subgroups, as obtained from Statistics Sweden 1989, as weights (table I). 13

The defined daily doses are, however, technical units and the average prescribed daily doses may vary for each drug below or above the respective defined daily dose. We have therefore recalculated the defined daily doses to prescribed daily doses as obtained from the Swedish diagnosis and therapy survey. A prescribed daily dose is considered to be one person day at risk (table I). Thus the formula for (standardised) person years at risk is: number of defined daily doses standardised factor prescribed daily dose factor/365.

By relating the number of cases to the number of person years at risk for each antidepressant we were able to calculate a risk index. As we were studying the associations of different antidepressants with deaths (not causes of death), we used as numerator the total number of detections of each antidepressant. This is in contrast with the studies of fatal toxicity index, in which only single intoxications were included. 9 10 By comparing this risk index for each antidepressant with that for amitriptyline, the antidepressant most often used in Sweden, we calculated standard mortality rates with 95% confidence intervals. 15

## Results

Antidepressants were detected 585 times in the toxicological screenings over the two years, corresponding to 542 cases as more than one antidepressant was found in 43 cases (metabolites excluded). This corresponds to 265 cases in 1990 and 277 in 1991. In 190 of the 585 findings antidepressants were detected in toxic concentrations. Concentrations of  $\geq 3.5 \,\mu\text{mol/l}$  of the older antidepressants and  $\geq 11 \,\mu\text{mol/l}$  of moclobemide and  $\geq 1.9 \,\mu\text{mol/l}$  of mianserin were considered to be toxic.

For cases in which we detected the two newly introduced drugs, moclobemide and mianserin (n=89), review of death certificates showed that 69 (78%) were certain cases of suicide. Overdose by drugs was the cause of death in 21 of these. Only three deaths were due to single intoxication with moclobemide and none with mianserin, although these drugs were detected at toxic concentrations in 10 cases. The remaining were 12 uncertain cases (four of which were probably suicides<sup>17</sup>) and eight deaths due to illness or accident (table II).

In relation to their use trimipramine, mianserin, and moclobemide were found to have twice the risk compared with amitriptyline, whereas lofepramine had a seventh of that risk. The other drugs did not differ significantly from amitriptyline (table III).

## Discussion

This study covers all toxicological screenings in Sweden during 1990-1. The fact that only about two thirds of cases of suicide were the subject of forensic toxicological screening in one region, with an estimated

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national screening rate of 85%, does not invalidate our main findings by introducing any bias. Furthermore, all cases with detectable concentrations of antidepressants were included, thus representing the availability of the drugs for the cases investigated, including current treatment. The information on drug use was obtained from reliable databases. Within its limits the study therefore provides reliable results regarding the association between suicide and treatment with antidepressants in real life. It is, however, a non-experimental study with many possible confounders, and the results must be cautiously interpreted.

#### THE CASES

Less than 16% (542/3400) of subjects who committed suicide had detectable concentrations of antidepressants in their blood. As deaths due to illness and accidents are included in the 542 cases, 16% is a maximum figure (table II). Autolysis is a problem in a few cases, mostly in summertime, but is of minor importance. Low therapeutic concentrations, however, will escape detection. For some drugs this may be more important-for instance, lofepramine and mianserin, for which the therapeutic concentrations are mostly below 0.4 µmol/l.18 Thus the number of cases in which these two drugs were detected may be falsely low. By contrast, moclobemide and trimipramine have relatively high therapeutic concentrations,18 implying that the sensitivity to detect these antidepressants is probably better than for the others, tending to give relative risks that are too high. The true number of patients taking antidepressants immediately before suicide may therefore be somewhat greater than we found, probably restricted to patients taking lofepramine, mianserin, or, in low dosage, any of the others. Owing to reduced tissue binding after death, however, the blood concentrations of antidepressants will increase substantially, sometimes giving a false impression of intoxication.16 This effect will reduce the problem of undetected cases. About 15% of the cases of suicide were not subjected to forensic toxicological. screening. We have no reason to believe that the pattern of use of antidepressants was substantially different in that population. Thus, as different studies have found that about half of patients who commit suicide are depressed,124 our result suggests that a substantial number of these are not correctly diagnosed or treated (including non-compliance). This is also consistent with our finding in a record linkage study, in which only 12 of the 80 people who committed suicide (15%) had received antidepressant treatment during their last three months.6

## USE OF ANTIDEPRESSANTS

When risks with drugs are calculated the ideal denominator is the number of patients using each drug for comparable conditions and durations. If at all available these data are found only in a few population based drug databases in the world. <sup>19</sup> We have therefore estimated the number of person years at risk for each drug by using the purchased volumes in average prescribed defined daily doses from an unbiased 4% sample of all prescriptions <sup>14</sup> indirectly standardised for age, sex, and county with respect to the different suicide rates within these subgroups. <sup>13</sup>

## COMPARING DIFFERENT ANTIDEPRESSANTS

Rank orders for the mortality risks of different drugs have been created to give a fatal toxicity index by relating fatal intoxications to the estimated use of each antidepressant. 9 10

This kind of ranking list can be criticised as it rests on the assumption that all substances are used in comparable patients and under otherwise similar circumstances. Another assumption is that all anti-

