Antidepressants and the risk of suicide in young persons – prescription trends and toxicological analyses

Isacsson G, Ahlner J. Antidepressants and the risk of suicide in young persons – prescription trends and toxicological analyses.

Objective: To assess trends in the use of antidepressants among young suicides after the warning that these drugs might increase the risk of suicide.
Method: Individual data of all 845 suicides in the 10- to 19-year age group in Sweden in the time period 1992–2003 (baseline), and in 2004–2010 (after the warning). Outcome data are prescriptions of antidepressants prior to death and detections of antidepressants in *post-mortem* toxicology.
Results: After the warning, suicide in this age group increased for five consecutive years (60.5%). The increase occurred among individuals not treated with antidepressants.
Conclusion: This study provides further support for the hypothesis that the warning, contrary to its intention, may have increased young suicides by leaving a number of suicidal young persons without treatment with antidepressants.

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Significant outcomes

- The 'black box' warnings for that antidepressants would carry an increased risk of 'suicidality' in young people were followed by an increase in suicide.
- The increase in suicide occurred among young persons without antidepressant treatment.
- This supports the *a priori* hypothesis that the warnings might be counterproductive.

Limitations

- The causes of variations in suicide rates can never be definitely proven.

Introduction

In 2003, signals from randomized controlled trials of selective serotonin reuptake inhibitors (SSRI) suggested that these drugs might increase the risk of suicide in young persons. Both American and European authorities therefore issued warnings for the increased risk of suicidal thoughts and behaviour (suicidality) in children and adolescents being treated with antidepressant medications, and in 2004, it was decided that each package of antidepressants had to carry such a warning in a 'black box' (1). In the USA, this resulted in a prompt decrease in the use of antidepressants among the younger age groups (2–5). Similar decreases were also reported in Canada and UK (6, 7).

In 2007, reports were published indicating that the suicide warnings might have been counterpro-

ductive, because young suicides in USA showed a sudden 14% increase (girls 33%) in 2004, after previously having been continuously decreasing since 1988 (3, 7, 8). This negative association on the ecological level between the use of antidepressants and the incidence of suicide does not however allow conclusions to be drawn regarding causality. It is not known whether the increase in suicide had occurred among persons treated with antidepressants or among persons who were not treated. Such knowledge is a prerequisite for an interpretation that the reason for the increase in suicide was that a number of depressed and suicide-prone young persons were not taking antidepressant medication due to the 'black box'.

Aims of the study

Because suicide among young persons in Sweden had also increased since 2003, we decided to test the hypothesis that this increase had occurred in individuals who were *not* treated with antidepressants. The rationale for the hypothesis was that depression is the main risk factor for suicide and consequently that, if depression is treated to a lesser degree, the population at risk of suicide will increase and ultimately also the occurrence of suicide.

Material and methods

In the Swedish population, there are about 1.1 million persons in the 10- to 19-year age group.

The National Board of Forensic Medicine provided toxicological data relating to all individual suicide cases aged 10–19 years in the period 1992–2010 ($N = 845$). Apparently unnatural deaths in Sweden are investigated by forensic pathologists. 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 poisoning (9). Such undetermined cases may preferably be considered to be suicides and are so in the present study (15.4%). A routine procedure in these forensic investigations is to search for foreign substances in the body. All such toxicological analyses are performed at the same laboratory in Linköping, Sweden. In the analyses, around 200 substances are screened for. All antidepressants can be detected at therapeutic concentration levels. We consider in this study individuals in whom an antidepressant is detected in toxicology as 'treated' and the other as 'untreated'. The date of the forensic investigation was considered as the date of death.

The Swedish Board of Health and Welfare provided aggregated data on the annual use of antidepressants in the 10- to 19-year age group in 1999–2010. These data originate from sales on prescription in Swedish pharmacies regarding all specific antidepressant medications. The volume unit is defined daily doses per thousand inhabitants per day (DDD/TIND). Each medication has a specific defined daily dose corresponding to a 'normal' dosage of the drug (e.g. 1 DDD of fluoxetine is 20 mg, while 1 DDD of sertraline is 50 mg), and this facilitates the summation of drugs of different strengths.

Since 1 July 2005, all prescriptions filled at Swedish pharmacies have been registered in an individual-based database run by the Swedish Board of Health and Welfare, from which it was possible to retrieve individual-level medication data for the period 2006–2010. The registered variables include the patient's personal identification number, which permitted linkage to the toxicology data, the ATC code of the prescribed drug, the amount purchased in defined daily doses, the date of purchase and other variables that are not considered in this analysis. We calculated from these a variable regarding dispensation in the last 6 months prior to suicide.

