Consumption of antidepressants in Italy: recent trends and their significance for public health.

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Consumption of antidepressants in Italy: recent trends and their significance for public health.

Maria Rosaria Gualano[a*], MD, Fabrizio Bert[a], MD, Alice Mannocci[b], PhD, Giuseppe La Torre[b], MD, Patrizia Zeppegno[c], MD, Roberta Siliquini[a], MD

[a] Department of Public Health, University of Turin, via Santena 5 bis, 10126, Turin, Italy

[b] Department of Public Health and Infectious Diseases, Sapienza University of Rome, P.le Aldo Moro 5, 00185 Rome, Italy.

[C] Department of Translational Medicine, Institute of Psychiatry, Università del Piemonte Orientale Amedeo Avogadro, Via Solaroli n° 17, Novara 28100, Italy.

Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

***Corresponding author**:

Maria Rosaria Gualano, MD, Assistant Professor

Department of Public Health, University of Turin, via Santena 5 bis 10126 Turin, Italy

e-mail: mariarosaria.gualano@unito.it

tel.: 0039-0116705809

fax: 0039-0116705889

Abstract

Objective

The present study was conducted in order to assess the consumption and to describe the past trends (from 2000 to 2011) of antidepressants use in Italy.

Methods

Based on the Italian Medicines Agency database, data on antidepressant drugs use have been collected. Data have been expressed in daily defined dose (DDD) per 1,000 inhabitants. The formula ln (rate) = b × years was applied for logarithmic transformation of the consumption rates to estimate past time of drugs consumption. Time changes are expressed as expected annual percentage change (EAPC). The significance level of 0.05 was chosen.

Results

A drastic increase of antidepressants consumption is showed (from 8.18 to 36.12 DDD/1.000, EAPC=56.4% in 2000-2002 and EAPC=6.2% in 2002-2011), with a single joinpoint (time point with a significant trend change). Concerning the trend analysis stratified by type of drugs, SSRI and other products show a huge increase of consumption, on the contrary tryciclic drugs usage decreased.

Conclusions

Mental disorders are now less stigmatized than in the past. Antidepressants use is growing and it would be important to monitor trends, especially considering the possible current economic crisis effects on mental health. In this scenario, the role of public health in mental health promotion has become fundamental.

Keywords: antidepressants; trends; Italy; depression; drugs.

Background

Depression is a common mental disease worldwide, affecting more than 350 million people of all ages [1]. Related to this disorder, suicide is a top ten cause in the eight regions with the most advanced health transition [2]. Globally, the World Health Organization (WHO) has estimated that neuropsychiatric disorders contribute to 13% of the global burden of disease and this percentage is projected to rise to 14.7% by 2020 [3].

In this scenario, depression represents a relevant public health issue worldwide, given the remarkable diffusion of this illness in the population and the possible consequences in terms of disability [4].

Recent data have estimated that about 21 million people in Europe (accounting for the 4.5% of the total population) are affected by depression, with a cost for the health sector of around € 120 billion, equivalent to 1% of the region's Gross Domestic Product (GDP) [5].

An Italian study involving 4,712 subjects between 2001 and 2003 reported that one person in five have experienced a mental disorder life-time, 1 out of 14 had such a disorder in the prior year and 1 out of 31 in the prior month. In addition, the risk of any mental illness reported in women was almost three times larger than in men [6].

Consequently, as it was reported worldwide in the last decade [7-11] an increase of neuropsychiatric drugs consumption such as antidepressant medication treatments, is expected in Italy.

Trends of antidepressant consumption are, indeed, increasing worldwide: almost doubled or tripled during one decade in the UK, France and other European countries, as well as in the USA [7; 12-14]. In addition, it was documented an increase in health expenditure for this drugs category also [15].

Italian trends of neuropsychiatric drugs have been previously studied for the periods between 1955 and 2000 and between 1995 and 2003. All these analysis, however, focused their attention only on antidepressant drugs investigating the relationships with the suicides rates [16-18].

The main purpose of the present study is to assess the consumption and to describe the past trends (from 2000 to 2011) of consumption of antidepressant drugs in Italy.

