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Pharmaco-epidemiological description of the population of the Marche Region (central Italy) treated with the antipsychotic drug olanzapine

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Abstract

Background. In Italy, even though olanzapine has been discouraged for treatment of behaviour disorders in older patients affected by dementia, some physicians chose to prescribe for them. In response to this situation, the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) promulgated a cautionary note.
Materials and methods. This study examined epidemiological indices for olanzapine prescriptions between 2004 and 2007 in the Marche Region of central Italy and in its provinces, to assess physician compliance with the AIFA note, and to determine whether there were differences in drug prescription between populations of the same territory, or differences based on gender or age group.
Results. Our analyses revealed high olanzapine use among young men and mature women, suggesting that these groups are most prone to psychotic symptoms. Analysis revealed that olanzapine prescription in elderly patients was reduced in some provinces, in line with the AIFA note.
Conclusions. Prudent use of olanzapine prescription, in compliance with the AIFA note, was noted throughout the Region. Furthermore, this work offers details that may be useful in future studies of adverse drug reactions.

Key words
• psychiatric drug
• prevalence index
• incidence index
• defined daily dose index

INTRODUCTION

Psychotic symptoms can result from a wide range of pathological conditions including primary psychiatric disorders (such as schizophrenia), medical conditions (such as trauma, temporal lobe epilepsy, dementia) and substance abuse problems. Psychotic symptoms are characterised by loss of contact with reality, hallucinations and bizarre behaviour.

First-generation antipsychotic drugs (FGAs) have often been prescribed to treat psychotic symptoms, but in recent years newer, so-called second-generation or atypical antipsychotic (SGAs) drugs have emerged [1]. These drugs, used to treat conditions such as schizophrenia, agitation, anxiety, mania and aggression, are considered atypical because, unlike conventional antipsychotic drugs, they have increased specificity of action against negative symptoms and cause a lower incidence of extrapyramidal side effects, thus offering better tolerability than FGAs [2, 3].

Because of these advantages, prescription of atypical antipsychotic drugs has shifted in the last decade from secondary use after the failure of conventional antipsychotic drugs, to primary treatment for psychotic disorders [4, 5].

In different practice guidelines, SGAs have been considered as the first therapeutic option in schizophrenia [6, 7], despite the growing concern about their metabolic effects, including diabetes, hyperlipidemia and obesity [8, 9].

These concerns have prompted healthcare authorities to issue cautionary notes about use of SGAs as first choice drugs in the treatment of psychotic symptoms

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[10, 11]. Indeed, several national regulatory agencies have published official warnings on this topic [12-14]. Even so, several studies reported a substantial increase of atypical antipsychotic prescriptions in primary care over recent years in several countries [15-18].

Among second-generation antipsychotics, the outcome and adverse events of the most used drugs, olanzapine and risperidone, have been analysed with particular attention [19-22]. Recently, the Committee on Safety of Medicines (CSM), after reviewing the available data from clinical trials of risperidone and olanzapine, has highlighted an increased risk of stroke and transient ischemic attacks in elderly patients with dementia who are treated with these drugs [23, 24]. Further concern was prompted by recent studies that have shown that olanzapine causes hyperglycaemic complications that may aggravate the incidence of diabetes in the population [21, 25, 26]. In Italy, the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) discouraged use of olanzapine to treat psychosis and/or behavioral disorders related to dementia in elderly patients, a population in whom the drug was often used and called for attentive monitoring of cases in which physicians chose nonetheless to prescribe the drug to these patients [27, 28].

In particular, the July 21, 2005 AIFA "Note" [29] called for a program of active pharmacovigilance, and dictated the following measures: i) administration of the lowest clinically effective dose, ii) avoidance of co-administration with benzodiazepine or with two different kinds of antipsychotics, and iii) care in administering the antipsychotic to patients affected by cardiovascular diseases [30]. Several studies in Italy have dealt with the prescription of olanzapine at the national and regional levels [17, 27, 28, 31, 32]. The first purpose of the present work was to verify whether the AIFA note changed the prescription rate of olanzapine for psychosis and behavioural disorders related to dementia in elderly patients.

