Translated from ***Rev Prescrire*** **February 2012; 32 (340): 116-118**

Gabapentin and pregabalin: abuse and addiction

Abstract

● **In Europe, in mid-2011, about 30 cases of dependence, abuse or withdrawal symptoms attributed to *pregabalin* had been reported to Swedish and French pharmacovigilance centres and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). About 20 cases of *gabapentin* addiction were published in detail.**

● **The most frequently reported disorders were withdrawal symptoms. More than half of the patients were hospitalised for withdrawal. Cases of excessive increases in the doses of *gabapentin* or *pregabalin*, unauthorised routes of administration, and combination with other substances were also reported.**

● **Some patients had no known history of substance abuse.**

● **In practice, it is better to avoid exposing patients to these risks when the expected benefits are not properly documented. Healthcare professionals should take care to prevent and detect addiction to *pregabalin* or *gabapentin*. When necessary, assistance with tapering off the medication should be offered.**

Rev Prescrire **2012; 32 (340): 116-118.**

Pregabalin, a GABA analogue, is authorised in the European Union for partial epilepsy, neuropathic pain and generalised anxiety disorder (1-3). It is chemically related to *gabapentin*, a second-line drug for partial epilepsy and also neuropathic pain, on which it has a moderate impact (1,4).

The mechanism of action of these drugs is not fully known (5,6). Their adverse effect profiles are very similar, and include neuropsychiatric disorders, gastrointestinal disorders, weight gain, oedema, and liver damage (1). *Pregabalin* can also cause skin rash, hypersensitivity reactions and heart failure.

In 2010, the Swedish pharmacovigilance system published an analysis of reports of *pregabalin* dependence and abuse received in 2008 and 2009 (7). It provides useful information on the potential risk of abuse and addiction with *pregabalin* and *gabapentin*.

Reports of pregabalin dependence and abuse

An analysis of the Swedish national register of adverse drug reactions (Swedis) identified 16 cases of *pregabalin* addiction or abuse, all reported in 2008 or 2009, out of 198 reports of addiction or abuse of medications reported over a 20-year period (**a**)(7). The patients included 9 men and 7 women with a median age of 29 years. The indications for *pregabalin* were known in 6 cases (anxiety in 5 cases, pain and anxiety in 1 case). The maximum daily doses ranged from 300 mg to 4200 mg, whereas the authorised doses were 150 mg to 600 mg per day (3).

One patient had seizures and 2 patients were hospitalised for tapering off the medication. Memory disorders and suicidal ideation occurred in a patient using high doses of *pregabalin* (doses not specified).

Since 2009, an unspecified number of cases of *pregabalin* abuse have also been reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) via the Finnish, Swedish and Norwegian pharmacovigilance systems (8).

In response to a request from *Prescrire*, the French drug regulatory agency (Afssaps) provided access in 2011 to cases implicating *pregabalin* in the French pharmacovigilance database. Twelve reports of dependence, abuse or withdrawal syndromes were identified (9).

Twenty-one cases attributed to gabapentin

Our literature search identified 21 published cases of *gabapentin* addiction (10-19), in patients aged 28 to 81 years, including 12 men and 4 women (gender not specified in 5 cases).

The patients took *gabapentin* at doses ranging from 600 mg to 27 000 mg per day, for recreational use (7 times), obsessive-compulsive disorder (5 times), mood disorders (4 times), or pain (3 times).

In the UK, 18 withdrawal syndromes and 2 cases of *gabapentin* abuse have been reported to the pharmacovigilance system (20).

Increasing the dose

Some patients took up to 7.5 g per day of *pregabalin* or 27 g per day of *gabapentin*. Most patients said they were trying to control pain (7,10,11,21,22).

A 35-year-old woman increased the dose of *pregabalin* prescribed for pain, from 600 mg per day during the first 2 months to more than 3000 mg per day. She went to several different prescribers and pharmacies to obtain this amount of *pregabalin*. She was finally admitted to a rehabilitation centre (22).

A 67-year-old woman with polyneuropathy and a history of alcohol dependence gradually increased her dose of *gabapentin* to 7200 mg per day for pain relief (10). To obtain this quantity, she asked her pharmacist to dispense the drug without a prescription, exaggerated her symptoms to her doctor, changed prescribers, and visited multiple pharmacies (that refused to dispense the drug). She was hospitalised with tremor,

sweating, agitation, pallor and exophthalmos (10).

