Research report

The sales of antidepressants and suicide rates in Norway and its counties 1980–2004

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Abstract

Background: Suicide is a major public health problem and depression is among the most important risk factors for suicide. Treatment of depression might prevent suicide. To study this hypothesis further we conducted an ecological study.

Methods: An ecological study using sales data for antidepressants and numbers of suicides in Norway and Norwegian counties 1980–2004 was performed. Data on alcohol consumption and unemployment rates were registered and taken into account. Data were analyzed using Cochrane-Orcutt time series for the country as a whole. The county specific data were analyzed with a random coefficient model with county as subject and intercept and time (slope) as random variables using an unstructured covariance matrix.

Results: Sales of non-tricyclic antidepressants (non-TCAs) and suicide were clearly negatively related, even when controlling for alcohol and unemployment (adjusted $r^2$: 0.57). There was an effect modification between time and level of sales of non-TCAs. Studying the relationship between the sales of non-TCAs and the suicide rate, we found that it was significant and stronger for the low sales figures, but non-existent for the high sales figures.

Limitations: Ecological studies cannot infer causality.

Conclusions: The fall in suicide rates in Norway and its counties was related to the increased sales of non-TCAs. The effect was mostly a result of a sales increase in the lower sales segment, indicating that a change from the more toxic TCAs, or heightened awareness of depression and its treatment, could explain the relationship found between sales of newer antidepressants and a decrease in suicide rate.

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1. Introduction

Mental health disorders are important causes of suicide (Harris and Barraclough, 1997), and particularly important are affective disorders, because different subtypes are found among about 60% of suicides in the general population (Cavanagh et al., 2003). The risk of suicide also increases with the severity of the
depressive episode (Kessing, 2004). Treatment of such conditions is thought to be beneficial in the prevention of suicide. The introduction of newer antidepressants, and especially the selective serotonin reuptake inhibitors (SSRIs), at the start of the 1990s accelerated the diagnosis and treatment of depression. Far more people were exposed to drugs that could alleviate depression. Together with this increase in sales of antidepressants, many western countries experienced a decline in their national suicide rates. Several researchers, particularly Isacsson (Isacsson, 2000), have promoted the idea that these two phenomena are related and increased treatment of depression has led to the observed decline.

Although suicide is a major public health issue, it is a rare phenomenon at an individual level. Only very large, possibly unsustainable, randomized controlled trials (RCTs) would, by themselves, have enough power to demonstrate any difference in suicide rate between a treatment and a placebo. Meta-analysis of such studies could, to some extent, overcome this (Khan et al., 2003; Gunnell et al., 2005). The follow-up time of RCTs included in the meta-analysis is, however, too short to capture the whole at-risk period for suicide in connection with depression. Furthermore, suicidality is usually an exclusion criterion in such trials, because of ethical constrains and practical difficulties.

Ecological investigations into the relationship between the sales of newer antidepressants and suicide rates have been performed in several countries, with varying time spans, different age groups, and various types of co-variates and statistical approaches (Table 1). With the exception of the studies in Iceland, Italy and Slovenia, which have not shown a decline in suicide rates, most of these studies find that the increased sales of newer antidepressants seem to be related to the decrease in suicide rate. This is also found in other communications from Hungary (Rihmer et al., 2001; Rihmer, 2003) and Britain (Gunnell and Ashby, 2004). What separates them are the result interpretations, ranging from a belief in a causal relationship to stating that sales figures are indirect measures of better diagnosis of depression and more treatment optimism, or even that the relationship is purely spurious.

The aim of the current study was to investigate the relationship between antidepressant sales and suicide rates as seen in Norway as a whole, and in its counties, on the basis of observations made from 1980 to 2004. As a completed suicide is not just a matter of mental illness and its treatment, we also included data on alcohol consumption and unemployment as confounders, both of which have been found to be related to national suicide rates (Rossow, 2005; Platt and Hawton, 2006).

