

# Atypical antipsychotic prescribing patterns in an Italian district 2001-2009 and the impact of regulatory warnings

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## Abstract

**Purpose** To evaluate the epidemiology and patterns of use of this class of drugs among a population in real clinical practice, in the real world, and the impact of regulatory warnings on antipsychotic prescribing patterns, we analyzed the prescription patterns of atypical antipsychotics and haloperidol in an Italian Health District between January 1, 2001 and December 31, 2009. **Methods** Data of 10,556 subjects who received at least one prescription of an antipsychotic drug during the above period were obtained from the Local Health Unit database, which allowed tracking of each individual's prescribing history. Data recorded included age, gender, drug information, strength, and number of packs prescribed. Prescription dates allowed us to evaluate the incidence and prevalence of prescribing of each antipsychotic drug. The adopted indicators for drug utilization included the Defined Daily Dose (DDD), Received Daily Dose (RDD), and a surrogated Prescribed Daily Dose (sPDD), extrapolated from available prescription data. **Results** All drug-utilization indicators showed an increase in the use of atypical antipsychotics over the period of time covered, especially among older patients ( $\geq 65$  years old, 476 prescribed out of 70,998 people of similar age in one town in 2001, versus 1,409 prescribed vs. 76,205 in the same town in 2009) and women, despite the warnings issued by Regulatory Agencies, and no corresponding decrease in use of haloperidol. Nonetheless, surrogated Prescribed Daily Dose and Received Daily Dose remained lower than Defined Daily Dose for all molecules. **Conclusions** We found an increase in the consumption of atypical antipsychotic drugs, despite the warnings issued by Regulatory Agencies. Furthermore, prescribed and received doses are lower than the corresponding Defined Daily Doses, perhaps suggesting an inappropriate use of these drugs.

## Keywords

Antipsychotics, Defined Daily Dose, Drug Utilization, Warnings, Pharmacoepidemiology

## 1 Introduction

Antipsychotics are widely used drugs for the treatment of major psychoses such as schizophrenia. Their use is a major item of expenditure in most pharmaceutical care budgets in developed countries, including Italy (1). The last two decades have seen the market entry of the so-called "atypical antipsychotics" (e.g. olanzapine, among others),

which in some respects (i.e. improved extrapyramidal tolerability) display a better therapeutic profile than older, "typical" agents such as haloperidol (2); (3). But more recently, data from routine clinical practice pointed out adverse reactions not reported by the clinical trials, including a dose-dependent risk of cerebrovascular events, especially in elderly patients (4), dyslipidemia and obesity (5), diabetes, ketoacidosis and hyperglycemia (6), and a risk of community-acquired pneumonia (7). As a result of

these adverse effects, regulatory agencies in North America warned about the risk of stroke and cerebrovascular events associated with risperidone (8); (9) in 2003, and about an association between atypical drug use and hyperglycaemia and diabetes in 2004 (10) The European Medicines Evaluation Agency (EMA) issued warnings about the use of olanzapine in elderly patients with dementia related psychosis or behavioral disturbance; these were disseminated by the Ministry of Health and local health authorities in Italy (11); (12). In 2005, the US Food and Drug Administration (FDA) issued a warning regarding the risks of atypical-antipsychotic use among elderly patients with dementia (13) and in June 2008 extended this warning to older typical antipsychotic medications (14). Dorsey and colleagues in the USA subsequently documented a decrease in consumption of atypical antipsychotic drugs in elderly patients with dementia (15).

The aim of our study was to investigate the patterns of use of atypical and typical antipsychotic drugs in patients living within Treviso (Italy) region, and who received drugs directly from the hospital pharmacy or the community pharmacy during 2001-2009 in terms of consumption, appropriateness, and number of patients who stopped therapy. The effect of warnings on the prescription of these drugs was also evaluated as the time frame straddles the publication of the warnings.

## 2. Methods

### 2.1. Setting

Data on antipsychotic prescriptions were retrieved from the Pharmaceutical Service of Treviso Local Health Unit, which collects all the records of publicly funded prescriptions from both local and hospital pharmacies in the Treviso area, which had a population of 362,363 inhabitants in 2001 and 403,182 inhabitants in 2009. The computer-based prescription database included details on identification and demographic characteristics (sex, age) of the patients; information on the drug treatments, by the Anatomical Therapeutic Chemical classification system (ATC) for each drug, and tablet strength and number. The prescribed typical and atypical antipsychotic drugs were those defined by the ATC category N05A\* (WHO Collaborating Centre for Drug Statistics Methodology, 2011). These were haloperidol (ATC code, N05AD01) (depot and oral preparations were considered together) for typical antipsychotics and aripiprazole (N05AX12), clozapine (N05AH02), olanzapine (N05AH03), quetiapine (N05AH04), and risperidone (N05AX08) for atypical antipsychotics. Other typical and atypical antipsychotics were very rarely used. Patient diagnosis was not included in the database. The prescription of atypical antipsychotics to patients requires a therapeutic plan (*piano terapeutico*) by a Psychiatrist, sent to Pharmaceutical Services. This plan includes information such as duration of the treatment, dosage, drug and diagnosis. We checked these plans to see

