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Antidepressant prescription and suicide rates: Effect of age and gender

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Abstract

To determine whether the effect of antidepressant exposure on suicide rate is modified by age and gender in Hungary, annual antidepressant use and suicide rates of 10,000,000 inhabitants were analyzed by age and gender groups. The suicide rate correlated negatively with increased use of antidepressants in both genders. The strongest association was found in the oldest age groups, where the increase in antidepressant use was highest, while there was no association in the under-20 or 50–69 age groups in either gender. Antidepressant rate predicted suicide rate after controlling for divorce rate or unemployment rate but not after covarying for alcohol consumption rate.

Keywords

suicide; antidepressant; age; gender

Since selective serotonin reuptake inhibitors (SSRIs) were introduced, many countries have seen an increase in prescription rates for antidepressants (Barbui et al., 1999; Carlsten et al., 2001; Hall et al., 2003). A number of studies have found a relationship between this increase in national antidepressant prescribing and declining suicide rates, with general agreement but some notable exceptions. In part, this may be because the efficacy of antidepressants in reducing suicide rates may vary by age and gender, in addition to other socio-economic and cultural factors, and in part because national rates may disguise important differences in prescription trends in some age groups and between sexes.

Investigating the suicide rates of the 27 countries with data on sales of all antidepressants between 1980 and 2000, Ludwig and Morcotte (2005) have reported that after controlling for some relevant sociodemographic factors (unemployment, GDP, gender, divorce rate)

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only the increase of antidepressant (mostly SSRI) utilization correlated significantly with declining national suicide rates. Studies in specific countries report that age and sex may affect the relationship. In Australia between 1991 and 2000, the national suicide rate did not fall significantly, despite a marked increase in prescriptions for antidepressants. However, suicide rates among older males and females, the two groups with the highest exposure to antidepressants, were significantly lower; this decrease was offset by an increase in suicide rates among young males and females, in particular young males who were less exposed to antidepressant prescriptions (Bremner et al., 2003). The limitation of this important study was that estimates of antidepressant use for the different age groups were based on survey data from Australian general practitioners. Similarly to Australia, in Japan national prescriptions and suicide rates have increased but in fact the suicide rate declined in the group where the prescription rate increase has been concentrated, mainly older males (Nakagawa et al., in press). In Italy between 1988 and 1996, a 53 percent national increase in antidepressant sales was recorded. This was accompanied by an increase in male suicide rates, and a decrease in female suicide rates (Barbui et al., 1999). In Sweden, the national suicide rate decreased over two decades, while antidepressant prescriptions increased across all age groups. The elderly had the highest rates of antidepressant prescriptions, but the most statistically significant reduction in suicide rates occurred among young adults (Carlsten et al., 2001). In the county of Jamtland, where the increase in the use of antidepressant prescriptions was greater than the overall increase seen in Sweden, the suicide rate decreased more steeply compared to the national average (Henriksson & Isacson, 2006). In the United States between 1985 and 1999, females received twice as many antidepressant prescriptions as males, and the decline in suicide rate in females was almost double that of males (Grunebaum et al., 2004).

Since the effect of a given intervention may be greater if the baseline condition is more serious (Rihmer & Akiskal, 2006), the impact of improved and more widespread treatment of depression in reducing suicide may be easier to detect in countries with high baseline suicide rates. Hungary has had the world's highest suicide rate when averaged over the last 100 years. Despite a decline in suicide mortality since 1998, it is still among the ten countries with the highest suicide rates; in 2004 its suicide rate was 27 per 100,000 persons, almost two and a half times the U.S. national rate. Hungary also has the world's highest reported suicide rate among the elderly in both genders (in 1999: 225/100,000 and 65/100,000 for men and women aged 80 and older respectively).

The aim of the present study was to determine the effect of increased antidepressant prescriptions in a country with high suicide rate and to investigate whether the efficacy of antidepressants in reducing suicide rates may vary by age and gender. We chose Hungary, because in addition to having one of the highest suicide rates in the world, the centralized health care system provides reliable prescription data on all 10,000,000 inhabitants. Annual national data of antidepressant use and suicide rate were analyzed for a seven-year period. Additional data on potential suicide risk factors (alcohol consumption, unemployment, divorce rates), and other cause of mortality that can bias reporting of suicide rates (motor-vehicle accidents) were also collected.