2. Method

2.1. Sources of data

Suicide rates were provided by Statistics Norway. The figures are given in deaths by suicide per 100,000 inhabitants. Suicide rates were available for the country as a whole from 1980 to 2004, but only up to 2003 when dealt with by the county. Statistics Norway also supplied data on sales of alcohol for the years 1980–2004, although data from 1998 were missing. Alcohol sales data were available only for the country as a whole. Figures are given in liters of pure ethanol sold through official channels per person in Norway (all ages). Unemployment figures were taken as a proxy for the state of the economic climate, and were provided by the Norwegian employment agency through Statistics Norway. These data were available for 1980–2004 across counties. The figures are presented as the number of people registered unemployed as a percentage of the total population.

Drug sales data were taken from the wholesale register at the Norwegian Institute of Public Health. All data were per county and calendar year for the years 1980–2003. County-specific data for 1981 were not available. Data on wholesale figures for drugs were collected from all drug wholesalers in Norway, and represent total sales to pharmacies, institutions, etc. Even if these data were complete, drugs sold are not of course necessarily consumed. However, for the purpose of comparing regions or countries, and looking for trends, these figures will probably provide reliable information. All drugs on the Norwegian market are classified into groups according to the Anatomical Therapeutic Chemical (ATC) classification. The sales figures were calculated and presented as numbers of defined daily doses (DDDs)/1000 inhabitants per day at the group level for the active ingredient (ATC fourth or fifth level) (WHO Collaborating Centre for Drug Statistics Methodology, 2005). Sales figures were calculated for the following groups of drugs: tricyclic antidepressants (TCAs) (ATC code N06AA: desipramine, imipramine, clomipramine, opipramol, trimipramine, amitriptyline, nortriptyline and doxepin), selective serotonin reuptake inhibitors (SSRIs) (N06AB: fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine and escitalopram) and other antidepressants (N06AG: moclobemide and N06AX: mianserin, nefazodone, mirtazapine, venlafaxine and reboxetine). In the analysis all these sales figures were either grouped together (all antidepressants) or the SSRIs and other antidepressants were grouped together as the non-TCAs.
Table 1
Ecological studies addressing the relationship between sales of antidepressants (ADs) and suicide rates in different countries and by different models

<table>
<thead>
<tr>
<th>Reference</th>
<th>Years studied</th>
<th>Study area</th>
<th>Co-variates in addition to ADs</th>
<th>Statistical methods</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbui et al. (1999)</td>
<td>1988–1996</td>
<td>Italian regions</td>
<td>Gender</td>
<td>Poisson regression</td>
<td>Increase in SSRI sales gave higher AD sales, but no effect on suicide rate</td>
</tr>
<tr>
<td>Carlsten et al. (2001)</td>
<td>1977–1997</td>
<td>Sweden</td>
<td>Age, gender</td>
<td>Quasi-Poisson model</td>
<td>A significant change in suicide rate coincided with the introduction of SSRIs, but preceded the high increase in SSRI sales</td>
</tr>
<tr>
<td>Gibbons et al. (2006)</td>
<td>1996–1998</td>
<td>5–14 year olds, USA county comparison</td>
<td>Age, gender, income, race</td>
<td>Mixed effect</td>
<td>Increases in prescriptions for non-TCAs were associated with lower suicide rates between counties and over time. Increases in prescriptions for non-TCAs were associated with lower suicide rates between counties and over time.</td>
</tr>
<tr>
<td>Gibbons et al. (2005)</td>
<td>1996–1998</td>
<td>USA county comparison</td>
<td>Age, gender, income, race</td>
<td>Mixed effect</td>
<td>Increase in AD sales did not explain the decrease in suicide rate and the possibility for suicide prevention.</td>
</tr>
<tr>
<td>Guijana et al. (2005)</td>
<td>1955–2000</td>
<td>Italy</td>
<td>Gender</td>
<td>Descriptive</td>
<td>The increase in AD sales did not explain the decrease in suicide rate.</td>
</tr>
<tr>
<td>Hall et al. (2003)</td>
<td>1991–2000</td>
<td>Australia</td>
<td>Age, gender</td>
<td>Spearman’s rank correlation</td>
<td>Changes in suicide rates and exposure to ADs are significantly associated.</td>
</tr>
<tr>
<td>Helgason et al. (2004)</td>
<td>1950–2000</td>
<td>Iceland</td>
<td>Alcohol consumption, psychiatric admissions and outpatient visits, disability pension</td>
<td>Quasi-Poisson model</td>
<td>Increased prescribing of ADs is not related to lower suicide rates.</td>
</tr>
<tr>
<td>Isacsson (2000)</td>
<td>1978–1996</td>
<td>Sweden (compared with Denmark, Norway and Finland)</td>
<td>Age, gender, unemployment rates, alcohol consumption</td>
<td>Spearman’s rank correlation coefficient</td>
<td>The increased use of ADs appears to be associated with the decrease in suicide rates.</td>
</tr>
<tr>
<td>Ludwig and Marcotte (2005)</td>
<td>1980–1999</td>
<td>26 European countries (including Norway and the USA)</td>
<td>GDP/capita, divorce and unemployment rate</td>
<td>Logistic regression with fixed effects</td>
<td>The increased sales of SSRIs may have saved lives.</td>
</tr>
<tr>
<td>Oravecz et al. (2003)</td>
<td>1985–1997</td>
<td>Slovenia</td>
<td>Correlations</td>
<td></td>
<td>No correlation was found between sales of antidepressants and suicide rate.</td>
</tr>
</tbody>
</table>

