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The effect of safety warnings on antipsychotic drug prescribing in elderly persons with dementia in the United Kingdom and Italy: a population-based study

Running title: Effect of safety warnings on antipsychotic prescribing in dementia in the UK and Italy

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Compliance with Ethical Standards The authors contributed to the present study as follows: Literature search: JS, JI, CB, SS; study design/writing of protocol: JS, AF, GT; data extraction/data management: JS, FG, AP; data analysis: AF, JS, FG; writing and revision of manuscript: JS, AF, FG, AP, CB, CC, SS, ES, GG, JI, CF, MM, MS, GT; conception of study: GT. GT has access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

JS, AF, FG, AP, CB, CC, SS, ES, GG, JI, CF, MM, MS, GT have no competing interests to declare directly related to the present study. CC has received consulting fees/honoraria from Bayer unrelated to this study. ES has received grants unrelated to this study, consulting fees/honoraria from Eli Lilly unrelated to this study, payment for lectures unrelated to the study and is a board member for Astra-Zeneca and Lundbeck. MM has received funding from Pfizer, Astra-Zeneca and the international Adverse Events Consortium for studies unrelated to this study. CB has received grants and personal fees from Arcadia, Lundbeck, Napp, Roche, Orion, Bial, Bristol Myer Squibb, Otsuka and Novartis unrelated to this study.

Abstract

Background: Antipsychotic (AP) drugs are commonly used to manage behavioural symptoms of dementia. Nevertheless, international (European Medicines Agency - Europe) and national (Medicines and Healthcare products Regulatory Agency – UK and the Italian Drug Agency) regulatory agencies issued safety warnings against antipsychotic (AP) use in dementia in 2004 and 2009.

Objective: The aim of this study is to investigate short- and long-term impact of safety warnings on AP use in UK and Italian persons with dementia using two nationwide databases, The Health Improvement Network (THIN) from the UK and Health Search Database-Cegedim-Strategic Data-Longitudinal Patient Database (HSD-CSD-LPD) from Italy.

Methods: The quarterly prevalence of AP use was calculated overall, by class and by individual drug in persons with dementia aged ≥ 65 years. Generalized linear models were used to explore the effect of the safety warnings.

Results: Over the period 2000-2012, 58,497 and 10,857 persons ≥ 65 years with dementia were identified from the THIN and HSD-CSD-LPD databases. After the 2004 warnings, atypical ~~and AP use~~ conventional AP use decreased while conventional AP use increased in Italy and the UK until 2009; however, the trend for APs individually showed that risperidone/olanzapine use decreased while quetiapine increased in both countries. After the 2009 warnings (until 2012), atypical and conventional AP use decreased in the UK (11% to 9%, and 5% to 3%, respectively), but such use increased in Italy (11% to 18% and 9 to 14%, respectively).

Conclusion: The 2004 warnings led to a reduction in olanzapine and risperidone use and increased quetiapine/conventional AP use in both countries. From 2009, AP use fell in UK but not Italian persons with dementia. Possible reasons for the difference in AP use between the two countries include a more proactive approach towards reducing AP use in the UK compared to Italy.

Key points

- This study is the first to present the short- and long-term effects of the safety warnings on the use of antipsychotic (AP) drugs in dementia in the UK and in Italy in a general practice setting on a national level.
- The safety warnings combined with proactive national initiatives in the UK may have contributed to the significant reduction in AP use since 2009. Equally, the less proactive approaches to reduce AP prescribing in Italy may be one reason why AP prescribing did not decrease in this country.

