ORIGINAL RESEARCH ARTICLE

Drug Saf 2009; 32 (11): 1075-1087
0114-5916/09/0011-1075/$49.95/0

Effectiveness of Safety Warnings in Atypical Antipsychotic Drugs

An Interrupted Time-Series Analysis in Spain

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Abstract

Background: Studies conducted to obtain drug authorization are often of short duration and based on small sample sizes in selected populations. Policies on drug safety rely on the validity of the methods used to achieve rapid and effective communication of new information. No formal evaluation has ever been made of the Spanish communications system, although indirect data have raised questions about its effectiveness.

Objective: To evaluate the impact of two safety warnings issued by the Spanish Drug Agency, and of a later prior authorization requirement involving the use of atypical antipsychotic drugs in the elderly.

Methods: The study was based on a time-series analysis constructed with data corresponding to monthly invoicing from 2000 to 2006 for olanzapine and risperidone in the Region of Valencia, Spain. Because the safety warnings and the prior authorization policy applied exclusively to prescriptions of these drugs for elderly patients with dementia, we investigated whether these interventions were successful and therefore changed prescription patterns for pensioners receiving low-strength formulations (the available proxy for elderly subjects with dementia), without altering patterns for those receiving the highest-strength formulations (typically used in schizophrenic patients) or for prescriptions for non-pensioners (any strength formulations). These two latter groups were therefore established as the control groups.

Results: Defined daily doses (DDDs) for olanzapine in low-strength pharmaceutical forms showed a clear levelling off after the first warning, while that for risperidone showed less pronounced decline. The prior authorization policy had a dramatic effect on the consumption of risperidone, but not on that of olanzapine. DDDs for low-strength formulations between the 12 months prior to the

first warning and the 12 months following the prior authorization showed a substantial reduction (22% for risperidone and 33% for olanzapine). In the high-strength forms and in non-pensioners the upward trends in DDDs remained unaltered after both interventions.

Conclusion: The safety warnings concerning atypical antipsychotic drugs were effective in reducing the prescribing of risperidone and olanzapine in low-strength doses in pensioner prescriptions, and the implementation of a prior authorization policy had a dramatic effect on the prescribing of risperidone.

Background

Studies conducted to obtain drug authorization are often of short duration, based on small sample sizes in selected populations and seldom take into account concomitant treatments. This means that certain adverse events (AEs) may go undetected when a drug is launched on the market.[1,2] Not infrequently, important information about safety is made public only after a drug has become widely used. Providing information to physicians, pharmacists and patients about new safety parameters that have arisen after the drug has been marketed is critical in maintaining the optimum drug risk-benefit balance. Policies on drug safety rely on the validity of the methods used to achieve rapid and effective communication of new information.[3] If communication is inadequate, forms of treatment that have been proven harmful may be retained or, alternatively, drugs with a good benefit-risk profile may be underused.[4-6]

The national drug agency of most countries uses communication instruments to warn of risks. Health authorities may require the inclusion of warnings in the insert that accompanies a drug package (the 'black-box warning'), and disseminate safety warnings. The agencies may also require the manufacturers to send letters to doctors explaining newly recognized risks and precautionary measures ('Dear Doctor letters'). These communications procedures vary considerably in intensity and effectiveness,[6] and assessments of their impact on medical practices are not conclusive.[7-10]

In Spain, when the Spanish Agency for Drugs and Health-Care Devices (Agencia Española de Medicamentos y Productos Sanitarios [AEMPS]) considers that doctors need to receive rapid information about a safety issue, it publishes a warning in the form of an 'informational note'. The dissemination of these notes sets in motion what is known as the 'warnings network'. It acts as a cascade mechanism: the AEMPS informs the healthcare institutions operated by the Central Government and the Healthcare Departments of each of the autonomous regions. These, in turn, inform the healthcare services in their own regions (along with all other Regional healthcare institutions such as official professional colleges and other professional associations), which inform the healthcare professionals within their jurisdictions. No formal evaluation has been made of this communications system, although indirect data have raised questions about its effectiveness.[11,12] The aim of this study was to evaluate the impact of two warnings issued by the AEMPS about the safety of atypical antipsychotic drugs in the elderly, and of the later implementation of a measure requiring prior authorization before dispensing these drugs for patients older than 75 years.