if the prescription was for an off label indication, e.g. dementia or behaviour disturbances.

### 2.2. Inclusion Criteria

A cohort study was performed by identifying all the patients who, between January 1, 2001 - December 31, 2009, received at least one prescription for any of the defined antipsychotics. Incident patients were those who, with no antipsychotic prescriptions in the previous years, received their first antipsychotic prescription in the considered year. Patients dropping out of therapy were also recorded, although we did not investigate the reasons. In this study, we defined a drop-out as any termination of prescription of the antipsychotic from January 1, 2002 to December 31, 2009.

### 2.3. Drug Utilization

To evaluate the quantity and appropriateness of antipsychotics used, we used the following drug-utilization indicators:

**Defined Daily Doses (DDD)** (WHO Collaborating Centre for Drug Statistics Methodology 2001, 2004, 2009). The DDD values (unchanged over this period) were 8, 15, 300, 10, 400, and 6 mg for haloperidol, aripiprazole, clozapine, olanzapine, quetiapine, and risperidone, respectively, throughout this study.

**Surrogated Prescribed Daily Doses (sPDD)**. Since the database used to retrieve drug information did not contain data on the actual daily dose prescribed, a sPDD was calculated, in mg: this assumes that doctors prescribe in units reflecting the dosage forms available of a given antipsychotic e.g. prescription of 1680mgs of haloperidol in a six month period is probably 30 mg/day. The formula used to calculate the sPDD is:  $\sum [\text{number of units in the pack prescribed} \times \text{dose of the unit} \times \text{days at that dose}] / [\text{length of therapy}]$ .

**Received Daily Doses (RDD)**. RDD is the average quantity of drug apparently actually taken by the patient each day: it reflects compliance as well as dose prescribed. It is based on dose prescribed e.g. 28x10mg tablets=280mg divided by number of days over which it is taken (e.g. 35 days between prescriptions: RDD = 280/35, or 8mg).

During the follow-up period, RDD values were calculated for each antipsychotic from the ratio between the total dose (in mg) of all the packs prescribed to each patient during the observation period, and the length of therapy (assumed to last from the first to the last prescription date, extended by a number of days therapy in the last prescription). In case of hospitalization, we assumed that antipsychotic therapy was administered directly by the hospital staff at the same dosing schedule actually prescribed by the general practitioner, and this was included in RDD calculation.

### 2.4. Statistical Analysis

To compare trends of the consumption of atypical

antipsychotic drugs vs. haloperidol, we used linear regression.

### 3. Results

#### 3.1. Patient Cohorts

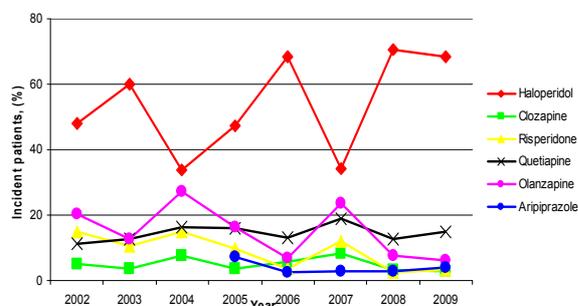
We identified 10,556 unique patients (mean age 53 years, range 16-98) who received at least one prescription for an antipsychotic during the observation period.

The number of patients prescribed antipsychotics increased over the years (1678 pt/362,363 population, 0.4% of population in 2001, vs 2849/402,182, 0.7% in 2009). There was no change in the rate of prescribing for those under 17, about 0.1% of the total of all patients prescribed antipsychotics in each year, but an increase in the use in the elderly (65 years or older) in particular, from 28% of all pts prescribed antipsychotics in 2001 to 49% in 2009; and in absolute terms, from 0.67% of all elderly in 2001 to 1.85% in 2009 (Table 1).

