Eur J Clin Pharmacol (2011) 67:1189–1198
DOI 10.1007/s00228-011-1067-7

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Prescribed drugs and violence: a case/noncase study in the French PharmacoVigilance Database

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Received: 3 March 2011 / Accepted: 20 May 2011 / Published online: 8 June 2011

Abstract
Aim Our aim was to identify prescribed drugs associated with violent behaviours using the French PharmacoVigilance Database (FPVD).
Methods All reports of adverse drug reactions (ADR) recorded in the FPVD between 1January 1985 and 31July 2008 and including the terms aggressiveness or violence were selected. We compared proportion of exposure to different drugs between cases (reports with violence) and noncases (other reports in the database).
Results Among 537 cases, 56 were included (48 men, mean age 46 years). Misuse was observed in ten cases (18%). In 25 cases (44.6%), a previous psychiatric history was documented. Main drugs involved were nervous system (63.6%) followed by respiratory (7.8%), alimentary tract and metabolism (7.8%), dermatological (5.2%) and anti-infective (5.2%) agents. Case/noncase analysis found an association with dopaminergic agonists (pergolide, pramipexole, bromocriptine, piribedil), benzodiazepines (alprazolam, bromazepam) and serotoninergic antidepressants (taken as a whole), but not antipsychotics or antiepileptics. Association was also found with varenicline, isotretinoin, interferon alpha-2b, rimonabant, benfluorex, topiramate and antiviral drugs (ribavirin, efavirenz).
Conclusion Dopaminergic agonists, benzodiazepines and serotoninergic antidepressants are the main pharmacological classes able to induce aggressive behaviour. This study also emphasises the putative role of other drugs less known to be involved in such ADR.

Keywords Violence · Drug safety · Adverse drug reactions · Pharmacovigilance · Database · France

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Introduction

As emphasised by the 2002 World Health Organisation (WHO) report World Report on Violence and Health [1], violence is now a universal challenge and a public health priority that has been largely ignored for several reasons—one being the lack of clear definition. WHO defines violence as the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation [2]. WHO divided violence into three broad categories according to who commits the violent act: self-directed violence, interpersonal violence and collective violence [1]. Each year, more than 1.6 million people worldwide lose their lives to violence, leading to a rate of around 30/100,000. Around 50% of these deaths are suicides, nearly one third homicides and about one fifth consequences of armed conflicts [1]. In particular, violence is one of the leading causes of death for people aged 15–44 years worldwide, with values around 14% in males and 7% in females [1, 2]. In fact, violence is often considered an inevitable part of the human condition and a law-and-order issue, with a limited role by health professionals.

Several risks factors have been identified, such as growing up in a violent or broken home, substance (i.e. alcohol or illicit drugs) abuse, especially during childhood, social isolation, rigid gender roles, poverty, income inequality or personal characteristics (poor behavioural controls, low self-esteem, previous history of depression or suicide…) [1, 2] . Among these factors, the potential role of drugs in such behaviour is poorly understood [3]. The drugs more frequently suspected are benzodiazepines [4] or antidepressants [5].

Thus, to investigate this relatively unknown adverse drug reaction (ADR), this study evaluated associations between drugs and reports of violence in the French PharmacoVigilance Database (FPVD) using a descriptive approach, followed by the case/noncase methodology. This method was found to be useful in a context of signal detection.

Methods

Case—noncase method

The case/noncase approach measures disproportionality of the combination between a drug and a particular ADR in a pharmacovigilance database [6–10]. Cases are reports corresponding to the ADR, and noncases are all other reports. The method allows comparison of drug exposure among cases and noncases and calculation of an ADR reporting odds ratio (ROR) with its 95% confidence interval (CI) [11].