METHOD

Number of suicides

The annual number of suicides and the annual population count for each age group by gender were obtained from the Hungarian Office of Statistics. Based on these data we calculated the suicide rates in each age group in a given year. Reporting of suicides in Hungary is based on an autopsy, required in every case of suspected suicide.

Antidepressant use

Change in antidepressant use was evaluated by comparing the level of treatment calculated as defined daily dose of antidepressants (DDD) per 1000 people per year. The Hungarian National Health Insurance Company, which has data on filled prescriptions linked to personal identification numbers, provided indicators of antidepressant use: the days of treatment (DOT) using DDD (Norwegian Institute of Public Health, 2006). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The advantage of the DDD is that it provides a fixed measurement unit enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups. However, the DDD only gives a metric of prescriptions per patient; that level does not always represent an adequate amount of medication for the individual patient (e.g., DDD of duloxetine 60mg; fluoxetine 20mg). We calculated DDD/per 1000 people per year ($DDD \times 1000 / 365 \times \text{population}$).

Alcohol consumption, unemployment, divorce rates, motor-vehicle accidents, and all-cause mortality

Data were obtained from the National Statistical Office and were available for the 1999–2004 period, except for the divorce rate and motor vehicle accident death rate, which were available for 1999–2005.

Statistical analysis

Separate generalized regression models of antidepressant levels on suicide rate were performed, covarying for other factors that potentially affect suicide rate. Spearman's rank correlations were used to assess the associations between annual trends in antidepressant use and suicide rates in each age group and within genders. A Spearman's Rho correlation is significant at $p < 0.05$ with a value of 0.75 with 7 observations, one for each year.

RESULTS

During the investigated period the overall suicide rate decreased by 20% in Hungary from 32.5 to 26.0 per 100,000 (see the annual stratified suicide rates in Table 1) and the antidepressant prescription rate increased 62% from 14.4 to 23.4 DDD per 1000 people per year (see in Table 2 for the annual antidepressant levels by age and gender groups). Antidepressant exposure was higher in women in each age group compared with men.

National per capita sales data on wine, beer, and other spirits as indicators of alcohol use were increased from 9.9 to 11.1 liters of 100% alcohol per year per capita from 1999 to 2004, while the number of alcohol-related liver deaths, the most fatal complication of alcohol misuse, decreased between 1999 and 2004 from 58.7 per 100,000 people to 29.7 per 100,000. These numbers reflect alcohol consumption that started often decades prior to death. Motor vehicle accidents death (MVA) slightly decreased and rates of divorce remained unchanged during the observed period (MVA: 13.7 vs. 12.6 per 100,000; divorce rate: 2.50 vs. 2.46 per 1000 inhabitants in 1999 and 2005 respectively). During the investigated period all cause mortality rate decreased modestly from 14% to 13.5% per 1000 people and average life expectancy increased (male: 66.3 vs. 68.6; female: 75.1 vs. 76.9 yrs).

Separate generalized regression models of antidepressant levels on suicide rate were performed covarying for rates of alcohol consumption, divorce rate or unemployment rate. Antidepressant use remained a significant predictor of reducing suicide rate after controlling for divorce rate ($F(1,4) = 24.02$, $p = 0.0080$) or unemployment rate ($F(1,3) = 19.50$, $p = 0.0216$).

but was no longer significant after covarying for alcohol consumption rate ($F(1,3)=7.42$, $p=0.072$).

A negative correlation was detected between antidepressant use and overall suicide rates in both genders (men: $p<0.05$, Spearman's $Rho=-0.90$; women: $p<0.05$, Spearman's $Rho=-0.92$). However the strength of the association was different in different age groups and by gender (see Table 3, Figure 1). There was no association in the under-20 or 50–69 age groups in either gender. Among women in the 30–49 groups there was only a trend for negative correlation. In both genders, strong associations were found in the oldest age groups (70–79 and 80+). The increase in antidepressant use was the highest in men and women aged 80 and older (140% and 149% respectively) (see Figure 2), and the lowest in men younger than 20 (26%).

