Psychotropics and suicide prevention

Implications from toxicological screening of 5281 suicides in Sweden 1992–1994

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Background Systematic clinical investigations of consecutive suicides have found psychiatric disorders in 90–95% of subjects (depressive disorder 30–87%).

Aims To investigate use of psychotropics in men and women of different ages who commit suicide.

Method Results of toxicological screening in 5281 suicides in Sweden 1992–94 were studied.

Results Psychotropics were detected in 45.3% of the suicides. Antidepressants were detected in 12.4% of the men and 26.2% of the women (7.2% and 14.2%, respectively, of those under 30 years of age). Neuroleptics or antiepileptics (in the absence of antidepressants) were detected in 8.3%, and anxiolytics/hypnotics alone in 20.5% of the subjects. Overdose by an antidepressant was the probable cause of death in 2.1% of the men and 7.9% of the women.

Conclusions The pattern of psychotropics detected in toxicology was incongruent with the pattern of diagnoses found in the clinical investigations of suicides mentioned above. Depression appears to be undertreated in individuals committing suicide, especially in men and in subjects under 30 years of age.

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The systematic clinical study of consecutive suicides has shown that suicide almost invariably occurs in people with psychiatric disorders (Robins *et al*, 1959; Dorpat & Ripley, 1960; Barraclough *et al*, 1974; Beskow, 1979; Chynoweth *et al*, 1980; Rich *et al*, 1986; Arató *et al*, 1988; Runeson, 1989; Åsgård, 1990; Cheng, 1995; Foster *et al*, 1997). Most frequent are depressive disorders (30–87%) and substance misuse (19–50%), while anxiety disorders are seldom found in cases of suicide (<5%). Schizophrenic disorders are diagnosed in 2–13% of suicides. Many of these disorders are treatable, particularly depression, and epidemiological data suggest that antidepressant medication has the potential to prevent suicide in depressed people (Isacsson *et al*, 1996, 1997). For this report, we analysed toxicological findings of psychotropic drugs in suicides. The questions we sought to answer were:

(a) To what extent is the pattern of psychotropics in toxicological screening consistent with the pattern of diagnoses in systematic studies of consecutive suicides?

(b) Are there any disproportions in treatment for depression based on age and/or gender?

(c) How often were antidepressants and psychotropics used for overdose as a method for committing suicide?

METHOD

Subjects

During 1992–1994, 5406 deaths in Sweden (population 8.6 million) were due to certain (n=4056) or uncertain (n=1350) suicide according to Statistics Sweden (data online). Unnatural deaths are investigated by the Swedish National Board of Forensic Medicine regardless of citizenship of the victims. (Official Statistics Sweden provides data only for Swedish citizens committing suicide, but includes cases occurring abroad.) Cases of suspected suicide subjected to forensic investigation are routinely screened for about 200 substances at the Department of Forensic Chemistry. During 1992–1994, 5281 (98%) out of all 5393 forensically investigated suicides were subjected to such screening. These 5281 cases were our study sample (3895 certain and 1386 uncertain suicides according to the final verdict). We decided to include the uncertain cases in order not to overlook suicides committed by means of drug overdoses, because the suicidal intent often cannot be determined in these cases. Data on age, gender, cause of death, suicide method and toxicological results were retrieved from the Swedish forensic medicine and forensic toxicology databases (Druid *et al*, 1996).

Toxicological methods

Body fluids were analysed using head space gas chromatography and capillary gas chromatography with a nitrogen-specific detector (Druid & Holmgren, 1997). Blood samples were collected from the femoral vein when possible. Only liver tissue was analysed in 302 subjects (5.7%) investigated (1992–1993). Psychotropics are usually detected at therapeutic concentrations. However, some drugs, such as high-potency neuroleptics (e.g. haloperidol) and the antidepressants lofepramine and paroxetine, may escape detection at such concentrations. Lithium is not detected by routine screening. Metabolites were not counted in the presence of their parent compounds (Isacsson *et al*, 1997). Detections of antidepressants in femoral blood at the following concentrations were considered toxic: tricyclic antidepressants ⩾3.5 μmol/l, maprotiline ⩾11 μmol/l, citalopram ⩾3.1 μmol/l, paroxetine ⩾9.1 μmol/l, fluvoxamine ⩾11 μmol/l, mianserin ⩾3.8 μmol/l, moclobemide ⩾11.1 μmol/l (Baselt & Cravey, 1995; Druid & Holmgren, 1997). In the few cases (n=36) where antidepressants were detected only in liver, the limits for toxicity were assumed to be 25 times higher (Baselt & Cravey, 1995). A case of antidepressant overdose was defined as a toxic concentration of an antidepressant and the cause of death being overdose, as ruled by a forensic pathologist, although other substances may have been of equal importance for the intoxication.