Withdrawal symptoms and difficulty stopping

Seven of the 12 cases of dependence, abuse or withdrawal symptoms attributed to *pregabalin* in the French pharmacovigilance database mentioned withdrawal symptoms when discontinuing use of *pregabalin* (9).

Four patients were hospitalised, for nausea, vomiting, sweating, agitation, confusion, delusions, violence, hyperarousal, sadness, emotional vulnerability, constant crying, depression, or ("coming down" feelings.

In a patient with Alzheimer's disease, these problems were associated with a worsening of pre-existing disorders (aggression, agitation with logorrhoea, delusion, and treatment refusal).

Two patients resumed taking *pregabalin* when withdrawal symptoms occurred. *Pregabalin* had been prescribed for pain (9 cases) or epilepsy (1 case).

Similar withdrawal symptoms were seen in 10 patients during the week following *gabapentin* withdrawal, with sweating, pallor, exophthalmos, pain, excitement, irritability, anxiety, agitation, confusion, disorientation, palpitations, tremor and seizures (10,13-19). Seven patients were hospitalised and two patients had to take time off work (17). Five patients were taking *gabapentin* for obsessive-compulsive disorder and anxiety. After they stopped taking the drug, they experienced a worsening of their pre-existing disorders and the onset of obsessive thoughts, depression and insomnia (17).

Euphoria

A systematic review with meta-analysis identified adverse effects related to *pregabalin* in 38 double-blind, randomised, placebo-controlled trials lasting at least 4 weeks. Euphoria was experienced by 6 times more patients with *pregabalin* than with placebo (relative risk (RR) = 6.2, 95% confidence interval: 2.76 to 13.87), and occurred with doses as low as 300 mg per day (23).

A qualitative analysis of 108 websites in English, German, Spanish, etc. yielded information on how *gabapentin* and *pregabalin* was perceived among drug users. *Pregabalin* was described as "ideal" for recreational use, with effects similar to those of alcohol or benzodiazepines. Users reported that the effects of *pregabalin* were dose-dependent and similar to those of *gabapentin* (24).

Out of the 16 reports identified in the Swedish national pharmacovigilance database, 4 patients reported using *pregabalin* to "get high" or described the effect as an "amphetamine trip" with euphoria (7).

Euphoria and impaired judgment led to problems at work (7).

Injection, inhalation, combination, resale

Patients not only took the drugs orally, but also used intravenous, rectal and intramuscular delivery (24). Among the 16 Swedish reports of *pregabalin* dependence with "abuse" or "tolerance", one patient injected *pregabalin* dissolved in water, and another inhaled the crushed contents of the capsules (7).

Five American prison inmates with a history of drug abuse said they stole their fellow inmates' *gabapentin* capsules and inhaled the contents. Four of them said they experienced cocaine-like effects (12).

Alcohol, benzodiazepines, cannabis, heroin, are sometimes combined with *pregabalin* or *gabapentin* (7,11,24,21).

Since 2007, the French network of Centres for Evaluation and Information on Pharmacodependence (CEIP) has received 4 reports of *pregabalin* addiction, once for recreational use and 3 times after *pregabalin* prescription at high doses (not specified). Three patients had no history of substance abuse (9).

In addition, 3 forged *pregabalin* prescriptions have been detected since 2006 (9).

Even without a known history of substance abuse

In France, none of the 12 cases of *pregabalin* addiction reported to regional pharmacovigilance centres involved patients with a known history of substance abuse (9). However, 10 patients were taking other medications, including psychotropic drugs such as opioids and benzodiazepines. In Sweden, however, only 1 of the 16 reports of *pregabalin* addiction involved a patient with no known history of substance abuse (7).

Among the 18 published cases of *gabapentin* withdrawal symptoms, 12 patients had no known history of substance abuse (10,13-19).

In practice

Pregabalin and *gabapentin* use can lead to dependence and abuse, even in patients with no known history of substance abuse.

The expected benefits and potential risks should be carefully considered on a case by case basis before prescribing these drugs. They should be avoided in situations in which the benefits are unproven, as in generalised anxiety disorder, for example (3). Patients must be fully informed, and healthcare professionals should be on the alert for excessive requests for these drugs. Assistance with tapering off the medication may be necessary.

It provides an important service to patients to think of withdrawal as a possible cause if patients have symptoms when they discontinue medication use.