The three parameters we studied were the use of antidepressants in the population, the number of suicides in the population and the use of antidepressants in individual suicides. As age has been an important variable in the question of antidepressant-induced suicidality, we separately analysed the relatively few suicides in the 10- to 14-year age group.

The study period was divided into the baseline time period before the warnings for an increased risk of suicidality 1992–2002, and the outcome period 2003–2010.

The statistical procedures included Poisson regression for trends and the comparison of trends. If not otherwise specified, one-sided tests were considered, because it was an *a priori*-hypothesized, and actual, *increase* in suicide that should be tested. Chi-squared test was used for comparing the rates of suicide in the two periods.

Results

Baseline period 1992–2002

During this period, the use of antidepressants in the population aged 10–19 years increased from 3.5 DDD/TIND in 1999 to 7.3 DDD/TIND in 2002 (Fig. 1, Table 1).

In the whole period, there were 407 cases of suicide (16.2% undetermined cases). The annual numbers varied in the range from 29 to 47
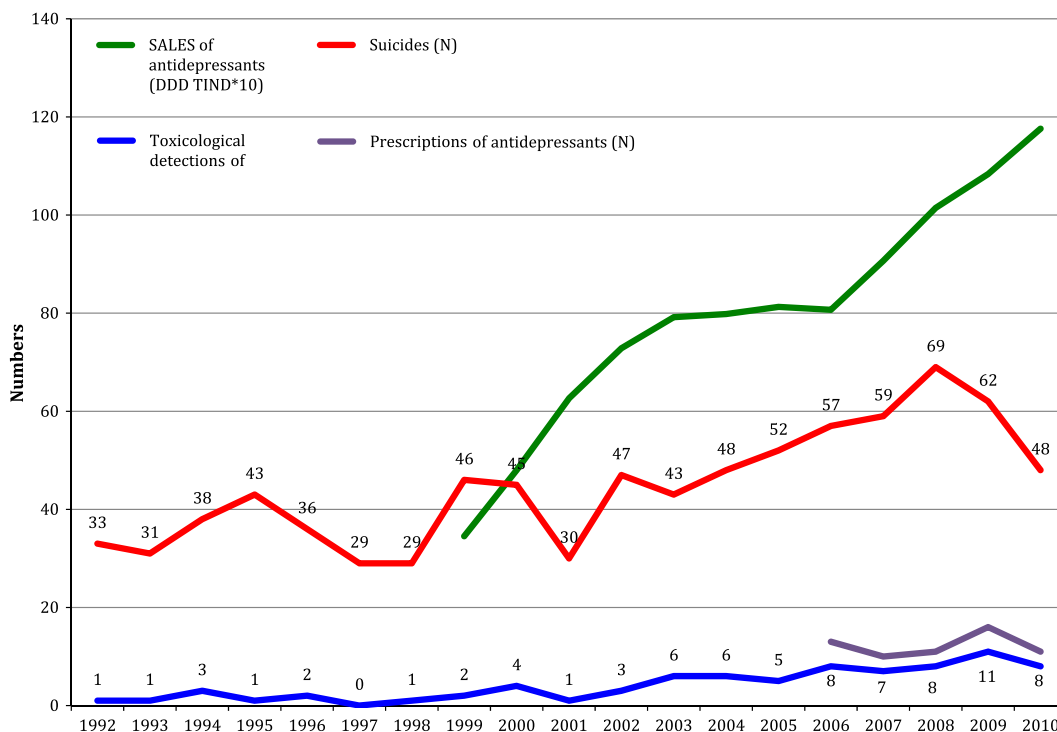
Fig. 1. Group-level sales of antidepressants (1999–), numbers of suicides, numbers of suicides with toxicological detections of antidepressants and number of suicides who had purchased at least one prescription of antidepressants in their last 6 months prior to death (2006–).

without any obvious trend ($P = 0.18$, two-sided test). Antidepressants were detected in *post-mortem* toxicology in 0–4 of these individual suicides per year.

Among the 52 cases in the 10- to 14-year age group, antidepressants were detected in toxicology in only one case during the whole period, and it was uncertain whether suicide or accident.

