

**Association between seasonality of suicide and increase in
antidepressant consumption in Hungary between 1998 and 2006
from the aspect of gender differences**

PhD theses

Beáta Sebestyén

**University of Pecs
PhD School of Health Sciences**

Leader of PhD School: József Bódis MD DSc professor
Consultant: József Bódis MD DSc professor
Zoltán Rihmer MD DSc professor

2010

Pécs

1. INTRODUCTION

Self destructive behavior is a complex, typically human behavior with several medical-psychiatric and psychosocial components.

According to international and Hungarian studies more than 90% of suicide suffers from a psychiatric disorder at the time of their suicide, and the most frequent psychiatric diagnosis is major depression (mostly untreated). Since, just like in other countries the one year prevalence of major depression in Hungary is 7.1%, efficient treatment of depression may have a significant impact on suicide mortality. Suicide mortality rates in Europe were always higher compared to other continents, and both in Europe and in North America, but also in other parts of the world showed a slow but uniform increase in the second half of the 20th century. Although (in part also due to the spreading of the more efficient treatments for psychiatric disorders and mainly depression) there is a steady decrease in the suicide rates in the majority of countries since the 1990s, in several European countries including Hungary the mortality due to suicide per year per 100 000 habitants (suicide rate) is still above 20. Suicide rate in Hungary from 1986 until 2006 showed a continuous decrease from 45 to 24, which is nearly 50, meaning the second highest decrease in the world after Denmark. During this period the increase in antidepressant consumption was nearly tenfold, while unemployment, divorce rate and alcohol related mortality showed a rather negative tendency (increase) after the 1990s. Since suicide – even in case of depressed patients – is related to several psychosocial factors as well, understanding psychological and social processes leading to the suicidal act, and developing effective prognostic and preventive strategies and monitoring the effectiveness of these strategies is a fundamental public health priority, which has also been declared as such by the European Union.

2. AIMS

The aims of our study were defined as follows:

1. Antidepressant consumption significantly increased during the past two decades all over the world including Hungary, while suicide related mortality gradually decreased in the majority of countries including Hungary. In our study we set out to investigate the structure of the increase in antidepressant consumption: agents in which pharmacological groups showed increase or decrease, and what were the patterns of structural change in antidepressant consumption by gender, age groups, regions and countries.
2. Since there are significant differences in county and regional suicide rates in Hungary, in our present study our aim was to investigate the association between the national, regional and county-wide change in antidepressant consumption and changing national, regional and county suicide rates.
3. Since the incidence of depression shows a well-known seasonal variation, which is also followed by the trend of suicide-related deaths, and according to a previous study the decrease of seasonality may be a potential marker of the suicide-preventive efficacy of antidepressants, we collected data concerning the monthly and quarterly distribution (seasonality) of suicides and antidepressant consumption to investigate the association between national, regional and country wide suicide rates and the seasonal fluctuation of suicides with respect to the increasing antidepressant consumption.

Thus the aim of our present study was to provide a detailed analysis of the relationship between the increase and structural change of antidepressant consumption and suicide rates in Hungary during the period between 1998 and 2006 with respect to gender, regional and country wide differences and also taking seasonality into account.

3. METHODS

Drug consumption data

Our drug consumption data were derived from the National Health Insurance Bursary (OEP) database registering prescription drugs. The database was prepared with the approval of the Legal Department of OEP and did not contain any data which would have allowed for the identification of patients. The provided data showed antidepressant consumption during the period of 1998-2006 in quarterly divisions, in the 0-19 year, 20-39 year, 40-59 year and 60+ year age group divisions, distributed according to gender and indicating microregion/county/region.