Methods

Design

The study was based on an interrupted time-series analysis.[13,14] This was designed to examine possible changes in dispensing patterns of two atypical antipsychotic drugs (olanzapine and risperidone) resulting from safety warnings issued by the AEMPS and the prior authorization policy. Since both measures applied exclusively to prescriptions of these drugs for elderly patients

with dementia, we hypothesized that, if these interventions were successful, they would change prescription patterns for pensioners receiving low-strength formulations (the available proxy for elderly subjects receiving treatment for dementia [the 'study group']), without altering patterns for those receiving the highest-strength formulations (typically used in schizophrenic patients) or for prescriptions for non-pensioners. These two latter groups were therefore established as the control groups. Pensioners, in this context, define people with exemption from pharmaceutical co-payment, eligible because they are aged ≥65 years, have a disability or are part of deprived collectives or their co-dependents.

Setting

In January 2000, when the time series began, there were 4 120 729 inhabitants in the Autonomous Region of Valencia, Spain, 16.6% over the age of 65 years and 6.9% over 75 years. Like all of the regional healthcare systems in Spain, the Valencia Health Agency (VHA) operates an extended hospital and healthcare centres network, which covers about 97% of the population. Care in this network is free of charge, with coverage extending to substantial pharmaceutical benefits: all medicines prescribed to pensioners (eligible because of either age or disability) and underprivileged collectives are free of charge. The remaining population, referred to in this study as non-pensioners, pays for only part of the costs of the pharmaceuticals it uses, through a co-payment system wherein the patient pays 40% of the cost of medication, and only 10%, with a ceiling of €2.45 for long-term treatments, such as the antipsychotic drugs discussed here.

Some characteristics of the prescription and dispensing system in Spain that are relevant to our study include:

1. Prescriptions must be filled in on specific Spanish National Health System forms, with different formats, depending on whether the recipient is a non-pensioner or a pensioner.
2. Drugs are always dispensed in commercial packages, not in unitary doses customized for each patient. This requires that a separate prescription form must be used each time and that the drug must be dispensed within 10 days after the doctor has signed the prescription form.
3. Prescriptions, even when the original is written by a specialist, must be renewed by the general practitioner throughout the duration of treatment.

Interventions (Safety Warnings and Prior Authorization Requirement)

This study evaluated the effect of three interventions: two safety warnings for atypical antipsychotic drug use in elderly people with dementia, issued by the AEMPS on 9 March and 10 May 2004, and a prior authorization requirement for prescriptions for patients older than 75 years that came into force on 1 February 2005. Since the two safety warnings were close in time, in this study they were treated as a single intervention and considered to have come into force on the date of issue of the first warning. For practical purposes, the impact of any other interventions that may have taken place during the same period (articles published on the topic in scientific and professional journals, bulletins or communications circulated by the health authorities, etc.) have been considered to be part of the respective interventions.

The aim of the first of the safety warnings was to provide information about the use of olanzapine in psychotic or behavioural disorders associated with dementia in the elderly. The warning pointed out that the use of this drug in this group of patients had not been shown to be effective in the clinical trials conducted prior to its approval, and that the use of this drug was associated with an increase in mortality and adverse cerebrovascular events, which was most apparent in patients over the age of 75 years. The AEMPS reminded physicians that olanzapine was not authorized for use in psychosis and behavioural disorders associated with dementia and that "it should not be used in this group of patients, calling for a review of treatment of patients who were receiving olanzapine … for this indication". For risperidone, which had been authorized in the management of elderly patients with dementia, the AEMPS stated that

there was "an increase in the risk of adverse cerebrovascular events" and recommended using risperidone "according to the package insert specifications".

Two months later, in the second safety warning, the AEMPS restricted its indication for these patients to the treatment of severe aggressive behaviour or severe psychotic symptoms that did not respond to non-pharmacological measures, after other aetiologies had been ruled out. The AEMPS further established that risperidone could be used only under the supervision of experienced physicians, for as short a period as possible and that patients should be under special observation if they had a diagnosis of ischaemic stroke.

The requirement of obtaining prior authorization for the dispensing of atypical antipsychotic drugs for the elderly was announced with a considerable lead time before it came into force on 1 February 2005. This measure not only affected the drugs involved in the two previous safety warnings, but it also included all of the atypical antipsychotic drugs on the Spanish market in 2005 (amisulpride, clozapine, quetiapine and ziprasidone), although this applied only to prescriptions for patients over the age of 75 years.