Review produced collectively by the Editorial Staff: no conflicts of interest

a- The authors scanned the reports for the following terms: "addiction", "drug addiction", "dependence", "tolerance increase" and "drug abuse", as well as "intoxication", "overdose", and "pathological inebriation" (ref 7).

Literature search and methodology

Our literature search was based on continuous prospective monitoring, at the *Prescrire* library, of the summaries of major international journals, Current Contents-Clinical Medicine, and member bulletins of the International Society of Drug Bulletins (ISDB); and routine consultation of clinical pharmacology textbooks (Martindale The Complete Drug Reference). We also accessed the following databases: Medline (1948-August week 1 2011), EMBASE/Excerpta Medica (1991 to 2011 week 32), The Cochrane Library (CDSR: 2011, issue 8, DARE, HTA: 2011 issue 3), and the following websites: Afssaps, EMA, FDA, Emcdda, Inami and MHRA, up to 6 August 2011.

This review was prepared using the standard *Prescrire* methodology, which includes verification of the choice of articles and their analysis, external review, and multiple quality controls.

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Translated from ***Rev Prescrire*** **March 2012; 32 (341): 192-195**

HPV vaccines and pregnancy: the situation in early 2012

Abstract

● **Vaccines against human papillomavirus (HPV) types 6/11/16/18 (Gardasil°) and 16/18 (Cervarix°) are non-viable vaccines composed of recombinant HPV proteins. As a precaution, they should not be given during pregnancy. However, some women are vaccinated shortly before conceiving or early during an undiagnosed pregnancy. What are the risks for the unborn child exposed in utero to these vaccines? We examined data available in late 2011.**

● **After in utero exposure to the HPV 6/11/16/18 vaccine during the first trimester, animal studies, only conducted in rats, showed no increase in the risk of malformations. Five clinical trials and the latest annual update of the Pregnancy Registry for Gardasil°, released in 2010 and including more than 1000 vaccinated pregnant women, showed no particular pattern of malformations with the quadrivalent vaccine. A few reports of very rare abnormalities are troubling, but they do not clearly implicate the vaccine.**

● **Most data on the HPV 16/18 vaccine come from two clinical trials comparing this vaccine with hepatitis A vaccine or placebo vaccination. Fewer than 400 pregnancies exposed to the HPV 16/18 vaccine have been studied. The rate of congenital malformations was similar to that in the control population.**

● **In practice, there are few data on exposure to HPV vaccines during the first trimester of pregnancy. There are more, relatively reassuring, data on the HPV 6/11/16/18 vaccine. Women who are vaccinated just before conceiving or early in pregnancy should receive appropriate information. Active pharmacovigilance must continue.**

Rev Prescrire **2012; 32 (341): 192-195.**

HPV vaccines against types 6/11/16/18 (Gardasil°) and types 16/18 (Cervarix°) are composed of recombinant HPV proteins and do not contain live virus (1). They are authorised in the European Union for immunisation of women and girls as young as 9 years of age (2,3).

As a precaution, these vaccines should not be used during pregnancy (4-7), but women are occasionally vaccinated shortly before conceiving or during an undiagnosed pregnancy (6,8).

In late 2009, no particular signals of a safety concern had been observed in France, where about 70 women had been exposed to the HPV 6/11/16/18 vaccine during pregnancy or less than one month before conception (8).

In early 2012, what is known about the possible risks to the unborn child exposed to an HPV vaccine?

Our literature search (summarised on page 155) identified several published series of pregnancies exposed to HPV vaccines. Here are the main results.

6/11/16/18 vaccine: no clear risk of specific malformations

Teratogenicity data on HPV vaccines are based on animal studies, clinical trials, and the Pregnancy Registry for Gardasil°, established by the company that markets the HPV 6/11/16/18 vaccine (9,10).

Studies in rats showed no teratogenic effects, even at doses 200 to 300 times higher than those used to vaccinate women. We found no animal studies using other species (1,9,11-13).

Clinical trials: more than 200 first-trimester exposures. According to an article published by Merck, 4206 pregnancies occurred during 5 double-blind clinical trials, resulting in 1447 live births among women immunised with the HPV 6/11/16/18 vaccine and 1424 among women in the placebo group (**a**). Forty children born to HPV-vaccinated women and 30 children born to sham-vaccinated women had birth defects (**b**), a difference that was not statistically significant (10). A wide variety of birth defects were observed, but no specific malformative syndrome was identified.