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Drug use

Extensive information on drug use in the Swedish population was used to estimate the number of person-years at risk (Isacsson *et al*, 1997). All prescription drugs, including hospital use, are purchased at pharmacies belonging to the National Corporation of Swedish Pharmacies. From this corporation, data on the total sales on prescription during 1992–1994 could be obtained by age and gender for all drugs in the technical volume unit of defined daily dose (DDD), which roughly approximates a daily dose for a particular drug. This approximation was refined further by adjusting for the average actually prescribed daily dose (Isacsson *et al*, 1997). One person-year of use was considered equivalent to 365 adjusted DDDs.

Statistics

Chi-squared statistics were calculated for tables describing toxicological findings. When the toxicological findings were related to drug use data, rates of risk for sold medications to be detected in suicides were calculated for each subgroup (suicides per person-year of use). By comparing such rates, risk ratios were calculated with 95% confidence intervals.

RESULTS

Psychotropics were found in 2392 of the 5281 subjects (45.3%) (Table 1). Eighteen per cent (n=932) were positive for several classes of psychotropics (497 men and 435 women, 13% and 27%, respectively, $P<0.001$), therefore the findings are reported here in a hierarchical manner: subjects positive for antidepressants, because these may have been aimed as treatment of the disorder most frequently found in suicides, namely depression; subjects negative for antidepressants but positive for neuroleptics or antiepileptics, which may have been aimed as treatment of schizophrenia and epilepsy (or bipolar disorder), which also are disorders found in suicides; subjects positive only for anxiolytics and/or hypnotics, drugs that, taken alone, are usually not recognised to be an adequate treatment of any syndrome found in suicides.

Antidepressants

Antidepressants were found in 874 subjects (Table 1). In 315 of these, antidepressants

Table 1 Detections of psychotropic drugs in 5281 suicides in Sweden 1992–1994, distributed according to age and gender

	Antidepressants		Anxiolytics		Hypnotics		Neuroleptics		Antiepileptics		Any psychotropic		Subjects
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
Men													
Age range													
0–14	0	0	1	11.1	0	0	0	0	1	11.1	1	11.1	9
15–29	39	7.2	61	11.3	73	13.6	31	5.8	22	4.1	152	28.3	538
30–44	106	10.5	178	17.6	194	19.2	68	6.7	71	7.0	409	40.5	1009
45–59	163	15.5	140	13.3	226	21.4	63	6.0	66	6.3	444	42.1	1054
60–74	97	15.1	46	7.2	120	18.7	28	4.4	18	2.8	234	36.5	641
75–89	53	12.7	33	7.9	95	22.8	12	2.9	8	1.9	159	38.2	416
90+	0	0	5	19.2	6	23.1	0	0	1	3.8	9	34.6	26
Total men	458	12.4	464	12.6	714	19.3	202	5.5	187	5.1	1408	38.1	3693
Women													
Age range													
0–14	0	0	0	0	0	0	0	0	0	0	0	0	5
15–29	26	14.2	28	15.3	34	18.6	12	6.6	3	1.6	69	37.7	183
30–44	84	24.2	76	21.9	115	33.1	51	14.7	23	6.6	215	62.0	347
45–59	146	30.7	116	24.4	174	36.6	60	12.6	27	5.7	304	64.0	475
60–74	103	29.9	67	19.5	127	36.9	34	9.9	11	3.2	234	68.0	344
75–89	56	25.1	34	15.2	112	50.2	14	6.3	7	3.1	156	70.0	223
90+	1	9.1	0	0	6	54.5	2	18.2	1	9.1	6	54.5	11
Total women	416	26.2	321	20.2	568	35.8	173	10.9	72	4.5	984	62.0	1588
Total	874	16.5	785	14.9	1282	24.3	375	7.1	259	4.9	2392	45.3	5281
Certain suicide only	702	18.0	488	12.5	878	22.5	256	6.6	131	3.4	1685	43.3	3895
Overdoses excluded	445	12.9	293	8.5	459	13.3	140	4.1	105	3.1	1071	31.1	3441
χ^2													
Men *v.* women (d.f.=1)	153 ($P<0.001$)		51 ($P<0.001$)		163 ($P<0.001$)		50 ($P<0.001$)		0.7 (NS)		255 ($P<0.001$)		
Age groups (d.f.=6)	69 ($P<0.001$)		43 ($P<0.001$)		68 ($P<0.001$)		20 ($P<0.001$)		37 ($P<0.001$)		85 ($P<0.001$)		