Study and Control Groups

Initially we had intended to use the group of pensioners as the study group and non-pensioners receiving the same drugs as the control group. However, closer analysis of these groups indicated that patients with psychiatric conditions likely to be treated with antipsychotics are usually pensioners, independent of age, and this may have led to an under-estimation of the effect of the safety measures in the elderly. Because both antipsychotics are marketed in different doses, and the lowest dose ranges are often used to treat symptoms of dementia in the elderly, we opted to construct a more selective study group using prescriptions for pensioners containing the lowest doses (risperidone tablets with 0.5 and 1 mg and the oral solution with 1 mg/mL; olanzapine tablets 2.5 mg). We established two control groups: those pensioners with prescriptions for higher-dose formulations (risperidone 2, 3 and 6 mg tablets and the 1.8 mg injectable depot; olanzapine 5, 7.5 and 10 mg tablets) and non-pensioners receiving risperidone or olanzapine in any dose formulation, including both lower and higher doses.

Sources of Data

Data reflecting consumption of the drugs was extracted during the 84 months of the study (2000–6) from the claims that the region's pharmacies submitted to the VHA on a monthly basis. Among other data, these claims include information about the drug dispensed (brand name, formulation, dose, number of units per package, price) and the coverage characteristics of the patient: pensioner (free of charge) or non-pensioner (under the co-payment scheme). The claims do not include any information about the age, sex, diagnostic features or reason for prescription concerning the patient. Since drug packages do not necessarily contain the same quantities of the drugs, the VHA's information system transforms information about quantities into defined daily doses (DDDs), the amount that corresponds to the average maintenance dose per day for a medication used in its principal indication in adults, as established by the WHO's Collaborating Centre for Drug Statistics Methodology:[15] 5 mg/day (1.8 mg for the depot formulation) for risperidone[16] and 10 mg/day for olanzapine.[17]

Main Outcome Measure

The main outcome measure was the number of DDDs of risperidone and olanzapine dispensed monthly in the intervention and control groups. Ideally the analysis would have been of DDD/1000/day (instead of number of DDDs), but because of a substantial change in the region's demographics, this was deemed unsuitable. During the study period, the population of the region of Valencia increased substantially (with foreigners accounting for 80% of the population growth), and some of the newcomers were eligible for free medical care on the basis of low income. This produced an increase in the 'pensioners' denominator with

the addition of people (mainly young men) who were very different from our target group (the elderly). Because we have no age or sex information to standardize the DDD/1000/day, we considered it preferable to use DDDs rather than DDD/1000/day.

Analysis

First, we describe the monthly raw series of prescriptions for risperidone and olanzapine (low- and high-strength formulations) for pensioners and non-pensioners by dose strength, and the annual monthly average DDD. Second, the raw time series corresponding to the DDDs of the drugs analysed were built into the study and the control groups. The Autoregressive Integrated Moving Average (ARIMA) methodology was then used to model any stationarity from the series and correct any possible autocorrelation.[18,19] The Ljung-Box and Box-Pierce statistics were used on the residuals and squared residuals, and the normality test was performed to evaluate the adjustment of the series. The forecast called for rejecting the adjustment if any of the statistics were significant at 0.01, if three of them were significant at 0.05 or if there were more than 5% extreme values.[19] To build the adjusted series, the stationarity and the autocorrelation were modelled depending on the case, but the extreme values were not adjusted since, in theory, they may have reflected an effect produced by the interventions.

After adjusting the values of the series with the respective ARIMA models, a segmented regression analysis was performed to detect any level or slope changes that may have occurred in the DDDs dispensed during the span of the study, and that may have been associated with the interventions. Segmented linear regression detects the occurrence of level or slope changes by comparing the segment, after a given cut-off point, with the segment immediately preceding it. Level changes (evaluated on the basis of their respective constants) or slope changes (evaluated on the basis of the β coefficient) related to the interventions analysed were considered statistically significant when $p < 0.05$. Three segments were established that corresponded to the three different study periods: January 2000–March 2004 (pre-warnings period), April 2004–February 2005 (post-warnings period, up until the entry into force of the prior authorization requirement) and March 2005–May 2006 (post-prior authorization period). The DDDs for each of the antipsychotic drugs were incorporated as the dependent variable, and two variables indicating the period of each intervention, and two dichotomous variables indicating the occurrence of change, or lack thereof, were incorporated as the independent variables.

Analysis of the time series was carried out using the TRAMO-SEATS procedure with the DEMETRA® statistical program, 2.04 version (European Communities). The STATA® mkspline procedure (College Station, TX, USA) was used to prepare the variables for the segmented regression analysis. In the regression analysis, which was also carried out using STATA, all of the independent variables were included.