Methods

Data collection

Based on the Italian Medicines Agency (AIFA) database, the openly available data of the antidepressant drugs consumption in Italy during the 2000-2011 period have been extracted. Data have been expressed in daily defined dose (DDD) per 1,000 inhabitants and stratified by type of drugs (Tryciclics – TCAs; Selective Serotonin Reuptake Inhibitors – SSRIs; other products). Other products include S-Adenosylmethionine (ademetionine), bupropion duloxetine, hypericum, trimipramine, mirtazapine, oxitriptan, reboxetine, trazodone, venlafaxine. The DDD is the unit of measurement defined as the assumed average maintenance daily dose for a drug, approved and recommended by the WHO for drug use studies and surveys. The DDDs/1000/day measures how many subjects have received a standard dose of a specific drug or drugs category daily. This measure has been used for many years in drugs consumption studies and comparisons at national and international level [19,20].

The AIFA agency is the national public authority responsible for drugs regulation in Italy. AIFA promotes its activities through observatories and databases, that are essential tools through which the Agency controls and analyses drug utilization at national, regional and local level.

Data of drugs consumption and expenditure are presented every year in an official report, the annual report of the Drug Utilisation Monitoring Centre, elaborated by the Medicines Utilization Monitoring Centre (OsMED), thus called “OsMED report”. OsMED monitors drug prescriptions financed by the National Health Service and provides with monthly reports to the Regional Authorities according to pre-defined indicators on drug consumption and expenditure. The same data are also re-analyzed by the National Observatory on Health Status in the Italian Regions that publish each year the “Osservasalute Report - Health status and quality of the

health assistance in the Italian regions", adopting a comparative methodology analysis and indicators validated at international level [14,21].

Study population

Osmed report data refer to around 40 millions of Italian citizens, equal to 63% of Italian Population (ISTAT 1.6.2011). Demographic characteristics of this population are representative of the whole population: 51% are women, the median age is 43 years, and the 21% of the sample is older than 64 years.

Statistical analysis

Rates of antidepressants consumption were computed as follows:

$$\frac{\text{Antidepressants consumption in defined daily doses}}{\text{Average population-weighted}} \times \frac{1000}{365}$$

The total DDDs used (for active principle or therapeutic category) were computed making the sum of all the DDDs for each prescribed package. In order to obtain antidepressants consumption time trends, then, the following formula, according to Kim's method [22] for the logarithmic transformation of incidence rates was applied:

$ln(y)=b*x$,

where x represents the calendar years, b is the regression coefficient and y the incidence rate. In particular, a joinpoint represents the time point when a significant trend change is detected. Time changes are expressed in terms of Expected Annual Percent Change (EAPC) with respective 95% Confidence Interval (95% CI); significance level of time trends is also reported. The null hypothesis was tested using a maximum of three changes in slope with an overall significance level of 0.05 divided by the number of join-points in the final model. Linear graphs were realized to represent trends. Statistical analysis was conducted by using Joinpoint

Regression Program software Version 3.5.3. To control heteroskedasticity of the population, a Poisson model was used [23].

Results

Antidepressants consumption and trends

In the year 2000 the antidepressant drugs consumption age-weighted (measured as DDD/1000 inhabitants/day) was equal to 8.18. The following year the consumption doubled (16.24) and it started a growing and continuous trend. Last data shows for the year 2011 an antidepressants consumption accounting for 36.12 DDD/1000 inhabitants/day. In the first nine months of 2011 the expenditure for the central nervous system drugs account for 17.9 euro per person, the third drugs category most represented in the territorial expenditure and the fourth in the prescription by physicians (58.2 DDD/1000 inhabitants/day) [24]. Among these, the most prescribed drugs are the antidepressants (36.1 DDD/1000 inhabitants/day, of them 27.5 for SSRI).

Regarding antidepressants trends analysis, a drastic increase in their consumption is showed in Italy, after analyzing data through the Joinpoint regression software (from 8.18 to 36.12 DDD per 1.000, EAPC=56.39% between 2000 and 2002 and EAPC=6.17% from 2002 to 2011). A single joinpoint (time point when a significant trend change is detected) was found in 2002 with a reduction of annual percent change (APC) but without a real inversion (Table 1). All the results were statistically significant ($p \leq 0.05$). The 2000-2011 trend of antidepressant drugs is showed in Figure 1.

