Antidepressant Drug Consumption and Public Health Indicators in Italy, 1955 to 2000

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Objective: This study investigated the impact of the increasing consumption of selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants on the following public health indicators: (1) suicide rates, (2) proportion of completed suicides by poisoning with solid or liquid substances, and (3) hospital admissions for depression and proportion of admissions for depression that were first admissions.

Method: Data collected by IMS Health on antidepressants dispensed in Italy from 1983 to 2000 were obtained from the Italian Ministry of Health, while data on suicide deaths from 1955 to 2000 were obtained from the Italian National Institute of Statistics.

Results: In Italy from 1983 to 2000, the use of tricyclic antidepressants remained substantially stable, and the use of SSRIs and newer agents dramatically increased. In contrast, suicide rates for males decreased from 1955 to 1974 and subsequently increased, reaching a peak in 1985 and then declining. In females, suicide rates remained substantially stable until 1978. A subsequent increase occurred up to 1985, followed by a steady decline. Suicide by poisoning using solids or liquids dropped by nearly 50% from 1986 to 2000. Admissions to the hospital for depression showed an erratic pattern; however, no decline was observed. No change was observed in the rate of first admissions for depression.

Conclusion: Despite a reduction in suicides by poisoning using solids or liquids, the analysis of long-term trends in suicide did not suggest that increases in antidepressant prescribing lie behind recent reductions in population suicides. Furthermore, in Italy, newer antidepressants had no impact on the total number of admissions for depression or on the proportion of all admissions that were first admissions.

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Over recent years, antidepressant prescribing has markedly increased in many developed countries, mainly after the introduction of selective serotonin reuptake inhibitors (SSRIs) in the early 1990s.[1–5] This increase might reflect better recognition of and prescribing for depression[6,7] and might therefore have relevant public health implications. In particular, a reduction in the rates of completed suicides and a reduction in the number of suicides by poisoning would be expected as a consequence of better recognition and treatment of subjects with depressive symptoms and because newer antidepressants are rarely lethal in overdose.[8] In addition, a decrease in the number of subjects hospitalized for depression would be expected, given that SSRIs and newer antidepressants should theoretically be associated with better patient adherence and therefore lower relapse rates.

In the present study, we investigated the relationship between the increasing consumption of SSRIs and newer antidepressants and the following public health indicators: (1) suicide rates, (2) proportion of completed suicides by poisoning with solids or liquids, and (3) hospital admissions for depression and proportion of admissions for depression that were first admissions.

MATERIALS AND METHOD

Data Source

This study was carried out in Italy, a country with nearly 60 million inhabitants. National data on numbers of suicide deaths according to the Ninth Revision of the

Figure 1. Suicide Rates per 100,000 Inhabitants and Antidepressant Drug Prescribing in Italy[a]
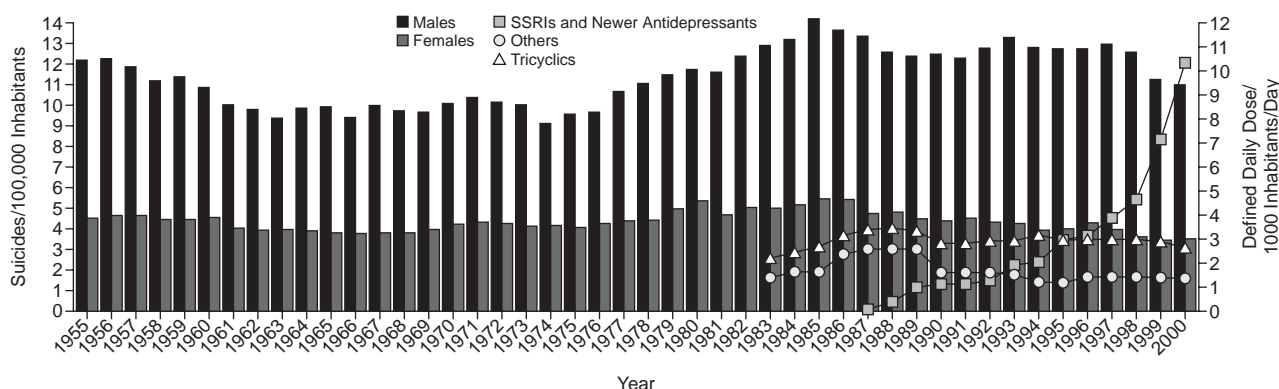
[a]Drug prescription data are from IMS Health, London, England. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Italian *International Classification of Diseases* (ICD-9) in each sex and age group and estimates of the Italian resident population were collected from the Italian National Institute of Statistics (ISTAT) for the years 1955 to 2000. Data after 2000 are not yet available. ISTAT data on suicide methods were extracted according to ICD-9 and include the following categories: 950 = poisoning by solid or liquid substances, 951 and 952 = poisoning by gas, 953 = hanging, 954 = submersion, 955 = firearms and explosives, 956 = cutting and piercing instruments, 957 = jumping from high places, 958 = other nonspecified method. Hospital discharge data were collected from ISTAT, as published in the health care statistics yearbook[9] for the corresponding period. We extracted the total number of admissions for depression and the proportion of admissions for depression that were first admissions up to 1998. Data after 1998 are not yet available.