Values of χ^2 are calculated for gender differences and for differences between age groups with the two genders combined.

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were the only psychotropics found. Antidepressants were found together with one other class of psychotropics in 296 subjects and with two to four other classes in 263 subjects. Antidepressants were found twice as often in women (26.2%) as in men (12.4%). In both genders the maximum detection rate was in the age group of 45–59 years.

Neuroleptics or antiepileptics in the absence of antidepressants

Among the subjects negative for antidepressants, there were 147 men and 103 women positive for neuroleptics (4.0% and 6.5%, respectively, $P<0.01$) and 158 men and 51 women positive for antiepileptics (4.3% and 3.2%, respectively, NS). Carbamazepine, which is used also for bipolar disorder, was found in 129 men and 45 women (69% and 63%, NS). Clonazepam was detected in 17 men and five women (9% and 7%, NS). The subjects who were positive for neuroleptics and/or antiepileptics were 291 men and 145 women (7.9% and 9.1%, respectively, NS, in total 436, 8.3%).

Anxiolytics and/or hypnotics

There were 1082 subjects (20.5%) who were positive for anxiolytics and/or hypnotics but negative for antidepressants, neuroleptics and antiepileptics. This group consisted of 659 men and 423 women (17.8% and 26.6%, respectively, $P<0.001$).

Antidepressants in suicides in relation to their use in the general population

Men were more often positive for antidepressants than women when related to the use of antidepressants in the Swedish population (308 *v.* 133 per 100 000 person-years, Table 2). Likewise, men and women (combined) under the age of 30 years were more often positive than those over 30 years of age when related to the population use.

Table 2 Detections of antidepressants (subjects) related to use of antidepressants in the population (person-years)

	Subjects positive	Person-years	Rates of risk	Risk ratios[1]	95% confidence intervals
Men					
Age range					
15–29	39	10 305	378	1.2	0.9–1.7[2]
30–44	106	36 393	291	0.9	0.8–1.2
45–59	163	48 723	335	1.1	0.9–1.3
60–74	97	34 291	283	0.9	0.7–1.1
75+	53	19 225	276	0.9	0.7–1.2
Total men	458	148 937	308	1	[3]
Women					
Age range					
15–29	26	14 984	174	1.3	0.9–1.9[2]
30–44	84	62 721	134	1.0	0.8–1.3
45–59	146	96 719	151	1.1	0.9–1.4
60–74	103	82 506	126	0.9	0.8–1.2
75+	57	55 809	102	0.8	0.6–1.0
Total women	416	312 289	133	1	[3]
Total	874	461 226	189		

1. Note that risk ratios in male age groups are related to the risk for total men and risk ratios in female age groups are related to the risk for total women.
2. Risk ratio in the combined group of 15–29-year-old men and women *v.* all older men and women was 1.4 (95% CI=1.1–1.8).
3. Risk ratio in men *v.* women (308/133) was 2.3 (95% CI=2.0–2.6).

Fatal overdoses

A drug overdose was the cause of death for 1840 subjects (35%). Because more than half of the subjects who died due to drug overdoses were uncertain suicides (n=941), certain and uncertain cases are presented separately in Table 3. Overdose was 2.5 times more often the cause of death in women than in men, but only in the certain suicides. An antidepressant overdose was the cause of death in 3.8% (2.8+1.0%) of the total sample, more frequently in women. Uncertain suicide by overdose was more common in those who were middle aged.

