

Relationship between antidepressant sales and secular trends in suicide rates in the Nordic countries

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Background The effect of recent increases in antidepressant prescribing on population suicide rates is uncertain.

Aims To investigate the relationship between antidepressant sales and trends in suicide rates.

Method Graphical and quantitative assessment of trends in suicide and antidepressant sales in Norway, Sweden, Denmark and Finland.

Results Suicide rates declined in all four countries during the 1990s, whereas antidepressant sales increased by 3- to 4-fold. Decreasing suicide rates in Sweden and Denmark preceded the rise in antidepressant sales by over 10 years, although the reductions accelerated between 1988 and 1990. In Norway, a modest but short-lived decline in suicide rates began around the time of the increase in antidepressant sales. In Finland, decreases in male suicide rates and to a lesser extent in female suicide rates began around the time of increased antidepressant sales. In all four countries decreases in suicide rates appeared to precede the widespread use of SSRIs.

Conclusions We found mixed evidence that increases in antidepressant sales have coincided with a reduction in the number of suicides in Nordic countries.

Declaration of interest D.G. was a member of the Medicines and Healthcare products Regulatory Agency Expert Working Group on the Safety of SSRIs. He was an independent advisor, receiving expenses and an attendance fee.

There are concerns that selective serotonin reuptake inhibitors (SSRIs) may precipitate suicidal behaviour in some individuals (Healy, 2003). In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) recently concluded that a modest increase in the risk of self-harm in SSRI users could not be ruled out, but that there was too little evidence available to assess the suicide risk (Medicines and Healthcare products Regulatory Agency, 2004). In contrast, an analysis of secular trends in antidepressant prescribing and suicide in the Nordic countries, based mainly on data for the period 1990–1996, suggests that reductions in the suicide rate coincided with increased antidepressant prescribing (Isacsson, 2000). However, time trends in antidepressant prescribing and suicide in other countries provide conflicting evidence for this hypothesis (Gunnell & Ashby, 2004). In this paper we update Isacsson's analysis with more recent data on antidepressant sales and suicide rates in the Nordic countries. In addition, we extend his time series further back in time to investigate whether the reductions in suicide in these countries coincided with or pre-dated the increases in antidepressant sales.

METHOD

Data on suicide rates from the year 1961 and levels of antidepressant prescribing for as long a time period as was available (in all cases before 1990) were obtained from Statistics Norway, the Norwegian Institute of Public Health, Statistics Sweden, the National Board of Health and Welfare (Sweden), the National Board of Health (Denmark), the Danish Association of the Pharmaceutical Industry (Lif), Statistics Finland and the National Agency for Medicines (Finland).

The data on suicide rates for Norway and Sweden were available up to 2002,

the data for Denmark were available up to 2000 and the data for Finland were available up to 2003. We were also able to obtain age-specific suicide trend data for Sweden and Norway. Antidepressant sales data, expressed in terms of defined daily doses (DDDs) for SSRIs and other antidepressants, were available up to 2003 for all four countries. Data on total antidepressant and SSRI prescribing were available from 1974 and 1990 respectively for Norway, from 1977 and 1991 respectively for Sweden, from 1990 for both for Denmark and from 1985 and 1989 respectively for Finland.

We plotted separate graphs for each of the four countries to enable us to compare the time trends in levels of antidepressant prescribing with the trends in overall and gender-specific suicide rates. For Norway and Sweden we also plotted age- and gender-specific suicide rates for three age groups (15–24, 25–44 and >45 years), as data from other countries suggest that time trends in suicide rates vary with age (Cantor, 2000).

To estimate the years (with 95% CI) in which changes in trends in suicide rates occurred we used Joinpoint software version 2.7 (available from <http://srab.cancer.gov/joinpoint>). Join-point regression is a form of analysis in which trend data are described by a number of contiguous linear segments and 'join points' where trends change (Kim *et al*, 2000). Permutation tests are used to determine the minimum number of join points required to provide an adequate fit to the data.

RESULTS

In all four countries, SSRI sales rose rapidly from around 1991–1993 onwards (Fig. 1). In Sweden and Norway there was some evidence of a brief compensatory decline in the sales of other antidepressants, but this effect was short-lived. The net effect on overall antidepressant sales of the increase in the use of SSRIs in the 1990s was that by 2000 overall levels of antidepressant sales in all four countries were 3- to 4-fold greater than in 1990.

