Drugs Associated With Restless Legs Syndrome
A Case/Noncase Study in the French Pharmacovigilance Database

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Background: Several case reports have suggested that drugs could induce restless legs syndrome. However, no systematic review of this adverse drug reaction (ADR) in a pharmacovigilance database has been published.
Objective: To assess the frequency of restless legs syndrome in the French Pharmacovigilance Database.
Methods: We selected all ADR reports from January 1, 1984 to December 31, 2009 coded as restless legs syndrome. Restless legs syndrome diagnosis was validated from case descriptions. Using a case/noncase approach, reporting odds ratio and 95% confidence interval were calculated for "suspected" drugs with 2 or more observations.
Results: Twenty-six ADR reports were found. Four cases were excluded because of alternative diagnosis. Fourteen cases were women (64%). Median age was 57. Most frequently suspected drugs were antidepressants (reporting odds ratio, 15.9 [6.4–39.7]; amitriptyline, escitalopram, mianserine, mirtazapine, duloxetine), neuroleptics (17.8 [6.1–51.7]; thioridazine, loxapine, risperidone, aripiprazole) or tramadol (18.2 [6.3–52.8]).
Conclusions: Restless legs syndrome is a very rare ADR that was more frequently reported in association with antidepressants, neuroleptics, or tramadol.

Key Words: restless legs syndrome, pharmacovigilance, adverse drug reactions, drug-induced movement disorders, sleep-related movement disorders

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R estless legs syndrome (RLS) is characterized by an urge to move the legs and by unpleasant paraesthetic sensations deep in the legs, occurring unilaterally or bilaterally, usually occurring during periods of rest or inactivity, particularly in the evening and at night.[1] Two subgroups of RLS phenotypes have been identified: primary (idiopathic) and secondary (symptomatic).[2] The former usually starts before age 45, and patients have a significantly higher incidence of affected relatives compared with symptomatic patients. In the symptomatic group, secondary causes of RLS, such as iron deficiency or uremic syndrome, among others, should be investigated.[2]

Restless legs syndrome has been also found to be an adverse drug reaction (ADR) to a range of drugs as discussed by a few number of case reports.[3] Analysis of spontaneous reports to health authorities, available in pharmacovigilance databases, represents a unique opportunity for detecting signals of unexpected ADRs.[4] Therefore, we set up this study to assess the frequency of RLS in the French Pharmacovigilance Database (FPVD).

MATERIALS AND METHODS

The French pharmacovigilance system was first established in 1973 and consists of a network of 31 regional centers. The reporting of ADRs has been compulsory in France since 1984. According to the law, physicians must report "serious" (ie, when the ADR results in death, requires initial or prolonged hospitalization, results in persistent or significant disability/incapacity, or is life threatening) or "unlabeled" (ie, when it is not reported in the summary of product characteristics) ADRs to their regional pharmacovigilance centre. The FPVD was established in 1985 to record spontaneous reporting of ADRs, but reporting serious or unlabeled ADRs became mandatory in 1995.[4] For each report, information about patient (age, sex, and medical history), ADR (date of occurrence and evolution), and drug exposure (date of introduction and withdrawal) are recorded in the FPVD. A summary of clinical description is added at the end of each pharmacovigilance case report. Adverse drug reactions are coded according to the Medical Dictionary for Drug Regulatory Activities. For all reports, a causality assessment ("imputability" or "imputation") is done for each drug using the French imputability method.[5] If causality was found between the drug and the occurrence of the ADR, drugs were defined as suspected.[6]

In the present study, spontaneous reports of RLS contained in the FPVD were extracted from January 1, 1984 to December 31, 2009. For each notification, diagnosis, sex, age, drug dechallenge and names of suspected drug(s) were extracted. Restless legs syndrome diagnosis validity was evaluated by one of the authors (S.P.L.L.), a trained clinical neuropharmacologist using the International Restless Legs Syndrome Study Group (IRLSSG) criteria.[7]

Statistical Analysis

Characteristics of patients are described with percentages or means.