Source: French PharmacoVigilance Database (FPVD)

The reporting of ADRs has been compulsory in France since 1984. According to the law, physicians must report serious or unlabelled ADRs to their regional pharmacovigilance centre (31 in France). All suspected ADRs are registered in the FPVD [12]. For each report, information about the patient (age, gender, medical history) and drug exposure (suspected and other associated nonsuspected drugs) and ADR (date of occurrence, duration, imputability score) are recorded. Causality assessment is performed according to the French method used by all regional pharmacovigilance centres [12]. A detailed summary of the clinical description is added at the end of each case report. ADRs are coded according to World Health Organisation terminology (WHO-ART) [13]. Serious ADRs are defined as leading to death, hospitalization (or prolongation of hospitalization), persistent or significant disability or incapacity or life threatening [14]. We investigated ADRs recorded in the FPVD between 1 January 1985 and 31 July 2008.

Selection of cases and noncases

In a first step, we identified all cases recorded in the FPVD during this period that included the terms violence or aggressiveness. Only cases with physical aggressiveness were studied. Secondly, we only included reports describing physical violence or aggressiveness against others, thus excluding reports of verbal violence, oral aggressiveness and pure self-aggressiveness (excluding, for example, pure case reports of suicide without previous aggressiveness). Further, cases were revised for a more stringent selection by a group of three clinical pharmacologists (two specialists in pharmacovigilance and drug safety, one in AddictoVigilance) and two physicians from the department of forensic medicine (specialists in violent behaviours). This expert group worked according to the consensus method. When the reporting form was not sufficiently informative or when the characteristics of ADRs could not be completely defined, the report was not included in the analysis. All other reports (i.e. those not defined as violence or aggressiveness) registered since 1985 in the FPVD were used as controls and defined as noncases. Reports included all ages and both genders. Drug exposure, coded according to the Anatomical Therapeutic Chemical (ATC) classification system, was defined by the presence in the report of the drug of interest, whatever the level of causality assessment. We did not include drug dose, as this detail is not exhaustively recorded in the reports.

Statistical analysis

The null hypothesis for this study assumed that a case with violence could be attributed to a drug by pure chance and that drugs with a greater total number of ADR reports might be exposed to a greater risk of violence. Patient characteristics and drug number and type were compared between reports defined as violence (cases) and all other reports (noncases) in the database. Only drugs for which two or more reports of physical violence were registered were investigated. We calculated an ADR ROR to compare the risk of exposure to the drug classes in cases and noncases [8, 11]. RORs are given with their 95% CI as crude RORs.

Results

Case characteristics

Of the 314,320 reports recorded in the FPVD between 1 January 1985 and 31 July 2008, 537 were reported as violence. Among them, 60 were reports of physical violence. After exclusion of poorly described cases, 56 cases were included in the study. Thus, cases of violence represented 1/5,000 reports in the FPVD. Table 1 shows the main characteristics of these 56 case reports. Most of them (48; 85.7%) were observed in males, and 25% (n=14) occurred between the ages of 31 and 40 years. Ten were reported in patients older than 69 years. Mean age was 46.2 years±22.1 [standard deviation (SD)] years (extreme values 4–86 years).

Delay of ADR occurrence widely varied after drug introduction from 1 day to some years. Misuse was observed in ten cases (18%). In 25 cases (44.6%), a previous psychiatric history was documented; in eight cases, simultaneous intake of alcohol was recorded. Eleven of the 56 reports of heteroaggressiveness also included secondary episodes of self-aggressiveness, including seven cases of suicide). Four cases led to medicolegal consequences. Among the 56 case reports, 76 drugs were suspect. The most frequently involved ATC classes were N nervous system (n=49, 63.6%) drugs, followed by A alimentary and metabolism (n=6, 7.8%) and R respiratory system (n=6, 7.8%), D dermatological (n=4, 5.2%), J anti-infectives for systemic use (n=4, 5.2%), P antiparasitic products (n=3, 3.9%), G genitourinary system and sex hormones (n=2, 2.6%), L antineoplastic and immunomodulating drugs (n=2, 2.6%) and S sensory organs (n=1). Among the 49 drugs from the N group, the most frequent classes were benzodiazepines and related compounds (zopiclone, zolpidem, alpidem) (n=16, 32.6%) followed by dopaminergic antiparkinsonian drugs (n=13, 26.5%), antidepressants (only serotoninergic and none imipraminic, n=4, 8.2%), antipsychotics (n=4, 8.2%) and antiepileptics (n=4, 8.2%). Among the 76 suspect drugs, 58 received a causality score defined as possible (I1), 13 as plausible (I2) and five as likely (I3) related. Drugs defined as plausibly (I2) related were pergolide, pramipexole, alprazolam, zopiclone, zolpidem, fluoxetine, gabapentin, Glatimer, varenicline, prednisone and cyclopentolate (ophthalmic preparation). A likely (I3) score of causality was found for bromazepam, isotretinoin, zolpidem, zopiclone and interferon alpha-2b (Table 1).