To this end, we examined the records of olanzapine use, prevalence, and incidence in the Region from 2004 to 2007. Secondly, we wanted to offer highly detailed analysis that would help verify whether there are differences in drug prescriptions among the populations of the same territory, stratified for gender, age and provinces, to offer information that should prove useful, in particular, for studies of adverse drug reactions (ADR).

METHODS
Study population and data sources
The 1 500 000 residents of the Marche Region of central Italy formed the reference population for the present study. The region has four provinces, from North to South: Pesaro-Urbino (PU), Ancona (AN), Macerata (MC), and Ascoli Piceno (AP). The populations of the four provinces were analysed separately. In the Marche Region, once the specialist (a neurologist, psychiatrist, or geriatric physician) has defined a treatment plan, olanzapine can be dispensed to patients from hospital pharmacies and public pharmacies.

All olanzapine prescriptions (ATC: N05AH03)

dispensed during the period 2004-2007 were identified using the Regional Agency of Health (RAH) prescriptions database.

We included all patients who received at least one olanzapine prescription during the years 2004-2007, divided into two age groups (0-74 years and ≥ 75 years).

During this period, the RAH supplied 56 506 prescriptions, from which the patients' name and surname, date of birth, residence and fiscal code could be ascertained.

The RAH also labeled each prescription with a code that could be used instead of patient name, to ensure the anonymity of the data, and from which researchers could obtain clinical data and information about the pharmaceutical prescription such as quantity and defined daily dose.

Evaluation of olanzapine prescribing
In order to evaluate olanzapine prescribing, the DDD per 1000 inhabitants per day was used as unit of measurement. 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 [33].

The standardized DDD (DDDst) was stratified by gender, age group, and province of residence according to data of the Italian Office of National Statistics (http://demo.istat.it/) for the years 2004, 2005, 2006 and 2007.

Prevalence/incidence of olanzapine prescribing
Patients who received at least one recorded prescription during the study period were included.

Prevalence was calculated by dividing the number of olanzapine users by the resident population (per 1000), by gender, age group, province of residence, and year of prescription.

New users were defined as those receiving the first olanzapine prescription without any recorded olanzapine treatment in the previous year. The cumulative incidence was defined as the number of new users divided by the resident population (per 1000), by gender, age group, province of residence, and year of prescription. As it was not possible to analyse data before 2004, incidence was calculated for 2005 and onwards.

Statistical significance was evaluated with CI 95%; lower and upper limits were calculated using Poisson distribution.

RESULTS
Assessment of epidemiological indices by year
During the period 2004-2007, a total of 1 244 404 DDD of olanzapine were prescribed in the Marche Region; in particular, 56 506 prescriptions of olanzapine were issued for 5207 patients, 54% of whom were female and 46% male. More than 50% were aged 54 or younger.

Total DDDst increased about 84% from 2004 to 2007 (Figure 1A). The prevalence index remained constant during the period examined, while the incidence index decreased (Figure 1A). No differences were observed between men and women (data not

Table 1
Cumulative incidence index of olanzapine users. The index has been reported separately for the four provinces of Marche Region, stratified by gender and calendar year

Province	2005		2006		2007	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Pesaro-Urbino	0.86 (0.73-1.01)	0.91 (0.77-1.05)	0.54 (0.44-0.66)	0.45 (0.36-0.56)	0.46 (0.37-0.57)	0.37 (0.29-0.47)
Ancona	0.75 (0.64-0.87)	0.82 (0.71-0.94)	0.62 (0.52-0.73)	0.80 (0.69-0.92)	0.47 (0.39-0.57)	0.59 (0.49-0.69)
Macerata	0.89 (0.74-1.05)	1.13 (0.98-1.31)	0.59 (0.48-0.73)	0.73 (0.61-0.88)	0.73 (0.60-0.87)	0.72 (0.59-0.86)
Ascoli Piceno	0.51 (0.41-0.69)	0.53 (0.44-0.65)	0.38 (0.29-0.47)	0.40 (0.32-0.50)	0.38 (0.30-0.48)	0.50 (0.40-0.61)

Data are reported as cumulative incidence per 10 000 inhabitants; in parentheses 95% confidence interval is expressed.

shown). Collectively, these findings seem to indicate an increase of olanzapine consumption after 2004, caused by increased prescription for old consumers and not for new patients entering into therapy.