Norway

The Norwegian statistics show that after a steady rise in suicide rates throughout the 1970s and 1980s, the rates began to decline around 1990, which partly coincided with the period when SSRIs were introduced

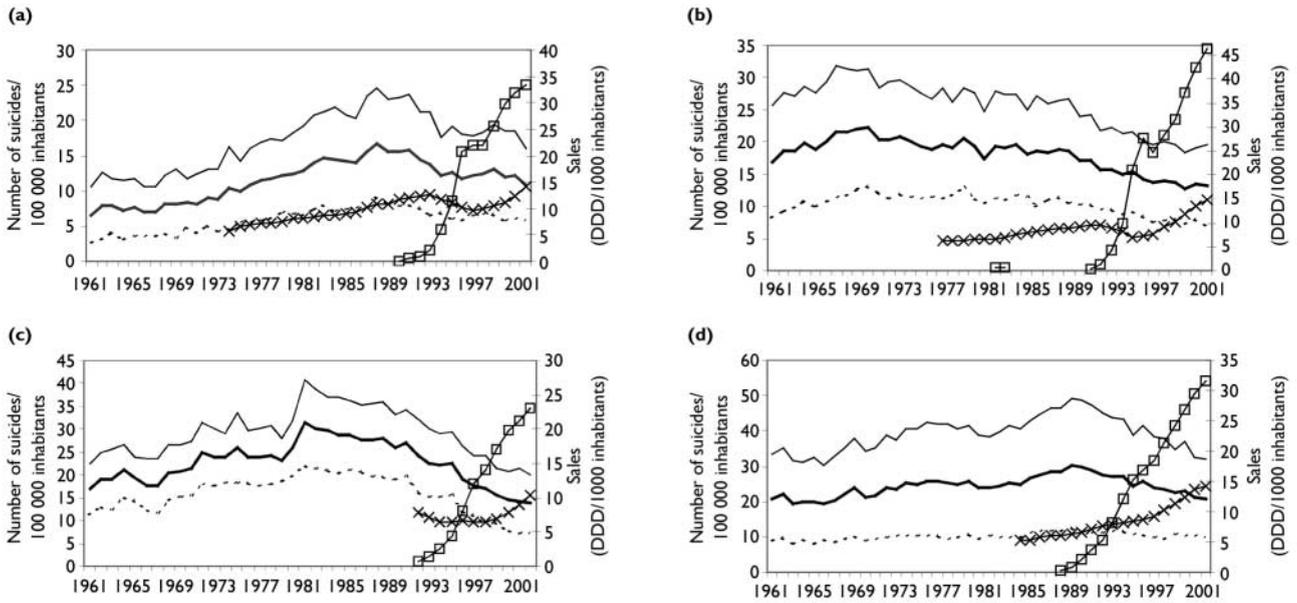


Fig. 1 Number of suicides v. SSRI and other antidepressant sales in (a) Norway (1961–2002), (b) Sweden (1961–2002), (c) Denmark (1961–2000) and (d) Finland (1961–2003). SSRI, selective serotonin reuptake inhibitor; DDD, defined daily dose. —, total; —, male; ·····, female; —□—, DDD (SSRI); —x—, DDD (other antidepressant).

and sales of antidepressants increased markedly (Fig. 1a). However, after 3 years of decline (1992–1994), suicide rates then stabilised, despite large increases in SSRI sales (Fig. 1a). In age-specific analyses (Fig. 2a and b) it is clear that this reduction and subsequent levelling out of previously rising suicide rates occurred in all age/gender categories except for female individuals aged 15–24 years.

Sweden

In Sweden, in contrast to Norway, suicide rates have been declining steadily since the 1970s, many years before the rise in SSRI sales in the early 1990s (Fig. 1b), but the decline (again in contrast to Norway) also continued after the introduction of SSRIs in Sweden. It is noteworthy that although age-specific

decreases in suicide rates continued in men and women aged over 25 years throughout the period of increased SSRI sales, any such declines were less marked or absent in individuals aged 15–24 (Fig. 2c and d). As in Norway, there was a reduction in the sales of other antidepressants in the years after the introduction of SSRIs in Sweden (Fig. 1b).