Results

Figure 1 shows the raw time series for the DDDs of olanzapine and risperidone dispensed with prescriptions for pensioners and non-pensioners by dose strengths. For both drugs, prescriptions of low-strength formulations for pensioners increased from 2000 until the publication of the warning in the first quarter of 2004. From this time on, consumption started to decrease until a dramatic drop occurred in 2005, coinciding with the prior authorization policy. Prescribing of the high-strength formulations showed a continuous increase during the entire period, although for risperidone the introduction in mid 2003 of an injectable depot formulation had a marked impact on the prescribing of high-strength oral formulations. In non-pensioners, prescription numbers also rose, although risperidone injectable formulations appear to have had a competitive edge over oral 6 mg tablets. Note that olanzapine (not authorized for dementia in the elderly) shows very limited prescribing of the low-strength formulations to pensioners.

Table I presents the average monthly consumption of the antipsychotic drugs in all the

Fig. 1. Monthly raw series of risperidone and olanzapine, in pensioners' and non-pensioners' prescriptions, by dose strength of commercial formulations. Region of Valencia, Spain, 2000–6. All quantities are defined daily doses (DDD). The vertical dotted lines indicate the initial warnings (2004) and prior authorization (2005). (**a**) Risperidone prescriptions for pensioners; (**b**) risperidone prescriptions for non-pensioners; (**c**) olanzapine prescriptions for pensioners; (**d**) olanzapine prescriptions for non-pensioners. **Inject** = injection depot formulations.

study groups. DDDs of low-strength risperidone in pensioners increased from 62 248 DDD/month in 2000 to 92 581 in 2004, then decreased to 74 173 DDD/month in 2006. Low-strength forms of olanzapine in pensioners showed similar behaviour, with 3805 DDD/month in 2000, close to 14 000 in 2003 and 2004, and 9421 in 2006. For pensioners, high-strength forms showed a continuous increase in DDD during the study period (from 84 165 DDD/month in 2000 to 230 353 in 2006 for risperidone, and from 87 466 to 178 500 DDD/month for olanzapine). In non-pensioners, olanzapine showed a continuous increase in DDD, but risperidone showed an initial increase, then a plateau after 2003.

Figure 2 shows the raw and adjusted time series for the DDDs for olanzapine and risperidone in all the study groups. ARIMA models 0,1,1 or 0,1,2 were used, depending on the series. The adjusted series surpassed all the pre-established statistical requirements and were very similar to the raw series. For both drugs, DDDs for low-strength formulations for pensioners rose until the publication of the safety warning. From this point on, DDDs for risperidone declined slightly, but then dropped abruptly the month after prior authorization became compulsory in patients older than 75 years; olanzapine, however, experienced a sharp decline in DDDs between the two interventions, so that when prior authorization was established its impact was minor. After the last intervention, the series appears to have stabilized. For high-strength formulations of both drugs in pensioners and olanzapine in non-pensioners, there was an upward

trend in DDD during the entirety of the period, while risperidone in non-pensioners showed a decline prior to the safety warnings, and ultimately levelled off.

According to the segmented regression models (tables II and III, figure 3), low-strength risperidone in pensioners increased from the intercept initial value of 57 463 DDDs by 785 DDDs/month during the pre-warning period. The first warning was associated with a sudden drop of 2897 DDDs and a downturn in the trend, with a decrease, relative to the previous period, of 1338 DDDs monthly during the post-warning period. Compulsory prior authorization was associated with a sudden decline of 18 070 DDDs the month after the measure came into force, to ultimately recover, relative to the previous period, by 739 DDDs/month. In high-strength risperidone, changes during the intervention periods were positive or non-significant, while in non-pensioners the fit of the model was worse, and although significant changes were detected that were associated with the safety warning, these occurred prior to the intervention (see dotted line on figure).