GDP: gross domestic product; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants.

2.2. Statistical analysis

2.1. Model for sales of antidepressants

The relationship between suicide rate and antidepressant sales was studied using a random coefficient model, with county as subject, sales of antidepressants and time as fixed effects and intercept and time (slope) as a random effect using an unstructured covariance matrix. The antidepressant group used for further analysis was chosen on the basis of the lowest value for the Akaike information criterion (AIC) (Lindsey and Jones, 1998).

2.2. The whole country

For the country as a whole we performed a Cochrane-Orcutt time series analysis (Cochran and Orcutt, 1949). Models were run with antidepressants, alcohol consumption and unemployment rates as independent variables. The regression coefficient ($\beta$) with 95% confidence interval (95% CI) and the ability of the independent variables to explain variation in the dependent variable ($R^2$) was calculated.

2.3. The 19 counties

When studying the 19 different counties of Norway, a random effect model was used with county as subject, suicide rates in counties as the dependent variable, sales of antidepressants, unemployment rates and time as fixed effects, and intercept and time (slope) as random effects using an unstructured covariance matrix. We did not have alcohol figures for each county and the analyses were performed without this variable. We checked for interactions between two and two variables (time*AD sales, time*unemployment rates and AD sales*unemployment rates) adding one interaction to the mixed model at a time.

3. Results

3.1. Model for sales of antidepressants

Three models using drug sales figures as independent variables and suicide rate as dependent variable were used:

1. The relationship between suicide rates and sales figures for all antidepressants.
2. The relationship between suicide rates and sales figures for non-TCAs.
3. The relationship between suicide rates and sales figures for SSRIs.

Only the main effects were studied. The model giving the best fit was option 2: the relationship between suicide rate and sales of non-TCAs. We chose this model because it produced the lowest AIC value, even if the differences between the models were moderate (Raferty, 1995). Model 2 was therefore used throughout.