Case/noncase comparison

When pharmacological classes were investigated (Table 2), a significant association was found with dopaminergic antiparkinsonian drugs, benzodiazepines, including related compounds such as zolpidem and zopiclone, and serotoninergic antidepressants but not with antipsychotic [ROR=2.1 (0.6–6.0)] or antiepileptic [ROR=1.3 (0.3–4.3)] drugs taken as a whole pharmacological class.

Table 3 shows ROR values for individual drugs in these 56 patients. Significant associations were found for dopaminergic agonists (pramipexole, pergolide, bromocriptine, piribedil), benzodiazepines (alprazolam, bromazepam), varenicline, rimonabant, topiramate, benfluorex, interferon alpha-2b and antiviral drugs (ribavirin and efavirenz). Other statistical evaluations with other drugs were not significant (not shown).

Labelled characteristics of the ADR

Using the 2009 Summary of Products Characteristics (SPC), we found that this kind of suited ADR was unlabelled for pramipexole and ropinirole.

Discussion

This study was undertaken to identify drugs possibly involved in violent behaviours. In fact, as previously discussed, the role of drugs in such behaviour is poorly understood and investigated. For this purpose, we worked in the FPVD, a large national database corresponding to the French spontaneous reporting system and including more than 300,000 case reports of ADRs from 1985. Cases were carefully checked by both clinical pharmacologists and forensic physicians to restrict our analysis to true validated cases of violent and aggressive behaviour. Firstly, our results indicate that violence is a relatively rarely reported ADR in a national pharmacovigilance database: around 1/5,000 reports in the FPVD. Secondly, significant relationships were found, as expected, with some drugs (dopaminergics, benzodiazepines, antidepressants) but also with

Table 1 Main characteristics of the 56 cases of aggressiveness registered in the French PharmacoVigilance Database and included in the study. Causality level was determined using the French method [12], with level 1=possible, 2=plausible, 3=likely and 4=very likely