DDDs for the low-strength formulations of olanzapine started with an intercept value of 1976 and a faster growth (compared with risperidone) of 277 DDDs monthly. The safety warnings were associated with a sudden decrease of 1204 DDDs and, during the post-warning period, a relative decrease of 664 DDDs/month compared with the previous trend. The introduction of the

Table I. Monthly average defined daily dose (DDD) for olanzapine and risperidone in pensioners' (low- and high-strength formulations) and non-pensioners' prescriptions (any strength formulation)

Year	Risperidone			Olanzapine		
	pensioners		non-pensioners	pensioners		non-pensioners
	low strength[a]	high strength[b]	all strengths[b]	low strength[a]	high strength[b]	all strengths[b]
2000	62 248	84 165	11 958	3 805	87 466	1350
2001	71 841	100 897	13 106	6 769	103 422	2142
2002	82 052	111 556	16 691	10 937	128 125	2921
2003	91 215	128 002	18 706	13 700	143 763	3462
2004	92 581	175 125	16 895	13 521	155 259	3864
2005	73 549	201 173	16 649	9 701	161 454	4083
2006	74 173	230 353	16 895	9 421	178 500	4526
Change in relation to the previous year (monthly average previous year = 1)						
2000	1.00	1.00	1.00	1.00	1.00	1.00
2001	1.15	1.20	1.10	1.78	1.18	1.59
2002	1.14	1.11	1.27	1.62	1.24	1.36
2003	1.11	1.15	1.12	1.25	1.12	1.19
2004	1.01	1.37	0.90	0.99	1.08	1.12
2005	0.79	1.15	0.99	0.72	1.04	1.06
2006	1.01	1.15	1.01	0.97	1.11	1.11
Change in relation to the year 2000 (monthly average 2000 = 1)						
2000	1.00	1.00	1.00	1.00	1.00	1.00
2001	1.15	1.20	1.10	1.78	1.18	1.59
2002	1.32	1.33	1.40	2.87	1.46	2.16
2003	1.47	1.52	1.56	3.60	1.64	2.56
2004	1.49	2.08	1.41	3.55	1.78	2.86
2005	1.18	2.39	1.39	2.55	1.85	3.02
2006	1.19	2.74	1.41	2.48	2.04	3.35

a Study group.

b Control group.

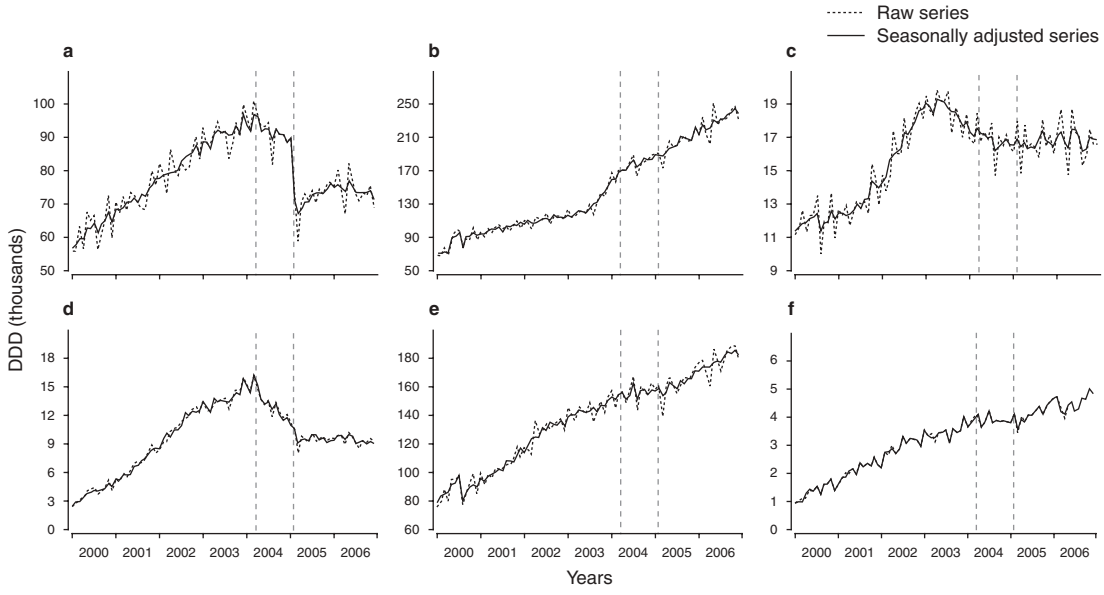

Fig. 2. Monthly raw and adjusted time series of risperidone and olanzapine, in pensioners' and non-pensioners' prescriptions, by dose strength of the formulations. Region of Valencia, Spain, 2000–6. Adjusted series constructed by ARIMA (Autoregressive Integrated Moving Average) models. All quantities are defined daily doses (DDD). The vertical dotted lines indicate the initial warnings (2004) and prior authorization (2005). (**a**) Risperidone low strength for pensioners (study group); (**b**) risperidone high strength for pensioners (control group); (**c**) risperidone any strength for non-pensioners (control group); (**d**) olanzapine low strength for pensioners (study group); (**e**) olanzapine high strength for pensioners (control group); (**f**) olanzapine any strength for non-pensioners (control group).