Analysing olanzapine use in the four provinces, we have observed that olanzapine prescription (DDDst) increased between 2004 and 2007 in three provinces (PU, AN, MC), confirming the trend for the Region as a whole, but remained fairly steady in the province of AP *(Figure 1B)*. Analysing the prevalence index, we have observed that in 2004 it was similar for three provinces (PU, MC, AP) and lower than that detected in the regional analysis; instead, the AN province showed higher values than the other provinces and the regional index *(Figure 1C)*. From 2005 to 2007, the prevalence index increased in the provinces of MC and PU, while it decreased in that of AN and strongly decreased in the AP province *(Figure 1C)*. Analysis of the incidence index in the four provinces showed a moderate decrease of values in the provinces of AN and MC *(Figure 1D)*. A more pronounced decrease was observed in the PU province, while a small decrease was observed in the AP province *(Figure 1D)*. Differences between men and women emerged in the incidence values of the MC province for 2005 and 2006 and the AN province for 2006 *(Table 1)*. Collectively, these findings seem to confirm an increase in olanzapine prescription starting in 2005 in the individual provinces. In particular, in the provinces of PU and MC, drug prescription (DDDst) was linked to an increase of the number of patients between 2004 and 2005, but after 2005 we observe rather an increase of dosage only. In the PU province, the high values of the DDDst and prevalence index, accompanied by a strong decrease of the incidence index, seemed to indicate that there were more olanzapine prescriptions here than in the other provinces *(Figure 1B, C, D)*. Similarly, in the AN province, the epidemiological indices indicated a general increase of drug prescription for old consumers and not of new patients admitted into therapy. Also, in the AP province, where a decrease of the number of patients (prevalence index) was detected, the constant drug usage index (DDDst) confirmed an increase in prescription levels, starting in 2004 *(Figure 1B, C, D)*.

Assessment of epidemiological indices by population age group

The maximum value in the olanzapine use index for men was in the 25-34 age group and for women in the 45-54 age group, while the minimum value was in the 65-74 age group for both men and women *(Figure 2A, B)*. It can be noted that, before and after 2005, drug prescription was greater for men than for women until the 45-54 age group, while the opposite was observed in the older age groups. Furthermore, an increase of drug use after 2005 can be noted in all age groups for both men and women *(Figure 2A, B)*.
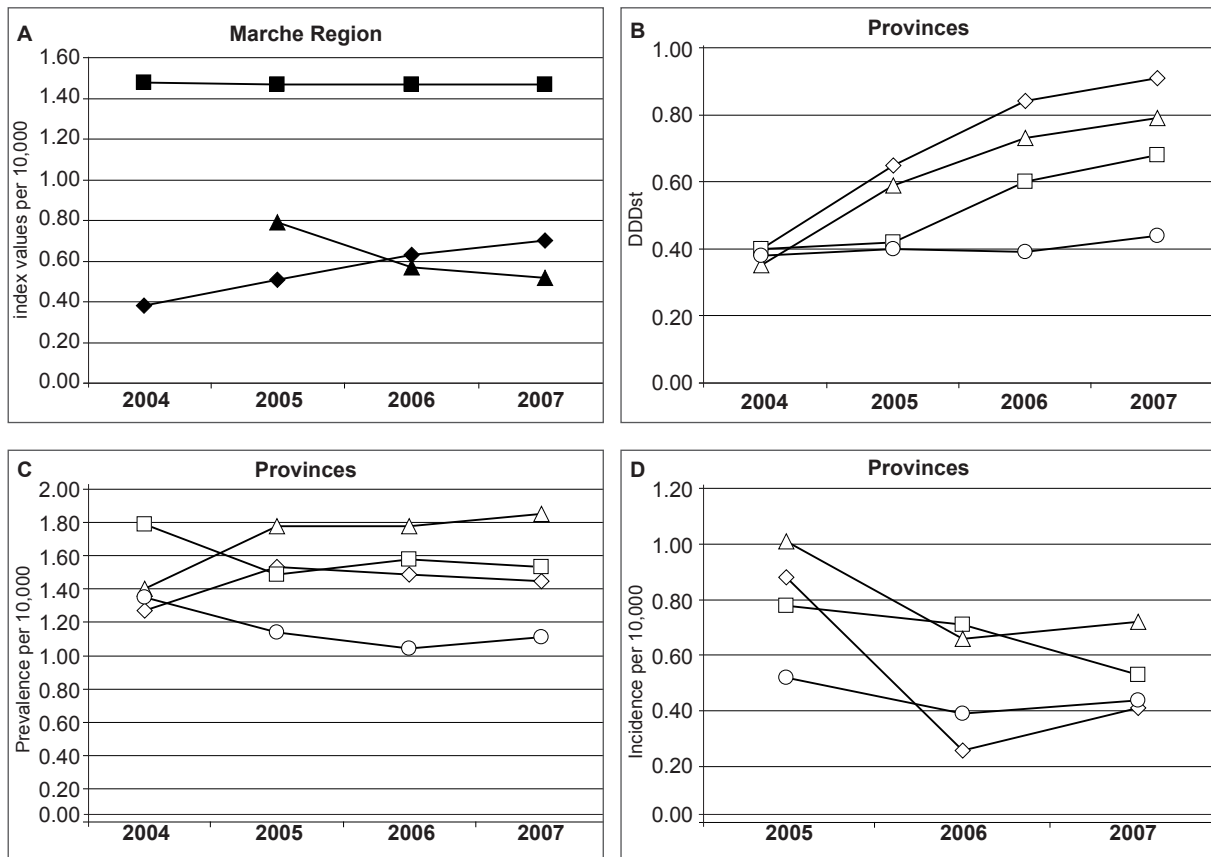
The prevalence index showed a profile quite similar to that of the use index (DDDst), confirming that drug use was well related to the number of patients. By comparing the prevalence index with the drug use index, it is evident that high olanzapine consumption occurred in the young patients, while there was modest consumption in the old age groups. In particular, drug use in the old age groups increased after 2005, particularly in men *(Figure 2A, B)*. These findings seem to indicate poor acceptance of the AIFA note by physicians. Analysis of the drug use and prevalence index in the four provinces showed a profile similar to that observed analysing the whole regional population (data not shown).