Calculation of dose equivalent values

From the basic data we calculated drug sales (F), i.e. we summarized in each study year (e) the prescribed amount of each agent (h) per gender (n), in each age group (k). We transformed drug sales into dose equivalents (D) based on the defined daily dose (DDD) as defined by the WHO.

$$D_{h,n,k,e} = F_{h,n,k,e} / DDD_h$$

DDD/1000 persons/day shows that on each given day of the year, calculated for 1000 persons, how many people take antidepressants in the dose defined by WHO. Dose equivalent per 1000 person (E) was calculated using the midyear population number according to age and gender for the given year:

$$E_{h,n,k,e} = D_{h,n,k,e} / N_{n,k,e} \times 1000$$

Values for each agent was summed for pharmacological groups (nonselective monoamine reuptake inhibitors – N06AA; Selective monoamine reuptake inhibitors – N06AB; monoamino oxidase inhibitors – N06AG; other new antidepressants – N06AX), and we carried out the same summation for all antidepressants.

Population data

The headcount of the Hungarian population corresponding to January 1 in each study years by ageyears and gender were provided by the Central Office of the Administrative and Electronic Public Services. After aggregation according to gender and age groups corresponding to the age groups of our study we created midyear population numbers (as a simple mean of the headcount of the given stratum in the beginning and end of the year). We calculated dose equivalents per 1000 persons based on this.

Suicide data

The number of suicides (ICD-10 X65) is published every year in the Demographic Bulletin of the Central Statistic Office given for 5-year age groups. Suicide rates (for the country, for genders, for age groups, etc) were given as the number of suicides committed in the given year per 100 000 inhabitants. Based on the stratum-specific mortality data for age groups (0-19, 20-39, 40-59, and above 60) and genders and the population structure of the year 1998 showing a similar distribution we calculated standardized suicidal mortality by gender and also for both genders together for each study year. Results were given for 100 000 persons.

Seasonality, seasonality index

Based on the number of suicidal cases by month (N/month) we calculated a yearly variation coefficient as a seasonal index.

Mean number of cases per month:

$$M_{\text{months}} = \sum N_{\text{month}} / 12$$

Standard deviation of mean number of cases per month:

$$S_{\text{month}} = \frac{\sum (N_{\text{month}} - M_{\text{month}})^2}{11}$$

Variation coefficient (seasonality index):

$$V_{\text{month}} = \frac{S_{\text{month}}}{M_{\text{month}}}$$

Calculation of ARIMA, correlation

Auto-Regressive Integrated Moving Average (ARIMA) is a method for the time series analysis of independent variables. We investigated the relationship between drug prescription and seasonality with the help of time trend analysis.

Pearson's correlation coefficient: Investigates the relationship between two changing quantities. The coefficient describing the closeness of the correlation is denoted by r , and it measures the closeness of the linear relationship between the measures. It can be applied to interval scale data.

Spearman's rank correlation coefficient: Can be applied to data which are either not normally distributed or cannot be measured on interval scale. Rank correlation coefficient is the Pearson's correlation coefficient between the rank numbers, if there are no linked ranks. Therefore the correlation coefficient calculated this way can also have values between -1 and +1, and it can be interpreted the same way except that in this case we compare rank numbers instead of the original numbers.

Kolmogorov-Smirnov test: Tests the identity of the distribution of two samples. The test can only be used for continuous variables.

SPSS 11.0 was used for that statistical analysis of our data.

4. RESULTS

1. Suicide related mortality in Hungary in the study period

Between January 1, 1998 and December 31, 2006 there were 26290 suicides in Hungary (20096 males and 6194 females), and during the study period suicide mortality significantly decreased in case of both males and females in all age groups and geographical areas. The national suicide rate decreased from 31.4 in 1998 to 24.3 in 2006 (-23%), while antidepressant consumption increased from 11.5 DDD/1000 persons/day to 24.5 (+113%). In case of women the decrease of suicidal mortality (21%) was significant also during the 9 years of the study. In the background of this phenomenon mainly the relatively significant decrease in old age (above 60 years) and young adult age (20-39 years) suicide mortality can play a role. In case of those younger than twenty years and in the middle age group (40-59 years) mortality remained relatively unchanged. The decrease of suicide mortality was relatively similar in case of men (23%), but due to the greater number of cases, the significance of mortality decrease was higher. In case of the middle age group the same trend was observable as in the other age groups. Only the mortality rates of those younger than 20 years did not change in the period between 1998 and 2006. Total mortality calculated by inner standardization (using a direct standardization method based on 1998-2006 mean headcount data for age groups) decreased by 0.47 hundred thousandths for women and 1.52 hundred thousandths for men. According to our aims we summarize our results below.

