PM2-020

Pregabalin abuse in France: results of a national retrospective and comparative cohort study

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Introduction: Abuse of pregabalin has been suggested in a few pharmacovigilance studies and in a small population-based survey among opiate users in Europe. Today, no data suggest any potential for pregabalin abuse in the general population in France. We aimed to assess pregabalin abuse in the general French population, in comparison with other similarly indicated drugs, and its associated factors.

Material and methods: A cohort study was set up based on the EGB (General Sample of Beneficiaries), a national 1/97th representative sample of the insured French population, from June 2006 to December 2012, including new users of pregabalin, compared to 2 control groups of new users of gabapentin or duloxetine. The main outcome confirmed abuse, defined as daily use above the maximum recommended dose. Time to abuse was described using the Kaplan-Meier survival model. Factors associated with abuse were investigated through a Cox proportional hazard regression model with time-dependent covariates.

Results: 13 869 subjects were included: 8692 (62·7%) for pregabalin, 1963 (14·2%) for gabapentin and 3214 (23·2%) for duloxetine. Drug abuse was assessed for 1112 (12·8%) patients in the pregabalin group, 130 (6·6%) in the gabapentin group, and 313 (9·7%) in the duloxetine group, with a significant difference between groups (log-rank: $P < 0{\cdot}0001$). Factors associated with pregabalin abuse were young age ($P < 0{\cdot}0001$), high number of distinct prescribers ($P < 0{\cdot}0001$), methadone exposure (HR = 4·44; 95%IC (1·7–11·9); $P = 0{\cdot}003$), cancer (HR = 1·31; 95%IC (1·12–1·53); $P = 0{\cdot}001$), multiple sclerosis (HR = 1·97; 95%IC (1·35–2·88); $P = 0{\cdot}0004$), and neuropathy (HR = 1·82; 95%IC (1·09–3·04); $P = 0{\cdot}02$). In other groups, young age, psychostimulant drugs or depressive disorders were associated with abuse.

Discussion/Conclusion: Abuse of pregabalin was more frequent than abuse of gabapentin or duloxetine in France. Moreover, our results suggest an increased risk of pregabalin abuse among opiate maintained and hyperalgic patients. [1–3]

References:

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PM2-021

Pregnancy outcome among partners of male patients receiving imatinib, dasatinib or nilotinib in chronic myeloid leukemia (CML): reports collected by the French regional pharmacovigilance (PV) centers

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Introduction: Imatinib, dasatinib and nilotinib, the 3 first selective BCL-ABL tyrosine kinase inhibitors (TKI) in CML, are also inhibitors of "off-target" tyrosine kinases as PDGFR and c-kit expressed by various cells during embryogenesis and adult life, in particular in gonads. Thus they are involved in male and female reproductive function.

Because of the mechanism of action and teratogenicity risk, women of childbearing age should use effective contraception. In men, no consensus exists for systematic sperm banking prior to initiating a TKI.

Material and methods: Spontaneous reports of pregnancy following paternal exposure to these 3 TKIs registered in Terappel or French PV databases up to 07 July 2015 were analyzed.

Results: Cases, notified between 2001 and 2013, concerned 14 male patients. Reports were retrospective in 5 cases.

Mean age: 32 years [19–42], unknown (4)

TKI: 12 imatinib (one conceived twins; switched to dasatinib 4 days after the estimated conception date), 1 dasatinib and 1 nilotinib; no other treatment mentioned

Daily dose: imatinib 400 mg (6), 600 mg (2) and unknown (4); dasatinib 140 mg; nilotinib 800 mg

Median treatment duration at conception: 34 months [9–79], unknown (5)

Pregnancy outcomes were known for 13/14: 1 early miscarriage (imatinib), 2 induced abortions (imatinib and dasatinib) and 10 births (6 boys, 5 girls).

6 children were born without any defect or neonatal pathology.

2 (twins) had neonatal complications (intrauterine growth retardation, respiratory distress).

3 had anomalies (all retrospectively notified):

- complex cardiopathy discovered during pregnancy requiring surgery (imatinib)
- pyelouretral junction syndrome discovered in a 20-month-old child following a pyelonephritis (imatinib)
- mild pulmonary valve stenosis diagnosed in a 1-month-old infant requiring surveillance, acute myeloid leukemia with translocation t(4;11) and MLL rearrangement was also diagnosed at the age of 19 months, in complete remission 1 year after allograft (nilotinib).

Discussion/Conclusion: Literature provides reassuring data on pregnancy outcome among partners of male patients treated with imatinib (over 150 pregnancies); however, data are limited for other TKIs. In our little series, a relationship between the TKI taken by the father and anomalies observed in the offspring cannot be formally established. It seems important to keep on notifying these pregnancies to better assess the risk of paternal exposure, especially with 2nd and 3rd generation TKIs. Long-term follow-up of the offspring is also essential.