DISCUSSION

Validity

In this nationwide toxicological analysis of almost all suicides during three years in Sweden, we studied psychotropic medications detected in post-mortem blood. Toxicology data, although of high quality, do not give the full picture concerning which drugs the subjects have (or have not) taken at the time of death, but we consider them to be the best available estimate.

The inclusion of 1350 uncertain suicides probably means that about 500–600 subjects in our sample were not suicides but accidents and a few homicides. Conversely, if the uncertain cases were excluded, approximately 800–900 true suicides, mostly by overdoses of prescribed medications, would have been lost. The sample will probably be less distorted by inclusion than exclusion of the uncertain cases, particularly as our interest is focused on medication. Some data are further presented for certain and uncertain cases separately.

The data concerning sales on prescription of antidepressants cover all prescriptions in out-patient as well as hospital use in Sweden during the same period of time. Also, without knowledge of the indications for the prescriptions, these data provide a good estimate of the maximal number of person-years of depression treated.

Psychotropics in toxicology

Women were more likely than men (62% *v.* 38%) to be detected with any kind of psychotropic medication in toxicology (Table 1) except antiepileptics. Subjects under 30

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Table 3 Certain and uncertain suicides by any overdose and by overdose of antidepressants[1]

	Certain suicides (E950)				Uncertain suicides (E980)				Subjects
	All		Antidepressants		All		Antidepressants		
	n	%	*n*	%	*n*	%	*n*	%	(*n*)
Men									
Age group									
0–14	0	0	0	0	0	0	0	0	9
15–29	61	11.3	9	1.6	67	12.5	1	0.2	538
30–44	137	13.6	19	1.9	237	23.5	9	0.9	1009
45–59	137	13.0	18	1.7	227	21.5	10	0.9	1054
60–74	55	8.6	4	0.6	94	14.7	5	0.8	641
75–89	42	10.1	0	0	22	5.3	2	0.5	416
90+	4	15.4	0	0	1	3.8	0	0	26
Total men	436	11.8	50	1.4	648	17.5	27	0.7	3693
Women									
Age group									
0–14	2	40.0	0	0	0	0	0	0	5
15–29	43	23.5	5	2.7	22	12.0	2	1.1	183
30–44	106	30.5	5	6.6	22	22.2	2	2.6	183
45–59	147	30.9	43	9.1	104	21.9	6	1.3	475
60–74	89	25.9	19	5.5	71	20.6	7	2.0	344
75–89	72	32.3	10	4.5	18	8.1	2	0.9	223
90+	4	36.4	0	0	1	9.1	0	0	11
Total women	463	29.2	100	6.3	293	18.5	26	1.6	1588
Total	899	17.0	150	2.8	941	17.8	53	1.0	5281
χ^2									
Men *v.* women (d.f.=1)	237 ($P<0.001$)		98 ($P<0.001$)		0.6 (NS)		9 ($P<0.01$)		
Age groups combined gender (d.f.=6)	12 (NS)		16 ($P<0.05$)		122 ($P<0.001$)		6 (NS)		

1. Additional 29 subjects had toxic concentrations of antidepressants but died because of means other than overdose.

years of age were less likely than the older subjects to be positive for psychotropic drugs. These gender and age differences might reflect varying morbidity as well as varying actual access to adequate healthcare, compliance, etc. Psychotropics were not found at all in 54.7% of the subjects. In a toxicological study of 1635 suicides in New York City in 1990–1992, psychotropics were found in only 16.4% of the victims (Marzuk *et al*, 1995). Women were 2.8 times more likely than men to be positive for a psychotropic drug (cf. 1.8 in our study), with no age differences. These international differences may reflect varying access to healthcare, demographic differences in the suicidal population, differences in efficacy of toxicological screening and other factors.

Anxiolytics and/or hypnotics

Anxiolytics were found in 14.9% and hypnotics in 35.8% of cases. Similarly, in an investigation of 1348 suicides in Finland 1987–1988, benzodiazepines were found in 18.7% of the men and 37.7% of the women (Ohberg *et al*, 1996). Symptoms of anxiety and insomnia are common in people with psychiatric disorders. Anxiety or sleep disorders as principal diagnoses are, however, rarely found in clinical studies of suicides. The rates of detections are not remarkably high, but it is remarkable that in 20% of all cases these drugs were the only psychotropics detected (1082/5281). This may be explained partly by misuse of these drugs, particularly of benzodiazepines. Two findings support this. In men, the detections of anxiolytics showed a maximum in the age group 30–44 years, and hypnotics were almost as frequently detected in younger and in older men. This is in contrast with the general use of benzodiazepines in Sweden, where use increases with age (two-thirds of the use in those over 60 years) (Bergman & Myrhed, 1993).

