

Antidepressants and public health in Iceland

Time series analysis of national data

TÓMAS HELGASON, HELGI TÓMASSON and TÓMAS ZOËGA

Background Major depressive disorder is the second leading cause of disability-adjusted life-years in developed regions of the world and antidepressants are the third-ranking therapy class worldwide.

Aims To test the public health impact of the escalating sales of antidepressants.

Method Nationwide data from Iceland are used as an example to study the effect of sales of antidepressants on suicide, disability, hospital admissions and out-patient visits.

Results Sales of antidepressants increased from 8.4 daily defined doses per 1000 inhabitants per day in 1975 to 72.7 in 2000, which is a user prevalence of 8.7% for the adult population. Suicide rates fluctuated during 1950-2000 but did not show any definite trend. Rates for out-patient visits increased slightly over the period 1989-2000 and admission rates increased even more. The prevalence of disability due to depressive and anxiety disorders has not decreased over the past 25 years.

Conclusions The dramatic increase in the sales of antidepressants has not had any marked impact on the selected public health measures. Obviously, better treatment for depressive disorders is still needed in order to reduce the burden caused by them.

Declaration of interest None.

Antidepressants were introduced in the late 1950s and their use was relatively limited until the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the late 1980s. Since then

'widely publicized emphasis on recognition and treating depression and... development of many new pharmacotherapies have contributed to explosive growth in antidepressant prescribing and increasing pharmacy costs for health plans' (Williams *et al*, 2000).

Major depressive disorder is the second leading cause of disability-adjusted life-years in developed regions of the world (Murray & Lopez, 1996) and antidepressants, the third-ranking therapy class worldwide, experienced an 18% sales growth in 2000, with North America being the dominant market (IMS Health, 2002). However, the question remains: has this had any impact on public health and the burden of depression? Analysis of official data from Iceland, with its extensive use of antidepressants, can contribute to answering this question. We have examined the data in order to address the following questions: how much has the sale of antidepressants increased since SSRIs were introduced in Iceland by the end of 1988, and what is the proportional increase in the sale of these and other more recent antidepressants; has the increased use of antidepressants affected the number of psychiatric out-patient visits and the extent of hospital treatment; and has the increased use of antidepressants affected suicide rates or the prevalence of disability?

METHOD

Setting

Iceland has a population of 286 000 (in 2001) with one active physician per 290 inhabitants, including 195 physicians in primary care and 55 psychiatrists. The State Social Security Institute covers the majority

part of the cost for medication and out-patient visits.

Data

The following nationwide data were collected from a range of official sources.

- The Ministry of Health provided data on the amount of medication sold nationwide annually in standard units, daily defined doses per 1000 inhabitants per day (DDD/1000/day), from 1975 to 2000 as well as on the retail price of each type of medication. Antidepressants include tricyclic and tetracyclic antidepressants, monoamine oxidase inhibitors, SSRIs and other antidepressants such as venlafaxine, but exclude stimulants.
- The number of out-patient visits was collected from psychiatric department reports and State Social Security Institute reports for the period 1989-2000.
- The number of admissions to psychiatric departments, the number of in-patient days and the number of in-patients annually for the period 1989-2000 were obtained from hospitals.
- The State Social Security Institute supplied information on the prevalence of the disability pension in 1976 and 2001.
- Official statistics on suicides (Skýrsla, 1996) and information from the Department of Forensic Medicine were obtained for the period 1950-2000.
- Increasing consumption of alcoholic beverages might influence the number of suicides, so data on the annual sales of alcohol per capita for the period 1950-2000 were obtained (Statistics Iceland, 2002).

Until 1993, very few children and adolescents under the age of 15 years were prescribed antidepressants, and in that same year only 0.8% of prescriptions were issued to children under this age. According to a recent limited prescription survey, 6.7% of the antidepressants were filled for this age group (Skýrsla, 1999). Therefore a 1% annual increase was assumed and deducted from the total quantities sold when estimating the number of daily defined doses per 1000 inhabitants aged 15 years or more during 1994-2000.