PM2-022

Risk mapping in the Burgundy regional pharmacovigilance center

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Introduction: Drug adverse effects are a public health concern. The French Medicines Agency (ANSM) relies on a network of 31 regional centers of pharmacovigilance (CRPVs). One of the tasks of the CRPVs is to alert about drug induced new adverse effects. The efficiency of this alert requires the use of quality process to detect these adverse effects. Hence, the aim of our study was to perform a Risk mapping in the Burgundy CRPV based on a process, in order to have a risk management tool. Our study took place in a context of current national pharmacovigilance reorganization and recent results of audits performed in the CRPVs.

Material and methods: First, we formalized the process "From receiving a call in the Burgundy CRPV to the transmission of a drug side effect to the ANSM". A multidisciplinary committee of the Burgundy CRPV, composed of pharmacists, physicians, a secretary, a quality engineer and pharmacy and medical students, evaluated the process. Then, according to the failure modes, effects and criticality analysis (FEMCA) method, the failure modes were defined and their criticality were calculated on the basis of the likelihood of occurrence (from 1 to 5), the potential severity for drug safety (from 1 to 5), and the detection probability (from 1 to 5).

Results: Through consensus, the committee identified 20 failure modes, 47 causes and 8 potential effects. We chose to implement an action for a criticality ≥20. An action plan has been identified with regard to the five following main axes: 1- Awareness, training and information for healthcare professionals; 2-Case report informativeness; 3-Unusual case report; 4-CRPV medical staff training; 5-CRPV organization.

Discussion/Conclusion: For the first time, we carried out a Risk mapping in the Burgundy CRPV. FEMCA is a useful approach to improve risk assessment and provide directions for prioritizing improvement actions in our daily activity. Moreover, this Risk mapping is a tool for risk management and allows us to establish measures in response to CRPVs audits.

PM2-023

Gynecomastia drug-induced: analysis of the French pharmacovigilance database

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Introduction: Gynecomastia is an enlargement of the mammary glands in male breast, attributable to the proliferation of the glandular tissue. Etiologies are multiple: drug is the second etiology of gynecomastia with 20% of cases. The main objective of our study was to characterize rare and unknown cases of drug-induced gynecomastia reported to the French Network of PharmacoVigilance Centers.

Material and methods: We performed a retrospective analysis of gynecomastia registered in the French Pharmacovigilance DataBase (FPVDB) and spontaneously reported between January 1st, 1985 and December 31th, 2013. We retrieved cases registered under the MedDRA terms « gynecomastia » (PT) and « mammary increase » (PT), which concerned men over 18 years old. We excluded cases corresponding to another medical diagnosis or those without sufficient data.

Results: We analyzed 1126 cases of gynecomastia concerning 2230 drugs out of 1427 registered, which represent 0.27% of cases registered in the FPVDB, (301 excluded cases). Some drug classes which induce gynecomastia are well known and this adverse reaction is mentioned in the Summary Product Characteristics: neuroleptics, antidepressants, antiretrovirals, antihypertensives, hypocholesterolemiants and antiacids. In our study, the most frequent known ATC drug class was antiretroviral drugs (30.5%), followed by cardiovascular drugs (19.3%), antiacids (5.5%) and some nervous system drugs as neuroleptics (5.1%) and antidepressants (3.5%). Some drugs were mentioned in literature, the most frequent retrieved in our study was retinoid drugs (0.8%) followed by fibrates (0.72%), antihistamine drugs (0.4%), fluoroquinolones, metronidazole and isoniazide. The most frequent unknown drugs was benzodiazepines derivatives drugs (3.9%), followed by beta blocking agents (1.6%), angiotensin II antagonists (0.94%) and antiepileptic drugs (0.76%). Other unknown drugs involved were: glucocorticoids, cicletanine, minoxidil, clopidogrel and tamsulosin. For these drugs, some complementary studies must be conducted to confirm this adverse reaction. For some drugs gynecomastia drug-induced is a class effect, it concerns antiretrovirals, statins, or proton pump inhibitors.

Discussion/Conclusion: This is to our knowledge the first study based on a large pharmacovigilance database that provides data about drug-induced gynecomastia in routine clinical practice.

PM2-024

Impact of cholinesterase inhibitors dereimbursement in France: a study using data from the National Healthcare Insurance System

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Introduction: In case a drug reevaluated by regulatory agencies is attributed a decreased benefit-risk ratio, its reimbursement rate can be lowered. Thus, the use of the drug should decrease as: i) clinicians decrease their prescription of a drug considered of low interest; ii) patients will assume a bigger part of the drug price. In the case of cholinesterase inhibitors (ChI) in Alzheimer's disease (AD), a wide controversy arose in France, some advocating that ChIs, even of poor efficacy, allowed structuring patients' trajectory of care. This study focussed on the public health impact of ChI reevaluation campaign (2011) and following dereimbursement (ChID) from 65% rate to 15% in France (03/2012). It considered i) trends