Number	Age (years)	Gender	Suspect drug(s)	Associated drug(s)	Delay of occurrence (days)	Medical history	Comments	Medicolegal consequences	Misuse	Causality level
1	52	M	Varenicline	None	14	None	During dose escalation	No	No	1
2	57	M	Rimonabant	None	19	Previous aggressiveness towards family	Assault and battery, rape	Yes	No	1
3	19	F	Rimonabant	None	30	None	Disappearance after rimonabant withdrawal	No	No	1
4	54	M	Varenicline Clobazam	None	10	Hyperthyroidism	Heteroaggressiveness + suicide	No	No	1
					1					1
5	69	M	Pergolide	Levodopa	1	Previous treatment with ropinirole without ADR	Aggressive behaviour towards wife	No	No	2
6	18	M	Biperidene	Cyamemazine olanzapine	2	Previous treatment with trihexyphenidyl without ADR	Disappearance after biperidene withdrawal	No	No	1
7	64	M	Varenicline	Venlafaxine	1	Depressive for 15 years+chronic alcoholism	Bad dreams, several crimes. Disappearance after varenicline withdrawal	No	No	2
8	71	M	Prednisone	Ramipril	15	Pulmonary fibrosis	Disappearance after prednisone withdrawal	No	No	2
9	44	M	Varenicline	None	?	None	Normal dosage	No	No	1
10	33	M	Glatimer	None	6	Paraplegia+multiple sclerosis for 9 years	Heteroaggressiveness+suicidal thoughts	No	No	2
11	76	M	Alprazolam Zopiclone	None	1	Depressive symptoms+alprazolam and zopiclone abuse	Disappearance after withdrawal of alprazolam and zopiclone	yes	No	2
					1					2
12	21	F	Alprazolam	None	2	Chronic anxiety	Partial disappearance after alprazolam withdrawal	No	No	1
13	39	F	Alprazolam	Paroxetine	150	Chronic alcoholism	Car crash+violent words to police	No	Yes	1
14	33	M	Topiramate	Valproic acid Clobazam	14	Previous suicidal behaviour+ generalized epilepsy	In the context of epilepsy exacerbation. Hospitalization	No	No	1
15	36	F	Venlafaxine	None	150	none	Decrease after dose reduction	No	No	1
16	61	M	Topiramate	None	120	Major depressive symptoms		No	No	1
17	26	M	Ritonavir, atazanavir	Lamivudine, tenofovir	21	HIV positive	Disappearance after ritonavir+atazanavir withdrawal	No	No	1
					21					
18	65	M	Gabapentin	None	60	None	Gabapentin for diabetic neuropathy. Strangulation of his wife. Disappearance after gabapentin withdrawal	No	Yes	2
19	45	M	Benfluorex	Bromazepam	28	One previous suicidal attempt with anorectic drugs	Dismantling of house+lewd words+suicidal attempts	No	Yes	1
20	31	M	Benfluorex	Haloperidol	180	Chronic psychosis	Benfluorex abuse	No	Yes	1
21	36	M	Bromazepam, buprenorphine	None	15	Alcoholism	Hetero-+self-aggressiveness	No	No	3
										1
22	52	M	Mefloquine	None	3	None	Hetero-+auto-aggressiveness	No	No	1
23	34	M	Alpha-2b interferon	None	90	Posttransfusion chronic hepatitis	Attempt to murder wife	Yes	No	3
24	34	M	Zopiclone	Tropatepine, alimemazine, propericiazine, flupentixol, methadone	60	Multiple drug abuse including zopiclone	Violence, multiple assaults, hallucinations…	No	Yes	3
25	70	M	Pantoprazole	None	3	Previous similar episodes with other proton-pump inhibitors	Disappearance after pantoprazole withdrawal	No	No	1
26	15	M	Isotretinoin	None	240	Alcoholism for some months	Heteroaggressiveness+Autolysis attempt	No	No	1
27	35	F	Bromocriptine	None	7665	Chronic muscular dystonia	Imprisonment	No	Yes	1
28	79	M	Lansoprazole Memantine	None	480	Alzheimer's disease	Attempt to murder wife	No	No	1