DISCUSSION

Greater antidepressant exposure was associated with lower suicide rates in Hungary. We found a strong correlation between antidepressant use and overall suicide rate in both men (Spearman's $Rho=-0.90$; $p<0.05$) and women (Spearman's $Rho=-0.92$ $p<0.05$). There was evidence of age effect, with a negative correlation between rising antidepressant prescription rates and a decline in suicide rate in the older groups (70 and above) and no association in the youngest groups (under 20) in both genders. However, the age by gender effect was mixed in the middle age groups, where the interaction was significant or there was evidence of a similar trend, in most of the age groups in men, and less so in women. The clear exceptions were the age groups of 50–59 in women and 60–69 in men, where there was not even a trend for association. Antidepressant rate remained a significant predictor of reducing suicide rate after controlling for divorce rate or unemployment rate, although the association no longer significant after covarying for alcohol consumption.

This study extends a previous finding that in Hungary an increase in antidepressant prescriptions corresponded to a significant overall decrease in the national suicide rate. Between 1982 and 2000, unemployment and alcohol consumption increased, thus the contributing role of unemployment and alcoholism could be excluded for that investigational period. Between 1999 and 2005 socio-economic and health-care factors may have contributed to the decline in suicide rates, as there was a small decrease in the unemployment and all-cause mortality rates. Although there was an increase in alcohol consumption, there was a decline in the number of alcohol-related liver deaths, probably reflecting the improvement in health care, similarly to the increased life-expectancy. We performed a psychological autopsy in the highest suicide rate region of Hungary; (Szanto and Mann, unpublished data) alcoholism was present in 75% of male and 21% of female suicides, and suicide victims aged 60 and over were less likely to have alcohol use disorder even when adjusted for the lower rate of males in this age group. The highest decline in alcohol-related liver deaths was in the 30–49 year old age groups in both genders and the smallest decline in the group aged 80–89 yrs. Thus, it is unlikely that the change in alcohol-related liver deaths had a major role in the magnitude of the decline in suicide rate in elderly suicide (aged 80 and older men: 224 to 155 per 100,000/yr; women: 65 to 25 per 100,000/yr in 1999 and 2005 respectively).

Other suicide risk factors such as the national divorce rate did not change, the GDP increased, and there was no change in the access to lethal means. In Hungary, the majority of suicides are carried out by hanging, there is minimal gun ownership, and there was no change in access to medications.

Our findings of a correlation consistent with a protective effect of antidepressant in reducing suicide rate in the elderly is in agreement with two studies (Hall et al., 2003; Nakagawa et al., in press), and also the recent U.S. Food and Drug Administration (FDA) meta-analysis of about 100,000 patients in its data base of randomized control trials of antidepressants (Valuck, 2006) that found the odds ratio for suicidality in individuals aged 65 and older who were taking antidepressant was 0.37 ($p=0.007$), showing a strong protective effect of antidepressants. The same FDA study reported that the odds ratio was 1.62, $p=0.07$ for subjects under 25, and 0.79, $p=0.03$ in the 25–64 age group; suggesting less efficacy in young adults and youth. One possible explanation for the apparently protective effect of antidepressants in the 65 and older age group is a larger proportion of uncomplicated depression in suicidal elderly (Conwell et al., 1996), while the role of substance use disorders, other AXIS I pathology, and personality disorders in suicidality is stronger in the younger age groups. Further, as the baseline rate of antidepressant use was lower in the elderly than in the middle-age groups, the same magnitude of change in the older groups might have had a bigger impact.

