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Drug-induced Depression: a Case/Non Case Study in the French Pharmacovigilance Database

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Abstract – Depression is a complex disorder with heterogeneous clinical anomalies whose neurobiological understanding still remains unclear. Medications have been implicated as potential causes of depression but for many of them, data are controversial. The present study aims to investigate association bet ween drugs and reports of depression. We used the case/non case method in the French pharmacovigilance database (FPVD) to identify drugs associated with depression. Cases were reports of depression in the FPVD between January 2007 and December 2011. Non cases were all other reports during the same period. Data were expressed as reporting odds ratio (ROR) with their 95% confidence interval. Of the 114 692 reports recorded in the FPVD during the studied period, we identified 474 cases of depression. For the majority of the patients, they were considered as "non serious" (56%) and evolution was favorable (64%). Significant RORs were found for antiepileptics (topiramate, levetiracetam), anti-infective and especially anti-retroviral drugs (efavirenz, emtricitabine, tenofovir, etravirine, raltegravir), interferons and other agents including isotretinoin, methylphenidate, sodium oxybate, varenicline, montelukast, flunarizine, adalimumab, anastrozole. Taking into account the limits of the methodology, the present study described associations with mainly expected drugs belonging to various therapeutic classes but it also found a signal with some anti-retrovirals. On the contrary, we did not find some assumed associations like cardiovascular medications, antimalarial. For most of the drugs, one or more mechanisms were found to explain these depressogenic effects on the basis of animal and human literature. Even if such associations need to be confirmed by further prospective studies, cautions are necessary for many drugs to early detect depressive symptoms.

Mots clés :
dépression ;
médicament ;
effet indésirable ;
étude cas/non cas

Résumé – Dépression induite par les médicaments : étude cas/non-cas dans la banque nationale de pharmacovigilance. La dépression est une pathologie complexe, aux signes cliniques hétérogènes et dont les mécanismes neurobiologiques restent encore mal connus. Les médicaments peuvent être à l'origine de dépression mais pour beaucoup d'entre eux, les données sont controversées. L'objectif de cette étude est d'évaluer l'association entre les médicaments et les notifications de dépression. Nous avons utilisé la méthode cas/non-cas dans la banque nationale de pharmacovigilance (BNPV) afin d'identifier les médicaments associés à la survenue de dépression. Les cas étaient les notifications de dépression enregistrées dans la BNPV entre janvier 2007 et décembre 2011. Les non-cas correspondaient à toutes les autres notifications enregistrées pendant la même période. Les données étaient exprimées par un *reporting odds ratio* (ROR) avec son intervalle de confiance à 95 %. Sur les 114 692 notifications enregistrées dans la BNPV au cours de la période d'étude, nous avons identifié 474 cas de dépression. Pour la majorité des patients, ils étaient considérés comme non graves (56 %) et l'évolution était favorable (64 %). Des ROR significatifs étaient retrouvés pour des anti-épileptiques (topiramate, lévétiracétam), des anti-infectieux et notamment des antirétroviraux (éfavirenz, emtricitabine, ténofovir, étravirine, raltégravir), des interférons et d'autres molécules incluant l'isotrétinoïne, le méthylphénidate, l'oxybate de sodium, la varénicline, le montélukast, la flunarizine, l'adalimumab et l'anastrozole. En tenant compte des limites liées à la méthodologie, cette étude a décrit des associations avec principalement des médicaments attendus appartenant à des classes thérapeutiques diverses mais il a également été retrouvé un signal avec certains antirétroviraux. A l'inverse, nous n'avons pas retrouvé les associations précédemment décrites avec des médicaments cardiovasculaires ou antipaludéens. Pour la plupart des médicaments, un ou plusieurs mécanismes ont été retrouvés pour expliquer ces effets dépressogènes. Même si ces associations nécessitent d'être confirmées par des études prospectives, des précautions sont nécessaires pour de nombreux médicaments afin de détecter précocement des symptômes dépressifs.

Abbreviations: see end of article.