Data on antidepressant prescriptions were collected by an independent source for pharmaceutical market intelligence (IMS Health, London, England). In Italy, IMS Health gathers data from 251/256 Italian wholesalers (98%); these data are then extrapolated for the whole country. IMS Health provides prescribing information to manufacturers, health care providers, and the Italian Ministry of Health, but is not itself involved in the production or sales of drugs. IMS Health data on drug sales included in this analysis were obtained from the Italian Ministry of Health, which supports the use of the data for research purposes. For each agent, IMS Health records the number of packages sold. From 1983 to June 2000, pharmacologic agents from the N06A group of the anatomical therapeutic chemical (ATC) classification system were extracted and included in the analysis.

Data Analysis

Sex- and age-standardized death rates for all suicides were computed. Standardization was done by the direct method on the basis of the Italian population of the 2001 census year.[10,11]

For each antidepressant, the number of packages sold was converted into defined daily doses (DDDs) per 1000 inhabitants per day (DDDs/1000/day). The DDD is the international unit of drug utilization approved by the World Health Organization for drug use studies.[12] The DDD is a theoretical unit of measurement defined as the assumed average maintenance daily dose for a drug, used for its main indication in adults. The measurement of DDDs/1000/day indicates how many people per 1000 of the population have in theory received a standard dose (i.e., the DDD) of a particular medication or category of medication daily.

For each year, the total number of admissions for depression was divided by the Italian resident population, and figures per 100,000 inhabitants were calculated. Finally, the proportion of admissions for depression that were first admissions was calculated.

Data Presentation

Since statistical methods for assessing possible relationships between antidepressant use and public health indicators are highly controversial and sometimes based on unproven assumptions,[13,14] a descriptive approach to data presentation was employed.

RESULTS

Antidepressant Drug Prescribing

The analysis of antidepressant prescribing revealed that, while the use of tricyclic antidepressants and that of other old agents (mianserin, trazodone, ademetionine) remained substantially stable or slightly declined from 1983 to 2000 (Figure 1), the use of SSRIs and newer agents (venlafaxine, mirtazapine, reboxetine) dramatically increased and accounted for 10.33 DDDs/1000/day in 2000