compulsory prior authorization produced a short lasting drop of 1214 DDDs, which recovered by 361 DDDs/month, relative to the previous post-warning period. DDDs of olanzapine in high-strength formulations showed little change during the pre-intervention period, and recovered after prior authorization became compulsory. Intercept changes associated with both interventions were not significant. The patterns with non-pensioners were similar, with non-significant intercepts associated with both interventions, reductions in the increase during the post-safety

Table II. Results of the segmented regression analysis for risperidone[a]

Parameter	Pensioners				Non-pensioners	
	low strength[b]		high strength[c]		all strength[c]	
	DDD	p-value	DDD	p-value	DDD	p-value
Intercept 1	57 463	<0.001	73 378	<0.001	10 674	<0.001
Slope prior to first warning	785	<0.001	1 390	<0.001	175	<0.001
Intercept 2 (warning)	–2 897	0.025	25 224	<0.001	–2 437	<0.001
Slope post-warning	–1 338	<0.001	462	0.530	–247	0.012
Intercept 3 (prior authorization)	–18 070	<0.001	–938	0.847	202	0.751
Slope post-prior authorization	739	<0.001	647	0.396	83	0.410

a Adjusted coefficient of determination: 0.97 (low strength, pensioners), 0.98 (high strength, pensioners) and 0.86 (non-pensioners, any strength); $p < 0.001$ in all models.

b Study group.

c Control group.

DDD = defined daily dose.

Table III. Results of the segmented regression analysis for olanzapine[a]

Parameter	Pensioners				Non-pensioners	
	low strength[b]		high strength[c]		all strength[c]	
	DDD	p-value	DDD	p-value	DDD	p-value
Intercept 1	1976	<0.001	77 338	<0.001	1041	<0.001
Slope prior to first warning	277	<0.001	1 559	<0.001	58	<0.001
Intercept 2 (warning)	−1204	0.002	−2 761	<0.320	−53	<0.722
Slope post-warning	−664	<0.001	−1 222	0.004	−70	0.002
Intercept 3 (prior authorization)	−1214	0.002	−3 901	0.157	33	0.820
Slope post-prior authorization	361	<0.001	1 069	0.015	52	0.027

a Adjusted coefficient of determination: 0.98 (low strength, pensioners), 0.98 (high strength, pensioners) and 0.97 (non-pensioners, any strength); $p < 0.001$ in all models.

b Study group.

c Control group.

DDD = defined daily dose.

warning period and the recovery of growth after compulsory prior authorization.

Discussion

The results of this study show considerable growth in the prescriptions of olanzapine and risperidone, both in pensioners and in non-pensioners, with prescribing almost doubling during the period analysed. A recent study of Spain's entire National Health System confirms this trend, indicating that consumption of atypical antipsychotic drugs grew from 665 000 packages in 1997 to 4 330 000 in 2004.[20] This increase cannot be attributed to an increase in the population or in the number of pensioners, or to changes in the prevalence of schizophrenia.[20] They suggest that over this span there was a widespread increase in the use of these antipsychotics in situations where they had not been previously prescribed.

The results of this study show that the interventions concerning atypical antipsychotics issued by the AEMPS in 2004 were effective in reducing the dispensing of low-strength forms to pensioners, although the effect was different depending on the drug. The growth curve for the use of olanzapine showed a clear levelling off after the warning was issued. This was probably due to the fact that the first and most explicit warning was addressed to olanzapine utilization. Risperidone showed a less pronounced decline. To the contrary, the prior authorization requirement had a dramatic effect on the use of risperidone, but not on olanzapine. As was expected, in the high-strength forms and in prescriptions for non-pensioners, the upward trends remained unaltered after the publication of the warnings applicable specifically to the elderly; nevertheless, DDDs of risperidone for non-pensioners started to decline from the first months of 2003, prior to the interventions by the AEMPS.

