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Antidepressant medication prevents suicide in depression

Isacsson G, Reutfors J, Papadopoulos FC, Ösby U, Ahlner J. Antidepressant medication prevents suicide in depression.

Objective: Ecological studies have demonstrated a substantial decrease in suicide in parallel with an increasing use of antidepressants. To investigate on the *individual* level the hypothesis that antidepressant medication was a causal factor.
Method: Data on the toxicological detection of antidepressants in 18 922 suicides in Sweden 1992–2003 were linked to registers of psychiatric hospitalization as well as registers with sociodemographic data.
Results: The probability for the toxicological detection of an antidepressant was lowest in the non-suicide controls, higher in suicides, and even higher in suicides that had been psychiatric in-patients but excluding those who had been in-patients for the treatment of depression.
Conclusion: The finding that in-patient care for depression *did not increase* the probability of the detection of antidepressants in suicides is difficult to explain other than by the assumption that a substantial number of depressed individuals were saved from suicide by postdischarge treatment with antidepressant medication.

G. Isacsson[1], J. Reutfors[2], F. C. Papadopoulos[3], U. Ösby[1], J. Ahlner[4]

[1]Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institute, Stockholm, Sweden, [2]Department of Medicine, Clinical Epidemiology Unit, Karolinska Institute, Stockholm, Sweden, [3]Department of Neuroscience, Psychiatry, Uppsala University Hospital, Uppsala, Sweden and [4]Department Forensic Toxicology and Forensic Genetics, National Board of Forensic Medicine, Linköping, Sweden

Key words: suicide; prevention; depression; antidepressants

Göran Isacsson, M.D., Ph.D., Department of Clinical Neuroscience, Division of Psychiatry, Karolinska University Hospital Huddinge, M59, S-141 86 Stockholm, Sweden.
E-mail: goran.isacsson@ki.se

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Significant outcomes

- The patients most likely to be prescribed antidepressants are those hospitalized for depression. This was not reflected among suicides, however, which indicates that many of them may have been prevented from suicide.
- This supports the hypothesis that antidepressant medication prevents suicide among depressed patients.
- It is, therefore, likely that the substantial decreases in suicide in many countries have been caused by the increased use of antidepressants.

Limitations

- Naturalistic study. Definitive conclusions cannot be drawn.
- Individuals prevented from suicide cannot be identified, only their absence among suicides can be estimated.
- Assumptions necessary for estimating expected numbers of suicides among depressives treated with antidepressants.

Introduction

Depression seems to be the common denominator in most suicides. Logic and clinical experience as well as early studies suggested that an improved treatment of depressed individuals should be a powerful suicide–preventive strategy (1, 2). Before 1990, when the new generation of antidepressants was introduced, only a fraction of depressed individuals were treated. Based on epidemiological studies of suicides until 1991, it was estimated that a 5-fold increase in the use of antidepressants should reduce suicide by 25% (3).

In a later study of Swedish suicides until 1996, this estimate received empirical support (4). By then the use of antidepressants in the population

had increased 3.4 times and suicide had decreased by 19%. Although these data were in support of an *a priori* hypothesis, causality cannot be inferred from an ecological study. The influence of unknown causal factors cannot be excluded. The finding was however consistent in both sexes, in all age groups, in 23 of 25 Swedish counties, as well as in the neighboring countries of Norway, Denmark, and Finland, and the degrees of freedom for unknown factors was restricted.

Since then, more than 20 ecological studies, with different designs have confirmed the inverse correlation between suicide rate and the use of antidepressants, including the *increase* in child suicide that followed official warnings that antidepressants might induce suicidality in children and the subsequent *decrease* in their prescription (5, 6). These studies have presented data from Australia, Sweden, Denmark, Finland, Great Britain, Hungary, Israel, Italy, Japan, New Zealand, Norway, Slovenia and USA, as well as across 26 countries (7). Only a study from Iceland (about 30 suicides annually) has failed to demonstrate a decrease in suicide parallel to the increased use of antidepressants (8).

To prove a causal relationship, it has to be demonstrated that the individuals who have been saved from suicide were indeed exposed to antidepressants. Since individuals characterized by a non-event cannot be identified, a definite proof is impossible. If a certain number of individuals are saved from suicide by their use of antidepressants, this will, however, *exclusively* decrease the number of suicides in whom antidepressants can be detected in forensic toxicological screening.