2. Antidepressant consumption and its structural change between 1998-2006 in Hungary by gender, age groups and geographical areas

During the 9 years of the study 747479766 (males 235738985, females 511740781) regular daily dose equivalents (D_e) of prescribed antidepressant were purchased in pharmacies according to the register of the National Health Insurance Bursary. The slightly more than twofold excess in case of women was observable for every year. The majority of antidepressants (44%) was used by those between 40 and 59 years of age. In the age group of below 20 years, only 4% of antidepressants were consumed. In the youngest investigated age group the gender difference wasn't significant. There was a definite female excess in the young adult group, which increased further in the older age groups.

Yearly drug consumption per 1000 persons increased from 3758.9 D_e to 6981.5 in 2006 among men. In case of women, besides higher consumption we observed a similar increase from 7166.9 D_e/1000 to 14185.4 D_e/1000. These consumption data allow for an estimation of the prevalence of treated depression, or rather the ratio of those undergoing antidepressant treatment: in 1988 1.02% of men and 1.96% of women were treated, and this increased to 1.91% and 3.89% in 2006, respectively. The highest treatment frequency was observed in the 50-59 age group both in case of men (1998: 1.54%; 2006: 2.79%) and women (1998: 3.30%; 2008: 6.45%).

Medications in the different pharmacological groups contributed to the general increase in consumption data to a different degree. Utilization of nonselective monoamine reuptake inhibitors (N06AA) was significantly reduced in both genders. In case of children and young adults who account for only a small part of the consumption no substantial change was observable. There was, however, significant change in the older age groups. Altogether there was a 16.9 DDD/1000 yearly consumption decrease registered in men and a 54.4 DDD/1000 yearly consumption decrease registered in women.

Utilization of monoamino oxidase inhibitors (N06AG) slightly increased in the age groups below 60 years, which altogether wasn't fully compensated by the reduction of consumption above 60 years of age. Due to this among males a 7.7 DDD/1000 and among females a 4.1 DDD/1000 yearly consumption increase was registered. This can be considered as stagnation with respect to our present study.

A significant increase could however be detected in the consumption of other new antidepressants (N06AX) in both genders in all age groups, but particularly among those above 40 years of age (men: 116.7 DDD/1000; women: 262.2 DDD/1000 yearly increase in consumption).

The most significant change in all age groups and both genders was the drastic increase in the utilization of selective monoamine oxidase inhibitors (N06AB). A minimum of 110.3 DDD/1000 persons and a maximum of 884.4 DDD/1000 persons yearly increase in consumption was observable in the study groups by gender and age groups. Due to this, the change in antidepressant consumption during the study period was primarily determined by the 227.7 DDD/1000 persons in men, and 589 DDD/1000 persons in women increase in consumption.

3. Relationship between suicidal mortality and antidepressant consumption on national, regional and county level according to gender and age groups