Effective treatment of mood disorders is crucial for suicide prevention, as the most common psychiatric diagnosis in suicide victims is a major mood disorder (Rihmer et al., 1990; Waern et al., 2002; Cavanagh et al., 2003) which, in the majority of cases, is untreated or inadequately treated (Henriksson et al., 2001; Mann et al., 2005). Moreover in patients with mood disorders fatal suicide, suicide attempt, and suicidal ideation appear almost exclusively in the course of mood episodes, particularly when severe depression and hopelessness are present, and markedly decrease after clinical recovery (Valtonen et al., 2005; Sokero et al., 2006; Szanto et al., 2003; Szanto et al., 2007). Local intervention studies involving improved diagnosis and treatment of depression report declines in suicide attempt rates (Hegerl et al., 2006) and completed suicide rates (Rutz et al., 1989; Szanto et al., in press). However, not all studies support the protective role of antidepressants. A meta-analysis of randomized clinical trials by (Khan et al., 2003) found no difference in rates of suicide for patients treated with SSRI-s, non-SSRI antidepressants, or placebo. Although, our study suggests a possible causal association, this quasi-experimental design cannot prove that antidepressant medication in itself prevents suicide. Moreover, we agree with Hall and colleagues (Hall et al., 2003) that antidepressant use is a proxy measure for overall management of depression. Prescription of an antidepressant is carried out in a social context, in most cases accompanied by some form of psychosocial intervention, which maybe a powerful ingredient in itself. Medications still have an effect as reported in the United States, antidepressant medication prescription volumes, even after considering mean income level and number of physicians, perhaps reflecting access to health care, are still inversely correlated with suicide rates at the county level (Gibbons et al., 2005).

The strengths of the study include reliable data on completed suicides and antidepressant use over a 7-year period in a national data set which includes about 10,000,000 people. Both the Austrian and the Japanese studies used estimates for overall antidepressant levels and inferred survey data to calculate age and gender stratified antidepressant use. By using DDD per person-year data for the whole population of the country, we had a more accurate estimate of the proportion of the population who received adequate antidepressant treatment than studies who used pill counts or number of persons treated. Further, as national identifier number traced every prescription to a specific person, we had highly accurate data on antidepressant prescription and age and gender.

The main limitation of the study is the quasi-experimental design, and we acknowledge the impossibility of conducting this type of study as a randomized clinical trial. Although, there are no undetermined verdicts in Hungary, we cannot exclude the possibility that underreporting of suicides contributed to the decrease in suicide rates. However, it is

unlikely that there would be a differential proportion of suicides in the different age groups. As over the investigated period the number of motor vehicle accident deaths declined in Hungary, we do not suspect that there was an increase in the proportion of non-documented suicide cases. Our finding that increased alcohol consumption was associated with decreased suicide rate in our model was unexpected. In Hungary, no estimates are available on illegal spirit production and the increase in alcohol consumption was modest and of similar magnitude across the wine, beer, and hard spirits categories. As no alcohol consumption data by age groups were available, we cannot refute that there was a change in the alcohol consumption that differentially affected certain age groups and their suicidality, e.g., increased alcohol consumption in the younger groups and decreased consumption in the older groups.

In summary, our study suggested that antidepressants have a primarily age-dependent effect on completed suicide. While overall there was a strong association between antidepressant use and overall suicide rate in both men and women, the protective effect was most evident in the 70 and older age groups, and was absent in the youngest age group. The greatest increase in antidepressant use was in the elderly which corresponded with the greatest decrease in their suicide rates, showing promise that depression treatment may have a big impact on suicide rate in this age group. This association was strongest in late-life suicide perhaps because the increase in prescription rates was greater in that age group or because depression treatment was more effective. Future studies need to determine whether the benefit of antidepressants in suicide prevention is dependent on a sufficiently high rate of treatment of the at-risk population or an age-specific effect of antidepressant responsiveness. We conclude that prevention studies should take into consideration the age-specific effect of antidepressants.

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Figure 1. Annual Suicide Rate (1999–2005) by Gender and Antidepressant Use
The decrease in the overall national suicide rate correlated with the increase in antidepressant use in both genders

Figure 2. Annual Suicide Rates by Gender and Age and Annual Level of Antidepressant Treatment 1999–2005

The biggest decrease in the suicide rate in the 80 and older age groups correlated with their increased antidepressant exposure.