29	59	M	Clonazepam, olanzapine	None	730	Chronic psychosis	Attempt to murder	No	No	1
					730					1
30	84	M	Ropinirole	Levodopa, propranolol, omeprazole, carbimazole, ramipril	Several years	Advanced Parkinson's disease	Heteroaggressiveness+hallucinations Disappearance after ropinirole withdrawal	No	No	1
31	55	M	Levodopa, pergolide, entacapone, pramipexole	None	12	Advanced Parkinson's disease	Heteroaggressiveness+hypersexuality+pathological gambling	No	No	1
										1
										1
										1
32	39	M	Pramipexole	None	39	De novo Parkinson's disease	Heteroaggressiveness+pathological gambling+ hallucinations+pathological gambling	No	No	2
33	68	M	Oxazepam, cyamemazine, loxapine, aripiprazole	None	Several years	Chronic paranoid psychosis	Heteroaggressiveness towards other patients	No	No	1
										1
										1
										1
34	86	M	Piribedil, selegiline	Hydroxyzine, tiapride	Several years	Advanced Parkinson's disease	Heteroaggressiveness towards wife	No	No	1
										1
35	53	M	Proguanil, chloroquine	None	56	None	Heteroaggressiveness+confusion	No	No	1
										1
36	15	M	Isotretinoin	Cetirizine	360	None	Hetero-+self- aggressiveness	No	No	1
37	17	M	Isotretinoin	None	90	None	Anxiety+Hetero-+auto-aggressiveness (suicide attempt)	No	No	3
38	16	F	Isotretinoin	None	90	None	Hetero-+self-aggressiveness (suicide attempt)	No	No	1
39	75	M	Clonazepam, bromazepam	None	?	Recent alcohol withdrawal	Verbal and physical aggressiveness	No	No	1
40	54	M	Zolpidem	None	1	Acute alcoholism	Attempt of rape + Heteroaggressiveness	No	Yes	3
41	71	M	Zolpidem	Alprazolam	9	None	Physical aggressiveness	No	Yes	2
42	4	M	Cyclopentolate	None	1	None	Heteroaggressiveness Cyclopentolate by ophthalmic route for specialized exam	No	No	2
43	25	M	Budesonide, formeterol, montelukast, triamcinolone, terbutaline	Alprazolam, cetirizine	31	AM	Insomnia+aggressiveness towards wife	No	No	1
										1
										1
										1
										1
44	85	F	Levodopa, bromocriptine, piribedil	Furosemide, trinitrine, isosorbide	?	Advanced Parkinson's disease with alterations of mental functions	Confusion+physical and verbal aggressiveness Disappearance after bromocriptine and piribedil withdrawal	No	No	1
										1
										1
45	49	M	Efavirenz	Didanosine, lamivudine, stavudine	49	None	Attempt to murder wife's employer	No	No	1
46	37	M	Efavirenz	Alpha-2b interferon, ribavirin, diazepam, didanosine, zidovudine	360	HIV positive+hepatitis	Insomnia+depressive state+heteroaggressiveness Disappearance after efavirenz withdrawal	No	No	1
47	?	M	Bromazepam	None	?	Acute alcoholism	Attempt of wife's rape+harms	No	Yes	1
48	24	M	Alpidem	Moclobemide	1	Chronic alcoholism	Car fire	No	No	1
49	82	M	Cyproterone	None	2	Senile dementia	Heteroaggressiveness; violence towards wife	No	No	1
50	81	M	Fluoxetine	None	7	Only depressive state related to work as a caregiver of wife suffering from Parkinson's disease	Heteroaggressiveness; violence towards wife followed by a suicide attempt	No	No	2

Table 1 (continued)

Number	Age (years)	Gender	Suspect drug(s)	Associated drug(s)	Delay of occurrence (days)	Medical history	Comments	Medicolegal consequences	Misuse	Causality level
51	49	M	Sertraline, phenobarbital, bromazepam	None	12		Kill wife with a knife	No	No	1
52	32	M	Alpha-2b interferon	Ribavirin	70	Used cannabis and heroin several years before	Kill father+other violent and asocial behaviours	No	No	1
53	27	M	Fluoxetine, methyltestosterone	None	?	Depression without psychotic antecedent	Kill wife+suicide	Yes	No	1 1
54	35	M	Sevoflurane	None	1	Following general anaesthesia	Major agitation+violence+disorientation	No	No	2
55	16	F	Zolpidem	Sodium valproate paroxetine	26	Depression	Hetero-+auto-aggressiveness	No	Yes	
56	33	M	Efavirenz	Lamivudine, zidovudine, tianeptine, buprenorphine	182	HIV positive	Attempt to kill wife	No	No	2

drugs less well known to induce such an ADR, drugs such as isotretinoin, rimonabant, benfluorex, varenicline, topiramate and interferon alpha-2b. A relationship was also found with two antiviral drugs (ribavirin, efavirenz). In contrast, we failed to find any association with some classes of drugs, such as antipsychotics or antiepileptics.