Analysis of the incidence index for the regional population stratified by age groups showed decreasing profiles during 2005-2007 without changes in the curve profile itself, indicating a reduction of new admissions to drug therapy for all age groups, except the oldest one *(Figure 3A)*.

Analysis of the incidence index stratified by age group and gender for 2005-2007 showed for the men's curve profile a first peak at the 25-34 age group, while in women's curve profile a first peak was shown at the 55-64 age group; a second higher peak in both men and women was observed in the ≥ 75 age-group *(Figure 3B)*. The increase of the incidence index in the oldest patients does not testify to a careful use of the drug in old patients in accordance with AIFA note. In line with observations drawn from analysis of the DDDst and prevalence index, the men's curve showed values higher than those of the women's curve for the young age group. The opposite was observed for the mature/

Figure 1
Graph panel showing pharmaco-epidemiological indices of the Marche Region (A) and several provinces (B, C, D). In A: black diamond = defined daily dose standardized (DDDst) index; black square = prevalence index; black triangle = incidence index. In B, C, D white diamond = Pesaro-Urbino province; white triangle = Macerata province; white square = Ancona province; white circle = Ascoli Piceno province.

old age group, with the 35-44 age group being the curve inflection point *(Figure 3B)*. Analysis of the incidence index stratified by age in each province of the Marche Region showed that the AN and MC provinces had a rapid increase of the index value for the ≥ 75 age group, significantly higher than that of younger age groups *(Figure 3C)*. In comparison with curve values of the AN and MC provinces, the PU province showed smaller values for the 25-34 and 35-44 age groups and an evident decrease of the values for the oldest age group. The AP province showed a flattened curve profile with the smallest values for all age groups *(Figure 3C)*.