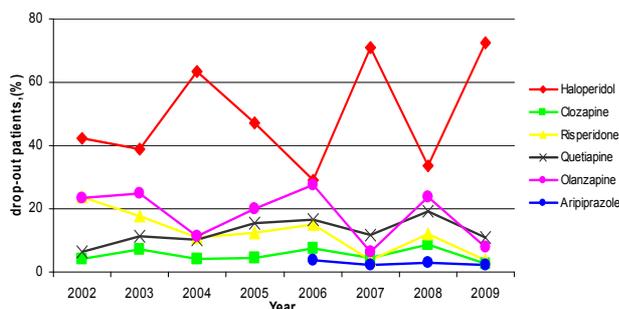
**Table 1.** Percentages and number of patients prescribed antipsychotic drugs stratified by age

Prescribed population vs total population (%)			
Year	0-17 years old	18-64 years old	≥ 65 years old
2001	0.03% (17)	0.51% (1185)	0.67% (476)
2004	0.03% (17)	0.57% (1474)	1.29% (968)
2009	0.06% (28)	0.51% (1412)	1.85% (1409)

Use by women was greater than in men, and increased further between 2001 and 2009 (1.07% vs. 0.75% and 1.10% vs. 0.73%, in 2001 and 2009 respectively).



**Figure 1.** Incident patients according to the antipsychotic drug first prescribed between 2002-2009



**Figure 2.** Frequency of patient drop-out according to the antipsychotic drug prescribed between 2002-2009

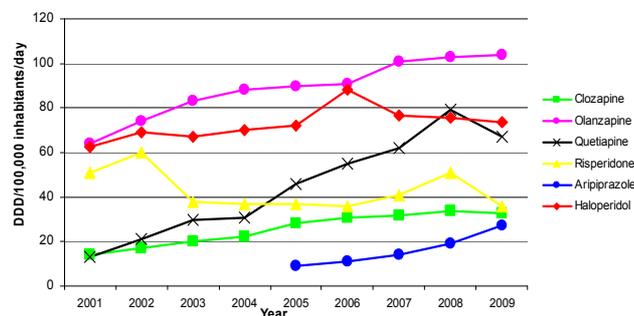
The choice of drug for new prescriptions changed over this period (Figure 1).

Haloperidol remained the single most widely used drug, but its use declined in some years while the use of atypical drugs increased e.g. in 2004 and 2007. Aripiprazole entered the European market in 2004, and in 2005 it accounted for about 7% of the total treated patients.

Patient withdrawals from atypicals showed three peaks (2003, 2006, 2008), which correspond with the timing of regulatory agency warnings (Figure 2). For haloperidol, the highest drop-out rate occurred in 2009 (72% of all drop-out patients in 2009 vs. 33.6% in 2008), the year after warnings were extended to typical antipsychotic drugs.

#### 3.2. Drug Utilization

Atypical antipsychotic utilization is compared to that of haloperidol in Figure 3, as DDD/100,000 inhabitants/day between 2001-2009. Overall, there was a 187% increase over nine years in atypical antipsychotic utilization, while total haloperidol utilization did not change significantly. There were changes between years: in 2006, there was a 4% decrease in the use of atypical antipsychotic drugs compared to the previous year (210 DDD/100,000 inhabitants/day in 2005 vs. 202 DDD/100,000 inhabitants/day in 2006), but an increase in consumption of haloperidol was observed (72.17 DDD/100,000 inhabitants/day in 2005 vs. 88 DDD/100,000 inhabitants/day in 2006).



**Figure 3.** Utilization analysis of each atypical antipsychotic vs. haloperidol between 2001-2009

Among atypical antipsychotics, olanzapine was the most prescribed from 2001 to 2009 (Figure 3b). Consumption of quetiapine increased 6-fold from 2001 to 2008 (13 DDD/100,000 inhabitants/day in 2001 vs. 79 DDD/100,000 inhabitants/day in 2008), but declined in 2009 (67 DDD/100,000 inhabitants/day).

The analysis of the sPDDs and RDDs showed values much lower than the official DDDs for both indices for all antipsychotic drugs between 2001-2009 (Tables 2 and 3).

The sPDD of haloperidol increased from 2001 to 2009, being a quarter of DDD in 2001 and then rising to 5 mg/day in 2004 and 2009 (Table 2). However, its RDD decreased by 1 mg/day between 2004 and 2009 (Table 3).

Looking at atypical antipsychotic drugs, both sPDD (Table 2) and RDD (Table 3) of olanzapine showed a

decreasing trend, with a sPDD and a RDD which in 2009 were the mid and about a quarter of the DDD, respectively.