Neuroleptics

The detections of neuroleptics (7.1%) appears to be in the same order of magnitude as the diagnoses of non-affective psychoses found in suicides (2–13%). These data thus provide no evidence suggesting that male or female suicides of any age with psychotic disorders were undertreated with neuroleptics,

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although this still may be the case (ecological fallacy). Therapeutic failure or untreated comorbid depressions might have been the therapeutic problems in psychotic patients committing suicide. Also, in New York City neuroleptics were found more seldom than antidepressants, whereas in Finland neuroleptics were found slightly more often than antidepressants in men as well as in women (Marzuk *et al*, 1995; Ohberg *et al*, 1996).

Antiepileptics

Antiepileptics (see Table 1) were the only class of psychotropic drug without significant gender differences in the number of detections. They were also the kind of psychotropic drug least often detected (4.9%). Although seizure disorder may be a risk factor for suicide, as reported in two investigations of consecutive suicide (Barraclough *et al*, 1974; Chynoweth *et al*, 1980), it is not clear to what extent it is the epilepsy as such or comorbid disorders that carry the risk for suicide (Barraclough, 1987). Many of the subjects positive for antiepileptics may have had comorbid epilepsy and alcoholism and some may have been prescribed carbamazepine for bipolar illness. These alternatives cannot be distinguished within the limits of this study.

Antidepressants

The gender difference was most pronounced for antidepressants, which were detected twice as often in women (26.2 *v.* 12.4%). In Finland, antidepressants were found in 19.0% of the women and 4.8% of the men (Ohberg *et al*, 1996). In an investigation of 251 suicides in Mobile County, Alabama, in 1990–1995 it was found that 34% of the women and 10% of the men were positive for antidepressants (Rich & Isacsson, 1997). The gender difference might simply reflect that antidepressants are more often prescribed to women than to men (Table 2), possibly because depression may be twice as common in women (Hagnell *et al*, 1993). Among suicides, however, women are only 15–25% more likely to be depressed (Robins *et al*, 1959; Barraclough *et al*, 1974; Arató *et al*, 1988; Rich *et al*, 1988; Åsgård, 1990). Hence, the twice as high probability for female suicides to be positive for antidepressants indicates that depressed suicidal women are more likely to seek medical help or are more likely to be correctly diagnosed and treated or to comply with antidepressant medications. This is consistent with the finding from the San Diego Study that 10% of the men and 17% of the women (NS) with a research diagnosis of major depression were positive for antidepressants (Isacsson *et al*, 1994). This supports the hypothesis that failure to recognise depression in men may be one factor behind men's higher suicide rates, despite lower rates of depression (Rutz *et al*, 1995). Detections of antidepressants were more rare in the age group 15–29 years (males 7%, females 14%). In this age group, depressions have been found in 31–41% of suicides (Rich *et al*, 1986; Runeson, 1989). Although this was slightly lower than among older subjects, the proportion of cases positive for antidepressants in this study was even lower. Prescription data (person-years in Table 2) suggest that the less frequent detection of antidepressants in the 15–29 year olds, as well as in men in general, depends on the lower prescription rates. When using prescription rate as a denominator, the suicide subjects of these subgroups were actually more likely to have taken antidepressants (risk in Table 2). Interpreting the toxicological finding as depending on lower compliance in these subgroups is therefore not warranted. Undertreatment thus seems to be the main problem with regard to suicide among depressed individuals of all categories, but it appears to be most pronounced in men and in individuals under the age of 30 years.

Suicides negative for antidepressants

Because we have previously concluded that antidepressants are the key issue in the prevention of suicide (Isacsson *et al*, 1997), it was of particular interest to analyse the subjects that were negative for antidepressants in toxicology. One category of these consisted of the 436 (8.3%) subjects who may have been adequately treated patients with psychotic or epileptic disorders. It is doubtful, though, if treatment with antiepileptics only may be considered adequate in suicidal patients, and to some extent this doubt may be valid also for treatment with neuroleptics only.