We recently analyzed the time trends in the detections of antidepressants in forensic toxicological screening of 16 937 Swedish suicides and 33 426 controls (deaths due to accident or natural causes) during 1995–2005 (9). From the time trend in the control group, expected trends among the suicides could be calculated under two hypothetical conditions:

i) If the actual decrease in suicide was *not caused* by the increased use of antidepressants, the proportional decrease would be expected to be the same in suicides with and without antidepressants detected in toxicology;
ii) If the decreasing trend was *caused* by antidepressants, however, the decrease should be found exclusively in the proportion of suicides in which antidepressants were detected.

The observed trend was consistent with the second condition and thus indicated that individuals using antidepressants were responsible for the general decrease in suicide. A limitation of the study was that we lacked information on diagnoses and other possibly confounding variables.

Aims of the study

The present record-linkage study was aimed at further investigating the hypothesis that individuals taking antidepressant medication have been prevented from suicide, by comparing the proportions of toxicological detections of antidepressants in non-suicide deaths and in suicides that had been: i) hospitalized for depression, ii) hospitalized for other psychiatric diagnoses, or iii) not hospitalized at all, controlling for social and sociodemographic factors.

Material and methods

Forensic pathologists investigate apparently unnatural deaths in Sweden. Their investigation leads to a conclusion as to whether the cause of death was homicide, suicide, accident or natural. In some cases, the cause of death cannot be determined. If investigated further, the majority of these undetermined cases are often found to be probable suicides, mostly because of intoxication. In epidemiological research, they may therefore be considered as suicides (10). A routine procedure in a forensic investigation is to search for foreign substances in the body. All forensic toxicological analyses are performed at the same laboratory. In the analyses, about 200 substances are screened. All antidepressants can be detected at therapeutic concentration levels. All analyses are entered into the toxicological database of the National Board of Forensic Medicine, from which we obtained toxicological data relating to all Swedish suicides during the period from 1992 to 2003 ($n = 18\,922$), whereof 22.6% were undetermined cases. By means of the personal identification numbers we could link the toxicological data regarding suicide to the registers of the Board of Health and Social Welfare. The records in these registers included information on the contingency of psychiatric in-patient care in the 5 years prior to the suicide, including the discharge diagnoses, information on the highest level of education, yearly income, civil status and country of birth, as well as age, gender, and year of death. The diagnoses were divided into three groups: depression only, depression with comorbidity, and other psychiatric diagnoses only. Bipolar Disorder was considered as an 'other' diagnosis, since the clinical role of antidepressants in bipolar is disputed. Toxicological data were also obtained from a control group

consisting of all screened cases which after the forensic investigation were judged to have been accidental or natural deaths (n = 34 165). The use of antidepressants among controls may be more similar to the use in the general population than is their use among suicides that to some extent have been selected for depression. The toxicological data of interest in this study was exclusively whether or not antidepressants had been detected (11, 12). The detection of an antidepressant may indicate that the individual had received treatment for depression.

The basic assumptions, or null-hypotheses, of this study were that antidepressants in toxicology could be expected to be more frequently detected:

i) In individuals who had committed suicide, than in individuals who had died by accident or of natural causes;
ii) In suicides who had received psychiatric in-patient care, than in suicides who had not;
iii) In suicides who had received psychiatric in-patient care for depression, than in suicides who had received psychiatric in-patient care for other psychiatric disorders.

The rationale for these assumptions was that antidepressants may be *more* common in those categories in which depressed individuals may have been more common. These three assumptions were analyzed with chi-squared tests with one degree of freedom (2×2 tables). The suicides were further analyzed by logistic regression in order to control for confounding by other factors, e.g. female sex may increase the probability of depression as well as the probability of treatment with antidepressants. Other psychiatric disorders may to some extent be comorbid with depression and these individuals were analyzed separately. SPSS 17.0 was used for these statistical procedures (13).

Results

Controls

The 34 165 *controls* (accidental and natural deaths) were 25 705 men and 8414 women, with mean ages of 55.7 and 60.5 years respectively.

Antidepressants were detected in 6.5% of the controls (5.1% in men and 11.0% in women).

Suicides

The 18 922 suicides were 13 274 men (70.2%), and 5,648 women (29.8%). The mean age was 50.4 years in men, and 52.6 years in women. The age range was 7–101 years. Their civil status was: married 35.4%, widowed 5.3%, divorced 15.8%, and never married 43.5%. In 88.3% of the cases, the place of birth was Sweden.

Among the 18 922 suicides, antidepressants were detected in 4,245 (22.4%). In men 2,395 (18.0%), and in women 1,850 (32.8%) (χ^2 = 493, $P < 0.001$).