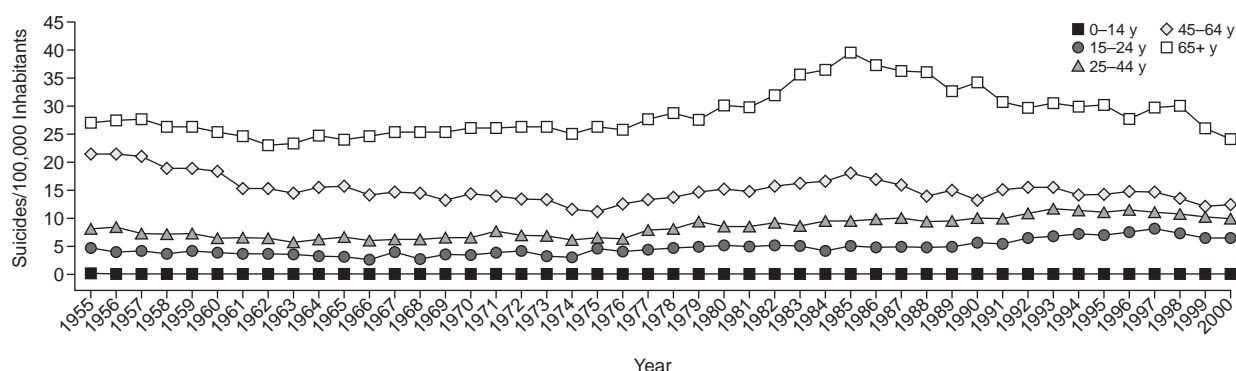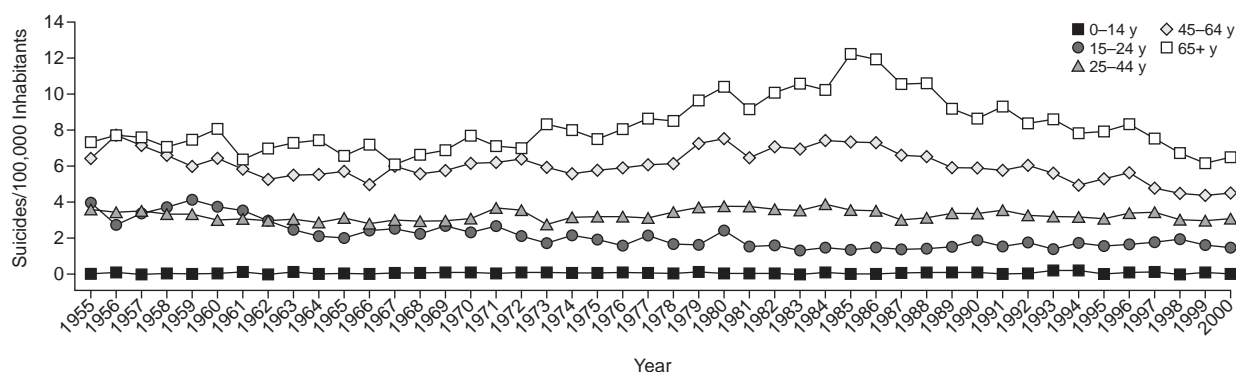Figure 2. Age-Specific Male Suicide Rates in Italy, 1955–2000

Figure 3. Age-Specific Female Suicide Rates in Italy, 1955–2000

(Figure 1). Overall, use of any antidepressant increased from 4.94 DDDs/1000/day in 1983 to 16.61 DDDs/1000/day in 2000.

Public Health Indicators

Standardized suicide rates from 1955 to 2000 are presented in Figure 1. Suicide rates for males decreased from 1955 to 1974 and subsequently increased, reaching a peak in 1985. After 1985, rates declined, from 14.12 to 10.98 per 100,000 in 2000. In females, suicide rates remained substantially stable until 1978. A subsequent increase occurred, followed by a steady decline from 5.42 to 3.54 from 1985 to 2000. Breaking down rates by age, a consistent decrease in suicides was observed during this period in males and females 65 years and older (Figures 2 and 3). In addition, there was a mild trend toward decline in males and females aged 45 to 64 and a slight rise in suicide rates for young men since the 1970s.

The most frequent methods of suicide were hanging, jumping from high places, and firearms and explosives (Table 1). While the proportion of suicides by these methods was substantially stable, suicide by poisoning using liquids or solids dropped by nearly 50% from 1986 to 2000.

Finally, admissions to the hospital for depression, available from 1986 to 1998, showed an erratic pattern (Figure 4); however, no decline was observed. The proportion of all admissions that were first admissions remained substantially stable.