Table 1. Use of antidepressants (AD) and suicide in the total population of 10–19 years of age in 1992–2010

Year	Population	Use of AD		Suicides	Dispensed AD	Disp >1 AD	AD in Tox	Suicide rate
	N	DDD TIND	Persons TIN	N	N	N	N	N/100 000
1992	1 028 115			33			1	3.2
1993	1 017 036			31			1	3.0
1994	1 011 206			38			3	3.8
1995	1 008 609			43			1	4.3
1996	1 013 995			36			2	3.6
1997	1 025 041			29			0	2.8
1998	1 046 252			29			1	2.8
1999	1 067 667	3.5		46			2	4.3
2000	1 095 616	4.8		45			4	4.1
2001	1 126 169	6.3		30			1	2.7
2002	1 154 616	7.3		47			3	4.1
2003	1 177 805	7.9		43			6	3.7
2004	1 192 801	8.0		48			6	4.0
2005	1 194 124	8.1		52			5	4.4
2006	1 188 705	8.1	11.0	57	13	7	8	4.8
2007	1 177 218	9.1	12.4	59	10	8	7	5.0
2008	1 158 093	10.1	13.2	69	11	9	8	6.0
2009	1 135 819	10.8	14.0	62	16	10	11	5.5
2010	1 106 119	11.8	15.1	48	11	7	8	4.3

The annual numbers of individuals aged 10–19 years in the total Swedish population in 1992–2010, the use of antidepressants in this age group (1999–), as well as the actual prevalence of treatment (2006–), the total number of suicides, the number of suicides that had at least one or more than one purchase of antidepressants in the last 6 months prior to death (2006–), the number of suicides with antidepressants detected in *post-mortem* toxicology, and the annual suicide rates. (DDD TIND, defined daily doses per 1000 individuals per day; TIN, per 1000 inhabitants) .

During this period, there was an obvious change in the use of antidepressants. The steeply increasing trend from the previous period was broken, and the use remained at the 2003 level during the following 3 years (7.9, 8.0, 8.1 and 8.1 DDD TIND, respectively, in 2003–2006). From 2007, the use of antidepressants again increased and had increased to 11.8 DDD TIND in 2010. From 2006, *individual-based* prescription data were available. These show that the DDD TIND data, based on sold volumes of antidepressants, corresponded to the actual treatment prevalence of 1.1% of the population in 2006 and 1.5% in 2010.

Suicides increased from 43 cases in 2003 to 69 cases (60.5%) in 2008 ($P = 0.0037$). In 2009 and 2010, however, suicides decreased.

Comparing the two periods

We defined 1992–2002 as period 1 and 2003–2009 as period 2 and performed Poisson regression analyses with the number of either *suicide* or *certain suicides* as the dependent variable and calendar year, period, and the interaction between year and period as independent variables. The interaction, estimating the difference in trend between period 1 and period 2, was significant regarding the *certain suicides* ($P = 0.045$). When including the undetermined cases, the interaction did not reach statistical significance ($P = 0.058$).

In a second Poisson regression analysis with the number of *suicides with antidepressants detected in toxicology* as the dependent variable and calendar year, period, population, use of antidepressants (DDD TIND), and the interactions between year and period as independent variables, the interaction was not significant ($P = 0.36$), not even if the undetermined cases were excluded ($P = 0.30$).

The cumulative number of suicides was 407 in the eleven years 1992–2002 and 438 in the 8 years 2003–2010, and the respective cumulative populations were 11 594 322 and 9 330 684 (person-years). Thus, compared with the rate in 1992–2002 (3.5 per 100 000), the suicide rate in 2003–2010 (4.7 per 100 000) was increased by 33.7% (chi-square 17.7, df = 1, $P < 0.001$). The average number of suicides in which antidepressants were detected by toxicology was 1.7 cases per year in 1992–2002 and 7.4 cases per year in 2003–2010.

The individual-based prescription data revealed that 61 (20.1%) of the 295 individuals who had committed suicide during 2006–2010 had been prescribed an antidepressant in the 6 months prior to suicide. Forty-one (67%) of these individuals had made more than one purchase, indicating actual compliance (10). In 36 (59%) of those who had made at least one purchase, the purchased antidepressant was detected by toxicology (i.e. 12.2% of all 295 cases).

There were 35 suicides in the 10- to 14-year age group in 2004–2010, but in only one case was an antidepressant detected by toxicology (fluoxetine). From the cases for whom individual prescription data were available (2006–2010), it was further revealed that another child had made two purchases of sertraline on prescription, but this drug was not found in the toxicological investigation.

Discussion

This is a study of all cases of suicide in the 10- to 19-year age group in Sweden during 1992–2010. It includes objective data showing whether or not the persons had taken antidepressant medication immediately prior to death. This information is highly relevant in attempts to determine the possible effects of antidepressant medication on suicide. To our knowledge, this is the first study where the exposure to antidepressants in suicides is estimated both by prescriptions *ante-mortem* and by toxicology *post-mortem*. Furthermore, both sets of data are obtained from databases covering the whole Swedish population.