In the last 5 years prior to suicide, 7,696 (40.7%) of the 18 922 suicides had been hospitalized with psychiatric diagnoses [men 4,899 (36.9%), women 2,797 (49.5%)]. Antidepressants were detected in 2,584 (33.6%) of the hospitalized cases. The in-patient diagnosis had been exclusively depression in 1,077 cases (14.0% of hospitalized cases), depression and additional psychiatric diagnoses in 1,237 cases (16.1%), and other diagnoses than depression in 5,382 (69.9%) cases.

The proportions of cases in each category in which antidepressants were detected are presented in Table 1 as well as in Fig. 1.

Multiple logistic regression

Since data on the highest achieved education level were missing in 2,610 cases, this variable was excluded from the analysis. If included, it had a minimal and non-significant influence on the result (OR = 1.025). All other sociodemographic variables, as well as the last hospitalization exclusively for depression, and exclusively for non-depression within 5 years prior to suicide were entered into a binary multiple logistic regression analysis, with toxicological detection of antidepressants as the dependent variable.

Female sex had an OR = 1.9, while the other sociodemographic variables had a minor influence on the probability of antidepressants being detected in the toxicology of the 18 922 suicides. A hospitalization within the last 5 years increased the probability more than three-fold (OR = 3.2),

Table 1. Detections of antidepressants, all suicides

	Total	Antidepressants detected		
Controls	34 165	2,243	6.5%	
Suicides	18 922	4,245	22.4%	$P < 0.001$ vs. Controls
Non-hospitalized suicides	11 226	1,661	14.8%	
Hospitalized suicides	7,696	2,584	33.6%	$P < 0.001$ vs. Non-hospitalized
Depression exclusively	1,077	164	15.2%	NS vs. Non-hospitalized
Non-depression	5,382	2,009	37.3%	$P < 0.001$ vs. Depression exclusively
Depression with comorbidity	1,237	411	33.2%	$P < 0.001$ vs. Depression exclusively

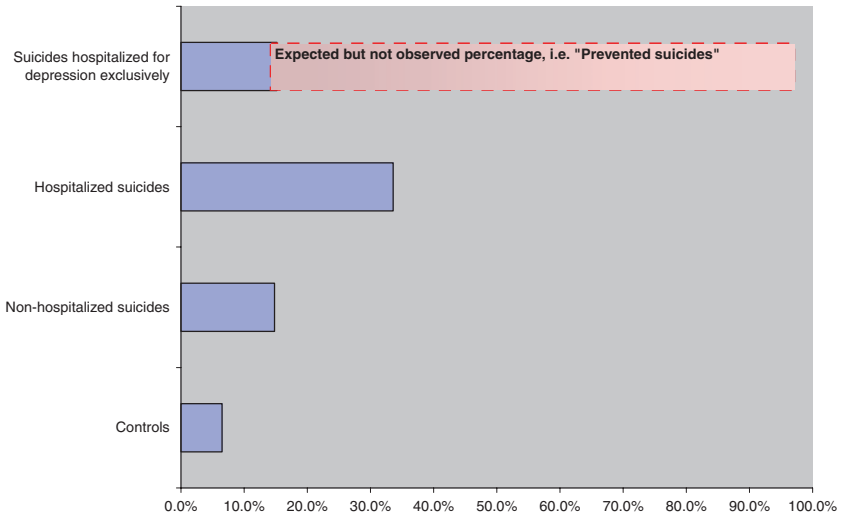


Fig. 1. Observed percentages of suicides and controls taking antidepressants at the time of death (blue bars). For suicides that had previously been hospitalized for depression, also a range of expected percentages is indicated (pink bar). The expected percentage may be between 40%–100%, since most if not all unipolar depressed patients usually are discharged with antidepressant medication.

Table 2. Multiple logistic regression. Dependent variable: toxicological detection of antidepressants

		95% C.I. for OR		
	OR	Lower	Upper	Probability
Year of death	1.090	1.078	1.102	$P < 0.001$
Sex (female)	1.946	1.803	2.101	$P < 0.001$
Age	1.013	1.011	1.016	$P < 0.001$
Employment	1.232	1.133	1.340	$P < 0.001$
Civil status	1.228	1.130	1.334	$P < 0.001$
Country of birth (Sweden)	1.217	1.080	1.371	$P < 0.001$
Hospitalized depression	1.024	0.858	1.223	NS
Hospitalized non-depression	3.188	2.948	3.447	$P < 0.001$

except when the discharge diagnosis was *depression*, in which case the probability was not higher than in the non-hospitalized suicides (Table 2).