Statistical analysis

For analyses of time series count data, a

logarithm of expected counts is expressed by Equation (1):

$$\begin{aligned} \log [E(N_t | N_{t-1}, N_{t-2})] \\ = \beta_0 + \beta_1 \log(\text{pop}_t) + \phi_1 \log(N_{t-1}) \\ + \phi_2 \log(N_{t-2}) \end{aligned} \quad (1)$$

where N_t denotes the count in year t ; pop_t is the population size in year t ; and $E(N_t | N_{t-1}, N_{t-2})$ denotes the conditional expected number of counts in year t given the counts in years $t-1$ and $t-2$. The purpose of the logarithmic terms $\log(N_{t-1})$ and $\log(N_{t-2})$ is to allow for possible cyclical behaviour, which could be due to several reasons (e.g. systematic effects in the registration of suicides or latent socio-economic variables). The autoregressive parameters ϕ_1 and ϕ_2 characterise possible cycles in the number of suicides. Spectral time-series analysis (Harvey, 1993) was used to estimate the length of such cycles. The model in Equation (1) assumes that the expected count is proportional to a power of the population size. Thus, the parameter β_1 describes the trend structure of the series and β_0 is an intercept. The diagnostics of the model were performed by analysing the scaled residuals, ν_t , defined by Equation (2):

$$\nu_t = [N_t - E(N_t)] / E(N_t)^{1/2} \quad (2)$$

The statistical inference was corrected for eventual overdispersion, i.e. the variance being greater than the mean, by estimating a quasi-Poisson model of type (1). Eventual misspecification of the model shows up in the scaled residuals. An important omitted variable should show association to them. The Ramsey-RESET test (Gujarati, 1995) was used to test the model specification, such as functional form and eventual missing variables.

The possibility of autocorrelation was addressed by inclusion of autoregressive terms (Cameron & Trivedi, 1998). The statistical program R was used for numerical calculations (Ihaka & Gentleman, 1996).

RESULTS

Sales of antidepressants and suicides

From 1989 the increase in sales of psychopharmacological medication was exponential by about 16.4% per year, with a close to perfect fit for the period 1995–2000.

Table 1 Medication sold in 1989 and 2000

Medication	Quantity (DDD/1000/day)		Cost (Million lkr, 2000 price)	
	1989	2000	1989	2000
All	664.5	983.8	6293	10 465
Psychopharmacological	84.5	162.2	503	1509
Antidepressants	14.9	72.7	184	1033

DDD, daily defined doses.

The increase can be ascribed to new antidepressants, mainly SSRIs, that were introduced to the market in Iceland by the end of 1988. During the period 1989–2000 the total quantity of medication sold increased by 48%, the quantity of antidepressants increased by 388% and the quantity of other psychopharmacological medication, mainly hypnotics, increased by 92%. The cost of all medication calculated according to the consumer price index in the year 2000 increased by 66%, whereas in the same year the use of antidepressants reached 72.7 DDD/1000/day and the cost had escalated by 461% since 1989 (Table 1). This is equivalent to an estimated user point prevalence of 8.7% for the adult population (aged 15 years or more) provided that all the patients are compliant in taking one defined dose per day. The sales of antidepressants in Iceland increased gradually from 1981, when tetracyclic antidepressants were introduced, up until 1985. Thereafter it remained relatively stable, at around 15 DDD/1000/day, up until 1990; since then it has increased very markedly, mainly due to the addition of SSRIs to older antidepressants. The sales of tricyclic antidepressants have been reduced gradually by 21% to 8.6 DDD/1000/day in the year

2000, whereas the sales of SSRIs have continued to escalate to 49.2 DDD/1000/day, as can be seen from Fig. 1. From mid-1996 venlafaxine and other new antidepressants have added to the constant increase in antidepressant sales (venlafaxine sales were 15 DDD/1000/day in the year 2000).