We found that the warnings for a possible antidepressant-induced risk of suicidality were followed not only by a distinct halting of the previous rapidly increasing trend in the use of antidepressants among children and adolescents, but also by a remarkable increase in suicide. The inclusion of the undetermined cases somewhat diluted this change in trend, which was expected because this category may also comprise other causes of death, foremost accidents, as well as suicides. The main finding of this study is, however, that this increase occurred in individuals who had been neither prescribed nor taking antidepressants, confirming the study hypothesis. At the most, in 2008, the number of suicides was 69 compared with 43 in 2003. The subset of suicides with antidepressants detected in toxicology was, however, only two more cases in 2008 than in 2003. In the separate analysis of suicides under the age of 15 years, antidepressants were detected in only two cases during the whole 19-year study period. Regarding suicides of individuals aged 10–14 years, it can, due to the few cases, only be concluded that antidepressant-induced suicidality appears not to have been part of the causation.

This result contradicts the rationale for the 'black box' that antidepressant treatment might be

a risk factor leading to suicide in children or in adolescents. The 2.1-fold increase in the use of antidepressants during 1999–2002 was not paralleled by any significant change in the annual number of suicides.

There is a possibility that the increase in suicide was caused by other factors than lack of treatment with antidepressants, but to our knowledge, no such alternative causal factor has been proposed. By demonstrating that the increase in suicide occurred among individuals who were not treated with antidepressants, however, this study goes one step beyond the correlation in time on the ecological level. It, therefore, provides further support for the conclusion that the increase in suicide after the 'black box' was actually a result of the limited prescribing of antidepressants thereafter. The fact that the study was a test of an *a priori* hypothesis based on a plausible biological mechanism and that it is consistent with previous US and Canadian findings also lends support to this interpretation. The effect of the 'black box' seems, however, to have come to an end in 2007, because the steeply increasing trend in the use of antidepressants then recovered. Thereafter, the annual number of suicides decreased and in 2010 approached prewarning levels. Therefore, we find it sound to exclude 2010 from the Poisson analyses of trends.

There is, however, also a trend over the two decades for antidepressants to be more often detected in the toxicology of suicides. This is to be expected regardless of any influence of antidepressants on the risk of suicide, as the use of antidepressants in the population increased by 240% between 1999 and 2010. As a consequence, the number of failed treatments must have increased because antidepressant medication is not 100% effective. We have actually in a previous study shown that the increase is far less than expected, and we have interpreted this as evidence for a suicide-preventive effect of antidepressants (11). Actually, any drug that becomes more common in the population must also be become more common among suicides. Our estimation of treatment from toxicology is an overestimation, however, because the prescription data for the period 2006–2010 showed that not all individuals with antidepressants in toxicology had been dispensed an antidepressant. Thus, the portion of treated suicides was in fact even smaller than that on which we based our conclusion.

It might somewhat obscure the correlation in time that the use of antidepressants after the warnings in 2003 did not decrease but became stationary and started to increase again already in 2007. A probable explanation for this is that depressed young people do not form a homogeneous group. Some might, for example, have expressed suicidal thoughts and others not. The readiness of physicians to prescribe antidepressants to children and adolescents in these two categories might have differed. The warnings in 2003 might have prompted a rapid withdrawal of the medication in young depressed patients with overt suicidal ideation, resulting in an immediate increase in suicide, while the prescribing to children and adolescents not expressing suicidality or judged not to be at risk might have been relatively unaffected by the 'black box'.

Comparison with other studies

Our result is consistent with the time series analyses of Gibbons et al. and Bridge et al. in the USA and by Katz et al. in Canada (3, 7, 8). They all demonstrated prominent increases in suicide after the black box. Several cross-sectional studies further demonstrate that suicide in young people is not associated with treatment with antidepressants, but with *no* treatment. Jick et al. (12) analysed all individuals in the UK General Practice Research Database who in 1993–1999 were prescribed one of the antidepressants fluoxetine, paroxetine, amitriptyline or dothiepin. Among the 6976 studied in the 10- to 19-year age group, none had committed suicide during the study period (at least 2 years) and the risk of non-fatal suicidal behaviour decreased continuously during antidepressant treatment. Leon et al. investigated youth suicides in New York City in 1993–1998 and 1999–2002 (13, 14). They found 66 and 41 cases, respectively, below the age of 18. Toxicological analyses were carried out in 58 and 36 of them, and among these, antidepressants were found in four and one case respectively (6.9% and 2.8%). Leon et al. further investigated prospectively 757 mood disorder patients with 6716 time periods being either exposed to an antidepressant or not exposed during a time period of up to 27 years. They found that, although those with more severe affective syndromes were more likely to initiate treatment, antidepressants were associated with a significant reduction in the risk of suicidal behaviour (15). Moskos et al. (16) found no antidepressants in the toxicology of 49 suicide cases aged 13–21 in Utah in 1996–1998. Sondergard et al. (17) found in a Danish nationwide prescription database that 'Among 42 suicides nationally aged 10–17 years at death, none was treated with SSRIs within 2 weeks prior to suicide'. Dudley et al. (18) found in six studies that 9 of 574 (1.6%) adolescent suicides had recent exposure to SSRIs. We have previously demonstrated with toxicological evidence that