Additionally, we performed trend analyses stratifying data by type of drugs (tricyclic antidepressants, SSRI, other products). Regarding TCAs, data show a reduction of consumption in the period between 2000 and 2011, without any joinpoints (from 1.40 in 2000 to 1.10 DDD/1000 inhabitants/day in 2011; EAPC=-2.81, $p<0.001$). Conversely, SSRIs and the other products registered a great increase of consumption, over time (EAPC=71.12 from 2000 to 2002 and EAPC= 5.38 from 2002 to 2011 for SSRIs; EAPC=13.72 from 2000 to 2011 for the other products). Interestingly, a joinpoint was showed for SSRIs, as for the overall data, in 2002. All these results were statistically significant.

Discussion

Our study was conducted in order to assess the consumption and to describe the past trends (from 2000 to 2011) of antidepressants use in Italy, by using the most recent data available in Italy. Our results show that the trend of antidepressants consumption in Italy is continuously increasing since 2000, quadrupling until the 2011. This rise affects SSRIs and the so called "other products", but not the TCAs. A possible explanation for our findings is that SSRIs and other antidepressants are largely being used in preference to TCAs to treat depression.

To date, the studies investigating the international trends indicate a huge increase in the use of antidepressants, especially after the introduction of selective serotonin reuptake inhibitors (SSRIs) in the early 1990s, the publication of practice guidelines to diagnose and treat depression and the development of efficient screening tools for depression in primary care [7; 25-30].

Interestingly, in parallel with the increasing awareness of depression as an important health issue, the past decade has seen an increase in the pharmacotherapy options for managing depression with the arrival of several new classes of antidepressants [31,32]. These new antidepressant drugs, more expensive, contribute to the rise in the total cost of these drugs [6]. These new antidepressant drugs, which have been proven effective [33] but are more expensive, contribute to the rise in the total cost of these drugs.

However, as recently reported by Connelly and Thase, none of the newer drugs that have been introduced have strongly addressed the unmet needs in this area of therapeutics. Among the newest treatment strategies, results of small studies of ketamine seem to conclude that drugs modulating the glutamatergic neurotransmission may be the useful way for exerting rapid and large antidepressant effects in patients who have not responded to SSRI [31].

Another possible explanation of our findings may be related to the increase of the Italian population, from around 57 million people in 2000 to more than 60 million in 2011, but this is unlikely to explain the trends completely. Additionally, the growing drugs use, as suggested by Ilyas & Moncrieff [34], may be attributed to an increased long-term prescribing or to antidepressant prescriptions addressed to people who are not diagnosed with depression, and to the fact that many antidepressants have been marketed for anxiety disorders over recent years. In USA, as example, there are data suggesting that the majority of people receiving antidepressant prescriptions do not have a diagnosable mental disorder. Furthermore, these drugs are often prescribed by general practitioners instead of psychiatrists, especially in the case of mild depression episodes as well as of anxiety and panic attacks [14,34].

Moreover, it is important to consider that, from the beginning of 2001, SSRIs are financed by the Italian National Health Service and this fact contributed to the huge rise of the consumption.

Specific programs aimed at educating health professionals and patients on a correct use of these drugs can obtain a huge change in the future consumption, with a relatively little change in the trend slope. This is a very important point to be considered by psychiatrists and public health professionals since the improvements in mental health may be consistent and the expenditure for the National Health Service will have remarkable benefits. Indeed, concerning antidepressants Expenditure Per Capita, current estimates show a constant increase (+0.7% for SSRI and +1.8% for the other antidepressants, considering the period 2010-2011) [24]. The role of prevention programs becomes further more important in order to contain and reduce these expenditure data, especially in this time of national and global economic crisis.