During the investigated period of 9 years we found a strongly significant ($p < 0.001$) relationship between the increase of antidepressant consumption and the decrease of the Hungarian suicide rate, and this relationship was 8 times stronger in case of men. In general, yearly antidepressant consumption and the standardized suicide mortality calculated for both genders showed to be very strong investigated by all statistical approaches. Correlation calculations supposing the normal distribution of variables (Pearson's coefficients) $r = -0.956$ and the corresponding linear regression coefficient $b = -0.597$ ($p < 0.001$) both indicated a strongly significant inverse relationship. The analysis not supposing the normal distribution of variables yielded similar result: Spearman $\eta = -0.917$ ($p < 0.001$). In case of men ($p < 0.001$) and women ($p < 0.001$) the same similarly strongly significant inverse relationship could be observed. Regression analysis also taking into consideration the time order of data, and corrected for autocorrelation with respect to time described a similar relationship: men $b_{ARIMA} = -1.660$ ($p < 0.001$); women $b_{ARIMA} = -0.215$ ($p < 0.001$); both genders $b_{ARIMA} = -0.623$ ($p < 0.001$). The similarity of trends in case of the two genders can be most straightforwardly demonstrated by analysis using the mortality rates and consumption data of the first year as point of reference. The parallel relative measures in the two genders emphasize the completely similar relationship between suicide mortality and drug consumption.

Analyzing separately the relationship between the antidepressants in the individual pharmacological groups and suicide related mortality with the same methods there is no significant relationship at either outcome in case of monoamine oxidase inhibitors. For nonselective monoamine reuptake inhibitors, statistical methods not correcting according to autocorrelation with respect to time showed a significant relationship between mortality and drug consumption. The direction of the coefficients indicated that the consumption of more medications is associated with a higher mortality rate. ARIMA however showed that there was no relationship between suicide-related mortality and nonselective monoamine reuptake inhibitor consumption in either genders and in the whole study population. In case of selective monoamine reuptake inhibitors and other new antidepressants all statistical methods yielded the same results. From all of these methods ARIMA yielded the most convincing results. The consumption data of both pharmacological groups showed an inverse relationship with suicide mortality.

In case of those younger than 20 years of age, neither statistical methods indicated an association between drug consumption and mortality, except for ARIMA which indicated an inverse relationship ($p=0.030$). All statistical methods indicated a significant inverse relationship between mortality and antidepressant consumption among those aged between 20-39 years ($p<0.001$), 40-59 years ($p<0.001$) and those older than 60 ($p<0.001$).

Suicide related mortalities calculated for Hungarian regions showed a significant variation in the beginning of the study period (minimum: 22.04/100000; maximum: 47.23/100000). In the 9 years observed in the study, mortality decreased in all regions. The yearly relative change was between -14% and -0.27%. The yearly change in antidepressant consumption also showed significant regional variation. Consumption significantly increased in all regions, due to the increase of selective monoamine reuptake inhibitor and other new antidepressant utilization. Utilization of nonselective monoamine reuptake inhibitors (tricyclic and tetracyclic antidepressants) decreased everywhere. Monoamine oxidase inhibitor consumption showed no significant change.

Regional changes in antidepressant consumption showed a significant association with the change in regional suicide related mortality ($p=0.023$). Instead of the inverse relationship seen in the time series analysis, at this regional difference analysis level higher drug consumption was associated with a smaller decrease in suicide mortality. The change of nonselective monoamine reuptake inhibitor ($p=0.337$) monoamine oxidase inhibitor ($p=0.482$) and other antidepressant ($p=0.094$) consumption was not associated with regional changes in mortality. The association observed for the regional changes in total antidepressant consumption was the result of the significant positive association observed in case of selective serotonin reuptake inhibitors ($p=0.052$).

Investigating the above variables at the level of counties we found trends similar to those observed in the regional analyses. No statistical method yielded a significant association between the change in antidepressant consumption and mortality rates neither in case of the total antidepressant consumption ($p=0.830$) nor in either pharmacological groups.

4. Association of decrease in suicidal mortality and increase in antidepressant consumption with respect to seasonality of suicides

As for the seasonality of suicides, spring/early summer peak and winter minimum observable at the end of the 1990s in both genders gradually disappeared by 2005/2006 in spite of the fact that this steadily decreasing tendency was significant only in males. Monthly case numbers of

suicide related mortality varied between 4.19 and 9.10 in men. In case of women the range was 0.94-3.00. In case of both genders we observed an April-July maximum and December-January minimum. Within-year variation was described by the variation coefficient for daily suicidal deaths ($VC = \text{within year variance} / \text{year mean}$). The value of the seasonality index defined this way was between 11.0% and 18.0% in men. In case of women a greater variation was observed (14.5%-22.5%).