<table>
<thead>
<tr>
<th></th>
<th>Crude Regression coefficient (95% CI)</th>
<th>p value</th>
<th>$R^2$</th>
<th>Adjusted* Regression coefficient (95% CI)</th>
<th>p value</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales of non-TCAs</td>
<td>$-0.090 (-0.136 to -0.042)$</td>
<td>0.001</td>
<td>0.47</td>
<td>$-0.105 (-0.180 to -0.028)$</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>$-1.239 (-2.712 to 0.393)$</td>
<td>0.129</td>
<td>0.12</td>
<td>$0.402 (-2.541 to 3.346)$</td>
<td>0.774</td>
<td>0.57</td>
</tr>
<tr>
<td>Unemployment figures</td>
<td>$-0.161 (-1.450 to 1.126)$</td>
<td>0.797</td>
<td>0.00</td>
<td>$-0.298 (-1.806 to 1.228)$</td>
<td>0.689</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for sales of non-TCA antidepressants, alcohol consumption, unemployment figures and time.

Fig. 1. Relationship between suicide rate (deaths in suicide per 100,000 inhabitants per year) and sales of non-tricyclic antidepressants (defined daily doses or DDDs/1000 inhabitants per day) in Norway, 1980–2004.

Table 2

Cochrane-Orcutt statistics for the relationship between the dependent variable of national suicide rate and the independent variables of sales of non-tricyclic antidepressants (non-TCAs), alcohol consumption and unemployment rate in the whole of Norway, 1980–2004.

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The whole country

The Cochrane-Orcutt statistics showed that the sales of non-TCAs were related to suicide rate (Fig. 1), even when adjusting for alcohol consumption, unemployment rate and time (Table 2). Alcohol consumption (Fig. 2) and unemployment rate (Fig. 3) were not significantly related to suicide rate (Table 2).

Norwegian counties

Using a random coefficient model, we also found an inverse relationship between suicide rates and sales figures for non-TCAs when the analysis was performed using all 19 Norwegian counties. We had no alcohol consumption data at a county level, but the inverse relationship between suicide rates and sales figures was clearly present after an adjustment for unemployment rate (Table 3).

When performing the analysis on the relationship between sales of non-TCAs and suicide rate at a county level, the interaction between sales of non-TCAs and time was significant (estimate fixed effect=0.049, 95% CI=0.009–0.089, p=0.018), indicating that the relationship between sales of non-TCAs and suicide rate was different at different times. To further address this interaction, we performed an analysis at the county level after stratifying the sales figures of antidepressants into

Fig. 2. Relationship between suicide rate (deaths in suicide per 100,000 inhabitants per year) and sales figures for alcohol (liters of pure alcohol per inhabitant) in Norway, 1980–2004. Figures for 1998 could not be obtained.

Fig. 3. Relationship between suicide rate (deaths in suicide per 100,000 inhabitants per year) and unemployment rates (number of registered unemployed per 1000 inhabitants) in Norway, 1980–2004.
low and high sales of non-TCAs, according to whether the sales were lower or higher than the mean sales of 16 DDDs/1000 inhabitants per day. These analyses showed that the relationship between sales of non-TCAs and suicide rates was significant and stronger for the low sales figures, but non-existent for the high sales figures (Table 3). To check for other possible explanations for this interaction the same analyses were also performed for different counties (low versus high sales counties) or different time periods (early versus late time period). The interaction was not explained by differences between high and low sales counties or between early years (with low sales) and later years (with higher sales).

4. Discussion

This ecological study of the increase in sales of antidepressants and fall in suicide rate in Norway and its counties found a clear, statistically significant association between these two variables. Suicide rates seemed to fall mostly in association with an increase in the sales of non-TCAs. The relationship was prominent for sales figures that were below average, and not for higher sales figures, indicating that an initial increase in sales was related more to a decrease in suicide rate. Adjustment for alcohol consumption and unemployment rates, which have both been reported to be associated with suicide rate in other studies, did not alter the relationship.