This study give an update knowledge on the past trends (from 2000 to 2011) of consumption of antidepressants in Italy. Alarmingly, our study shows a four-fold increase of use of these drugs in the study period. Thus, this study seems to suggest the need for the public health agenda to

address the issue of antidepressant consumption, not only in Italy but also in Europe. The interventions designed in order to reduce the consumption of antidepressants could be, for instance: a new regulation about the prescription off-label of these drugs categories, a more rigid monitoring of these drugs use, a welfare policy addressing the reducing risk factors for poor mental health (for example, reducing stress). In this regard, a meta-analysis showed that an improvement of 11% in depressive symptoms can be reached through specific prevention programs designed to reduce depression such as educational intervention, lifestyle intervention, anxiety management training, cognitive therapy [35]. Consequently, it is likely that, by providing these kind of interventions, the consumption of drugs addressing these depressive symptoms would decrease.

Surely, some limitations of this study should be considered. First of all, the measurement unit (DDD) is a proxy of consumption and does not necessarily reflect the real daily dose consumed. In this type of studies, if the real prescribed daily dose is lower than the DDD, the use of DDD leads to an underestimation of the prevalence of use; in contrast, if the prescribed daily dose is higher than the DDD, the use of the DDD overestimates the number of patients having this medication. Another limitation of our study is that the database of AIFA does not include drug consumption labelled as “out of pocket”, so our results refer exclusively to the consumption in the public and private settings that have an information flow monitored by the Regions. In addition, reported data contain no information on compliance with therapy and, therefore, the term ‘consumption’ is used figuratively; at no time we can assume that the medication dispensed was actually consumed. Finally, the data were stratified by geographic criteria (by Italian region, as performed by the Osservasalute working group, previously mentioned) and by type of drugs but not by age and gender (not available data).

Conclusions

Mental disorders, such as anxiety and depression, are now less stigmatized by the public opinion than in the past. This different perspective of neuropsychiatrics illnesses affects the compliance of drugs treatment, even because many of these drugs are often used also for the treatment of pathologies not strictly related to psychiatry, such as the pain management. Thus, the implementation and the monitoring of effective information flows is advisable, in order to easily identify the growing portion of patients that really need psychiatric treatment. Concerning the treatment, it could be very useful to implement the psychiatric support in the healthcare system, particularly in primary care [36]. Given the global increasing of the consumption, especially of antidepressants, and that good mental health is the basis for economic growth and social development in Europe, the role of public health in mental health promotion has become more and more fundamental. Moreover, considering that mental health problems are related to socioeconomic and environmental factors, it is important to monitor these trends, especially considering the possible current economic crisis effects on mental health.

Authors' contributions

MRG and RS conceived the research; MRG and FB drafted the paper; AM performed statistical analyses; GLT and RS revised the paper.