Our study suffers from some compulsory methodological drawbacks. The first problem is underreporting, a well-known phenomenon in spontaneous reporting schemes. Thus, for some drugs, the number of reports could be considered as being relatively low. Estimation could be biased according to several factors, one of the most important being the characteristic of seriousness of the ADR [15]. In fact, it is known that a serious and/or unlabelled ADR occurring with a new drug is more likely to be reported that another kind of ADR. Moreover, reporting a violent behaviour as being associated with a drug is not easy in most patients—especially those suffering from chronic psychiatric disease. In fact, a psychiatric history was found in around 50% of patients. Finally, it is important to emphasise that this study was performed in a context of signal detection: thus, we chose to be sensitive enough rather than unable to identify a true association. Thus, ROR values should be considered only as a signal and not as a true risk value.

Control group choice is another important limitation of case/noncase methodology. Results should only be inferred to patients who have suffered from an ADR. In fact, one of the limits of this study is that we did not account for some important factors, such as familial antecedents or illegal drug abuse. This is true for both cases and noncases. We did not show any data about illegal substance use, because the FPVD was not built to record this type of data. Thus, they were not always fully informed in cases (or in noncases). The same comments could be also made, at least partly, for alcohol and drug doses. Thus, we could hope that, in the future, pharmacovigilance centres and authorities could improve the information quality of case reports, including, for example, mandatory chapters concerning these important associated factors. Finally, our study should be considered as exploratory. However, despite its mandatory limitations, use of case/noncase methodology is now recognised as being useful for generating signals in pharmacovigilance and drug-safety research [11–16]. Taking into account these limitations, our study suggests that violent behaviours can be related to exposure to some drugs. These findings may have three explanations: the underlying disease or condition and/or personality for which these drugs are used could be a risk factor for violent behaviour; the drug could be an innocent bystander; the relationship could be causal. The first mechanism is particularly important for psychiatric diseases or illicit substance abuse, although a favouring role of drugs in

Table 2 Pharmacological classes involved in case reports of violence in the French PharmacoVigilance Database (FPVD) and risk of exposure calculated using the case/noncase method

Pharmacological class	Involved drugs	Number of violence cases in the FPVD	Number of total ADRs in the FPVD	ROR (95% CI)
Dopaminergic antiparkinsonians	Levodopa (+ benseraside or carbidopa±entacapone) bromocriptine, pergolide, piribedil, pramipexole, ropinirole	13	5,052	19.8 (10.1-38.2)*
Benzodiazepines and related drugs	Alprazolam, bromazepam, clobazam, diazepam, oxazepam, zolpidem, zopiclone	16	21,912	5.7 (3.1-10.6)*
Serotoninergic antidepressants	Floxetine…	4	6,217	3.9 (1.2-11.2)*

ADR adverse drug reaction, *ROR* reporting odds ratio, *CI* confidence interval

*$P<0.05$,

such violent behaviours is well demonstrated [3]. In fact, Table 1 shows that eight cases had alcohol abuse, three substance abuse and at least 13 an underlying psychiatric history. However, careful revision of cases (by specialists of clinical pharmacology and forensic medicine) allows us a better selection of cases.

First, our study confirms the risk of violence associated with benzodiazepines and related drugs (zopiclone, zolpidem). This pharmacological class was selected as a positive control in this study [6–11]. A recent review [4] discussed this ADR with benzodiazepines. This ADR includes reactions of disinhibition occurring during use of these drugs as anxiolytics or hypnotics. Physical aggressiveness, rapes, impulsive decision making and violence have been reported, as have autoaggressiveness and suicide. Prevalence remains a matter of discussion, although most studies indicate a value <1%. Among risk factors, besides alcohol, the role of low stress control (specifically high-trait anxiety) was suggested, whereas the importance of dose and type of benzodiazepine remains another matter of discussion. From a pharmacodynamic point of view, benzodiazepine-induced activation of the gamma-aminobutyric acid (GABA) ergic mechanisms could explain this ADR [3, 4].