The magnitude of the effect would be that an increase in the sales of non-TCAs by 12–13 DDDs/1000 inhabitants per day could save one suicide per 100,000 inhabitants. However, when considering only the low sales figures, the impact would be that an increase of only about 2 DDDs in the sales of non-TCAs would save one suicide per 100,000 inhabitants per year. For many counties, and for the country as a whole, this increase came soon after the introduction of non-TCAs at the start of the 1990s. It could be that the change from the more toxic TCAs was beneficial, or that groups not previously treated, despite clear depression, were now more likely to receive treatment for depression. The increased awareness and treatment optimism among general practitioners (GPs) could also have had an impact. From the mid-1990s, there has been a marked increase in alcohol consumption, with no corresponding increase in suicide rate. The relationship between alcohol use, antidepressant sales and suicide rates may have obscured any relation between antidepressant sales and suicide rates from that point on.

Ecological studies cannot infer causality. In the study of the public health impact of increased sales of antidepressants it may still be the best type of study obtainable. As suicide is a relative rare event, even in patients treated for depression (Gunnell et al., 2005; Simon et al., 2006), it could be difficult to conduct sufficiently large RCTs to investigate the relationship between suicide and antidepressant treatment. The problem of statistical power may be overcome by meta-analysis of RCTs. Two such comprehensive meta-analysis (Khan et al., 2003; Gunnell et al., 2005) reported no impact on suicide rate of active treatment and possibly an increase in self-harm in the treated patients. This increase may be attributable to the known clinical phenomenon of increased suicide risk associated with increased psychomotor activity, together with continuing depression in the first weeks after starting antidepressant therapy, or the induction of manic episodes in patients with bipolar disorder (Rihmer and Akiskal, 2006) and should probably not be regarded as evidence against the overall effect of antidepressants. On the other hand RCTs provide data on

<table>
<thead>
<tr>
<th>Estimate for fixed effects (95% CI)</th>
<th>p value</th>
<th>Estimate for fixed effects (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sales of non-TCAs</strong></td>
<td></td>
<td><strong>Unemployment figures</strong></td>
<td></td>
</tr>
<tr>
<td>-0.136 (-0.174 to -0.097)</td>
<td>&lt;0.001</td>
<td>-0.159 (-0.210 to -0.108)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.834 (0.341 to 1.328)</td>
<td>0.001</td>
<td>-0.409 (-1.025 to 0.206)</td>
<td>0.192</td>
</tr>
<tr>
<td><strong>Low sales of non-TCAs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sales of non-TCAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.462 (-0.635 to -0.290)</td>
<td>&lt;0.001</td>
<td>-0.466 (-0.639 to -0.293)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unemployment figures</td>
<td>0.502</td>
<td>-0.382 (-1.165 to 0.401)</td>
<td>0.337</td>
</tr>
<tr>
<td><strong>High sales of non-TCAs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sales of non-TCAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-0.024 (-0.130 to 0.081)</td>
<td>0.643</td>
<td>-0.026 (-0.135 to 0.083)</td>
<td>0.631</td>
</tr>
<tr>
<td>Unemployment figures</td>
<td>0.328</td>
<td>-0.584 (-1.718 to 0.549)</td>
<td>0.310</td>
</tr>
</tbody>
</table>

* Adjusted for sales of non-TCAs, unemployment figures and time.
an individual level and may pick up smaller effects than ecological studies, such as increased suicidality at the onset of treatment. Then again, even if meta-analyses may solve the problem of statistical power, most RCTs are too short to be able to predict the public health benefit of antidepressant treatment in the longer term. These factors may explain the possible discrepancy between RCTs and ecological studies.

Factors other than sales of antidepressants may explain the observed relationship. Such factors could be better diagnosis of depression and more treatment optimism among healthcare professionals. This is supported by earlier research. The Gotland study demonstrated that education directed at GPs rather than psychiatrists had an effect (Rihmer et al., 1995; Rutz, 2001). GPs see most of the depressed patients and prescribe most of the dispensed antidepressants. The effects seen in the Gotland study came at a time when the older antidepressants were still being used. Our findings indicate that the effect of increased antidepressant treatment was more pronounced when sales figures for antidepressants were low. Increasing the sales at this time point probably meant offering treatment to the individuals with the most apparent depression. There seems to be a dose–response relationship between severity of depression and suicide risk (Kessing, 2004), and the early increase might represent antidepressants being given mainly to those with the most severe depression. The relationship was not present when sales were increased beyond a certain level, indicating no effect when more marginal groups had been offered treatment. We must bear in mind that we used suicide as an outcome and that results may differ using other mental health outcomes.