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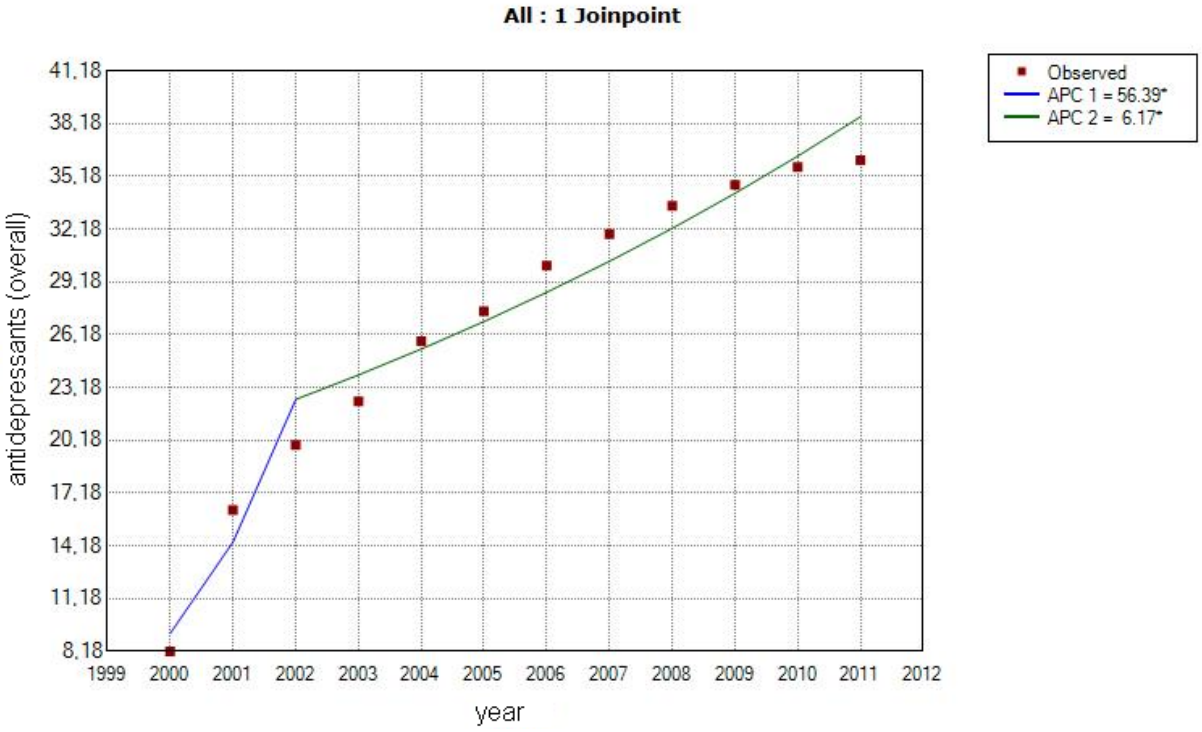
Table 1: Expected Annual Percent Change (EAPC) and 95% Confidence Interval (CI) of Antidepressants drugs consumption (overall data and stratified by type of drugs).

Expected APC[a] of Antidepressants drugs consumption				
Years range	**EAPC[a]**	**95%CI**	***p*-value**	
2000-2002	56.39	(20.8; 102.4)	<0.01	*Antidepressants (overall)*
2002-2011	6.17	(4.7; 7.7)	<0.001	
2000-2011	-2.81	(-3.8;-1.8)	<0.001	*Tryciclics (TCAs)*
2000-2002	71.12	(27.51;129.60)	<0.01	*Selective Serotonin Reuptake Inhibitors (SSRIs)*
2002-2011	5.38	(3.81;7.0)	<0.01	
2000-2011	13.72	(11.51;15.90)	<0.001	*Other products*

[a] APC = Annual Percent Change

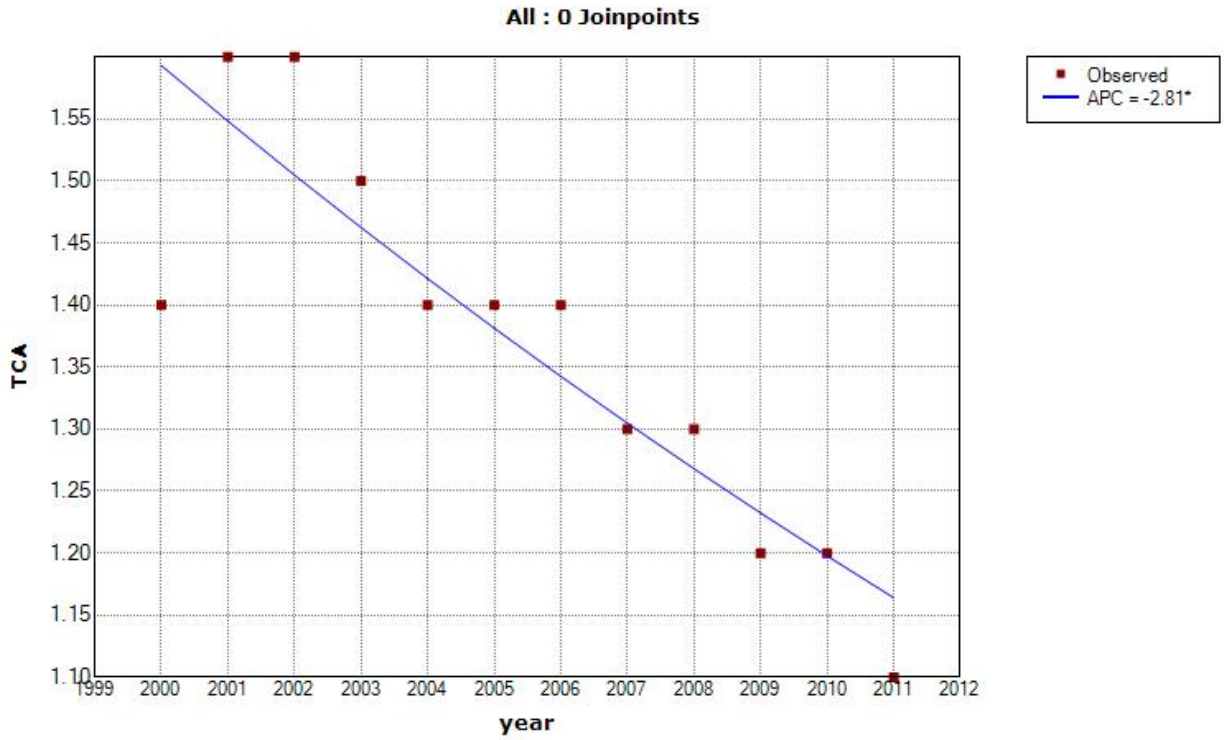
Figure 1 – Antidepressants consumption trend in Italy expressed as DDD per 1000 inhabitants (2000 – 2011)