1. Introduction

Over 90% of people with dementia experience behavioral and psychological symptoms of dementia (BPSD), including aggression, confusion and hallucinations [1], for which antipsychotics (APs) are commonly prescribed, usually off-label [2]. Eighteen placebo-controlled randomized clinical trials (RCTs) have shown significant but modest improvement of aggression (Standardized Effect Size: 0.22) and smaller but significant benefits in psychosis (Standardized Effect Size 0.18) over 6-12 weeks of treatment with risperidone and olanzapine in persons with BPSD in a systematic review by Ballard et al. [3]. In contrast, quetiapine appears ineffective according to the same systematic review as well as a meta-analysis [3-4]. In Europe, risperidone is the only AP indicated for the treatment of BPSD [for short-term (≤ 6 weeks) management of severe aggression in dementia, if unresponsive to other treatments][5]. Severe AP-related adverse effects in persons with dementia include pneumonia, stroke and all-cause mortality [6-8].

Following a pooled analysis of RCTs in 2004, the European Medicines Agency (EMA) reported an almost 2-fold increased risk of all cause-mortality and 3-fold increase in cerebrovascular events in persons with dementia treated with risperidone and olanzapine [9]. Thereafter, a series of safety warnings about AP use in dementia were launched by international/national agencies (**Table 1**). While the initial warnings pertained specifically to the atypical APs risperidone and olanzapine, in 2009 the regulatory safety warnings were extended to all APs. During this period there were also high-profile reports in England from the Alzheimer's Society and the All Party Parliamentary Group on Dementia targeting inappropriate AP prescribing [10]. An English Department of Health-commissioned review in 2009 indicated that unnecessary AP use was potentially leading to an additional 1,600 strokes and 1,800 deaths in older persons with dementia, annually [11]. Following the publication of this report, there was a proactive initiative in England with the government committing to reduce AP use in dementia by two-thirds by 2011. A ministerial working group was established and the reduction of AP prescribing became a key target of English dementia policy strategies [12]. The Dementia Action Alliance, formed between key stakeholders (government, professional bodies, and charities representing people with dementia) launched a call to action on inappropriate AP prescribing in June 2011. Toolkits were produced to support health/social care professionals in using alternative approaches [13].

[Table 1 here]

The UK Department of Health commissioned National Dementia and AP Prescribing (DAP) audit suggested a reduction in AP prescribing by half between 2008 and 2011 [14] but participation in the audit was voluntary, leading to potential biases. On the other hand, in 2005 the Italian Drug Agency launched an active pharmacovigilance initiative, targeted at Italian specialist dementia centers, but no assessment of AP prescribing trends was planned [15]. This activity involved completing a pharmacovigilance data sheet if APs were prescribed to a person with dementia. In Italy, the same warning in 2005 advised physicians to review their patients every two months and reminded them that the duration of AP use in persons with dementia should not exceed 90 days. Other AP-related initiatives in Italy were more advice-oriented rather than directly action-oriented compared to the UK initiatives while some had a technical-legal and/or a clinical nature. For example, the communication by AIFA in 2009 reminded prescribers that informed consent is required by law before the first AP is prescribed to a person with dementia. This warning also advised that APs should be used only where strictly needed in persons with dementia.

The effectiveness of risk minimization measures requires careful monitoring through observational studies [16]. The effect of safety warnings on AP prescribing has been investigated in several countries within [17-19] and outside Europe (**Appendix 1**) [20-21]. The two available Italian studies investigated only short-term effects of the warnings and one of those was limited to a restricted geographic area [22-23]. No nationwide studies have been conducted in the UK so far although a study by Guthrie et al. has described AP use after the Medicines and Health Products Regulatory Agency (MHRA) warnings in 2004 and 2009 using data from 87 Scottish general practices [24].

Given the lack of information on recent trends in AP utilisation in Italy and the UK, the aim of this population-based study was to investigate and compare the short and long-term effects of the safety warnings issued by international/national drug regulatory agencies on AP prescribing in older people with dementia in UK and Italy. Additionally, this study explored whether a 50% reduction in AP use in UK dementia people between 2008 and 2011, as documented by the DAP audit, was confirmed in a nationwide population.