The latter findings seem to reveal different physician behaviour in the four provinces for new cases after the AIFA note. In the MC and AN provinces, olanzapine prescriptions for elderly patients did not demonstrate the care requested in the AIFA note. However, a great increase of incidence values in the ≥ 75 age group was noted, which can arguably be attributed to a large number of new patients entering therapy. On the contrary, in the PU province, a slightly decreased incidence index for the ≥ 75 age group can be noted, pointing out a careful use of the drug for elderly patients. An interesting profile emerged in the Ascoli Piceno province, where the drug was used with care

with all age groups, including young patients, for whom olanzapine use was high in the other provinces. However, a slight increase in the ≥ 75 age group was also observed in the AP province.
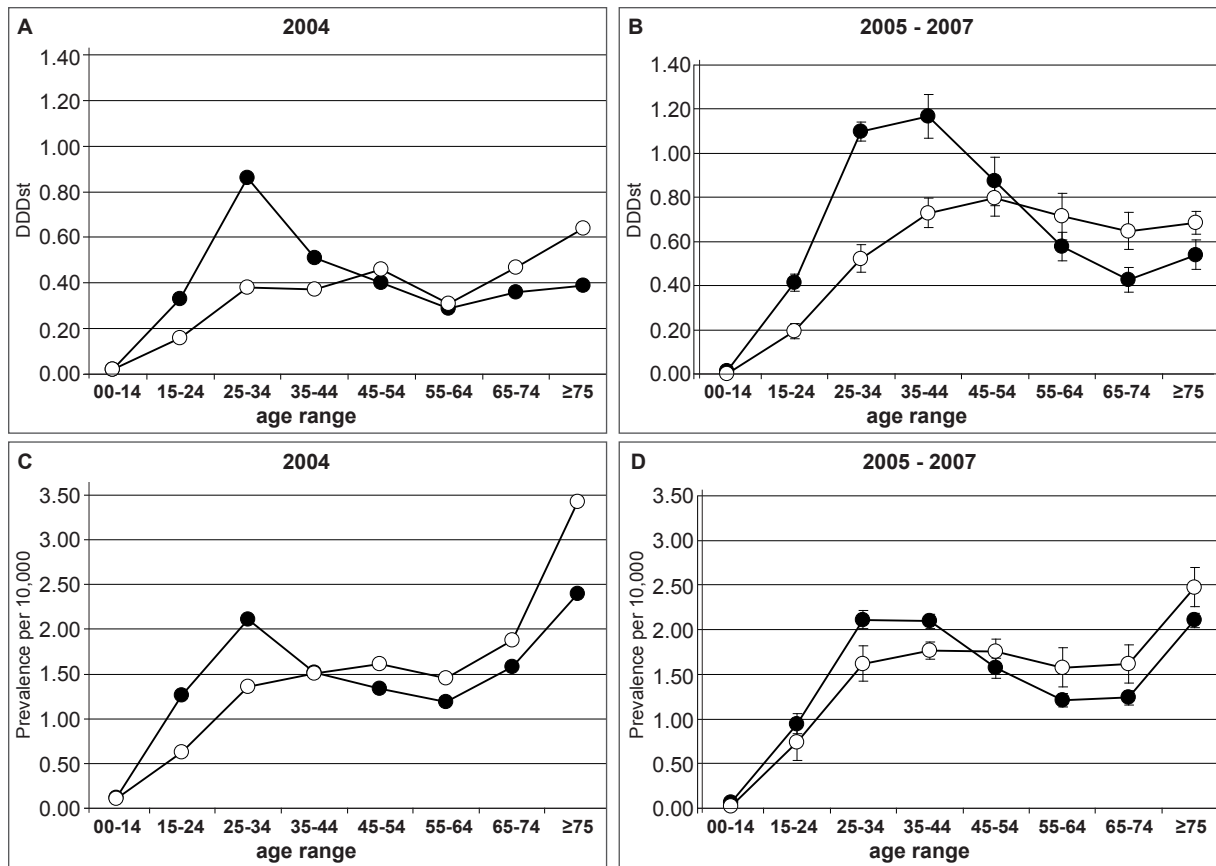
DISCUSSION

The data presented in this study showed a significant increase of olanzapine use (in terms of the consumption index, DDDst) by the Marche Region population from 2004 to 2007. This trend is of interest because, although olanzapine use in the Marche Region is below the national mean, it increased constantly during the years examined, while several sources indicate a recent decrease of olanzapine use on the national level (National Health System database). These findings indicate that the increase of olanzapine use (DDDst) was caused by the increase of the drug prescription. In particular, the wide reduction of the incidence index values observed in 2006 compared to 2005, and the permanence of the values in 2007, may have been due to the 2005 AIFA note about olanzapine use. The increase of olanzapine prescriptions alongside the steady values of the prevalence index seem to indicate that the note generated attention to the admittance of new cases under olanzapine treatment.