* Statistically significant results

APC = Annual Percent Change

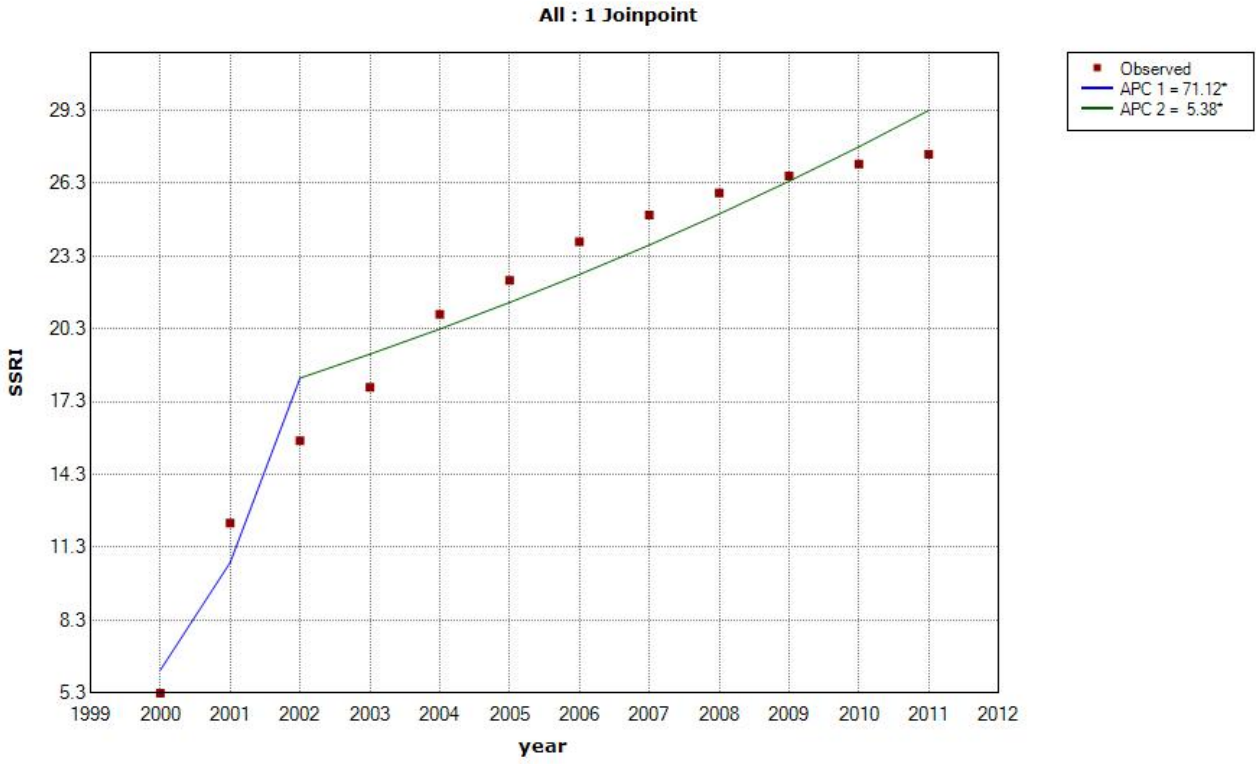
Figure 2 – Tryciclic (TCA) Antidepressants consumption trend in Italy expressed as DDD per 1000 inhabitants (2000 – 2011)