The case/noncase approach measures disproportionality of the combination between a drug and a particular ADR in a pharmacovigilance database.[8,9] The number and type of drugs were compared between reports defined as RLS (ie, cases) and all other reports in the database (ie, noncases or comparators) for all drugs with 2 or more RLS reports.[9] Exposure was considered as the presence in a report of the drug of interest. In this study, reporting

odds ratio (ROR) represents the ratio of the odds of the association of RLS reports with the drugs of interest in cases and noncases.[10] Therefore, RORs allow for comparisons of the risk of exposure to the different classes of drugs in cases and noncases. The null hypothesis is that the exposure rate in the cases is not different from that in the noncases, in which case, the 95% confidence intervals of RORs for the drugs of interest include 1.[9]

RESULTS

Twenty-six RLS reports of 372,001 ADRs were found in the FPVD (ie, 0.7 case per 100,000 ADR reports). Four cases were excluded because of alternative diagnosis (3 cases, peripheral neuropathy; 1 case, allergic reaction). Case descriptions of the other 22 cases evoked RLS, but only 8 cases fulfilled all 4 criteria; whereas the other 14 cases fulfilled 2 or 3. Fourteen (67%) out of 21 cases were women, with one case having missing data on sex and age. The median age was 57 years (range, 22–91 years). Figure 1 shows case frequency by sex and age. On average, 1 case per year was reported between 1990 and 2007, and 4 cases per year was reported since 2008. In 86% of the cases, only one suspected drug was reported, whereas 2 or 3 drugs were suspected in 9% or 5% of the cases, respectively.

The list of suspected drugs with RORs for RLS is provided in Table 1. Imputability was "possible (I1)" or "probable (I2)" in most cases, except for the cases with amitriptyline or alanine, which had a "likely (I3)" score. Cases with trimetazidine, amitriptyline, oxybate, or tramadol had positive dechallenge (ie, symptoms disappeared after discontinuation of the "suspected" drug).

Using the case/noncase analysis, it was observed that RLS was more frequently reported in association with drugs including antidepressants, neuroleptics, or tramadol than with other drugs (Table 1). It was not possible to calculate RORs for others drugs that had only 1 case report (Table 1).

DISCUSSION

Restless legs syndrome is being increasingly recognized as an ADR. Such reactions were not observed during the clinical development of such drugs, but only during postmarketing surveillance. This study used the FPVD for obtaining signals about drugs associated with RLS in France. Restless legs syndrome was found to be a very rare ADR, most frequently reported with antidepressants, neuroleptics, or tramadol compared to other
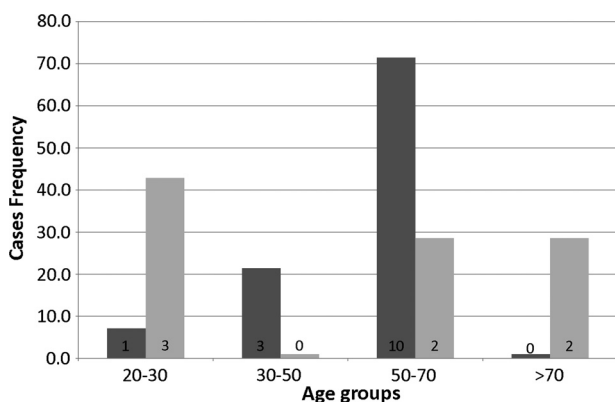
TABLE 1. Drugs Suspected to Cause RLS in the French PharmacoVigilance Database

	No. Cases	ADRs in the FPVD	ROR (95% CI)
Antidepressants[†]	6	6870	15.94 (6.40–39.72)*
Neuroleptics[‡]	4	3759	17.81 (6.13–51.71)*
Tramadol[§]	3	3680	13.05 (3.92–34.50)
Ropinirole	1	339	—
Trimetazidine	1	2454	—
Ornithine	1	12	—
Nicergoline	1	917	—
Nitrofurantoine	1	541	—
Fosfomycine	1	488	—
Docetaxel	1	1191	—
Leuprorelin	1	353	—
Valpromide	1	647	—
Oxybate[‖]	1	87	—
Beclometasone/ Formoterol	1	314	—
Alanine	1	861	—
Morphine	1	1235	—

Reporting odds ratios (ROR) with their 95% confidence interval (95% CI) are shown.

*$P < 0.05$.

[†]Antidepressants: amitriptyline, escitalopram, mianserine, duloxetine (n = 1 for each drug), mirtazapine (n = 2).

