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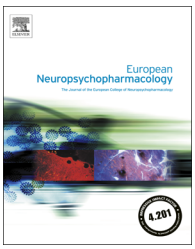

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Baclofen for alcohol dependence in France: Incidence of treated patients and prescription patterns—A cohort study

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Abstract
Recently, baclofen has been widely promoted for treatment of alcohol dependence in France. Our aim was firstly to describe the incidence of patients newly treated with baclofen for alcohol dependence in France from 2007 to 2011, and secondly to describe baclofen prescription patterns and prescribers. A retrospective cohort study of patients newly treated with baclofen was conducted using the "Echantillon Généraliste des Bénéficiaires" database (EGB). Patients with a first dispensation of baclofen between 01/01/2007 and 31/12/2011, followed by a second in the next 120 days, were included. Patients were considered treated with baclofen for neurological conditions if at least one of the following conditions was found to be true: (1) presence of a neurological condition for which baclofen could be prescribed, (2) dispensation of dantrolene, another anti-spastic drug, or (3) hospitalization for a neurological condition for which baclofen could be prescribed. We assumed that all the remaining patients were treated for alcohol dependence. During the 5-year period, 676 patients were incident users. While the annual incidence rate of patients newly treated with baclofen for neurological conditions remained stable, the annual incidence rate of patients newly treated with baclofen for alcohol dependence increased by a factor of 2.9 between 2007 (0.09/1000 person-years) and 2011 (0.26/1000 person-years). In the alcohol dependence group, median duration of baclofen treatment was 143.5 [74.0; 377.0] days; median daily dose was 24.4 [14.8; 39.5] mg. This study demonstrated the rapidly increasing use of baclofen in France for treatment of alcohol dependence.

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1. Introduction

Baclofen is an anti-spastic drug used in neurological disorders, which has recently been widely promoted in alcohol dependence in France (Rolland et al., 2012). It acts as a direct gamma-amino-butyric-acid-B (GABA-B) receptor agonist (Davidoff, 1985). In France as in many other countries, baclofen has marketing authorization for paraplegia, multiple sclerosis and serious central or spinal neurological diseases. The usual daily dose starts at 15 mg to finally reach 40–80 mg. Adverse drug reactions (ADRs), such as sedation, drowsiness, dizziness, confusion, or hallucinations, generally occur at doses of more than 60 mg daily.

In recent years, baclofen use for alcohol dependence has been debated. Baclofen has been demonstrated to have an anti-craving action in rats (Colombo et al., 2000, 2003, 2004). Clinical effects of baclofen may be improvement of withdrawal signs, abstinence achievement and decreased alcohol dose in non-abstinent patients (through its anti-craving action). Some human studies, the majority conducted by the same research team, have assessed the value of baclofen for both alcohol withdrawal and abstinence achievement. In view of methodological issues their results need to be interpreted with caution.

Regarding alcohol withdrawal, a randomized trial comparing baclofen with diazepam found that baclofen was slightly slower to act than diazepam, but found no difference in efficacy (Addolorato et al., 2006). The results of this single study were included in a recent Cochrane systematic review, which concluded that there was insufficient evidence to support the use of baclofen for alcohol withdrawal (Liu and Wang, 2013). Since this review was conducted, another randomized trial comparing baclofen with placebo found that baclofen led to lower doses of benzodiazepine in the management of symptomatic alcohol withdrawal syndrome (Lyon et al., 2011).

Regarding abstinence achievement, three randomized clinical trials (versus placebo) conducted by the same team in the last ten years have found that baclofen use was associated with decreased craving and alcohol consumption and with increased abstinence rates (Addolorato et al., 2002, 2007, 2011). One recent randomized, double-blind, placebo-controlled trial conducted by another team found that baclofen use did not reduce heavy drinking days and did not increase the days of abstinence, time to first drink, or time to relapse to heavy drinking (Garbutt et al., 2010). A recent systematic review extracted the essential facts from these trials and concluded that no sufficient evidence supports the use of baclofen for alcohol dependence (Muzyk et al., 2012). In particular, these trials were limited by their low number of subjects and selected population. A recent observational study showed positive results (de Beaurepaire, 2012), with half of the patients abstinent or drinking at low-risk level after 3 months of treatment. This result was consistent with the findings of randomized trials: 70% of patients were abstinent after 4–12 weeks of treatment (Addolorato et al., 2002, 2007). Nevertheless, this study did not include a control group and suffered from ethical issues (Braillon, 2012).

Finally, Tiffany and Wray (2012) recently discussed the difficulty of craving assessment in clinical trials.

Regarding safety of baclofen, a strong dose-response effect has been identified at high doses (Addolorato et al., 2011). The usual daily dose ranged from 15 mg to 300 mg (de Beaurepaire, 2012; Dore et al., 2011), with high doses of baclofen reported in a few papers (Greene, 1992; Smith et al., 1991). Nevertheless, doses higher than 200 mg daily led to serious adverse effects (Leung et al., 2006). A safety trial has found that baclofen alone had minimal abuse liability in heavy social drinkers, and that baclofen was relatively well tolerated and safe when given in combination with intoxicating doses of alcohol (Evans and Bisaga, 2009). By contrast, cases of serious adverse drug reactions were reported, such as neuropsychological disorders, rashes and hepatitis (Macaigne et al., 2011; Nasti and Brakoulias, 2011; Saddichha et al., 2011; Soufia et al., 2010).

In France, this scientific debate has rapidly escalated since Ameisen, a French physician, has widely promoted baclofen for alcohol dependence (Ameisen, 2005). He published his self-case report in 2005 after he had treated his own alcohol dependence and anxiety disorder with baclofen. He reported decreasing his alcohol consumption and achieving abstinence at a dose of 270 mg/day. He then published a best-selling book widely diffused in France (Ameisen, 2008). The media took up the story and presented baclofen as a miraculous drug for alcohol dependence (Rolland et al., 2012). The consequence was a great increase in the demand for baclofen prescription in alcoholic patients (Rolland et al., 2012).

Alcohol-dependent patients can be managed, in France, by specialist physicians (often psychiatrists, addictologists or gastroenterologists) or by general practitioners (GPs). As they are easily accessible, GPs are substantially involved in the management of alcoholic patients. In 2008–2009, 52% of a sample of French GPs reported seeing a patient for an alcohol problem in the last seven days (Beck et al., 2011). Three out of 4 GPs manage their patients for alcoholic problems themselves, whether or not they are in contact with a specialized center. Alcohol is a frequent reason for consulting a GP: 16% of patients consulting their GP had an alcohol problem (Malet et al., 2003). Even if GPs lack training (Charrel et al., 2010; Malet et al., 2003), no evidence of a different prognosis has been shown for patients who underwent detoxification in a hospital or outside (Malet et al., 2009). GPs are in a unique position to recognize, treat, refer and monitor patients with alcohol problems. So, physicians and GPs in particular may be in great demand for the off-label prescribing of baclofen in alcohol dependence.

To our knowledge, no study has yet explored this issue. We conducted a retrospective population-based cohort study, aiming to describe the incidence of patients newly treated with baclofen for alcohol dependence in France from 2007 to 2011. Our secondary aim was to describe prescription patterns and prescribers.

2. Experimental procedures

We performed a pharmacoepidemiological retrospective cohort study on patients newly treated with baclofen, using the "Echantillon Généraliste des Bénéficiaires" database (EGB, or permanent sample of beneficiaries) (Tuppin et al., 2010). The EGB is a permanent representative sample of subjects affiliated to the French health insurance system. It is obtained by 1/97th national random sampling with control for distribution of age, gender and area of residence. The EGB database includes approximately