Discussion

The result of this study gives evidence indicating that the substantial decrease in suicide in Sweden between 1992 and 2003 has occurred among individuals taking antidepressant medication. This supports the general hypothesis that antidepressant medication is a powerful means of preventing suicide on a large scale.

The main finding is that the category of suicides in which the detection of antidepressants could be expected to be most frequent, i.e. the suicides that had been diagnosed with depression prior to death, instead constituted the diagnostic category of hospitalized suicides that had the *lowest* frequency of detection of antidepressants (15.2%). It was about as low as the frequency among non-hospitalized suicides (14.8%). This is remarkable – the first category consisted of psychiatric patients diagnosed with severe depression, while the second category consisted of individuals who to a large extent may not have been diagnosed with depression or who had no contact at all with the health care system.

The use of antidepressants according to the toxicological analyses among the non-suicides, the controls, was found as could be expected to be of the same order of magnitude (6.5%) as the assumed prevalence of treatment in the general population (5%) (14). The frequency of detection of antidepressants in suicides was, also as expected, higher than in the controls (22.4%), and, not surprisingly, even higher in the subgroup of hospitalized suicides (33.6%). A frequency twice as high in women (32.8%) as in men (18.0%), was also expected, since the use of antidepressants in women is about twice as high as in men in the general population, as reflected among the controls. Thus, the rationale for the basic assumptions (null-hypothesis) was validated. The third null-hypothesis was, however, rejected with the implication that the frequency of detection of antidepressants cannot be fully explained solely by the frequency of depressed individuals.

When controlling for age, sex and social factors in the logistic regression analysis, a consistent result was found. A psychiatric hospitalization for depression during the last 5 years did not increase the probability of the detection of antidepressants compared with other suicides, whether hospitalized or not (OR = 1.0, NS). Psychiatric hospitalizations with other diagnoses, however, substantially increased the probability with an Odds Ratio of 3.2. The ORs for the covariates were found to be as expected: female gender, marriage, employment and being born in Sweden increased the probability of antidepressants being detected in suicides. This can be interpreted as meaning that women and

socially better integrated individuals more frequently have had the chance to respond to an antidepressant before committing suicide.

How is the rejection of the 3rd null-hypothesis, to be interpreted, i.e. the finding, that among those suicides who had been hospitalized in the last 5 years, those diagnosed with depression had the *lowest* frequency of detection of antidepressants instead of the *highest* as had been expected? The highly significant difference between the observed and the expected frequencies is based on at least 250–500 cases (see below). Are these 'expected cases' missing among the depressed suicides with antidepressants because they were misdiagnosed as non-depressed, did not receive or take antidepressants, or did not commit suicide? It seems unlikely that specifically depressed patients that received antidepressants were systematically misdiagnosed as non-depressives. It seems also unlikely that psychiatric patients diagnosed with severe depression should have received and complied with antidepressant medication to the same low extent as those individuals who might not even have had any contact with the health care system. We believe that the only reasonable explanation for this result is that many patients, when discharged from a psychiatric department after being treated for depression, were indeed prescribed an effective continuation treatment with antidepressant medication, or if they later relapsed into depression they were early prescribed an antidepressant, and that *because of this* they did not commit suicide, as was the hypothesis of the study. Each suicide averted by antidepressants will decrease the number of suicides in which antidepressants are detected in toxicology.

To estimate the absolute number of suicides that may have been prevented by antidepressants, it is necessary to make an assumption as to how frequently antidepressants would have been detected if they had not prevented suicide. A highly conservative estimate would be that antidepressants should be detected in suicides hospitalized for depression at least *as often as* in those suicides that were hospitalized for psychiatric disorders for which antidepressants are *not* indicated ('non-depression'). The difference between this expected percentage and the observed percentage [1,077×(37.3% – 15.2%)] suggests that 238 suicides were prevented among the patients discharged after hospital treatment of depression and 50 more among those with comorbidity [1,237×(37.3% – 33.2%)]. It is probably still conservative to expect that the proportion of antidepressant treatment would be twice as high in those treated for depression as in those treated for other disorders (15), and this would then suggest about 500 prevented suicides. During the 12-year-period studied, the cumulated actual decrease in suicide in Sweden was 2,900 cases, compared with the number of suicides if the suicide rate had been constant at the 1992 level (9). It seems to us quite possible that 500 (17%) of these 2,900 supposedly prevented suicides might have been hospitalized for depression.