Table 1**Annual Hungarian Suicide Rates 1999–2005**

Men	1999	2000	2001	2002	2003	2004	2005
<20	4.5	3.6	3.1	3.5	3.2	3.9	2.9
20–29	29.3	27.4	24.4	24.2	21.8	23.4	20.2
30–39	54.1	57.4	47.5	42.0	39.6	39.1	38.4
40–49	85.8	83.6	80.5	79.3	73.6	72.7	70.2
50–59	82.7	78.9	75.2	67.9	74.3	70.3	71.8
60–69	65.5	64.2	60.4	64.2	66.3	57.5	56.8
70–79	103.1	99.9	85.8	89.0	88.2	80.2	72.8
80+	224.7	182.3	188.1	151.9	150.4	148.8	155.0
Total	52.2	50.6	47.0	44.6	44.8	43.4	42.3

Women	1999	2000	2001	2002	2003	2004	2005
<20	0.9	1.1	1.1	1.3	1.1	1.1	1.0
20–29	5.7	4.9	5.0	3.6	3.1	4.3	3.3
30–39	11.8	10.0	8.4	10.2	6.9	7.8	8.3
40–49	16.7	19.4	16.0	17.9	15.7	18.5	13.5
50–59	18.5	16.6	19.5	16.8	16.8	17.8	18.0
60–69	23.1	24.2	16.3	13.5	17.0	17.1	16.2
70–79	28.0	32.5	27.2	21.8	25.4	22.4	23.4
80+	64.6	65.3	50.6	46.2	44.1	36.5	25.1
Total	14.5	15.0	13.0	12.1	12.0	12.3	11.2

Table 2

Antidepressant Use Annually (1999–2005), based on Defined Daily Dose (DDD) of antidepressants

Level of Treatment *	1999	2000	2001	2002	2003	2004	2005
Men							
>20	1.1	1.1	1.2	1.3	1.4	1.4	1.4
20–29	5.4	5.5	6.1	6.7	7.9	7.6	8.3
30–39	9.0	8.1	9.6	10.5	12.3	12.0	13.3
40–49	12.0	10.6	12.5	13.8	16.5	16.2	18.5
50–59	13.6	12.5	14.7	16.5	20.0	19.5	22.6
60–69	12.2	11.3	13.3	15.0	18.2	18.2	21.2
70–79	13.0	12.8	15.3	17.5	20.8	20.9	24.6
80+	9.5	9.5	12.3	14.9	18.3	18.6	22.8
Total	7.9	7.3	8.8	9.8	11.7	11.6	13.3

Level of Treatment *	1999	2000	2001	2002	2003	2004	2005
Women							
>20	6.2	6.1	7.2	7.8	9.3	8.9	9.5
20–29	9.6	9.2	10.6	11.2	13.3	12.7	13.6
30–39	23.8	21.7	24.5	25.4	29.1	27.4	29.2
40–49	35.7	31.7	36.8	39.5	46.4	45.1	49.8
50–59	34.4	31.9	38.4	42.6	51.7	51.1	59.1
60–69	29.1	27.2	31.9	35.0	41.1	40.2	46.8
70–79	26.4	25.6	30.6	35.3	41.9	42.6	50.3
80+	15.0	15.7	20.0	24.1	29.8	31.0	37.3
Total	20.3	18.9	22.3	24.5	29.1	28.6	32.6

* Level of Treatment per person per each day of the year (DDD×1000/ 365× population)

Table 3

Correlation of Level of Treatment and Suicide rates

	Men	Women
Total population	-0.90 *	-0.92 *
<20	-0.32	-0.25
20-29	-0.96 *	-0.82 *
30-39	-0.96 *	-0.71
40-49	-0.93 *	-0.68
50-59	-0.64	0.11
60-69	-0.29	-0.61
70-79	-0.86 *	-0.75 *
80+	-0.75 *	-0.96 *

Level of treatment was calculated as $(DDD \times 1000 / 365 \times \text{population})$

Suicide rates over the years were correlated with DDD rates with Spearman Rho,

* significant correlations at $p < 0.05$ with a value of 0.75 with seven observations