1. Introduction

Mood disorders represent one of the most prevalent forms of mental illness. Depression is a complex heterogeneous disorder with a wide spectrum of anomalies including depressed mood, anhedonia, sleep disorders, fatigue, loss of self-esteem, negative thinking and suicidality. Functional brain imaging and neurobiological techniques have revealed specific functional and structural brain abnormalities but the neurobiological understanding of depression still remains unclear.

Genetic and environmental factors such as stress and emotional trauma, viral infections, medical conditions have been implicated in depressive symptoms. Medications may also cause neuropsychiatric symptoms and, in literature, a wide variety of drugs have been implicated as potential causes of new-onset depression or worsening of established depression.[1] Unfortunately, contradictory data have been reported for many agents leading to the lack of conclusive data.[1,2] Indeed, it can be difficult to determine whether the suspected drug is truly causing the depressive symptoms or whether its use was concomitant with an endogenous depression on the basis of case reports. However, identification of drugs associated with depressive symptoms is important because untreated depression can evolve into suicidal ideation and suicide attempts and the lack of adherence to therapy is often closely related to the central adverse effects caused by drugs.

Thus the aim of the present study was to evaluate association between drugs exposure and reports of depression using the case/non case method in the French pharmacovigilance database.

2. Methods

The data source used is the French pharmacovigilance database (FPVD) that has been previously described.[3] Briefly, the French pharmacovigilance system was created in 1973 and, since 1985, all spontaneous reports of adverse drug reactions (ADRs) have been recorded into the FPVD. According to French law, every health professional must report "serious" and/or "unexpected" adverse drug reactions to their Regional Center of Pharmacovigilance (31 centers in France). "Serious" ADRs are defined as reactions resulting in death, life-threatening event, hospitalization (or prolongation of existing hospitalization), persistent or significant disability or incapacity, congenital abnormalities/birth defect or other significant medical event. ADRs are defined as "unexpected" if their nature, seriousness or evolution is not consistent with data given by the drug monograph. For each ADR report, information about the patient (age, sex, medical history), drug exposure (to the suspected drug and other associated non-suspected drugs) and ADR characteristics ("serious" or "non-serious", "expected" or "unexpected", causality score, outcome) are recorded in the FPVD. ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 15.1).[4]

2.1. Case/non case method

The case/non case method measures the disproportionality of combination between a drug and a particular adverse drug report (ADR) in a pharmacovigilance database.[5] This method can be used to generate signals from a pharmacovigilance database. Cases are defined as reports of the ADR of interest and non cases as all other reports of ADR. For each drug of interest, the association with the ADR was assessed by calculating an ADR reporting odds ratio (ROR) with its 95% confidence interval (CI). The ROR is the ratio of reporting of one specific event *versus* all other events for a given drug compound.[6]

2.2. Selection of cases and non cases

In our study, we collected ADRs notified between January 1st, 2007 and December 31st, 2011. Cases were identified using standardised MedDRA queries (SMQ) "Depression (excl. suicide and self injury)". After a careful analysis of the comments of spontaneous reports, we excluded all cases that were not "depression". Non cases, using as controls, were all the remaining ADR reports recorded in the database during the same period.

Drug exposition was defined by the presence in the report of the drug coded "suspect" according to the World Health Organization (WHO) criteria, whatever the level of causality assessment. We selected drugs for which four or more reports of "depression" had been registered in the FPVD.

If available, the following data were also collected from each report: age, sex, seriousness and evolution of the ADR.

2.3. Statistical analysis

Collected data were compared between reports defined as depression (cases) and all other reports in the database (non cases). We calculated a ROR to compare risk of exposure to different drugs in cases and non cases. The RORs are given with their 95% CIs. The 95% CIs were calculated using the Woolf's method.[7] A p value <0.05 was considered statistically significant. Statistical analyses were performed with Epi Info version 3.5.4.

3. Results

Of the 114 692 reports recorded in the FPVD from the January 1st, 2007 to December 31st, 2011, the SMQ allowed to identify 1691 cases and we validated 474 cases of depression, representing 0.41% of all reports (114 218 were non cases).

Among these cases, 255 (54%) were observed in women. Mean age was 44.6 years (median 44 years, range 5 – 93 years). The maximal