2. Methods

2.1. Setting

Two nationwide, general practice databases were used for this retrospective population-based study: The Health Improvement Network (THIN, UK) and Health Search Database -Cegedim-Strategic Data-Longitudinal Patient Database (HSD-CSD-LPD, Italy). THIN currently contains anonymized clinical data for 11 million persons with 3.7 million active patients (covering approximately a 6.2% representative sample of UK population) registered with 562 general practices across the UK. Data in HSD-CSD-LPD are recorded by approximately 900 general practitioners (GPs) from all over Italy, covering a population of 1,166,076 persons (approximately a 2% representative sample of the Italian population). Both THIN and HSD-CSD-LPD contain data on patient demographics, diagnoses (coded using Read codes in THIN and International Classification of Diseases, 9th revision, clinical modification (ICD-9 CM) in HSD-CSD-LPD) and drugs prescribed (coded using British National Formulary (BNF)/Multilex codes in THIN and Anatomical Therapeutic Chemical

(ATC) classification in HSD-CSD-LPD). Both databases have been used extensively for pharmacoepidemiological research [25-30].

2.2. Participants

Persons registered in both databases were considered eligible for inclusion if they were alive and had at least one year of database history. The study period ranged from January 1st 2000 to December 31st, 2012 in HSD-CSD-LPD and May 31st, 2012 in THIN, based on last data drawn at the time the study was conducted. Person contribution to the cohort was censored at the end of the study period, transfer out of database or death, whichever came first. Eligible persons from both databases who were ≥ 65 years and had a diagnosis of dementia (**Appendix 2**) were identified.

Persons who were < 65 years and those ≥ 65 years, irrespective of dementia diagnosis, were also identified in order to allow a broad comparison of crude prevalence of AP use in these two populations with respect to those ≥ 65 years with dementia. We also hypothesised that more marked change in drug utilisation among persons ≥ 65 years with dementia compared to the other two populations would suggest whether the safety warnings were specific to the former population.

2.3. Drug exposure

AP prescriptions were identified using specific Multilex/BNF codes in THIN (**Appendix 3**) and ATC codes (N05A*, except for lithium: N05AN*) in HSD-CSD-LPD. APs were grouped by therapeutic class: a) atypical APs (amisulpride, aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole, zotepine); b) conventional APs (all other APs). Prescribing patterns for the most commonly prescribed APs (quetiapine, risperidone, olanzapine and haloperidol) were also analysed individually.

2.4. Statistical analysis

The effect of safety warnings on the prevalence of AP use was assessed using generalized linear models (GLMs) for longitudinal data, which account for the effect of multiple measures over time collected by the same individual (cluster-level covariate) using the logit formula (specifically, the link function) and assuming a binomial distribution with first-order autoregressive covariance structure as regards subject error term. GLMs were used to model the probability of receiving an AP and included the time covariate as the main exposure. To account for the hierarchical data structure, a generalized estimating equation was used to calculate the parameters of GLMs and provided model-based robust standard errors. By means of GLMs, two main evaluations were carried out: 1) whether the mean prevalence of AP use changes 3, 6 and 12 months before and after the warnings (i.e. to assess whether the onset of the warning effect was immediate and whether the effect persisted); 2) whether the prevalence of AP use changes over each unitary increase of a quarter year, performing a test for linear trends within each time interval between two consecutive safety warnings. For instance, using THIN data, four possible time intervals can be defined: 1) from the start of the study until the first quarter of 2004, when the first EMA/MHRA warning was issued; 2) between the first quarter of 2004 and the third quarter of 2005, when the second EMA warning

was launched; 3) between the third quarter of 2005 and the first quarter of 2009, when the second MHRA warning was launched and 4) from the first quarter of 2009 until the end of the study.