A search of the literature uncovered a single study, carried out in Canada, which evaluated the impact of safety warnings on the prescribing of atypical antipsychotic drugs for the elderly.[21] In this paper, the safety warnings were effective, but not to the extent that overall prescription rates in patients with dementia were reduced. Each warning was associated with a small, relative decrease in the predicted growth in the use of atypical antipsychotic drugs, but the prescription rate increased by 20% overall, from September 2002, the month before the first warning, to February 2007, 20 months after the last warning. Our study is not comparable to the Canadian one for several reasons: we have no information about the patients' age or diagnostic features; we cannot calculate the overall prescription rate; and, in Spain, there was another type of intervention applied (the prior authorization requirement). However, we also detected a substantial decrease in low-strength formulations between the 12 months

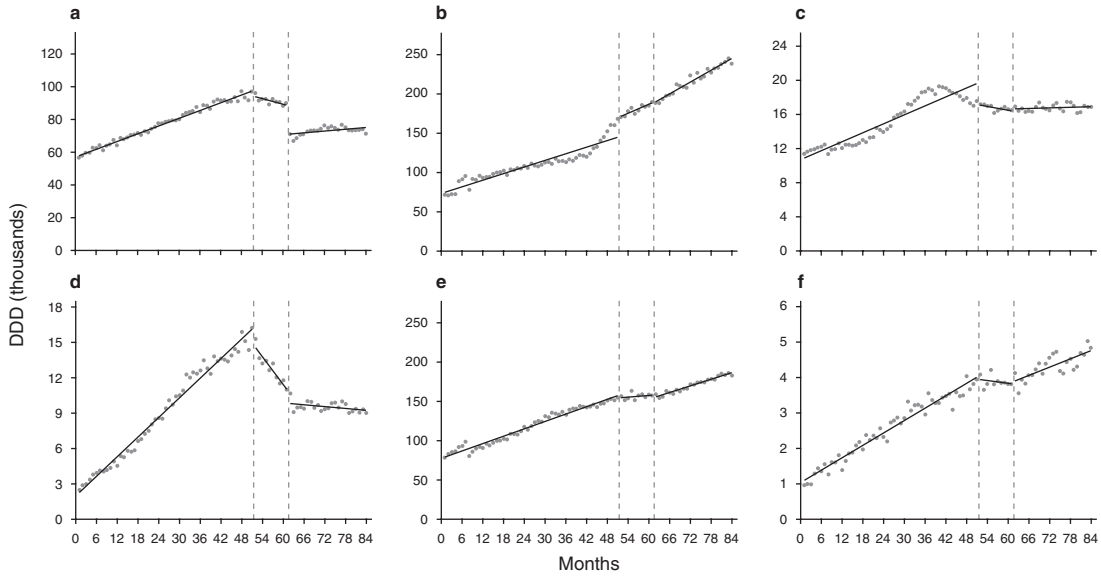

Fig. 3. Segmented regression analysis of seasonally adjusted time series of risperidone and olanzapine by low- and high-strength formulations (pensioners' prescriptions) and all formulations (non-pensioners' prescriptions). Region of Valencia, Spain, 2000–6. All quantities are defined daily doses (DDD). The vertical dotted lines indicate the initial warnings (2004) and prior authorization (2005). (**a**) Risperidone low strength for pensioners (study group); (**b**) risperidone high strength for pensioners (control group); (**c**) risperidone any strength for non-pensioners (control group); (**d**) olanzapine low strength for pensioners (study group); (**e**) olanzapine high strength for pensioners (control group); (**f**) olanzapine any strength for non-pensioners (control group).

prior to the first safety warning and the 12 months after the prior authorization requirement (22% for risperidone and 33% for olanzapine), and in 2005 the number of DDDs was very similar to those at the end of 2001 (numbers of DDDs were maintained through 2006).

The only references regarding the effect of other safety warnings found for Spain concern the widespread impact of the warning about the cardiovascular safety of cyclo-oxygenase (COX)-2 selective inhibitors ('coxibs') issued by the AEMPS in 2001 (although in this case the warning, coinciding with the withdrawal of cerivastatin, had exceptional repercussions in the media, and physicians were particularly sensitive to the subject),[22,23] and the warning about selective serotonin reuptake inhibitors (SSRIs) in paediatric populations.[12,24] In this second case, the warning issued by the AEMPS (several months after warnings in other countries) was not effective; there had, however, been a previous reduction in paediatric prescriptions for SSRIs immediately after the US FDA's warning.