Official figures on the sales of antidepressants have been available only since 1975 and are shown in Fig. 1, along with annual suicide rates and per capita sales of alcohol for the period 1950–2000. An example of model output according to Equation (1) is given in Table 2, which suggests that the number of suicides has increased slightly more than the corresponding increase in population and, by spectral analysis, estimates of the autoregressive parameters (0.45 and -0.33) suggest a cycle of about 5–6 years. The data do not allow us to determine whether this is due to some events within a year or whether there are genuine cycles in the process. The standard errors in Table 2 are corrected for overdispersion. Residual analysis showed that the process is remarkably constant over a 50-year period. The scaled residuals showed no autocorrelation after including the two autoregressive terms

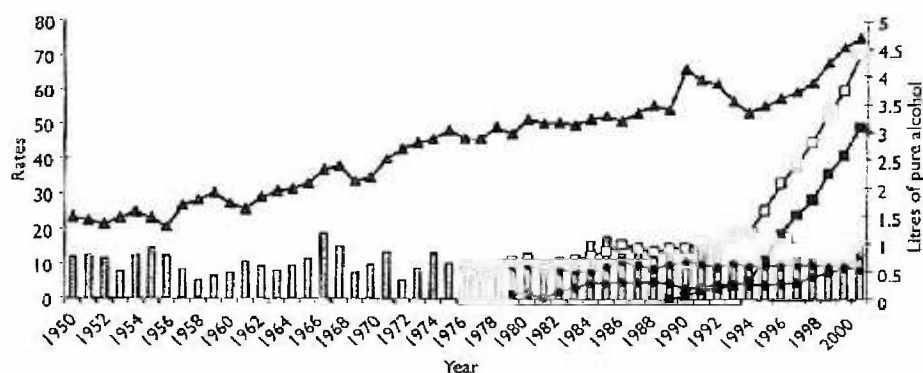


Fig. 1 Suicide rates per 100 000 inhabitants (bars), sales of pure alcohol per capita in 1950–2000 (\blacktriangle) and sales of antidepressants in daily defined doses/1000/day during 1975–2000: \bullet —tricyclic antidepressants; \blacksquare —selective serotonin reuptake inhibitors; \blacklozenge —other antidepressants; \square —total antidepressants.

Table 2 Estimates of a quasi-Poisson model (Equation (1)) for the number of suicides

Variable	Estimate	Corrected standard error	t	P
Constant	-12.44	3.38	-3.68	0.001
Log (Population at time t)	1.24	0.30	4.10	<0.001
Log (Number of suicides at time t-1)	0.45	0.14	3.20	0.003
Log (Number of suicides at time t-2)	-0.33	0.14	-2.36	0.023

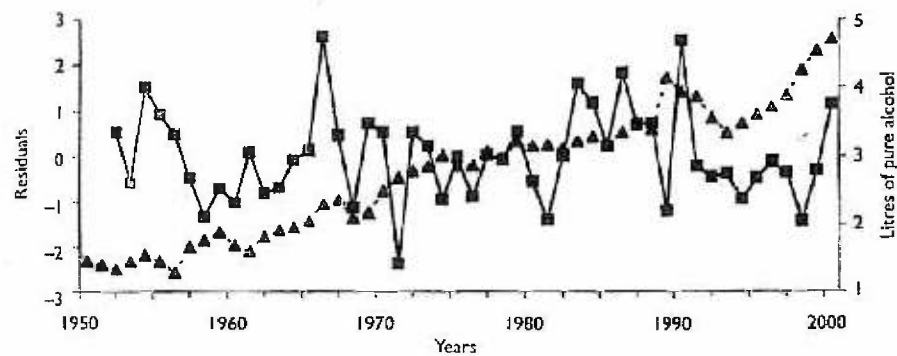


Fig. 2 Standardised residuals from the model used to explain the number of suicides (—■—) and annual per capita alcohol sales (---▲---) during 1950–2000.

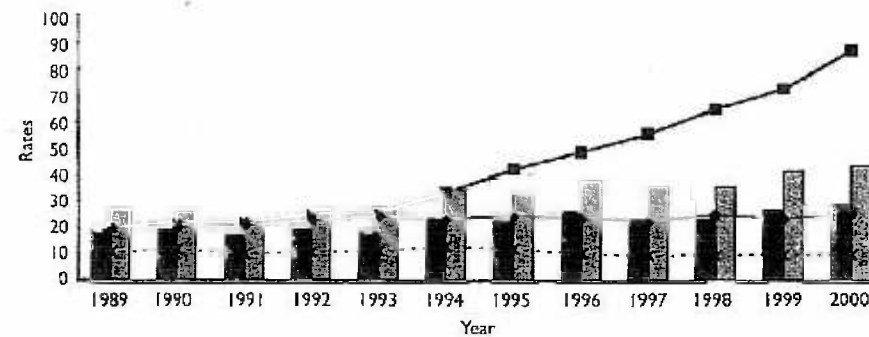


Fig. 3 Sales of antidepressants in daily defined doses per 1000 inhabitants aged 15+ per day (—■—) and use of psychiatric services by adults during 1989–2000: ■ patients admitted per 10 000 inhabitants aged 15 years or more; ▨ total number of admissions per 10 000 inhabitants aged 15 years or more; ···· in-patient days per 100 inhabitants aged 15 years or more; -◆- out-patient consultations per 100 inhabitants aged 15 years or more.