[‡]Neuroleptics: thioridazine, loxapine, risperidone, aripiprazole (n = 1 for each drug).

[§]One case after drug introduction and 2 cases after drug withdrawal.

[‖]Corresponds to a published case report.

medications. As far as we know, this is one of the first systematic studies to deal with drugs related to RLS. Previously, this ADR has been acknowledged mostly by case reports.

Case/noncase studies in pharmacovigilance databases offer a unique opportunity to detect signals of ADRs potentially connected to a given drug. In contrast to case series, which represent uncontrolled studies, case/noncase studies can disclose that an ADR has been more frequently reported with a given drug than with others during the studied period. Therefore, they allow for a better estimation of the ADRs' risk with the drug of interest. Conversely, they are not aimed at providing a proof of causality. Nonetheless, judgments about drugs' safety are sometimes made solely on the basis of studies like the present one.[11]

Studies on pharmacovigilance databases suffer from mandatory limitations related to underreporting of ADR, which can reach 90% of cases.[12] Nonetheless, underreporting affects all drug pharmacotherapeutic families equally,[13] and this technique has been further validated by our group with step 2 analgesic drugs[14] or for drugs causing dilated cardiomyopathy.[15,16]

Sufficient information to allow for full RLS diagnosis by IRLSSG criteria was present only in 8 cases, whereas in the other 14 information, approximately 1 to 2 criteria were missing. However, this may be a minor drawback, as each case was reviewed by expert pharmacologists and patients' treating physicians before recording it into the FPVD. Moreover, in published case reports, patients seldom fulfilled all IRLSSG criteria,[3] probably indicating that RLS connected to drugs may not present as the typical full-blown syndrome.

FIGURE 1. Histogram of cases frequency by age and sex. Females are shown in the dark columns and males in the lighter ones. Case numbers are given.

A few unsystematic case series have pointed out the involvement of drugs like antidepressants, neuroleptics, or tramadol in RLS. Impraminic selective serotonin uptake inhibitors or tetracyclic mixed-effect antidepressants have been connected with RLS.[17–20] Similarly, neuroleptics like olanzapine, haloperidol, or risperidone have been reported to cause RLS.[21–23] Two case reports have linked tramadol to augmentation,[24,25] which is a rebound of symptoms after idiopathic RLS treatment. Interestingly, tramadol has also been shown to potentiate the risk of mirtazapine-induced RLS.[26]

In our study, clear statistically significant signals of associations between drugs and RLS were detected for antidepressants, neuroleptics, or tramadol. Physiopathologically, RLS seems to be related either to decreased dopamine activity or increased serotoninergic tone,[2] which is the reason why we decided to group drugs in these classes. Nonetheless, further information is needed to confirm involvement of all particular drugs of each class.

None of the 3 tramadol cases was related to augmentation. In two of them, symptoms appeared after drug withdrawal, whereas in the other one, symptoms appeared after drug administration in a previously unaffected patient. Cases with ropinirole or trimetazidine were expected based on previous case reports, the former corresponding to augmentation and the latter probably caused by the antidopaminergic properties of this hidden neuroleptic.[27]

One of the advantages of studies based on pharmacovigilance databases is that they maximize the chances of detecting "unexpected" ADRs by collecting reports during long periods of time. In our study, cases connected with ornithine, nicergoline, nitrofurantoine, fosfomycine, docetaxel, leuprorelin, valpromide, beclometasone/formoterol, alanine, or morphine were reported for the first time. Reporting odds ratios could not be calculated for these drugs, as they only had 1 report, which could affect ROR stability. Therefore, further information is required to confirm their involvement in RLS genesis.

A surge in RLS frequency was noted in 2008–2009, probably reflecting increased recognition of this syndrome. Both female sex predominance (typical of RLS) and a sex-related difference in RLS onset age suggest a complex interaction between unknown genetic factors and drugs.

In summary, RLS was more frequently reported with antidepressants, neuroleptics, or tramadol. Additionally, several unexpected drugs were connected with RLS in this study. Therefore, physicians should question patients with RLS symptoms about their drug treatments, as withdrawal of such drugs usually leads to disappearance of symptoms.

AUTHOR DISCLOSURE INFORMATION

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