Studies evaluating the impact of safety warnings (or other drug-related risk-communication mechanisms) in other countries show mixed results. The interventions affecting SSRIs in children and adolescents have been effective in all papers published,[11,24-32] as have been interventions covering terfenadine,[33,34] the coxibs[22,23] and droperidol.[35,36] In contrast, the initial interventions affecting cisapride showed either no impact[37-40] or mixed results,[41-44] although later interventions, which were more stringent and followed up on prior warnings, were more effective.[45,46] Other studies have shown that warnings concerning dextropropoxyphene had no effect.[47] Warnings against the co-prescription of tramadol and antidepressants were also ineffective.[48] Finally, warnings associated with thiazolidinediones ('glitazones') demonstrated mixed results (resulting in a decrease in the concomitant prescribing of contraindicated drugs or leading to an increase in liver enzyme monitoring, but in an insufficient way).[44,49-51] These results show that safety warnings issued by national

health agencies can be effective, ''but not in all circumstances, not every time, and not always to the ideal extent'',[5] and suggest the need to develop (and test) new methods and novel combinations of techniques to communicate medical risks.

Certain limitations are inherent with a study of this nature. The first of these concerns the use of the total prescriptions of antipsychotics (for elderly patients with dementia and all other indications) as our measure of consumption in our target group, because this may underestimate the effectiveness of the intervention. This limitation is associated with restrictions intrinsic to the sources of data available during the study period, as they do not provide any information (age, diagnosis or reason for prescription) about the patients. Since our study was concluded, the VHA has implemented an electronic medical record with a prescription module that currently covers about 75% of general practitioners. Although the system still has several drawbacks in terms of diagnostic information, and still does not cover the elderly who are institutionalized, according to this source, of the 28 685 people with at least one prescription for risperidone or olanzapine registered on their medical records in 2007, half (51.1%) were aged 65 years or older, and half of this group were 75 or older. Note that these figures refer to 2007 and were thus affected by the interventions evaluated here. Additionally, a study conducted in Catalonia (5 healthcare centres, 592 patients) indicated that 31.1% of institutionalized geriatric patients were treated with antipsychotic drugs and that, of these, 74% received atypical antipsychotics, of which risperidone was the most widely prescribed (46% of treatments). Of these treatments, 68% were given to patients diagnosed with behavioural disorders due to dementia.[52] All of these figures suggest that the use of atypical antipsychotic drugs in dementia was widespread at the time the warnings were issued. In all events, limitations associated with the sources of data used did not make it possible to estimate the number of elderly patients with dementia treated with antipsychotics, and it was necessary to estimate this figure through the proxy of prescriptions of low-strength doses to pensioners. These are imprecise estimates, and would be even more so if there were a large group of young patients with schizophrenia considered 'pensioners', also receiving medical treatment free of charge.

Further limitations are those associated with observational studies that strive to establish a cause-effect relationship, as they may detect confounding factors that coincide during the span of the study. One of these may have been the launch of ziprasidone in 2003 that may have gained market share at the expense of olanzapine and risperidone, and may be a factor in the levelling off of the use of these two drugs. The possible effect of scientific papers alerting to the risks of the atypical antipsychotic drugs may also have had an impact. Conversely, the response of the pharmaceutical industry with the publication of promotional materials could have reinforced the positive image of the drugs. Moreover, the prior authorization requirement received considerable criticism, with claims that it did not pursue safety ends, but had been devised to save money.

Conclusions

The safety warnings concerning atypical antipsychotic drugs issued by the AEMPS between 2004 and 2005 were effective in reducing the prescribing of risperidone and olanzapine in low-strength doses to pensioners. The implementation of a prior authorization requirement had a dramatic effect on the prescribing of risperidone, but not of olanzapine. Further and improved research into communications methods that provide information about drug safety and efficacy is required to elucidate which methods have the optimum effects on modifying physicians' behaviour. Methods to explore include the dissemination of warnings through the general communications media or direct information to patients. Warnings provide an important tool in protecting patients, and will no doubt require the development of new strategies to ensure rapid communication that results, above all, in changes in physicians' prescribing habits.

Acknowledgements

Non-conditional funding for this study was provided by Merck Foundation, Whitehouse Station, NJ, USA, in the framework of the agreement between this Institution and the Research Center on Economics and Health (Centre de Recerca en Economia i Salut [CRES]) of the Pompeu Fabra University of Barcelona. The sponsor did not play any role in the study design, collection, analysis, or interpretation of data, in the writing of the manuscript, or in the decision to submit it for publication. The authors' work was independent of the funders.

Salvador Peiró and Beatriz González López-Valcarcel have received grants from Merck Sharpe & Dohme, and have received honoraria for participation in scientific meetings sponsored by pharmaceutical companies. The other authors have no conflicts of interest to declare that are directly relevant to this study.

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