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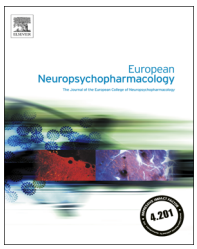

Trends in use of antipsychotics in elderly patients with dementia: Impact of national safety warnings

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Abstract
Based on evidence of an increased risk of death, drug agencies issued safety warnings about the use of second generation antipsychotics (SGAs) in the elderly with dementia. The French agency issued a warning in 2004. which was extended to all antipsychotics in 2008. Little is known about the impact of these warnings on use. We conducted a quasi-experimental study (interrupted time-series) in France, for 2003–2011, including subjects aged ≥ 65 with dementia and subjects aged ≥ 65 without dementia in the EGB database (1/97th representative random sample of claims from the main Health Insurance scheme). Outcomes were monthly rates of use of antipsychotics (by class and agent) and of five comparison drug classes (antidepressants, benzodiazepines, dermatologicals, antidiabetics, antiasthmatics). Trends were analyzed by joinpoint regression, impact of warnings by linear segmented regression. In patients with dementia ($n=7169$), there was a 40% reduction in antipsychotic use from 14.2% in 2003 to 10.2% in 2011. The reduction began before 2004 and was unaffected by the warnings. Use of first generation antipsychotics declined over the period, while use of SGAs increased and leveled off

Abbreviations: ATC, anatomical, therapeutic and chemical (classification); BPSD, behavioral and psychological symptoms of dementia; DDD, defined daily dose; EGB, échantillon généraliste de bénéficiaires; FGA, first generation antipsychotics; ICD, international classification of diseases; SGA, second generation antipsychotics

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from 2007. Use of the five comparison drug classes increased on the period. In subjects without dementia (n=91,942), rates of overall antipsychotic use decreased from 2.3% in 2003 to 1.8% in 2011 with no effect of the warnings. Meanwhile, use of SGAs continuously increased from 0.37% to 0.64%. Antipsychotic use decreased in the elderly between 2003 and 2011, especially in dementia. The timing of the decrease, however, did not coincide with safety warnings.

1. Introduction

Most patients suffering from dementia experience behavioral and psychological symptoms (BPSD) (Chan et al., 2003; Lyketsos et al., 2002; Lyketsos et al., 2000; Mega et al., 1996; Sink et al., 2004), many of which are particularly disruptive for the patient and her caregivers such as agitation, aggression, oppositional behavior, delusions or hallucinations. BPSDs are associated with increased hospital lengths of stay (Wancata et al., 2003), institutionalization (Steele et al., 1990; Stern et al., 1997; Yaffe et al., 2002), and caregiver distress and depression (Black and Almeida, 2004; Kaufer et al., 1998). Antipsychotics have been commonly used to treat aggression or psychotic symptoms occurring in dementia in spite of only modest evidence of their efficacy (Ballard and Waite, 2006; Schneider et al., 2006; Sink et al., 2005), and lack of regulatory approval for use in dementia. In fact, risperidone is the only drug labeled for BPSD and only in some countries (i.e. approved in July 2008 in France).

The reassessment of clinical trials data showed an increased risk of death with some second generation antipsychotics (SGAs) prompting some countries to issue safety warnings. The first safety reports were published in 2002 in Canada (Wooltorton, 2002). In 2003, the US MedWatch issued a warning about an increased risk of cerebrovascular adverse events with risperidone (US Food and Drug Administration, 2003) and further articles reporting the higher risk of death were published in 2005 (Gill et al., 2005; Schneider et al., 2005). National drug agencies in the US, UK, Italy, Spain, etc. issued warnings about the increased risk of mortality associated with SGAs between 2004 and 2005. Afterwards, articles have compared the mortality risk between SGAs and first generation antipsychotics (FGAs) and concluded that FGAs shared that increased risk (Gill et al., 2007; Schneeweiss et al., 2007; Wang et al., 2005). Numerous drug agencies then issued warnings for FGAs in 2008.

The French drug agency (Agence Nationale de Sécurité du Médicament, formerly known as Agence Française de Sécurité Sanitaire des Produits de Santé AFSSaPS) issued three safety warnings on antipsychotics in dementia the first one on March 9th 2004 concerned the use of two SGAs (olanzapine and risperidone), the second on February 3rd 2005 concerned another SGA (aripiprazole; as this drug was not available at the time of the first warning) and the last one on December 9th 2008 extended the warning to all antipsychotics. Warnings were spread through "Dear health care provider" letters sent to physicians and pharmacists by firms. The new safety information was added to the drugs' monographs and patient information leaflets found in every drug package. No study has so far assessed the impact of these warnings in France.

Few studies have investigated the impact of safety warnings on antipsychotic use in dementia patients abroad and only one provided information about the 2008 warning in the community or about all warnings. A study showed a modest impact of the warnings issued by Health Canada in Ontario (Valiyeva et al., 2008). Conflicting results have been published for the US. A first paper reported a huge decrease in antipsychotic use following the first US Food and Drug Administration warning (Dorsey et al., 2010), while another group reported only a small decline (Kales et al., 2011). In the region of Valencia in Spain, a decrease in doses of olanzapine and risperidone used by pensioners was seen following the 2004 safety warnings and 2005 prior authorization requirement (Sanfelix-Gimeno et al., 2009), and similar reductions have been reported in Scotland (Guthrie et al., 2013). Additionally, studies suggested a reduction in antipsychotic use in the US (Desai et al., 2012), and Italy (Franchi et al., 2012) but not in Germany (Schulze et al., 2013) following the 2004 warning and an audit found a reduction in antipsychotic use in elderly patients with dementia between 2006 and 2010 in England (Health and Social Care Information Centre, 2012), but these studies did not provide time series methodology. Last, one study found an impact of the 2008 warning on the use of antipsychotics in one teaching hospital in England (Thomas et al., 2013) and another one in 87 general practices in Scotland (Guthrie et al., 2013).

The aims of this study were to describe trends in the use of antipsychotics in elderly patients with dementia in France between 2003 and 2011 and to assess the impact of the French drug agency warnings on use. To take into account secular trends, we described trends in the use of other drug classes in dementia and of antipsychotics in elderly patients without dementia.

2. Experimental procedures

2.1. Design

We conducted a quasi-experimental study using interrupted time-series design for the period January 2003–July 2011.

2.2. Source of data

The EGB (Echantillon Généraliste de Bénéficiaires) database contains claims for a 1/97th random sample of the population living in France (Tuppin et al., 2010). From 2003, it contains claims for visits to physicians and other health care providers, drugs dispensed in retail pharmacies and submitted for reimbursement, and from 2005 onward it contains information about hospital stays in medicine and surgery wards (no information is available for psychiatric wards, rehabilitation

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