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Seizure risk associated with neuroactive drugs: Data from the WHO adverse drug reactions database

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ABSTRACT

Purpose: To explore the association between the use of neuroactive drugs and reports of epileptic seizures.
Material: Using the WHO adverse drug reactions (ADR) database, VigiBase, we surveyed reports of suspected seizures from 1968 until February 2006. Case reports of ADRs, that were classified as convulsions were collected and compared to the total number of ADRs reported.
Results: The total number of ADRs was 7,375,325. The number of convulsive events was 71,471. The ratio of convulsive ADRs to the total number of ADRs reported for each drug was evaluated and expressed as a percentage. The 10 drugs most frequently associated with convulsive ADRs were maprotilene (14.42%), escitalopram (9.78%), buproprione (9.49%), clozapine (9.0%), chlorprothiexene (8.89%), amoxapine (8.74%), donepezil (8.40%), rivastigmine (6.41%), quetiapine (5.90%) and trimipramine (5.69%).
Conclusions: Based on the reports in VigiBase, ADR reports relating to antidepressants, antipsychotic and cholinomimetic drugs included seizures more often than other neuroactive drugs.

1. Introduction

Many compounds that act on the nervous system are known to reduce the seizure threshold and provoke epileptic seizures. Although these adverse events have been described for almost every drug available, few systematic reviews have been published. The present study explored the occurrence of suspected seizure adverse events in relation to treatment with neuroactive drugs, in a large, global safety database.

Following the thalidomide disaster in the 1960s, the WHO Program for International Drug Monitoring was set up, with the aim of collecting and storing spontaneously reported suspected adverse drug reaction (ADR) reports in an international database. Since 1978, the Uppsala Monitoring Centre has maintained the WHO-ADR database, VigiBase. Case reports, are recorded in a common format, processed and stored in VigiBase. An ADR is defined as a response to a drug, which is noxious, and unintended; the ADR occurs at doses normally used in human patients for the prophylactic, diagnosis, or therapy of disease, or for the modification of physiological functions. These reports are forwarded spontaneously to the national pharmacovigilance centres for assessment and coding. The main aim of VigiBase is to detect previously unknown ADRs, so-called signals of unwanted side effects. The database is a unique source of international ADR information, and when this study was carried out (February 2006), the database contained almost 3.6 million case reports from 79 different countries. WHO-ADR data are not homogenous with respect to origin of the ADR or the probability that a particular drug causes a given adverse reaction. However, these reports have proven to be useful in the early detection of signals of unwanted drug side effects.[1] WHO defines a signal as reported information on a possible causal relationship between an ADR and a drug, when the relationship was previously unknown or has been documented incompletely. Usually more than one single report is required to generate a signal of unwanted side effects, and the signal is also dependent on the seriousness of the event and the quality of the information.[2] Previously, methods similar to ours have been used to study drug-related adverse events such in VigiBase, as headache[3] and sexual dysfunction.[4]

The purpose of the present study was to review VigiBase, for drugs belonging to the Anatomical Therapeutic Chemical (ATC) Classification System group "nervous system" and explore their association with reports of seizures. In this article, seizures and convulsions will be used as synonymous terms.

2. Methods

VigiBase was searched for spontaneously reported cases of suspected ADRs including the following WHO-ART terms: convulsions, aggravated convulsions, convulsions grand mal, and convulsions local. Individuals who experienced more than one

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seizure for a given drug were counted only once. Reports of drugs classified as an agent within the 'nervous system' (ACT groups N01-7) were collected and analysed with the terms of interest. Anaesthetic (N01) and analgesic (N02A and N02B) drugs were not included in this study since reports of convulsions are difficult to interpret in situations in which these drugs are indicated explicitly. Antiepileptic drugs (AEDs, ATC group N03) were also excluded because of the inherent difficulty in determining if a reported convulsion was caused by insufficient AED-medication or was an actual ADR. Drugs used for migraine (ATC group N0C2) were included, even though their main action is not directly on the central nervous system. Except in one case (L-dopa with decarboxylase inhibitor), reports were used only when the drug in question was given as single-component therapy. Consequently, ATC groups included were: neuroleptics and atypical neuroleptics (N05), antidepressants (N06), triptanes (N02), anti-Parkinson's drugs (N04), anxiolytics (N05) and miscellaneous neurotropic drugs (NO6B and D).

The reports were sorted according to the drug's generic name. The year of the first report, total number of ADRs for the drug in question, number of convulsive ADRs and the percentage of the total number of ADRs, that were convulsions (convulsive ADRs/total ADRs) were scrutinised.

3. Results

In total, there were 7,375,325 ADRs reported from the 3.6 million case reports in VigiBase, and 71,471 included

Table 1
Neuroleptics. Reports of suspected drug-related seizures in WHO VigiBase, 1968–2006.