In a previous work, Trifirò *et al.* [34] analysed the

Figure 2
Graph panel showing pharmaco-epidemiological indices of the Marche Region during the years studied, stratified by gender and age. Black circle = men; white circle = women. In graphs B and D the data are reported as mean ± SEM of the years examined.

prescriptions of antipsychotic drugs in the Italian general population during years 2000-2005. They found that the recent safety warnings led to an increasing trend in the use of typical agents, and a decreasing trend in the use of atypical agents in elderly outpatients with dementia (in Italy), but they did not find similar trends in the general population and the elderly as a whole. Their findings indicate that the AIFA note caused physicians to take care in the use of atypical antipsychotic drugs in elderly outpatients with dementia and in new cases, but they also indicate the continuation of a high level of atypical antipsychotic prescriptions for patients who had already been receiving these drugs, as emerged in our study on olanzapine as well.

Analysis of epidemiological indices stratified by gender and age helps us better examine the particular distribution of drug use in the population.

In male patients, a high rate of olanzapine use was detected in patients 25-44 years old, and a high level drug prescriptions was also noted for old and new patients.

It is arguable that males of this age range are more prone to psychosis or other conditions for which olanzapine is the drug of first choice [4, 5].

In particular, data on prescriptions of this drug to young men of the 25-34 age group may reflect their vulnerability to exhibit dangerous behaviour in family

or social settings when beset by these psychiatric illnesses.

The persistence of olanzapine prescriptions over the years in this age group and the gradual increase of olanzapine use suggest that physicians deem the drug efficacious and well-tolerated, as it indicated by several studies [2, 3]. However, an increase of drug prescriptions in male elderly patients (over 75 years) was also noted. The increase of the drug use index was very small in comparison to the increases of the prevalence and incidence index, indicating a high number of new patients receiving olanzapine, accompanied by a reduction of the dosage prescribed. This hypothesis is confirmed by the minor differences between the use index (DDDst) and the prevalence and incidence indices observed in the elderly, in comparison to those observed in younger patients. Indeed, this cautious behaviour by physicians may have been a consequence of the 2005 note about the off-label use of the drug in the elderly.

In women, the trend was similar to that observed in men: high values of drug prescription were accompanied by high values in the prevalence and incidence indices, thus the drug use was linked to the increase of the number of patients receiving olanzapine.