SSRIs were less associated with young suicides than were other antidepressants (19).

In England and Wales, Wheeler et al. (20) found no association between the notable reduction in the prescription of antidepressants after the black box and changes in suicide in the 12- to 17-year age group. This is at variance with our Swedish findings, but does not support the rationale for the 'black box'. Wheeler et al. (21) also investigated suicide rates in 23 countries during the period from 1990 to 2006 and concluded that there was no evidence for a change in trend in relation to the time for the warnings, although suicide in young women had increased by 8.1%. The study had, however, no data on the use of antidepressants in the different countries. It might also be that girls more than boys were actually vulnerable for the decrease in prescribing as the US data indicate (3). This study thus does not contradict our results. Hammad et al. (22) concluded from a meta-analysis that the use of antidepressants in paediatric patients is associated with a modestly increased risk of suicidality. This might be true if it is accepted that 'suicidality' is not necessarily a risk factor for suicide, which the term unfortunately implies. The TADS showed a two-fold risk of 'harm-related events' but not 'suicide-related' in the children treated with fluoxetine compared with those without antidepressants (23).

Whittington et al. (24) meta-analysed data from RCTs of SSRIs in the 5- to 18-year age group and concluded that, with the exception for fluoxetine, SSRIs had 'unfavourable risk-benefit profiles', and particularly so when including data from non-published trials in the meta-analysis. This conclusion was based on the limited evidence for antidepressants being effective against paediatric depression. The scarcity of evidence of efficacy may be due to the many weaknesses in the way RCTs are actually conducted, which is far from the ideal experimental situation (25–27). These weaknesses decrease the probabilities of demonstrating possible effects of antidepressant drugs because of a statistical type II error (i.e. the statistical power is insufficient). Gibbons et al. recently reanalysed 20 RCTs of fluoxetine or venlafaxine, however, and found that both were *more* effective in young people than they were in older patients and without evidence of increased suicide risk (28, 29). Recently, it has also been demonstrated that shortcomings of the universally used Hamilton Depression Rating Scale (HDRS-17) further increase the risk of false-negative results (type II error; 30). Because 'efficacy not demonstrated' is not the same as 'non-efficacy demonstrated', antidepressant medication in depressed children and adolescents might be more beneficial than it appears to be in RCTs. To our knowledge, no study has presented empirical evidence confirming an inference from the RCTs that antidepressants might increase the risk of suicide in youth, although Ghaemi et al. (31), based on several assumptions, recently estimated that 'antidepressants can be said to be, at the population level, neutral in their effects on suicide'.

Strengths and limitations

The strength of this study is that it included all young suicides in Sweden during the eleven years before the warnings for increased risk of suicidality and the 8 years thereafter. Individual data on prescriptions of antidepressants and post-mortem toxicology were available, as well as reliable data on the use of antidepressants in the whole Swedish population. It is a limitation that observational study cannot establish causality, and this study goes only one step beyond ecological study when illuminating the actual use of antidepressants among young suicides.

Conclusion

Youth suicide increased remarkably in Sweden in the 5 years after the 'black box' warnings. The cause of this increase cannot be determined. The fact that the increase in suicide occurred in young persons without antidepressant medication, however, is consistent with our hypothesis that these truly suicidal persons might have been denied antidepressants, or abstained from them, due to the 'black box' and then committed suicide because of untreated depression. Thus, the study supports the notion that antidepressants prevent suicide in youth and contradicts the rationale for the 'black box'. The prevalence of antidepressant treatment is still low in young persons compared with the prevalence of depression. It is a prospectively testable hypothesis that increasing treatment with antidepressants would correspond with further decreasing numbers of suicides. As antidepressant treatment is not 100% effective, however, a greater proportion of the persons who commit suicide would be expected to have antidepressants present *post-mortem*.

Acknowledgement

Declaration of interest

None.

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