DISCUSSION

Undoubtedly, the availability of SSRIs and newer antidepressants has increased the therapeutic options available for patients with depressive disorders. Their tolerability profile, different from that of tricyclic and related antidepressants, makes these agents particularly suitable in a wide range of situations in which conventional antidepressants are not appropriate. In addition, they are less toxic when taken in overdose and might increase patient adherence to treatment.[15] Although these advantages might be observed in individual patients, it is relevant to

Table 1. Distribution of Suicides in Italy by Method, 1986–2000 (%)

Year	Poisoning by Solids/Liquids	Poisoning by Gas	Hanging	Submersion	Firearms/ Explosives	Cutting, Piercing Instruments	Jumping From High Places	Others
1986	6.16	3.18	37.58	9.96	14.73	1.51	23.70	3.18
1987	4.92	3.28	38.35	8.52	14.77	1.88	25.07	3.21
1988	5.34	3.83	36.92	8.70	13.90	2.08	25.35	3.88
1989	5.62	3.80	37.20	7.72	13.86	1.36	26.76	3.68
1990	4.88	8.16	36.01	6.79	13.18	1.43	25.44	4.11
1991	4.99	8.89	34.62	7.59	13.88	2.00	24.10	3.93
1992	4.82	8.52	34.87	7.81	13.82	2.07	24.26	3.83
1993	4.51	8.64	36.48	6.28	15.07	1.89	23.40	3.73
1994	4.17	7.70	40.15	6.30	14.28	1.63	22.18	3.59
1995	4.22	8.78	39.97	5.65	13.92	1.62	21.27	4.57
1996	4.30	8.53	41.27	6.61	12.48	1.39	21.48	3.94
1997	4.07	6.95	43.20	6.30	13.34	1.34	21.09	3.71
1998	3.51	6.26	42.76	5.88	14.39	1.55	20.74	4.91
1999	4.10	5.93	41.85	5.69	14.92	1.63	21.75	4.13
2000	3.82	5.86	41.82	5.48	14.95	1.68	22.18	4.21

Figure 4. Hospital Admissions for Major Depression and Proportion of First Admissions in Italy, 1986–1998
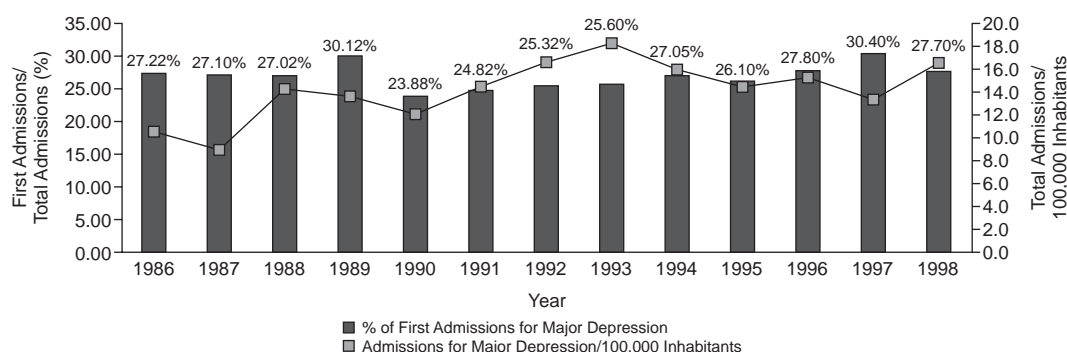
establish and monitor whether there are positive consequences in terms of public health measures.

A dramatic rise in SSRI and newer antidepressant prescribing was accompanied by a drop in suicides by poisoning using liquids or solids in Italy. Although a causal relationship between these 2 phenomena cannot be established by means of the present ecological analysis, in terms of public health, this is a relevant finding, the impact of which on overall suicide rates remains difficult to establish. In Italy, suicide rates have been declining in males and females 65 years and older, but not in young people. Interestingly, according to recent cross-sectional analyses of antidepressant prescribing conducted in selected areas of Italy,[16,17] males and females 65 and older account for the majority of antidepressant prescriptions, thus suggesting a possible impact of antidepressant prescribing in this age group. However, in late life, suicide rates were already declining before the introduction, and before a dramatic rise in prescriptions, of SSRIs and newer antidepressants.

This analysis has 2 main limitations. First, antidepressant sales data allow estimation of the consumption of drugs, but cannot provide information on their real use. Since a relevant proportion of the medicines prescribed for people with chronic conditions are not taken,[18] great caution is required in assuming that antidepressant prescriptions correspond to antidepressant utilization. Second, the naturalistic design of this analysis is subject to the ecological fallacy, and therefore no causal relationships can be established.