A second category consisted of the 1082 (20.5%) subjects positive only for anxiolytics or hypnotics. In the absence of specific treatment, various sedatives cannot be considered as adequate treatment of any disorder regularly found in suicides. The majority of these subjects were probably depressed patients receiving only symptomatic treatment for their depressive anxiety or depressive insomnia but no specific treatment for their depressive disorder (Isacsson *et al*, 1992).

A third category consisted of the 2889 (54.7%) subjects who lacked any psychotropic medication. These individuals might not have consulted a physician at all, did not mention their psychiatric problems to the physicians, were not prescribed psychotropics or did not comply with the prescriptions received.

Thus, in rounded numbers, it appears that maximally 20% of the suicides were treated with antidepressants, 10% might have been adequately treated for schizophrenia or epilepsy, 20% were only treated for anxiety or insomnia and at least 50% were not treated at all with medication. A few of the latter may have been treated with lithium or electroconvulsive therapy (ECT).

This pattern of psychotropics in the toxicology of suicides is in disagreement with the pattern of diagnoses found in clinical suicide studies. In the latter studies, the dominant diagnostic category was depression (30–87%). Schizophrenic disorders were found in 2–13% of the suicides, anxiety disorders in less than 5% and the absence of a psychiatric disorder in less than 10%. The pattern found is consistent with that from a study of drugs prescribed for patients later committing suicide (Isacsson *et al*, 1992) and with that from a study of drugs used for suicide attempts (Isacsson *et al*, 1995).

Overdoses with psychotropics

Women were more likely to commit suicide by means of overdose of medication (Table 3) than men. Among the uncertain suicides, however, gender differences were found only for antidepressant overdoses. These uncertain cases may include a minority consisting of accidental overdoses, probably occurring mostly among substance misusers. To outweigh the age and gender distribution of the certain suicides, the uncertain cases must have been men in the age range 30–59 years.

Antidepressant overdoses were uncommon methods for suicide (men 2.1%, women 7.9%). This is consistent with data from England, Ireland, Finland and the USA (Kelleher *et al*, 1992; Isacsson *et al*, 1994; Marzuk *et al*, 1995; Ohberg *et al*, 1996). As reported previously, only a few

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of these were pure antidepressant overdoses (Isacsson *et al*, 1997). Among all subjects who were positive for antidepressants, 17% of the men (77/458) and 30% of the women (126/416) had taken antidepressant overdoses (Tables 1 and 3). Although some of these subjects may have taken overdoses of antidepressants prescribed for others, the majority probably represent therapeutic failures due to therapy refractoriness or non-compliance. The risk that antidepressants may be taken in overdose constitutes an argument for prescribing new antidepressants of lower toxicity, such as the selective serotonin re-uptake inhibitors (SSRIs). There are data suggesting that some of the new antidepressants may have increased risk for therapeutic failure and suicide (Jick *et al*, 1995; Isacsson *et al*, 1997). The preferential use of SSRIs is, however, also supported by evidence that their greater tolerability has allowed a wider use of antidepressants more congruent with the prevalence of depression and with dosages and durations more in accordance with recommendations (Isacsson *et al*, 1999). This wider use has been paralleled by a decreased suicide rate in Sweden (Isacsson *et al*, 1997).

The risk that prescribed psychotropics may be used for fatal overdose should not prevent prescribing for cases of adequate indication but should prompt careful monitoring of the patient. It is the disease that makes the patient suicidal, not the medication. If suicidal patients have no drugs to overdose, other and usually more lethal methods for committing suicide are always abundant. Highly suicidal patients should be referred to psychiatric hospitals for supervision and often ECT.

CLINICAL IMPLICATIONS

- Suicidal people should be encouraged to consult physicians.
- Physicians must not overlook depressive syndromes.
- Diagnosis of depression, antidepressant medication and monitoring of compliance should be improved, particularly in men and younger people.

LIMITATIONS

- Actual diagnoses were not investigated.
- Actual treatment received was not investigated.
- Some medication might have escaped detection.

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