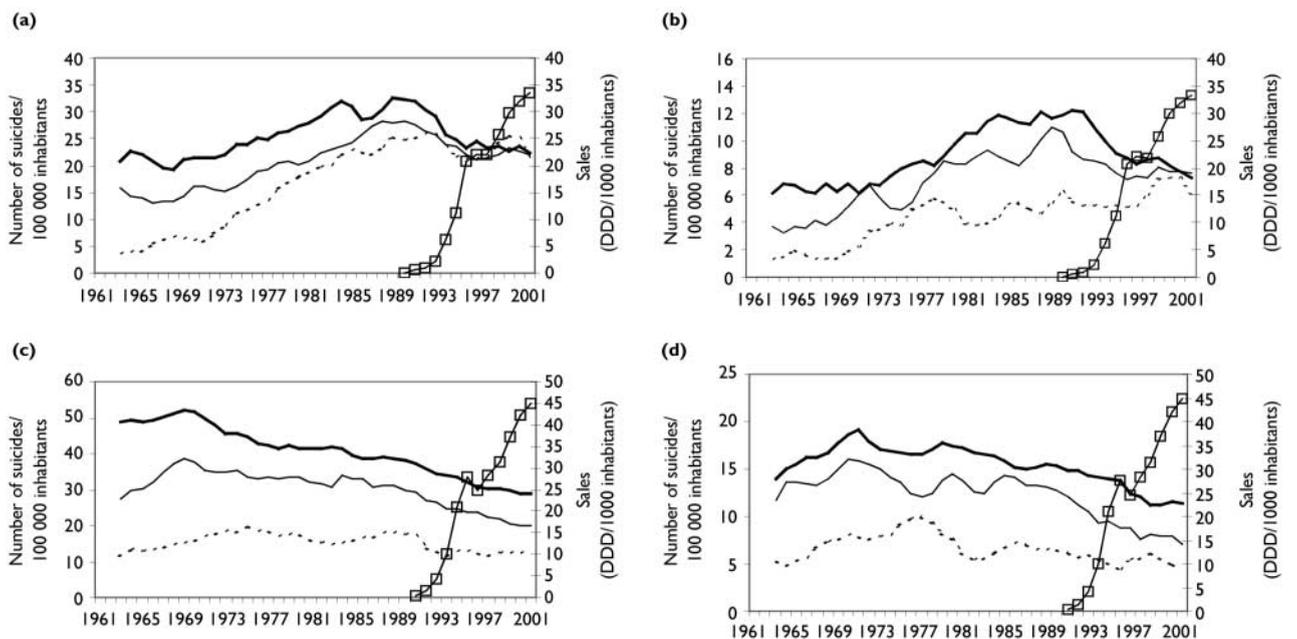


Fig. 2 Number of suicides (per 100 000 inhabitants, smoothed by 3-year moving averages) v. SSRI sales by age group in Norway for (a) males and (b) females, and in Sweden for (c) males and (d) females, for the period 1961–2002. SSRI, selective serotonin reuptake inhibitor; DDD, defined daily dose. —□—, DDD (SSRI); —, ≥45 years (3-year moving average); —, 25–44 years (3-year moving average); ·····, 15–24 years (3-year moving average).

Denmark

The Danish statistics (Fig. 1c) clearly show a steady rise in male and female suicide rates throughout the 1960s and 1970s, with a marked peak around 1980. Subsequently, suicide rates declined in both genders, around 10 years before the introduction of SSRIs in Denmark and the associated increase in levels of antidepressant use. The decline in suicide rates has continued over the period of increased SSRI sales. However, the rates of decline appeared to increase somewhat in the 1990s, particularly in women.

Finland

In Finland, after increases in suicide rates in the 1960s, 1970s and 1980s, declines in the overall and male suicide rates, and to a lesser extent in the female suicide rates, coincided with the introduction and increased sale of SSRIs (Fig. 1d).

Join-point analysis

For Norway, Sweden and Denmark the most appropriate model of secular trends in suicide rates included two join points whereas for Finland three join points provided the best fit to the data. The estimated join points and their 95% confidence intervals are shown in Table 1 for models with one, two and three join points, and the model of best fit is denoted in bold type. *P*-values for a test of the difference in slopes at each join point in the fitted model are also shown.

