Drug-induced panic attacks: Analysis of cases registered in the French pharmacovigilance database

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ABSTRACT

Background: The potential role of drugs in the onset of panic attacks (PAs) is poorly understood.
Aim: The objective of our study was to characterize drug-induced PAs.
Method: We performed an analysis of PAs registered in the French pharmacovigilance database between 01/01/1985 and 05/11/2014.
Results: Among the 163 recorded cases, 136 (83.4%) were directly related to drugs, mainly antidepressants (11.3%, mainly serotonin reuptake inhibitors), mefloquine (7.2%), isotretinoin (5.2%), rimonabant (3.6%) and corticosteroids (4.7%). PAs are labelled in the Summary of Product Characteristics (SmPC) for a minority (8.6%) of these drugs. In 31.4% of these cases, withdrawal of the suspected drug was performed more than a week after the onset of PAs. PAs could also be secondary to another adverse drug reaction (ADR; n = 14, 8.6%), mainly an allergy to antineoplastic or immunomodulating agents. In 13 cases (8.0%), PAs occurred during a drug-withdrawal syndrome, mainly after benzodiazepines or opioids. Most cases (73%) involved patients without any previous psychiatric disorder.
Conclusion: This is the first pharmacoepidemiological study about iatrogenic PAs. Beside antidepressants, the most often encountered drugs are not indicated for psychiatric diseases. This study also reveals that iatrogenic PAs mostly occur in patients without any psychiatric medical history and that PAs can be triggered by another ADR. Lastly, the many cases with delayed management underline the need to raise awareness of this relatively unknown ADR among physicians, especially since PAs are generally not labelled in SmPCs of the suspected drugs.

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1. Introduction

A panic attack (PA) is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, with occurrence of 4 or more of cardiovascular (palpitations …), autonomic (sweating …), pulmonary (sensation of smothering …), neurological (trembling …), gastrointestinal (nausea …) or psychological (derealization …) symptoms (American Psychiatric Association, 2016).

PAs occur across all cultures and nations and are common in the general population (Kessler et al., 2006; Yates, 2009). According to an American nationwide study, lifetime rates of PA prevalence are elevated, with almost a third of patients reporting at least one PA during their life (Kessler et al., 2006). Recurrent unexpected PAs can lead to panic disorder (PD), which is characterized by longer than 1 month of: (1) subsequent persistent worry about having another attack or consequences of the attack, or (2) significant maladaptive behavioral changes related to the attack (American Psychiatric Association, 2016).

Several factors could contribute to the origin of PAs, including genetic (genes conferring vulnerability), psychopathological (cognitive distorsions and misinterpretations of somatic

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experiences) and neurobiological ones (Dresler et al., 2013; Gorman et al., 2000; Millan, 2003; Roy-Byrne et al., 2006). In the widely acknowledged revised version of their 1989 neuroanatomical hypothesis for PD, Gorman suggested that panic originates in an abnormally sensitive "fear network" in the brain, that is centered in the amygdala which stands as the central point for dissemination of information and that coordinates fear responses (Gorman et al., 2000, Fig. 1). According to this model, the sensory input for the conditioned stimulus runs through the anterior thalamus to the amygdala, which in turn stimulates: (i) the parabrachial nucleus, producing an increase in respiratory rate; (ii) the lateral nucleus of the hypothalamus, activating the sympathetic nervous system and causing sympathetic discharge; (iii) the locus ceruleus, resulting in an increase in noradrenaline (NA) release and contributing to increases in blood pressure, heart rate, and the behavioral fear response; and (iv) the paraventricular nucleus of the hypothalamus, rising the release of adrenocorticoids (Gorman et al., 2000, Fig. 1). Consistent with Gorman's hypothesis, neuroimaging studies have subsequently reported in patients with PD an increased reactivity of the amygdala with volume reduction and structural deficit (Kim et al., 2012). Modern neuroimaging techniques since 2000 have also pointed to (i) the involvement of other cortical areas and other brain circuitry (e.g. the insula and anterior cingulate cortex) (Dresler et al., 2013; Pannekoek et al., 2013) and (ii) other neurochemical alterations within the fear network such as altered GABAergic [particularly in frontal and cingulate cortex (Long et al., 2013)] and serotonergic transmission [particularly in the raphe nuclei (Nash et al., 2008; Neumeister et al., 2004)].