To assess the change in mean prevalence of AP use before and after the warnings, separate GLMs (overall, within each AP drug class for the most commonly used APs) were built. These GLMs included an intercept term (this quantifies the logit of the estimated overall mean AP prevalence) and a categorical time variable where categories were ordered and defined according to the corresponding quarter year from the beginning to the end of the study (e.g. for THIN data, the time variable assumes value 0 for the first quarter of 2000, the value of 1 for the second quarter of 2000, and so on, until the end of the study). Comparisons between the estimated means of AP prevalence of use before and after each warning occurrence were statistically assessed using suitable comparisons (i.e. statistical contrasts), within the estimated GLMs, with respect to the quarter year at which each warning occurs (i.e. setting null coefficients for time points that must be ignored and setting contrasting non-null coefficients, with opposite sign and sum of zero, for all time points involved in the comparison with respect to the time point at which each warning occurs).

To evaluate whether the prevalence of AP user changes with every passing quarter year, separate GLMs were run which included the persons' presence in a specific time interval as a dummy covariate (e.g. three possible dummies if four time intervals are considered), the time covariate (i.e. the slope of the GLM, treated as continuous variable) and lastly, time-by-interval interaction terms. The person's presence in both databases was defined as the time between the person's registration in the database and their date of transfer out of the database, death or if none of these dates are registered, the end of the study. For each unitary increase of quarter year, the mean change in the log odds of AP use (i.e. log odds ratio) was estimated within each time interval between the warnings using the time-by-interval interaction terms. The presence of linear trends was identified by testing the statistical significance of the log odds ratios. Having included a continuous time covariate and the interaction terms, this model successfully mimicked a segmented regression analysis using longitudinal data, as different slopes were estimated with respect to each specific time interval, the start of which is marked by the launch of a warning.

Furthermore, to assess how much the expected prevalence of AP use changes in absolute terms within each defined time interval, the following approach was adopted: 1) the expected prevalence of AP use was derived from GLMs for each quarter year, using the inverse formula of the logit link function; 2) the absolute difference of expected prevalence between two consecutive quarters was calculated within each defined time interval; 3) the median (along with the 2.5 and 97.5 percentiles) of the distribution of all such differences, i.e. the slope representing the quarterly prevalence of AP use from the beginning to the end of one time interval, was estimated. This information complements that provided by the previously defined GLMs and may be more easily interpretable. As the corresponding 2.5 and 97.5 percentiles of the medians cannot formally represent a 95% confidence interval, their statistical significance was deduced from the corresponding log odds ratio. Plots of the observed and estimated quarterly prevalence of AP user over time were further reported.

Finally, to put the above findings in a broader context, the annual prevalence rate of AP use in the time interval between one warning and another was calculated by 1) summing all patients' follow-

up time (this represents the denominator in terms of person-years); 2) estimating the expected number of AP users (i.e. the numerator) by summing each persons' AP exposure time and dividing this by the person's total follow-up time for the whole population; 3) dividing the numerator by the denominator.

2.4.1. Sub-analysis

Persons aged ≥ 80 were identified irrespectively of a dementia diagnosis for a *post-hoc* descriptive analysis in order to compare the prevalence of AP use between the oldest old in the Italian and UK populations. AP use is very likely to be related to dementia even in absence of a dementia diagnosis in this population. In addition these persons are likely to have more severe dementia than their younger counterparts triggering more AP prescribing. Given these two assumptions, we hypothesised that a comparison of the prevalence of AP use in persons ≥ 80 in the Italian and English databases could indicate whether there was a differential use of these drugs in the two countries that could partly explain significant differences in drug utilisation pattern in the two countries.

A p value < 0.05 was considered for statistical significance. All statistical analyses were performed using SAS Release 9.3 (SAS Institute, Cary, NC, USA).

2.5. Ethical approval

The use of THIN and HSD-CSD-LPD for this study was approved by the THIN Scientific Review Committee (ref: SRC 13-085) and the Ethical Committee of the University of Messina respectively.

3. Results

Overall, 58,497 and 10,857 persons with dementia ≥ 65 years were identified in THIN and HSD-CSD-LPD, respectively. The gender distribution and mean age in the two databases was similar (**Table 2**).

The crude quarterly prevalence of AP use in persons < 65 years throughout the study period was approximately 0.6% in both countries (**Appendices 4 and 5**), increasing to approximately 2% in the general population ≥ 65 years in both countries (**Appendices 6 and 7**).