* Statistically significant results

APC = Annual Percent Change

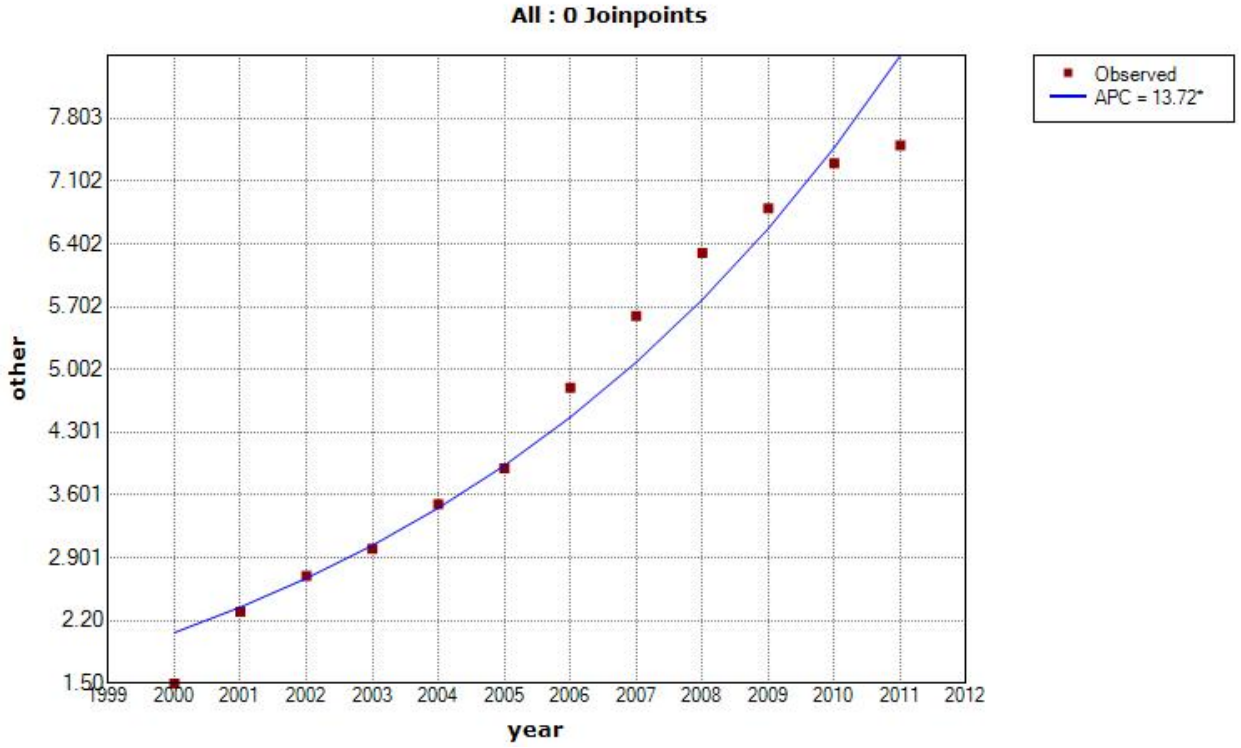
Figure 3 – Selective Serotonin Reuptake Inhibitors (SSRI) Antidepressants consumption trend in Italy expressed as DDD per 1000 inhabitants (2000 – 2011)



* Statistically significant results

APC = Annual Percent Change

Figure 4 –Antidepressants (other products) consumption trend in Italy expressed as DDD per 1000 inhabitants (2000 – 2011)



* Statistically significant results

APC = Annual Percent Change