For the best-fitting model for Norway, the 2 years in which changes in trends occurred were 1967 (95% CI 1963–1991), when suicide rates began to rise, and 1988 (95% CI 1985–1999), when suicide rates began to fall. A third change, namely the levelling out of rates described above, was also identified in 1995 (95% CI 1986–2001) in a model with three join points, although this is not the model of best fit. Similarly, for Sweden 2 years were identified, namely 1968 (95% CI 1965–1970), when rates began to decline and 1988 (95% CI 1985–1991), when there was an accelerated rate of decline as described previously by Carlsten *et al* (2001). The two join points that were identified in the Danish suicide data were 1982 (95% CI 1978–1986) and 1989 (95% CI 1985–1995), the latter year corresponding to an increase in the rate of decline that began around 1982. In Finland,

the best-fitting model included the following three join points: 1977 (95% CI 1972–1981), after which suicide rates rose; 1983 (95% CI 1979–1987), when rates rose again, and 1990 (95% CI 1988–1993), when they began to fall. In each of the final (best-fitting) models, *P*-values provide strong evidence ($P < 0.005$) for a difference in slopes at the most recent join point (1988–1990).

DISCUSSION

Trends in suicide rates in Nordic countries in the 10-year time period before and after the introduction of SSRIs provide mixed evidence that increased sales have resulted in a reduction in suicides. In Norway, the period when the greatest increases in antidepressant sales occurred was characterised by relatively stable suicide rates. The decline in suicide rates in Denmark and Sweden pre-dated the introduction of the SSRIs by more than 10 years, and the suicide rates in these countries continued to decrease thereafter. The strongest evidence of an association between increases in antidepressant sales and a decrease in suicide rates was seen in Finland, where reductions in suicide rates coincided with the introduction and increasing use of SSRIs. However, such

effects were most marked in men, despite the fact that women are the greatest consumers of antidepressants. The decline may be partly explained by Finland's vigorous national suicide prevention programme, which was initiated around this time (Annals of Internal Medicine, 2004), although more recent suicide prevention initiatives in Norway (in 1992) and Sweden (in 1995) do not appear to have influenced trends in suicide in those countries (Calgary Centre for Suicide Prevention, 2004).

Statistical analysis suggests that in all four countries a decline (or an acceleration of a pre-existing decline) in suicide rates began around 1988–1990. This period pre-dates the introduction of SSRIs (and certainly their widespread use), although the 95% confidence intervals for the year in which suicide rates began to decline extend to 1999 for Norway, to 1991 for Sweden, to 1995 for Denmark and to 1993 for Finland. These results are derived from models that fit linear segments to non-linear data. Although the positions of the join points of these segments provide useful estimates of the years in which trends in suicide rates changed significantly, they represent a simplification of the observed temporal trends, and should therefore be treated with caution.

Our findings contrast with a previous assessment of trends in antidepressant

Table 1 Results of join-point analysis of suicide rates in the Nordic countries from 1961 to 2000–2002¹

Number of join points	Join point (95% CI) <i>P</i> ²	Join point (95% CI) <i>P</i>	Join point (95% CI) <i>P</i>
Norway			
3	1967 (1962–1990) 0.04	1988 (1963–1998) <0.01	1995 (1986–2001) 0.04
2	1967 (1963–1991) 0.09	1988 (1985–1999) <0.01	
1		1988 (1986–1989) <0.01	
Sweden			
3	1970 (1962–1971) ³	1971 (1966–1992) ³	1988 (1982–2001) <0.01
2	1968 (1965–1970) <0.01		1988 (1985–1991) <0.01
1	1969 (1967–1972) <0.01		
Denmark			
3	1979 (1976–1980) ³	1980 (1979–1982) ³	1989 (1985–1994) <0.01
2		1982 (1978–1986) 0.01	1989 (1985–1995) <0.01
1			1985 (1983–1988) <0.01
Finland			
3	1977 (1972–1981) 0.04	1983 (1979–1987) 0.01	1990 (1988–1993) <0.01
2		1986 (1962–1993) 0.45	1990 (1988–2002) 0.05
1			1992 (1990–1994) <0.01

1. Bold typeface denotes best fit.

2. *P* values are for a difference in slope at each join point.

3. *P* values not calculated because the information matrix is singular.

prescribing and suicide rates in the Nordic countries (Isacsson, 2000). The limited period covered by the suicide data that were presented in Isacsson's study meant that it was impossible to distinguish between short-term and longer-term trends in suicide rate (Isacsson, 2000). Our analysis suggests that the favourable trends in two of the four countries studied reflect a longer-term favourable trend in suicide rates. However, we did find evidence that declining rates of suicide in Sweden accelerated around 1988, shortly before the widespread use of SSRIs in the 1990s. This finding is consistent with another assessment of the association between antidepressant prescribing and suicide rates in Sweden up to 1997 which reported that the introduction of SSRIs coincided with an increased rate of decline in suicide rates (Carlsten *et al*, 2001), but that this change pre-dated the large increases in antidepressant sales.