in the model. A Ramsey-RESET test did not indicate that the model was wrongly specified ($P=0.98$). Consequently, there is no indication that a trend or some simple function of time is missing from the model as an explanatory variable, particularly not the increased sales of antidepressants.

Figure 2 shows a graph of standardised residuals of the model. A possible explanatory variable that might add information on the frequency of suicides should have something in common with what is not

explained by the model, i.e. the residuals. To illustrate this point, a graph of the annual average sales of pure alcohol per inhabitant is also shown in Fig. 2. The Ramsey-RESET test did not suggest that the model was wrongly specified. To illustrate this further the model was re-estimated with alcohol consumption per capita and its lagged value added to the model. The impact was only marginal (a likelihood ratio test statistic of 0.42; $\chi^2=0.66$; d.f.=2), which is not surprising

considering the result of the Ramsey-RESET test.

The population in the year 2000 was about 283 000 and the average suicide rate was 11/100 000, so the expected annual number of suicides is around 30. The overdispersion coefficient in the model containing autoregressive terms is approximately 1.5, therefore the standard deviation of the yearly number of suicides is the square root of 1.5×30 , which is about 7. In a model without autoregressive terms the overdispersion is about 1.9, which gives a standard deviation in the region of 8. Thus, the autoregressive parameters have limited impact on predicting the number of suicides.

Sales of antidepressants and psychiatric out-patient visits and hospital admissions

In spite of the dramatic increase in the sales of antidepressants, the rates of psychiatric out-patient consultations and in-patient treatment for depressive disorders increased (Fig. 3). After correcting for the increase in the population aged 15 years or more, the number of patients admitted increased by about 3.9% annually. Similarly, after correcting for the increase in population the admission rates increased by 5.4% per year (i.e. each patient was admitted more often). Furthermore, the number of out-patient consultations increased by 2% per year during the period 1989–2000. The total duration of in-patient treatment for depressive disorders per 100 inhabitants decreased by 1.1% per year whereas that for psychiatric disorders in general decreased by 3.6% annually as the number of available beds decreased.

Disability

The proportion of the general population claiming disability pension because of depressive and anxiety disorders increased from 0.4% to 0.7%, as it did for other disorders over the 25-year period of 1976–2001; however, it remained similar as a proportion of all disability (i.e. about 13%).

DISCUSSION

The sales of antidepressants per capita in Iceland in 2000 were probably comparable to those in the USA (IMS Health, 2002). The retail cost of antidepressants increased in Iceland by 460% during the past 12

years but there are no data available to show that this has offset other costs. The increased cost can be ascribed to the SSRIs and other newer antidepressants because the cost of the older drugs has decreased. The marked worldwide increase in the use of antidepressants and their cost has been the source of much discussion in relation to the cost-effectiveness and possible advantages of the new medications versus the more traditional or other forms of treatment (Agency for Health Care Policy and Research, 1999; Williams *et al*, 2000).

Sales of antidepressants and the prevalence of depressive disorders

Recently, the International Consensus Group on Depression and Anxiety stated that depression was currently underrecognised and undertreated, particularly in young adults (Ballenger *et al*, 1999). The results of the present study hardly support this as regards treatment with antidepressants. The sales of antidepressants in Iceland in the year 2000 corresponded to a user prevalence of 8.7% among those aged 15 years or more, which is within the range of estimates for the community prevalence of depressive disorders: 4–10% among adults (Bebbington *et al*, 1998; Helgason, 1990). Depressive disorders cause considerable impairment, result in increased mortality, reduce the health-related quality of life (Simon *et al*, 1998) and are costly for the patients, their families and society. The direct cost of treating depressive disorders in Iceland, the population of which is approximately one-thousandth of that in the USA, was estimated to be equivalent to £18.6 million in 1998 (Skýrsla, 1999) and about 27% of this amount was ascribed to antidepressants, mainly SSRIs.