In contrast with most ecological analyses investigating the relationship between antidepressant prescribing and suicide, the present study looked at long-term trends. This is a crucial factor because the possibility that suicide rates were already declining before the dramatic rise in antidepressant prescriptions has to be considered.[19] Focusing on 10 to 15 years only, in fact, might give the wrong impression of an association between antidepressant prescribing and suicide rates while, in reality, the outcome of interest (decreasing suicide rates) might have preceded the exposure variable (antidepressant prescribing). Carlsten and colleagues,[20] to overcome this problem, carried out a time-series analysis using a

2-slope model to compare suicide rates in Sweden before and after the introduction of the SSRIs. This analysis found that antidepressant sales increased in men from 4.2 DDDs/1000 inhabitants/day during 1977–1979 to 21.8 in 1995–1997 and in women from 8.8 to 42.4 DDDs/1000 inhabitants/day between the same periods. In the 2 census periods, suicide rates decreased in men by 30.9% and in women by 34.0%. Similarly, in the United Kingdom, declines in suicide preceded increases in prescribing, and rises in antidepressant prescribing since 1991 in different age and sex groups did not consistently coincide with clear changes in previous suicide trends.[14]

Other analyses found contrasting results. Hall and colleagues[21] examined the association between changes in antidepressant prescribing in Australia from 1991 to 2000 and changes in suicide rates. Between 1991 and 2000, the suicide rate markedly decreased in older men and women and increased in young adults, especially young men, yielding a substantially stable total suicide rate. The analysis of antidepressant consumption in the same period showed that exposure to antidepressants was higher for women than men in all age groups and increased markedly for both men and women over the study period, with the largest increases among older adults. A significant negative association was observed between antidepressant consumption and suicide in women but not in men. Among both men and women, the largest declines in suicide occurred in the age groups with the highest exposure to antidepressant across the study period.[21] Similarly, Isacsson[22] analyzed national statistics on suicide, alcohol consumption, unemployment, and use of antidepressants for 1978–1996 in Sweden and for 1990–1996 in Denmark, Norway, and Finland. The suicide rate decreased by 19% in parallel with the increased use of antidepressants in Sweden, Denmark, Norway, and Finland. Moreover, in Sweden, there was no demographic group with regard to age, gender, or county in which the suicide rate decreased in the absence of an increased use of antidepressants. However, in women under 30 and over 75 years of age, and in 4 of the 23 counties, suicide rates remained unchanged despite an increased consumption of antidepressants. Another nationwide analysis of suicide mortality in Finland from 1990 to 1995 was carried out by Ohberg and colleagues[23] with the aim of exploring suicide mortality by various methods. Over the study period, the total suicide mortality decreased from 30.3 per 100,000 inhabitants to 27.2 per 100,000 inhabitants. In the same period, the total consumption of antidepressant agents more than doubled from 9.3 DDDs/1000/day in 1990 to 21.8 in 1995.[23]

Grunebaum and colleagues[24] who investigated the relationship between antidepressant prescribing and suicide rates in the United States, showed that the decline in the national suicide rate appeared to be associated with greater use of non-tricyclic antidepressants. However, only 15 years (1985–1999) were analyzed, and no data

were reported on trends in suicide before 1985. According to other analyses, suicide rates were already declining before 1985 in the United States, especially in females.[19]

In addition to suicide rates, admissions to the hospital is another public health measure that could theoretically have been affected by the introduction of SSRIs and newer antidepressants. We observed no changes in the 13-year period considered. Helgason and colleagues,[25] who carried out a similar analysis in Iceland, a country with only 286,000 inhabitants, found that although sales of antidepressants increased from 8.4 DDDs/1000/day in 1975 to 72.7 in 2000, suicide rates showed no definite trend, and rates for outpatient visits and hospital admissions progressively increased.

In conclusion, despite a reduction in suicides by poisoning using solids or liquids, the analysis of long-term trends in suicide did not suggest that increases in antidepressant prescribing lie behind recent reductions in population suicides. This relationship deserves further and more accurate investigation, for example by looking at the distribution of SSRI prescribing according to age and sex. Furthermore, in Italy, SSRIs and newer antidepressants had no impact on the total number of admissions for depression or on the proportion of all admissions that were first admissions.

Drug names: mirtazapine (Remeron and others), trazodone (Desyrel and others), venlafaxine (Effexor).