Suicide prevention plans have been offered as another explanation for the decline in suicide trends in many western countries. Such a national suicide prevention plan was implemented in Norway during 1994–2002, and could possibly provide an alternative explanation for our findings. However, the effect of national suicide prevention plans lacks sufficient evidence (De Leo, 2002). A recent systematic review of suicide prevention strategies indicated that GP education was one of the most powerful interventions for preventing suicide (Mann et al., 2005). It is reasonable to believe that GP education given at the time of introduction of newer antidepressants was important in increasing awareness of depression as a problem.

In our study, we control for a few important covariates that were thought to be related to suicide rates. Alcohol consumption has been shown, in some but not other studies, to be related to national suicide trends (Sher, 2005). In the current study we were not able to reproduce earlier results from Norway that indicated a increase in suicide rate coinciding with increasing sales in alcohol from 1975 to 1988 (Rossov, 1995). This illustrates the dilemma of ecological studies. We cannot refute the earlier studies, only accept the current results as additional information. The discrepancies in the results could possibly be explained by the sharp increase in alcohol consumption after 1993 (Fig. 2), together with the steady decline in suicide rates. It is also possible that increased rates of antidepressant sales have protected against the increased suicide rates expected with increased alcohol consumption, given that, in the general population, the combination of depression and alcohol abuse or dependence seems to be a potent risk factor for suicide (Cavanagh et al., 2003). The limitation within the data may also be an explanation, because the official sales statistics for alcohol are only an indicator of what is consumed. Much alcohol will be bought tax free abroad or come from illegal sources.

Our study has the advantage of covering a long time span (1980–2003), although not the longest of the cited studies (Table 1). There is a tendency for the studies including the longest time series (Italy and Iceland) not to have found any relationship between sales figures and suicide rate, mostly as a result of stable suicide rates despite increases in antidepressant sales (Barbui et al., 1999; Helgason et al., 2004; Guiana et al., 2005). In some of the countries without a relationship between sales of antidepressant sales and suicide rate there was only little increase in antidepressant sales (Barbui et al., 1999; Oravec et al., 2003), offering an explanation to the conflicting results. In the current study we found a relationship also with a longer observation period, but the largest effect seemed to be related to the introduction of non-TCAs.

Lastly, the observed relationship could be a spurious finding. Researchers have argued that suicide rates will vary over time for many unknown reasons (Gmel et al., 1998). In times of declining suicide rates, credit for this change will be taken by different interventions. The Gotland study has been criticized from this point of view (Berglund et al., 2001). When looking at the relationship between sales of newer antidepressants and suicide rates, choosing other time windows and other regions may also make the relationship disappear (Kahn et al., 1992). Both in Norway (Reseland et al., 2006) and in Sweden (Isacsson, 2000; Carlsten et al., 2001), there was a remarkable drop in suicide rates at the start of the 1990s, coinciding with the introduction of SSRIs.

Ecological studies cannot prove that a drop in suicide rates is related to increased treatment of depression. On the other hand, many ecological studies from different
countries, covering different time periods, using various statistical approaches and including different confounders, may be interpreted as increased support for the prevention effect of antidepressants on rates of suicide. The current study, covering a long time span and using adequate statistical approaches, adds to the previous studies that point to a possible relationship.

5. Conclusion

The fall in suicide rates in Norway and its counties was related to the increased sales of non-TCAs. The effect was mostly the result of a sales increase in the lower sales segment, indicating that an explanation might be a change from the more toxic TCAs or heightened GP awareness of depression and its treatment.

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References