The association between antidepressant consumption in each year and seasonality index was not significant in any statistical analysis in women ($p=0.559$). In case of men ARIMA corrected for autocorrelation showed a significant association between seasonality and drug consumption: increasing antidepressant consumption was associated with the decrease of the seasonality index ($p=0.017$). In the two genders analyzed together there was no significant associations between the two parameters, only a strong tendency was observed ($p=0.086$).

Slopes describing monthly variation run parallel in case of the two genders which is also indicated by male/female ratios with only a slight variation around -0.4 (in case of men, improvement increase at the same rate). This similar trend can in principle be explained by the similar rate of increase of antidepressant consumption. August-September shows a marked difference, where in case of women mortality showed no change during the investigated 9 years. Here we observed a marked gender difference. There may exist a risk factor leading to an increased vulnerability for women in August-September, which showed no substantial change during the 9 years. This result may support the supposition that the impact of the “regular” social influences is greater in women. It is also possible that the beginning of school in families which are in a critical situation constitute a “push” for the previously balanced women. The general trend can be explained by the increase of antidepressant consumption, while the August-September risk factor of women is important and independent of antidepressants.

4. THESES

1. During the 9 years of our study altogether 26290 completed suicides were registered in Hungary (20096 men and 6194 women) and yearly mortality decreased in both genders continuously between 1998 and 2006. In case of women the decrease in mortality was significant with respect to its ratio. In case of men, the level of decrease of suicide mortality was similar, however, due to larger case numbers the decrease in mortality had a much larger volumen. For women and men under 20 years of age and for women aged between 40 and 59 the decrease in suicide mortality was minimal, however, it was marked in case of men above 20 years of age and women aged between 20 and 39 and older than 60 years.
2. During the investigated time period antidepressant sales increased in both genders, all age groups and all geographical areas of Hungary, which was mainly due to an increase in selective monoamine reuptake inhibitor and other new antidepressant sales. There was no significant change in the prescription rates for monoamine oxidase inhibitor (nialamid and moclobemide) preparations, while utilization of nonselective monoamine reuptake inhibitor antidepressants (tricyclic and tetracyclic preparations) was reduced.
3. The relationship between the increase in yearly antidepressant consumption and the standardized suicide mortality calculated for both genders appeared very strong both nationally and according to geographical areas and age groups in all statistical analyses. Analyzing antidepressants separately according to pharmacological groups we found that only the increase in the sales of selective monoamine reuptake inhibitor antidepressants and other new antidepressants (dual action agents) showed a significant negative relationship with national and regional or countywide suicide rates in both genders and all age groups.
4. Yearly change in antidepressant consumption was significant at regional and county level, however, on the county level there was no significant relationship between the increase in antidepressant consumption and the decrease of suicide rates, that is we cannot state that suicide rates showed the highest decrease in those regions and counties where antidepressant sales showed the highest increase and vice versa. In the

study period, antidepressant consumption significantly increased everywhere in Hungary, due to an increase in selective serotonin reuptake inhibitor and other new generation antidepressant utilization.

5. The relationship between the increasing antidepressant consumption and decreasing seasonality index observed during the study period was highly significant for men, while in case of women this relationship was not significant in any statistical analyses.
6. The decrease of the seasonality of suicides is significantly related to depression, and may be a marker of decrease in depression-related violent suicides especially in men who are more prone to employ violent suicide methods.