The prevalence of subsyndromal depression or of depressive symptoms is considerably higher than that of depressive disorders, being 16–25% (Helgason, 1990). Depressive disorders and symptoms are very common in primary care and are often comorbid with physical disorders (Kisely & Goldberg, 1996); they are also mixed with anxiety disorders, for which antidepressants have been used increasingly in recent years.

During the past 10–15 years new generations of antidepressants have been developed and marketed energetically. At the same time, awareness campaigns have been launched to combat depression

(Paykel *et al*, 1998) and to prevent suicide in a number of countries (Taylor *et al*, 1997). In addition, guidelines for treating depressive disorders have been issued (American Psychiatric Association, 2000). These developments might have been expected to have a public health impact by reducing disability, morbidity and mortality due to depressive disorders, even more so as the new medications are simpler to administer and more likely to be given in adequate dosages than tricyclic antidepressants. However, the cost for society has not been reduced and the impact on public health is limited.

Far fewer antidepressants are taken than are sold (prescribed), therefore prevalence estimates based on sales data are too high due to limited compliance. In a recent community survey the self-reported use of antidepressants (in DDD/1000/day) was estimated to correspond to about 54% of the official sales figures (Helgason *et al*, 2003). The reasons for many of the prescriptions are not clear, as primary care physicians have probably not diagnosed depressive disorder in more than 40–50% of patients prescribed antidepressants (Skýrsla, 1999; Ornstein *et al*, 2000). It should be noted, however, that antidepressants are being used increasingly for other disorders, such as some anxiety disorders and chronic pain.

Admissions, out-patient visits and disability

Admission rates for in-patient treatment of depressive disorders have increased, partly because of more readmissions and partly because more patients are admitted. The number of in-patient days used for depressive disorders has decreased insignificantly but in contrast, the decrease in in-patient days for psychiatric disorders in general has been quite marked. At the same time as these trends were occurring, the availability of psychiatric hospital beds was also decreasing. The increased annual admission rate may indicate increasing acceptance of treatment and decreasing stigmatisation, as well as a possible lower admission threshold for depressive disorders because beds for other disorders might have been freed up owing to the tendency to treat people with psychosis in the community. The rates for psychiatric out-patient visits increased, thus it is conceivable that the new antidepressants have not stopped the

for speciality treatment. It has been found in clinical studies that adequate treatment can be expected to alleviate physical and psychosocial impairment in patients with depression and to improve their quality of life (Simon *et al*, 1998). Despite extensive pharmacological treatment, the prevalence rates for disability due to depressive and anxiety disorders increased, although not as a proportion of total disability. It should be noted that the increased prevalence of disability pension between 1996 and 2001 is related to changes in disability assessment.

Suicide rates

Suicide rates in Iceland have fluctuated roughly as an autoregressive Poisson process with a dispersion coefficient of 1.5 during the latter half of the 20th century, remaining on average about 11/100 000. The age and gender distribution of those who died by suicide may have changed during this period, but the overall rates have not been affected by the sales of antidepressants, which have increased ninefold since 1975. It is unlikely, according to our findings, that a reduction in the sales of antidepressants would affect the rates of psychiatric service use and suicide.

Unemployment has not been a problem in Iceland during the study period, with less than 1% of the labour force being out of work most of the time. However, in 1969 unemployment rose to 2.5%, only to decrease again and then rise to 5% in 1995. In 1999 it had fallen once more to less than 2%. One-third or less of those unemployed were out of work for more than 6 months (Statistics Iceland, 2002). The Ramsey-RESET test (Gujarati, 1995) does not indicate that unemployment and other unknown variables have had an effect on the number of deaths by suicide.

One of the main features of time series models is to filter out trends and cycles. It is conceivable that alcohol consumption, unemployment and other variables affect suicide rates. If that is the case, the residual diagnostics indicate that they are already sufficiently included in the trend-and-cycle component of the model. Thus, it is not likely that a counteracting effect of alcohol and antidepressants can be invoked as an explanation for not finding any effect of the huge increase in antidepressant use on suicide rates in Iceland.

Suicide rates in the population are a

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