It is an unavoidable weakness of this study that it has to be based on assumptions, even though these are credible and conservative. A prevented suicide is a non-event and the theoretical individuals who would have committed suicide if they had not received antidepressants are known to no one, not even themselves, and they cannot therefore be studied directly. The design does not allow for any conclusions as to whether antidepressants possess a direct antisuicidal effect or if they prevent suicide as an indirect effect of their undisputable antidepressant property. Similarly, we cannot conclude whether these suicides were prevented by the continuation treatment in recurrent depression, by the early treatment of mild relapses into depression, or by the treatment of severe depression with a high risk of suicide.

Besides antidepressants, lithium, which is currently not detected in the routine method of forensic toxicological analysis, may also be a part of the explanation of our result. A number of naturalistic studies indicate that long-term prophylactic treatment with lithium may lower the risk of suicide (16, 17). The use of lithium increased in Sweden from 1.3 to 1.6 Defined Daily Doses (DDDs) per 1000 Inhabitants per Day (i.e. prevalences $\approx$ 0.13 and 0.16%) from 1992 to 2003 (Apoteket AB, data on-line), but the absolute level of the use of lithium is still low compared to the prevalence of bipolar disorder (1%–2%). The increase may imply that there were 2,700 more lithium-treated individuals in Sweden (population 9 million) in 2003 than in 1992. The Standardized Mortality Ratio (SMR) for suicide in Bipolar one patients in Sweden has been found to be about 25, (18) suggesting an annual suicide rate of 500 per 100 000 inhabitants. If a 100% suicide-preventive effect of lithium is assumed, the increased use of lithium might as the most have prevented 14 suicides in 2003. Accumulated over the study period, this suggests that the progressively increasing use of lithium might account for less than 100 of the 2,900 'prevented suicides', while antidepressants with a use of 62.3 DDDs/1000 inhabitants per Day in 2003 might be responsible for most of the remaining 2,800, of

which 500 may have been hospitalized, according to our findings.

This interpretation is consistent with the results of our previous study where the number of suicides with detected antidepressant was found to be substantially lower in 2005 than the number estimated from time trends of the use of antidepressants in controls(9). It is further in line with some previous individual-based studies by other groups.

Tiihonen et al. identified from a national register all the individuals who had been hospitalized because of a suicide attempt in Finland during 1997–2003(19). They found during a mean follow-up time of 3.4 years that, among subjects who had previously used an antidepressant, the current use of medication was associated with a 32% decrease in the risk of suicide, compared with no current use of medication.

Jick et al., as well as Martinez et al., using the British General Practice Research Database identified respectively 159 810, and 146 095 patients with a first prescription of a tricyclic or SSRI (Selective Serotonin Re-uptake Inhibitor) antidepressant during the time periods 1993–1999, and 1995–2001 respectively(20, 21). When patients who received tricyclics were compared with those who received SSRIs, no differences were found regarding the risk of suicide (or non-fatal self-harm). Jick et al. found, however, that, compared with 90 days or more after the first prescription, the Odds Ratio for suicide was 38.0 times higher during the first 1–9 days, 5.1 times higher during days 10–29, and 2.0 times higher during days 30–89, which may suggest that the risk of suicide decreased during the treatment with antidepressants.

Angst et al. did a follow-up of 406 mood-disorder patients with and without long-term medication for 40 to 44 years (22). They found that the SMR for suicide was reduced by 59% among those treated with antidepressants (lithium 65%, neuroleptics 41%).

One individual-based study by Erlangsen et al. has, according to the authors, given contradictory results. That study was conceptually flawed, however, and the raw data clearly support the hypothesis that antidepressants do prevent suicide (23, 24).

Finally, it is a remarkable observation that, among patients who have been hospitalized for depression and have committed suicide within 5 years thereafter, only 15.2% had detectable concentrations of antidepressants. This suggests that much more might be achieved by long-term treatment with antidepressants in patients with recurrent depressive disorder.

In conclusion, the result of this study is difficult to explain otherwise than that a substantial number of patients previously hospitalized for depressive disorders have been saved from committing suicide by antidepressant treatment. In the absence of other explanations, in particular explanations supported by empirical evidence, this study adds to the evidence that the decrease in suicide being demonstrated worldwide is *caused* by the increasing use of antidepressants.

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Declaration of interest

Göran Isacsson has received fees for being a speaker at symposiums arranged by pharmaceutical companies like H. Lundbeck, Eli Lilly, GSK, and has attended an Astra Zeneca advisory board meeting. Johan Ahlner has been involved in a research project funded by H. Lundbeck. Urban Ösby has been involved in advisory boards for BMS and Pfizer, received fees as a consultant from Eli Lilly, Astra Zeneca and BMS, and has received research grants from BMS and Jansen-Cilag. Fotios C. Papadopoulos and Johan Reutfors declare no conflicts of interest.

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