An interesting finding of our study was the results obtained with dopaminergic drugs used in Parkinson's disease. We found a significant association with dopaminergic agonists (bromocriptine, pergolide, piribedil, pramipexole) but also case reports in the FPVD with levodopa, alone or in association with entacapone, a catechol-*O*-methyl transferase (COMT) inhibitor. Although the role of brain dopamine in aggressive and/or violent behaviours is largely described in the literature [17–19], few clinical data are, as far as we know, available. In fact, violent behaviours are part of the dopamine dysregulation syndrome (DDS) [20] that may complicate long-term symptomatic treatment of Parkinson's disease. These includes punding and impulsive control disorders, such as pathological gambling, hypersexuality, compulsive shopping or compulsive eating due to addiction to dopaminergic drugs. In a series of 202 parkinsonian patients, Pezzela et al. [21] described seven individuals who fulfilled the DDS criteria, three of whom presented violent or aggressive behaviour. Finally, ours appears to be one of the

Table 3 Individual drugs significantly involved in case reports of violence in the French PharmacoVigilance Database (FPVD) and risk of exposure calculated using the case/noncase method

Drugs	Number of violence reports in the FPVD	Total number of ADRs in the FPVD	Reporting odds ratio	95% confidence Interval
pramipexole	2	50	103.7*	26.3–409.0
alprazolam	4	334	16.2*	5.0–46.7
varenicline	4	362	29.2*	10.8–78.9
pergolide	2	197	26.3*	6.5–105.9
rimonabant	2	251	20.6*	5.1–83.2
topiramate	2	486	10.7*	2.6–43.1
isotretinoin	4	1,119	9.5*	3.5–25.6
benfluorex	2	750	6.9*	1.7–27.9
Interferon alpha-2b	3	1,214	6.4*	2.1–20.3
ribavirin	2	1,097	4.7*	1.2–19.1
bromocriptine	2	1,116	4.7*	1.1–18.7
piribedil	2	1,236	4.2*	1.0–16.9
efavirenz	3	2,441	3.2*	1.0–10.0
bromazepam	4	5,378	4.5*	1.4–13.0

Reporting odds ratios with its 95% confidence interval. Only drugs for which two or more reports of violence registered in the FPVD were included in the study

*$P<0.05$

few clinical studies indicating the role of dopaminergic drugs in violent behaviour.

In our study, four case reports described violent behaviour under isotretinoin. In fact, following recent reports [22–24], a controversy developed about the risk of psychiatric ADRs (mainly suicides) with isotretinoin [25]. Reviews concluded that, due the multiple biases observed in the published data [underlying disease (acne), psychopathological antecedents and study designs…], it is not possible to establish a definite relationship [25]. However, the link cannot be excluded, as suggested by a recent study [26]. Two other relationships were also found with two drugs recently withdrawn from the market. The first was rimonabant, a cannabinoid antagonist, withdrawn from the European market in January 2009 for an increased risk of suicide [27]. Our study shows that the drug was able to induce symptoms of heteroaggressiveness, which is a less well known ADR. The second was benfluorex, used in France as an adjunct in hyperlipidemias, and recently withdrawn for a risk of pulmonary hypertension and valvular heart diseases [28]. Due to the pharmacodynamic properties of this drug (an amphetamine-derived agent), this serious ADR was from type A (Augmented) [13, 14]. Another interesting result concerns data with interferon alpha-2b. In fact, the risk of psychiatric ADRs with interferon [29] is well documented. Irritability, agitation or paranoia commonly appear after 1–3 months and usually improves within few days after decreasing doses or drug withdrawal. The risk of suicide with interferon is also well described [30]. In contrast, the occurrence of aggressive behaviour remains poorly understood and, as far as we know, no report of violence has previously been published in the literature. Ribavirine is a synthetic nucleoside analog used as antiviral drug in association with interferon in hepatitis virus C (HVC). Its profile of psychiatric ADRs is similar to that of interferon. Thus, as expected, an association between violent behaviour and exposure to ribavirin was found in our study.