The quarterly prevalence of AP use in older people with dementia was initially similar in both countries: approximately 7% in 2000, followed by a comparable gradual increase up to around 10% in 2004 (**Figure 1**). The effect of the safety warnings on AP use in persons with dementia from 2004-2009 and 2009-2012 is described in more detail in the following sections.

[**Figure 1 here**]

3.1. Effects of the safety warnings on AP use in older people with dementia from 2004-2009

The 2004 warnings in the UK and Italy were associated with a marked short-term reduction of atypical AP use (**Figure 2**).

[**Figure 2 here**]

In the UK, the quarterly prevalence of atypical AP use decreased rapidly from a pre-warning peak of 8% to 6% within less than one year following the warning; in Italy, there was a similar pattern with a decrease from 6% to 5% over the subsequent year. In contrast there was an increase in prescribing of conventional APs in both countries. The prevalence of conventional AP use in the UK increased from 3.5% to almost 4.5% within less than one year after the warning, while remaining stable thereafter (**Figure 3**).

[**Figure 3 here**]

In Italy, there was a more sustained increase in conventional AP use from 6% at the time of the warning to 10% in 2009. The overall prevalence of AP use returned to pre-warning levels by 2005 in Italy and by 2007 in the UK. AP use continued to increase in both countries until 2009, more markedly so in Italy (**Figure 1**).

Statistical comparisons

The statistical comparison of the prevalence of AP use at 3, 6 and 12 months before and after the warnings allowed the identification of the onset of the warning effect (i.e. a decrease in the prevalence of AP use) and whether this was statistically significant (**Tables 3 and 4**). At 3, 6 and 12 months after the warning in the UK, atypical AP use decreased from 7% to 6% (p-value <0.001), while conventional AP increased significantly from 3% to 4% (p-value <0.001). In Italy conventional AP use increased at 3, 6 and especially 12 months after the warning (from 5.7% to 7.2% at 12 months; p-value <0.001), while atypical AP use did not significantly decrease at any of the time-points evaluated.

3.2. Effects of the safety warnings on AP use in older people with dementia from 2009-2012

AP use among persons ≥ 65 years with dementia was approximately 5% higher in Italy compared the UK in 2009 (**Figure 1**). The 2009 MHRA warning, EMA recommendations and parallel report from the UK Department of Health had a different impact as compared to the 2004 warning in the UK. There was a smaller change over the year following the warning, but over a 4 year period atypical AP use in the UK dropped from approximately 11% to 9%. In contrast to the pattern observed after the 2004 warning, the AP use did not increase again after the 2009 MHRA warning. Conventional AP use also decreased from approximately 5% to 3% over the same period in the UK. In contrast, atypical AP use in Italy increased steadily from 11% in 2009 to 18% in 2012, while conventional AP use also increased from 9% in 2009 to 14% in 2012 (**Figures 2 and 3**).

Statistical comparisons

No significant changes in the prevalence of AP use overall or by class was seen within 6 months after the 2009 warning in the UK, although atypical and conventional use by class increased slightly within 1 year (p-value 0.0011 and 0.01 respectively) (**Table 3**).

[Table 3 here]

AP use overall and atypical AP use increased slightly but significantly within 6 months after the warning in Italy. AP use overall also changed significantly 12 months after the warning when the prevalence increased from 19% to 22% (p-value <0.001) (**Table 4**), as a result of an increase of both conventional (from 10% to 11%) and atypical APs (from 10% to 13%).