REFERENCES

1. Isacsson G, Boethius G, Henriksson S, et al. Selective serotonin reuptake inhibitors have broadened the utilisation of antidepressant treatment in accordance with recommendations: findings from a Swedish prescription database. J Affect Disord 1999;53:15–22
2. Lawrenson RA, Tyrer F, Newson RB, et al. The treatment of depression in UK general practice: selective serotonin reuptake inhibitors and tricyclic antidepressants compared. J Affect Disord 2000;59:149–157
3. Middleton N, Gunnell D, Whitley E, et al. Secular trends in antidepressant prescribing in the UK, 1975–1998. J Public Health Med 2001;23:262–267
4. Ciuna A, Andretta M, Corbari L, et al. Are we going to increase the use of antidepressants up to that of benzodiazepines? Eur J Clin Pharmacol 2004;60:629–634
5. Olfson M, Marcus SC, Druss B, et al. National trends in the outpatient treatment of depression. JAMA 2002;287:203–209
6. Henriksson S, Boethius G, Hakansson J, et al. Indications for and outcome of antidepressant medication in a general population: a prescription database and medical record study, in Jamtland county, Sweden, 1995. Acta Psychiatr Scand 2003;108:427–431
7. Rich CL, Isacsson G. Suicide and antidepressants in south Alabama: evidence for improved treatment of depression. J Affect Disord 1997;45:135–142
8. Taylor D, Paton C, Kerwin R. The South London and Maudsley NHS Trust 2003 Prescribing Guidelines. London, England: Martin Dunitz; 2003
9. Annuario Delle Statistiche Sanitarie. Rome, Italy: Italian National Institute of Statistics; 2004
10. D'Avanzo B, La Vecchia C, Negri E, et al. Suicide mortality in Italy: an update from 1955 to 1987. Rev Epidemiol Sante Publique 1993;41:454–460
11. Doll R, Smith PG. Comparisons between registries: age-standardised rates. IARC Sci Publ 1982;42:671–675
12. WHO Collaborating Centre for Drug Statistic Methodology. Guidelines

for ATC Classification and DDD Assignment. Oslo, Norway: WHO Collaborating Centre for Drug Statistic Methodology; 2003

13. Moncrieff J. Antidepressant prescribing and suicide: analysis is misleading [letter]. BMJ 2003;327:288

14. Gunnell D, Ashby D. Antidepressant and suicide: what is the balance of benefit and harm. BMJ 2004;329:34–38

15. Masand PS, Gupta S. Selective serotonin-reuptake inhibitors: an update. Harv Rev Psychiatry 1999;7:69–84

16. Barbui C, Broglio E, Costa Laia A, et al. Cross-sectional database analysis of antidepressant prescribing in Italy. J Clin Psychopharmacol 2003; 23:31–34

17. Percudani M, Barbui C, Fortino I, et al. Antidepressant drug use in Lombardy, Italy: a population-based study. J Affect Disord 2004;83:169–175

18. Jones G. Prescribing and taking medicines [editorial]. BMJ 2003;327:819

19. Levi F, La Vecchia C, Lucchini F, et al. Trends in mortality from suicide, 1965–99. Acta Psychiatr Scand 2003;108:341–349

20. Carlsten A, Waern M, Ekedahl A, et al. Antidepressant medication and suicide in Sweden. Pharmacoepidemiol Drug Saf 2001;10:525–530

21. Hall WD, Mant A, Mitchell PB, et al. Association between antidepressant prescribing and suicide in Australia, 1991–2000: trend analysis. BMJ 2003;326:1008–1012

22. Isacsson G. Suicide prevention: a medical breakthrough? Acta Psychiatr Scand 2000;102:113–117

23. Ohberg A, Vuori E, Klaukka T, et al. Antidepressants and suicide mortality. J Affect Disord 1998;50:225–233

24. Grunebaum MF, Ellis SP, Li S, et al. Antidepressants and suicide risk in the United States, 1985–1999. J Clin Psychiatry 2004;65:1456–1462

25. Helgason T, Tomasson H, Zoega T. Antidepressants and public health in Iceland: time series analysis of national data. Br J Psychiatry 2004;184: 157–162