The sPDD of quetiapine increased (106.43 mg/day in 2001 vs. 126.33 mg/day in 2009) (Table 2), but its RDD dramatically decreased (156.8 mg/day in 2001 vs. 103.12 mg/day in 2009) (Table 3).

Clozapine sPDD remained largely unchanged (88.75 mg/day in 2001 vs. 90.38 mg/day in 2009) (Table 2) although its RDD, after a great increase in 2004, dramatically decreased (69.9 mg/day in 2001 vs. 46.14 mg/day in 2009) (Table 3).

**Table 2.** Comparison among DDD and sPDD values for each antipsychotic drug. Defined Daily Dose (DDD), surrogated Prescribed Daily Dose (sPDD)

Drug	DDD (mg)	sPDD (mg) 2001	sPDD (mg) 2004	sPDD (mg) 2009
Clozapine	300	88.75	87.82	90.38
Olanzapine	10	8	7.32	5.12
Quetiapine	400	106.43	114.99	126.33
Risperidone	5	4.38	4.42	5.08
Aripiprazole	15	-	-	12
Haloperidol	8	2	5	5

**Table 3.** Comparison among DDD and RDD values for each antipsychotic drug. Defined Daily Dose (DDD), Received Daily Dose (RDD)

Drug	DDD (mg)	RDD (mg) 2001	RDD (mg) 2004	RDD (mg) 2009
Clozapine	300	69.9	152	46.14
Olanzapine	10	5.1	6.9	2.85
Quetiapine	400	156.8	211.6	103.12
Risperidone	5	1.6	3.17	1.99
Aripiprazole	15	-	-	11
Haloperidol	8	2.29	3.1	2.14

Concerning the utilization of risperidone and aripiprazole, both sPDD (Table 2) and RDD (Table 3) in 2009 were lower than their DDD.

In 2009 compared to 2001, both sPDD (Table 2) and RDDs (Table 3) of risperidone increased.

22% of all patients treated with antipsychotic drugs have an off label indication, e.g. dementia, and not psychosis or schizophrenia.

## 4. Discussion

The timing of warnings about these drugs (8); (9); (10); (11); (12); (13); (14) seem to correspond to temporary declines in their use and possibly swapping between the typical haloperidol and the atypicals depending on which had had recent warnings. But despite these concerns and temporary decreases in use, overall the rate of use of antipsychotics, in particular atypicals, has increased, especially in elderly patients. Women were more likely to be prescribed atypicals than men, in accord with an earlier study in Italy by Trifirò *et al.* (16), but in contrast with an U.S.A. study by Menzin *et al.* (17). Exposure of younger patients (*i.e.*, under 18 years), has increased in line with

Cascade *et al.* (19) and reflecting an extension of licensed indications for atypical antipsychotic drugs during the years 2007-2009 (20); (21), but absolute numbers of patients affected remain low. The use in patients over 65 years old increased: the doses used were also low. This may suggest that the increased use is in keeping with the results of Valiyeva *et al.* (18) which showed an increasing use of atypical antipsychotic drugs in patients with dementia and probably behaviour disturbances, rather than treating psychoses. This use is off-label for all except risperidone.

A significant finding of this study is that sPDD and RDD were always lower than DDD over the course of the analyzed period. The fact that both of these indicators are below the reference DDD indicates that both the prescriber (generator of PDD) and the patient (generator of RDD) respectively fear or suffer the effects of the drugs in question (23), as highlighted by regulatory warnings in 2003, 2004 and 2005. After these warnings, several studies described a reduction in use of antipsychotic drugs in Italy, based on data taken from the electronic medical records of the Italian general practice database "Health Search/Thales". In contrast, our study shows the use of atypical antipsychotic drugs remarkably increased during the study period, while the consumption of haloperidol (a typical antipsychotic drug taken as comparator) did not change significantly over the same time. The data from "Health Search/Thales" may be an underestimate since it does not take into consideration direct supply by hospitals. Our results therefore differ from those of Trifirò *et al.* in an elderly dementia population which claimed a decreased trend in the use of atypical antipsychotic drugs and an increased trend in the use of typical agents following the recent safety warnings (27): this may reflect the longer time horizon of our study, or the more specific populations studied by Trifirò *et al.* Our data are however in line with the findings of Valiyeva *et al.* (18) and Saad *et al.* (28) who showed that despite FDA warnings, antipsychotics are still being widely used for the management of dementia-related psychosis in an elderly population.

In conclusion, between 2001 and 2009, the consumption of atypical antipsychotic drugs in a general patient population has almost doubled, despite the warnings issued by Regulatory Agencies and the resulting increase in drop-out patients registered in the same years for the same molecules.

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