[Table 4 here]

3.3. Prescribing trend of individual APs in older people with dementia

In the UK and Italy, the prevalence of olanzapine use after the 2004 warnings decreased from approximately 2% to 1% (**Appendix 8**). After the 2009 warning, olanzapine use in the UK started decreasing modestly but kept increasing in Italy. The prevalence of risperidone use before the 2004 warning was higher in the UK (5%) than in Italy (2%), but both decreased to roughly 1% after the 2004 warnings (**Appendix 9**). The use of risperidone did not appear to change after the 2009 warnings either in the UK or Italy. The prevalence of quetiapine use in the UK increased from 1% to 7% after the 2004 warnings, while gradually decreasing after the 2009 warning (**Appendix 10**). In contrast, quetiapine use increased steadily from its marketing year (2000) up to 14% in 2012 in Italy. The prevalence of haloperidol use in the UK remained stable at approximately 1% from 2000 to 2004, increasing rapidly thereafter from 1% to almost 2%, decreasing back to 1% after the 2009 warning (**Appendix 11**), while in Italy haloperidol use increased continuously from 2000 (1.5%) to 2012 (6%). The GLM statistical comparisons of individual AP prevalence 3, 6 and 12 months after the warnings confirmed the above results (**Appendix 11 and 12**).

The analysis of estimated mean changes in the prevalence of AP use and annual prevalence of use after the warning occurrences confirmed all the above findings (**Appendix 13 to 16**).

3.4. Sub-analyses

The results of the sub-analysis comparing AP use in persons ≥ 80 showed a comparable use of APs in the UK and Italy. Conventional APs initially had a higher prevalence of use (3% and 2% in the UK and Italy respectively in 2000) while atypical AP use was much lower (<1% in both countries in 2000); thereafter the use of both classes remained between 1%-2% in the UK and Italy (**Appendix 17**).

4. Discussion

To our knowledge, this is the first population-based, nationwide study which explored short- and long-term effects of the safety warnings on AP use in dementia from two European countries, Italy and the UK. The comparative pattern of change of AP use in dementia in both countries provides key insights. The initial EMA/MHRA warning regarding stroke and mortality risk associated with risperidone and olanzapine led to a significant short-term reduction in atypical AP use over 12 months, but with increased conventional AP use. By 2005, AP use was again increasing in both the UK and more so in Italy. Although the safety warnings in 2009 had a limited immediate impact on AP prescribing, there was a sustained 25% reduction in AP use between 2010 and 2012 in the UK

(from a quarterly prevalence of 14% to 11%), while a substantial increase in total AP use (to 32% in 2012) was observed in Italy. The prolonged reduction of AP use after the 2009 warning in the UK and the divergent pattern of AP use comparing the UK and Italy suggests that at a national level, the safety warning along with independent policy initiatives and proactive strategies of entities such as the National Dementia Alliance may exert a greater influence on curbing AP use in dementia than the safety warnings launched by regulatory agencies alone.

The elevated use of APs in dementia remains a concern in both countries and cannot be explained by changes in the yearly prevalence of dementia in persons 65 and over (**Appendices 18 and 19**). Although present data support a significant reduction of AP use in people with dementia since 2009 in the UK, the observed reduction was 25% rather than the 50% presented in the DAP audit results [14], and the level of AP reduction achieved is still considerably less than the target of a two thirds reduction that was proposed in the Bannerjee report for the UK Department of Health [11]. Nevertheless, it is clear that the change in AP use the UK is much more favorable than that seen over the last decade in Italy, where 1 in 3 people with dementia were still prescribed APs in 2012. This increased pattern of use in Italy is also consistent with reports from other European countries (**Appendix 1**), emphasizing the need for coordinated action at a national level, if sustained reductions in AP use in people with dementia are to be achieved. The reason why the warnings in the UK appeared to be relatively more successful in reducing AP use in dementia can only be speculated but may be related to several factors such as the mode of dissemination, directness of appeal to appropriate healthcare professionals, clarity and action-oriented nature of the directive and the clarity with which the risk in question is communicated. For example, the 2004 warning by the MHRA was clearly action-oriented, recommending immediate review of patients because of “an important concern” on the increased risk of stroke, and was sent to all healthcare professionals as an “Urgent message” encouraging them to spread the word. In Italy on the other hand, the risk communication in 2004 was conveyed only through EMA and not by the national regulatory agency, AIFA. The first AIFA communication on the topic was issued a year later in 2005 but the warning of drug-related risk as well as information on the associated pharmacovigilance project appeared to target mainly prescribers in specialist dementia centres rather than all prescribers potentially responsible for the care of persons with dementia. Other warnings in Italy such as the 2009 AIFA communication was a reminder of the legal context of AP prescribing in dementia but did not highlight a concrete drug safety risk associated with these drugs leading to more cautious prescribing (e.g., increased risk of stroke) and was not action-oriented. Similarly, the 2009 MHRA warning was not action-oriented but was limited to advice on drug prescribing; in addition it was not actively disseminated but was published on the MHRA webpage. Nevertheless, the combined effect of this relatively passive regulatory action supplemented by other continued actions aiming to reduce AP use in dementia is likely to have led to a sustained reduction in AP use among dementia patients in the UK.