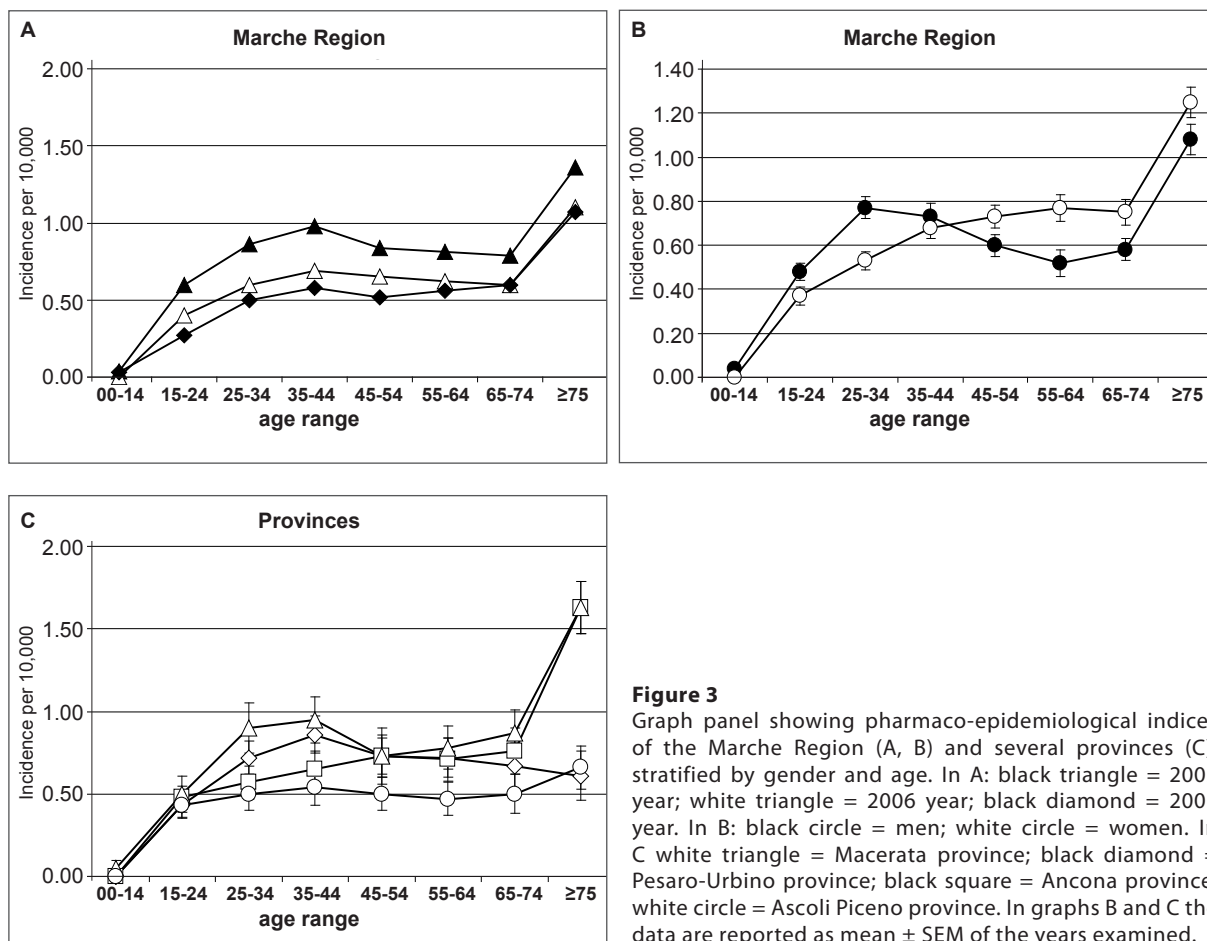For women, the highest olanzapine drug consumption was observed in the 45-54 age group. Indeed, this

A Marche Region

B Marche Region

C Provinces

Figure 3

Graph panel showing pharmaco-epidemiological indices of the Marche Region (A, B) and several provinces (C), stratified by gender and age. In A: black triangle = 2005 year; white triangle = 2006 year; black diamond = 2007 year. In B: black circle = men; white circle = women. In C white triangle = Macerata province; black diamond = Pesaro-Urbino province; black square = Ancona province; white circle = Ascoli Piceno province. In graphs B and C the data are reported as mean ± SEM of the years examined.

age range is typically associated with the beginning of menopause, and in this period women affected by behavioural disturbances may be more susceptible to a worsening of psychiatric conditions [35].

An interesting finding of our study is that the drug consumption was generally higher in men than in women, but the prevalence and incidence index were higher in women than in men, indicating that men were prescribed higher doses, particularly in the younger age range.

Analysis of the epidemiological indices for the different provinces showed a particular profile. The PU province showed a low incidence index for the elderly group (≥ 75), which seems to indicate the acceptance of AIFA note, unlike the other provinces, which therefore were responsible for the general regional profile in prescriptions for the elderly.

Another particular situation can be observed in the AN province where, unlike the other provinces, a low incidence index in the young/mature age group (25-34, 35-44) was detected. The fact that the values remained high in the elderly group might reflect a progressive aging of its population. The AP province presents a particular case: the low use of olanzapine in all age ranges accompanied a modest increase of values in the elderly group. However, the reduced use of new consumers of olanzapine after 2005, may well reflect the impact of the AIFA note.

CONCLUSIONS

Our findings reveal that in the Marche Region olanzapine is used as first choice drug to control psychiatric symptoms in young/mature patients. However, a general decrease in the use of the drug (especially in terms of new consumers) has been detected, indicating a substantial acceptance of the AIFA note, and its importance in encouraging physicians to use the drug more carefully. On the basis of these findings, although we do not have specific data, we may argue that similarly prudent behaviour may have been adopted by physicians for all atypical antipsychotic drugs.

Furthermore, the analyses performed for the four provinces of the Marche Region have provided useful information about olanzapine prescriptions, which hopefully will offer the basis for further analytical studies, particularly those examining adverse drug reactions related to long-term drug use.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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