This report also allows discussion of the putative link between varenicline, a drug used in smoking cessation, and violent behaviour. There have been reports of neuropsychiatric symptoms as well as exacerbation of preexisting psychiatric illness in patients who have taken varenicline. Patients should be monitored for such symptoms, including suicidal ideation or behaviour, agitation, depression or other changes in behaviour. A warning about the risk of suicide was recently sent by the Medicines and Healthcare Products Regulatory Agency (MHRA) [31]. Our results emphasise that, among neuropsychiatric ADRs elicited by varenicline, violent behaviour should be included. The mechanism of this ADR could include stimulation of brain dopamine release by this partially nicotinic agonist.

Topiramate is a sulfamate-substituted monosaccharide prescribed as an antiepileptic as adjuvant or monotherapy. The problem with psychiatric ADRs observed with topiramate appears to be multifactorial, as epileptic patients are at increased risk of cognitive and behavioural deficits. In children, hyperactivity and aggressiveness may occur [32]. In contrast, no significant association occurred with antiepileptic drugs as a whole.

Among antiretroviral drugs, our study found an association with the nonnucleotide reverse transcriptase inhibitor efavirenz. The profile of serious psychiatric events associated with efavirenz observed in clinical trials includes not only severe depression, suicidal ideation or attempts, psychotic reactions (paranoia, mania…) but also aggressive behaviour [33]. However, these associations could be multifactorial, involving both the underlying disease and drugs (efavirenz and/or other coadministered drugs).

Another interesting finding is the association with serotoninergic antidepressants. This is in agreement with Herxheimer's work, which clearly demonstrates such a relationship [5, 34] with, for example, a 2.1 odds ratio value for paroxetine in adult and paediatric placebo-controlled trials on therapy and in the withdrawal phase [5]. The exact mechanism remains unknown, although the role of antidepressant-induced adverse behavioural outcomes such as akathisia, emotional disinhibition, emotional blunting and manic or psychotic reactions has been suggested [5].

Finally, our study found no relationship with antipsychotics. In fact, this negative data could beg the question discussed above regarding the role of underlying disease [3]. It could also be explained by a lack of power in our study. Several works have linked the occurrence of violence under neuroleptic treatment with the induced akathisia [35].

It is interesting to compare our results with data coming from a recent study performed using the FDA Adverse Event Reporting System data and using a similar methodological approach [36]. Both studies found similar results for antidepressants (mainly serotoninergic agents, but also in the US study, bupropion and mirtazapine), benzodiazepines, interferon alpha-2b and varenicline. In contrast to our findings, the US study described association with antipsychotics and amphetamines but not with dopaminergic drugs. The associated antiepileptic drugs in the US study were levetiracetam and gabapentin (but not topiramate, as in France) [36].

In conclusion, our study identifies a relationship between some drugs and aggressive behaviour. This relationship involves some already suspected drugs (dopaminergics, benzodiazepines, serotoninergic antidepressants) as well as other drugs [(varenicline, isotretinoin, interferon alpha-2b, rimonabant, benfluorex, topiramate and antiviral drugs (ribavirin, efavirenz)], which are less well known to induce such an ADR. Despite the mandatory limits of this kind of

study (underreporting, confounding factors…), these data represent a pharmacovigilance signal and could contribute to establishing further prospective studies to confirm such signals. One of the interests of this kind of research is to find new associations between drug exposure and a relatively unknown (and rare) ADR. From a practical point of view, this study indicates that a systematic anamnesis about drugs should be involved in each aetiological research of violent behaviour. Finally, these data also emphasise the importance of data mining to detect new signals of rare ADRs in a pharmacovigilance database.

Contributors NR and HB performed the study in the FPVD. NR, NT, NF, AP, LS, DR, MLM and JLM analysed the data. JLM wrote the manuscript. NS, HB, NT, NF, AP, LS, DR and MLM revised the text.

Competing interests None

Funding The study was performed as a work of NR during her stay in the Department of Clinical Pharmacology of Toulouse University Hospital.

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