6. SUMMARY

During the 9 years of the study, we found a significant negative correlation between steadily increasing antidepressant consumption (+113%) and decreasing national suicide rates (-23%, $p < 0.001$). During this period antidepressant sales increased gradually in both genders, all age groups and all regions and counties of Hungary which showed a significant negative correlation with national, regional and county suicide rates. The increase in antidepressant consumption was exclusively the result of the increase in selective serotonin reuptake inhibitor and other new generation antidepressants while tricyclic and tetracyclic antidepressant sales decreased in both genders, all age groups and all geographical areas. According to previous studies seasonal incidence of suicides (spring/early summer peak, winter minimum) is a result of the seasonal variation of depression-related suicides. In our present study we analyzed the increase in antidepressant sales and the pattern of suicide seasonality in Hungary between 1998 and 2006. Although the increase in antidepressant sales and the decrease in suicide rates was very similar in men and women, the association between the increase in antidepressant consumption and suicide rates was 8 times stronger in men. Increasing antidepressant sales was significantly related to the decrease in the seasonal incidence of suicides in men. According to our results the decrease in the seasonality of suicides may be a good marker of the decrease of depression-related suicides.

ACKNOWLEDGEMENT

I would like to acknowledge my workplace leader Dr. Péter Brunner, who supported my scientific work from the beginning. I would also like to express my gratitude for my consultant Prof. Dr. József Bódis, leader of the PhD school of the University of Pécs, who accepted, supported and coordinated my research.

I am indebted to my consultant Prof. Dr. Zoltán Rihmer, who raised my attention to the association between depression and suicide, and supported my work with valuable professional advice, suggestions and patience.

I would like to acknowledge Dr János Sándor for his help during the statistical analysis. Finally I would like to thank Dr. Xénia Gonda and Andrea Balázsne for their help which contributed to increasing the quality of my thesis.

PUBLICATIONS

Publications related to the topic of the dissertation

Sebestyén B, Rihmer Z, Bálint L, Szokontor N, Gonda X, Gyarmati B, Bodecs T, Sandor J. 2010. Gender differences in antidepressant suicide mortality in Hungary 1998-2006. *World Journal of Biological Psychiatry* 2010; 11: 579-585. **IF: 5,564**

Torzsa P, Rihmer Z, Gonda X, Szokontor N, **Sebestyén B**, Faludi G, Kalaby L. 2009. Family history of suicide: A clinical marker for major depression in primary care practice *Journal of Disorders* 117: 202-204. **IF: 3,12**

Torzsa P, Rihmer Z, Gonda X, **Sebestyén B**, Szokontor N, Kalaby L. 2008. A depresszió prevalenciája az alapellátásban Magyarországon *Neuropsychopharmacologia Hungarica* 5: 265-270.

Sebestyén B, Gonda X, Berze H, Rihmer Z. 2006. Öngyilkosság és depresszió: az ápolók szerepe a felismerésben és megelőzésben *Nővér* 19: 13-20.

Presentations

Sebestyén B, Szokontor N. Relationship between antidepressant utilization and suicide rate of Hungary between 1994 and 2003. ECNP Seminar, Siófok, 2008.

Szokontor N, **Sebestyén B**. Analysis of epidemiology of suicide in Hungary in the past 15 years ECNP Seminar, Siófok, 2008.

Szokontor N, **Sebestyén B**, Gonda X, Rihmer Zoltán: Öngyilkosságok epidemiológiai vizsgálata Magyarországon az elmúlt 15 év távlatában. Magyar Neuropszichofarmakológiai Kongresszus, Tihany 2008.

Rihmer Z, **Sebestyén B**. Depresszió, antidepresszívumok és öngyilkosság Magyarországon, OSzMK Konferencia, Budapest, 2008.

Rihmer Z, **Sebestyen B**. The relationship between the spring peak of suicides and depression
Annual meeting of the SLTBR, Bécs, 2010.

Posters

Sebestyen B, Markó K. GroupTherapy In Painting for Guided Music 1st Art Therapy World
Congress, Budapest, 2003.

Sebestyén B, Szamosközi P, Brunner P, Rihmer Z. Unipoláris depresszió kezelésének
indikátorai Magyar Pszichiátriai Társaság XIII. Vándorgyűlése, Miskolc, 2007.