## Clinical implications

- In surveys of suicide about half the patients who commit suicide are depressed
- The availability of effective antidepressants has not substantially lowered the incidence of suicide
- In forensic toxicological screenings of 3400 (85%) of all 4000 suicides in Sweden in 1990-1 antidepressants were found in less than 16%
- In relation to their use compounds of lower toxicity were found more often than the more toxic tricyclic antidepressants
- Therapeutic failure may be a greater problem with antidepressants than toxicity, and all causes of death should be included in risk analyses of these drugs

depressants are equal in their antidepressive effects as no differences have been proved in clinical trials. This may, however, be due to a type II error. A multicentre controlled clinical trial in Denmark has challenged that question and found clomipramine to be more effective than the newer antidepressants moclobemide, paroxetine, and citalopram.<sup>11</sup>

The concept of fatal toxicity index has recently been criticised for shifting the focus from the majority of the suicidal patients in need of efficient treatment to the minority committing suicide by overdose of antidepressant.21 Our finding that less than 16% of the people who committed suicide had detectable concentrations of antidepressants (and less than 6% toxic concentrations) supports this view. A study from the United States and the United Kingdom reported on suicide among recent users of antidepressants in two population based drug databases. In both countries drug overdose as a method of suicide was in a minority. and antidepressant intoxications were even less common.19 Although that study is not strictly comparable with our survey, these findings are consistent with the conclusion that failure of treatment is a much bigger problem than toxicity with current antidepressants.

Amitriptyline, the most commonly used drug, showed a risk index of 294 per  $100\,000$  person years. Compared with this the standard mortality rates of the other drugs, with the exception of lofepramine, varied modestly  $(0.8-2\cdot0)$ . The outstandingly low standard mortality rate for lofepramine  $(0\cdot14)$  agrees with the studies of fatal toxicity index. Owing to low concentrations of the metabolite screened for (desipramine), however, at recommended doses of lofepramine this result may be biased.

Because of the modest differences and possible confounders we do not want to rank the drugs according to risk. It is, however, remarkable that the less toxic drugs mianserin and moclobemide had higher standard mortality rates than the other drugs. This may be due to a weaker antidepressive effect, as is suggested for moclobemide.11 In the case of moclobemide, but not of mianserin, the risk may be overestimated because of relatively higher and therefore more easily detected therapeutic concentrations (see above). Another nonexperimental study also suggests a greater risk for suicide with mianserin compared with other antidepressants.19 The denominator used, standardised person years, excludes the possibility that the differences in risk found are confounded by prescribing in different demographic categories and provides probably the best possible estimate of use. Compared with amitriptyline, however, the significant excess risks found are the same when crude person years are used as

the denominator (the 95% confidence intervals for trimipramine are 1.7 to 3.1, for mianserin 1.5 to 2.9, and for moclobemide 1.2 to 2.3). Risk calculations including only cases with one single antidepressant detected did not differ from the results presented, but the confidence interval for moclobemide was then at the border of significance. Given that depression is a recurrent disease a relatively high rate of detection of other antidepressants among patients treated with the newly introduced drugs mianserin and moclobemide can be expected. Exclusion of cases in which more than one antidepressant is found would therefore make comparisons less valid.

### Conclusion

Studies that have used the fatal toxicity index suggest that the risk:benefit ratios for newer antidepressants are better than for the older ones because of their lower toxicity. As intoxication with an antidepressant is a rare method of suicide, however, it is reasonable to include all methods in a risk analysis. The antidepressants of lower toxicity do not then seem to have lower risks than average, which suggests that therapeutic failure (relative benefit) may be of more concern than toxicity (relative risk) with antidepressants. Our most substantial finding, however, consistent with those of others is that few people are taking antidepressants at the time of suicide, although half of the people who commit suicides are depressed. This may be the reason why antidepressants have failed to reduce the suicide rate. Whether some drugs are relatively more effective in curing depressions or preventing suicide requires further studies.

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# Provision of consumer health information in general practice

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The term "consumer health information" is relatively new and refers to information about healthy living, medical conditions, and health and other services that is provided direct to consumers. There are arguments for developing consumer health information independently of providers of primary care and other health care. It could then be seen as impartial and as a source of empowerment for consumers of health care. On the other hand, people have traditionally gone to their general practitioner for advice on their health and find general practice surgeries convenient and appropriate places to seek information on health.1 Although there are several examples of innovations in the provision of health information to patients in general practice,25 there is no clear picture of the overall provision of consumer health information in general practices.

A brief questionnaire about consumer health information (written, on video tape, or on audio tape) was sent in April 1993 to all 312 practices in the East by the practice manager; 36 by a principal in general practice; and the remaining 19 by practice nurses, secretaries, or receptionists.

The table shows the types of information that were available for patients in general practice surgeries in East Anglia. Information about healthy lifestyles and medical conditions was available in most practices, but information about hospital waiting lists was available in less than a quarter. Information was usually given in a leaflet; in 98 practices books were available to patients, and in 60 practices videos were available. In addition to providing patients with leaflets produced by the health education authority and commercial companies, 91 practices said that they produced their own leaflets (as well as the leaflet about their practice); 36 had leaflets available in languages other than English.

Seventy four practices said that they had a library for

Consumer health information (written, on video, or on tape), according to subject, provided by 258 general practices in East Anglia

Subject	No	
Healthy lifestyle	244	
Life events (for example, the menopause)	239	
Medical condition (for example, diabetes)	236	
The practice and its services	226	
Claiming welfare benefits	222	
Self help groups	215	
Charities and voluntary agencies	210	
Support for carers	201	
Community health services	168	
Social services	163	
Local hospital services	115	
Hospital waiting lists	59	

Method and results

Anglian region. The final response rate was 83% (n= 258). Of the 312 questionnaires, 203 were completed

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