Prescribing trends and suicide rates in other countries

Evidence from other ecological investigations is mixed. Studies in the USA (Olsson *et al*, 2003; Grunebaum *et al*, 2004), Australia (Hall *et al*, 2003) and Hungary (Rihmer *et al*, 2001) report trends which suggest a favourable effect of antidepressants on suicide rates, whereas findings from Iceland (Helgason *et al*, 2004), Italy (Barbui *et al*, 1999) and England (Gunnell & Ashby, 2004) do not support this. The main limitation of those analyses, as well as those in the present study, is that there are many complex influences on national suicide rates, including the availability of lethal methods of suicide, changing social and economic conditions, changing levels of substance misuse and birth cohort effects (Gunnell *et al*, 2003). Distinguishing between the discrete effects of changing levels of antidepressant prescribing and those of these other influences on patterns of suicide is challenging, as many of the factors are strongly correlated with each other.

Person-based analyses of the association between antidepressants and suicidal behaviour

Recent meta-analyses of placebo-controlled randomised trials of SSRIs (Whittington *et al*, 2004; Fergusson *et al*, 2005; Gunnell *et al*, 2005) have provided evidence that SSRIs are associated with an increased risk

of non-fatal suicidal behaviour in children and adults. As most of these trials were of short duration, it is uncertain whether such increased risks may be offset by a longer-term reduction in risk among those taking antidepressants for the recommended period of up to 6 months. There were insufficient numbers of participants recruited to the trials to allow investigation of any beneficial or adverse effects of SSRIs on suicide deaths (Gunnell *et al*, 2005), highlighting the importance of using observational studies to investigate this issue. It is noteworthy that observational studies provide no strong evidence that SSRIs differ from tricyclic antidepressants with regard to the risk of suicidal behaviour (Martinez *et al*, 2005).

Limitations

Our analysis has several limitations. First, we employed an ecological study design using national sources of prescribing and suicide data. We have not investigated the influence of antidepressant treatment on suicide risk. Furthermore, because the prescribing data are sales data rather than data on person-based consumption of antidepressants, the number of individuals who took antidepressants will be overestimated. Second, we were unable to determine the extent to which increases in sales were a result of growing numbers of each of the following: people who had been newly prescribed an SSRI; long-term users; or a combination of the two. Third, we have not taken into account other influences on temporal trends in suicide rates (e.g. changes in the levels of unemployment, divorce or substance misuse) (Gunnell *et al*, 2003). Fourth, we were unable to obtain age- and gender-specific prescribing data for the four countries, so we were unable to investigate whether age-specific trends in suicide rates mirrored those for prescribing. However, analyses from other countries suggest that antidepressant prescribing increased by 2-fold or more in all age/gender categories in the 1990s (Middleton *et al*, 2001; Hall *et al*, 2003), which indicates that our use of all-age data will not seriously bias our interpretation of the overall trends within specific age/gender categories. Finally, our analysis was restricted to four countries. As highlighted above, there is mixed evidence from other countries concerning the effect of increased levels of antidepressant prescribing on suicide rates.

Implications

Although there is broad consensus about the effectiveness of SSRIs in treating depression, the evidence that the decline in suicide rates which was seen in Norway, Sweden, Denmark and Finland in the 1990s resulted from increased antidepressant prescribing is not clear-cut. A more detailed understanding of the factors that have contributed to recent declines in suicide rates in the Nordic countries is required. Elucidation of these factors will help to inform the development of evidence-based suicide prevention policies.

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CLINICAL IMPLICATIONS

- The evidence that increased antidepressant sales have had a beneficial effect on population suicide rates is equivocal.
- Explanations for the recent favourable trends in suicide rates in Norway, Sweden, Denmark and Finland should be clarified. These may help to inform national suicide prevention policies.
- Frequent and careful patient monitoring during the early stages of treatment with antidepressants is important.

LIMITATIONS

- This is an ecological study. We have not investigated the effect of antidepressant treatment on suicide risk.
- We have not taken into account other influences on temporal trends in suicide rates (e.g. changes in the levels of unemployment, divorce or substance misuse).
- We were unable to distinguish the extent to which increases in antidepressant sales were a result of growing numbers of people who had been newly prescribed a selective serotonin reuptake inhibitor, long-term users, or a combination of the two.

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