This study has several strengths. The databases used allowed us to sample a large number of primary care patients that can be considered representative of the two national populations. In addition, both countries have a universal healthcare system which further increases the comparability of findings in the two countries. GLMs were used to estimate the prevalence of AP use accounting for clustered data (i.e. multiple measures over time per individual), an approach similar to the interrupted time-series analysis. GLMs have several advantages compared to time-series analysis. For example, time-series analysis is limited with regards to data fitting and requires

the assumption of the stationary condition of the stochastic process, whereas this assumption is not required for GLMs. Interrupted time-series analysis may also be reliable in predicting future observations, provided that the model represents the stochastic process very well. However, GLMs can provide statistical evaluations based on robust statistical inference of comparisons between the prevalence of AP use in different time windows using statistical comparisons, whereas these evaluations are not possible using time-series analysis. The present study also has various strengths when compared to similar studies. Some published studies considered the effect of the safety warnings only on risperidone and olanzapine use [19], while others did not consider APs by class in their analysis [19,24]. In addition, other studies had a shorter observation period compared to the present study [19,22,23], did not use nationwide data [19,22] or did not consider haloperidol individually, the most commonly prescribed conventional AP [18,19,24].

A limitation of this study is that no information was available on AP dispensing in both countries [17,18]. In Italy, the use of atypical APs may be partly under-estimated since prescription drugs may be made available directly from Italian National Health Service (NHS) hospitals, thus bypassing GPs. The AP prescribing patterns described in the present study mainly reflect GP prescribing to elderly persons living in the community setting rather than nursing homes. Nevertheless we were able to trace the living arrangements of 3,746 persons ≥ 65 years with dementia, of whom 3,554 were living in nursing home in THIN. No information on whether persons were living in a nursing home were found in HSD-CSD-LPD although given the structure of the Italian NHS it is likely that GP prescribing in nursing homes is similarly partially covered in HSD-CSD-LPD. Another limitation is that the diagnoses of dementia as found in THIN and HSD-CSD-LPD were not validated in the present study; nevertheless, the prevalence of dementia in THIN was found to be comparable with national estimates in the UK [31]. The validity of dementia diagnoses in both databases was not tested in the present study.

It should also be noted that in an observational study such as the present one, findings can point to an association but not a causal link between changes in AP prescribing pattern and the safety warnings. The influence of other factors on AP prescribing apart from the warnings, such as the DAP audit or initiatives by the National Dementia Alliance in the UK, may have influenced prescribing activities. In addition, comparisons between the warning effects should consider the different content and different dissemination methods used, however this cannot be taken into account in the statistical analysis used.

5. Conclusion

The initial warnings targeting olanzapine and risperidone use in older people with dementia generally reduced the prescribing of these drugs in the short-term, but resulted in a shift towards quetiapine and conventional AP use. Although the warnings led to a decrease in overall AP use in more recent years in the UK, this was more modest than stipulated by the DAP audit. Nevertheless, this reduction suggests that the pressure exerted in the UK to decrease AP prescribing in dementia achieved a substantial impact as compared to Italy, where AP prescribing continued increasing throughout the study.

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