Currently, the potential role of drugs in the onset of PAs is poorly understood. No pharmacoepidemiological study has been performed to evaluate, at a population level, the characteristics of drug-induced PAs. Consequently, more information would be required for a better understanding of iatrogenic PAs in routine clinical practice. Our objective was to analyze characteristics of PAs registered in the French PharmacoVigilance Database (FPVD), especially involved drugs.

2. Material and methods

2.1. Data source

The French Pharmacovigilance system was first established in 1973 and consists of a network of 31 regional centers (Moore et al., 1995; Vial, 2016). The FPVD was subsequently established in 1985 to record any Adverse Drug Reaction (ADR) spontaneously notified by health professionals. Reporting ADRs to the French regional centers has been mandatory for any drug prescriber (physician, dentist, or midwife) or pharmacist in France since 1995 (Moore et al., 1995; Vial, 2016). Other healthcare professionals and more recently patients (decree of June 10th, 2011) can also report ADRs.

In 2016, more than 623,000 reports of ADRs are registered in this database. For each report, information about patient (age, gender, past medical history), ADR [type (coded according to the Medical Dictionary for Drug Regulatory Activities MedDRA (Brown et al., 1999), date of onset, duration and evolution], and drug exposure [name, intake dates, doses] are recorded. A detailed summary of clinical description is added at the end of each pharmacovigilance case report. For all reports, a causality assessment ("imputability" or "imputation") is done for each drug using the French Pharmacovigilance System's method (Miremont-Salamé et al., 2016). If causality is found between the drug and the occurrence of the ADR, drugs are defined as "suspected" and if not, they are defined as "associated" (non-suspected) (Miremont-Salamé et al., 2016).

2.2. Data analysis

We performed an analysis of spontaneous reports of PAs registered in the FPVD between 01/01/1985 and 05/11/2014 under the MedDRA terms "Panic attacks and disorders" (High Level Term) or "Anxiety attack" (Low Level Term). Clinical symptomatology of each reported case was thoroughly examined by 2 pharmacovigilance specialists (DA, JLM) and 1 psychopharmacologist (FM). Cases corresponding to another medical diagnosis or those without sufficient data were excluded. For each case, we systematically recorded variables related to the patient (age, gender and medical history),
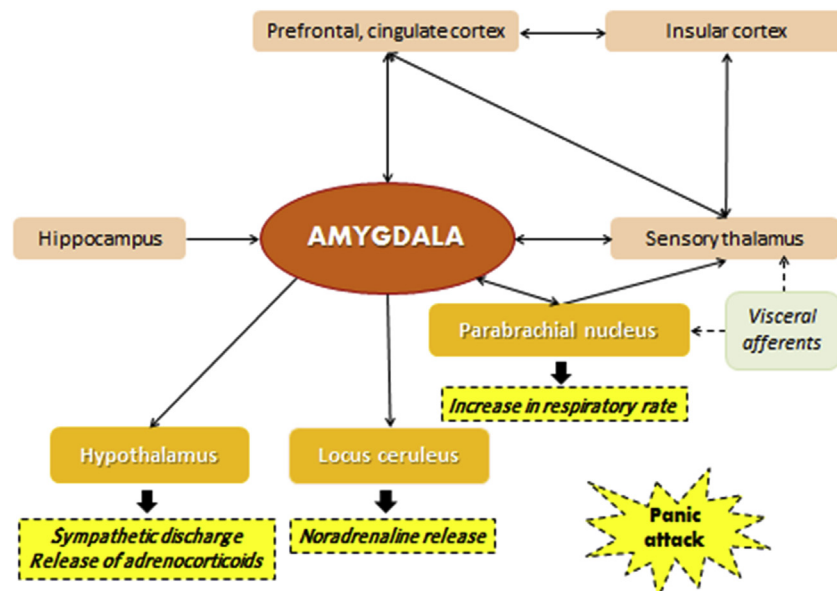

Fig. 1. Neuroanatomical pathways potentially involved in panic attacks according to Gorman's hypothesis (Gorman et al, 2000).