Drug name	ATC-code	Year of first report	Total no. ADRs	Total no. convulsions	Percentage convulsions of total no. of ADRs
Chlorpromazine	NO5AA	1968	6024	148	2.46
Chlorprothiexene	*NO5AF*	*1968*	*461*	*41*	*8.89*
Fluphenazine	NO5AB	1968	2707	84	3.49
Levomepromazine	NO5AA	1968	2207	94	4.26
Perphenazine	NO5AB	1968	1601	51	3.19
Procloperazine	NO5AB	1968	4376	137	3.13
Alimemazine	*NO5AA*	*1968*	*574*	*29*	*5.05*
Haloperidol	NO5AD	1968	10,046	329	3.27
Doxepine	NO6AA	1969	3212	119	3.70
Flupentixol	NO5AF	1969	1753	50	2.85
Dixyrazine	NO5AB	1970	142	2	1.40
Dosulepine	NO6AA	1971	1673	82	4.90
Melperone	NO5AD	1972	319	13	4.08
Zuclopenthizol	NO5AF	1979	962	46	4.18

Drugs with reports of convulsions expressed as percentage of total number of adverse drugs exceeding 5% are given in italic.

Table 2
Atypical neuroleptics. Reports of suspected drug-related seizures in WHO Vigibase 1968–2006.

Drug name	ATC-code	Year of first report	Total no. ADRs	Total no. convulsions	Percentage convulsions of total no. of ADRs
Clozapine	*NO5AH*	*1974*	*41 735*	*3758*	*9.00*
Risperidone	NO5AX	1993	16 808	618	3.68
Quetiapine	*NO5AH*	*1995*	*4 289*	*253*	*5.90*
Olanzapine	NO5AH	1997	14 261	700	4.91
Aripiprazol	NO5AX	2001	3 207	83	2.59

Drugs with reports of convulsions expressed as percentage of total number of adverse drugs exceeding 5% are given in italic.

Table 3
Antidepressants. Reports of suspected drug-related seizures in WHO Vigibase 1968–2006.

Drug name	ATC-code	Year of first report	Total no. ADRs	Total no. convulsions	Percentage convulsions of total no. of ADRs
Amitriptyline	NO6AA	1968	8545	342	4.00
Nortriptyline	NO6AA	1968	2828	111	3.93
Trimipramine	*NO6AA*	*1968*	*1150*	*66*	*5.69*
Clomipramine	*NO6AA*	*1969*	*5960*	*334*	*5.60*
Maprotilene	*NO6AA*	*1975*	*3243*	*468*	*14.43*
Mianserin	NO6AB	1977	4501	159	3.53
Trazadone	NO6AX	1978	5595	144	2.57
Amoxapine	*NO6AA*	*1981*	*1384*	*121*	*8.74*
Citalopram	NO6AB	1982	11,107	471	4.26
Fluvoxamine	NO6AB	1983	6974	303	4.34
Fluoxetine	NO6AB	1986	50,403	1689	3.35
Paroxetine	NO6AB	1988	34,078	991	2.90
Moclobemide	NO6AG	1988	3424	77	2.25
Sertraline	NO6AB	1991	29,375	949	3.23
Venlafaxine	NO6AX	1994	16,641	797	4.79
Nefazodone	NO6AX	1995	8203	121	1.48
Mirtazapine	NO6AX	1996	5748	243	4.23
Reboxitine	NO6AX	1998	1461	18	1.23
Ziprasidone	NO5AE	2001	2534	96	3.79
Escitaloprame	*NO6AB*	*2002*	*1994*	*195*	*9.78*
Duloxetine	NO6AX	2004	1201	36	3.00
Bupropion	*NO7BA*	*1985*	*28,170*	*2670*	*9.48*

Drugs with reports of convulsions expressed as percentage of total number of adverse drugs exceeding 5% are given in italic.

Table 4
Antimigraine drugs. Reports of suspected drug-related seizures in WHO Vigibase 1968–2006.

Drug name	ATC-code	Year of first report	Total no. ADRs	Total no. convulsions	Percentage convulsions of total no. of ADRs s
Dihydro-ergotamine	NO2CA	1968	830	20	2.41
Ergotamin	NO2CA	1969	312	6	1.92
Sumatriptan	NO2CC	1991	11,075	189	1.71
Naratriptan	NO2CC	1997	287	6	2.09
Zolmitriptan	NO2CC	1998	718	12	1.67
Rizatriptan	NO2CC	1999	398	11	2.76
Almotriptan	NO2CC	2001	64	1	1.56
Elitriptan	NO2CC	2003	359	4	1.11

Table 5
Anti-Parkinson's drugs. Reports of suspected drug-related seizures in WHO Vigibase 1968–2006.

Drug name	ATC-code	Year of first report	Total no. ADRs	Total no. convulsions	Percentage convulsions of total no. of ADRs
Omphenadrine	NO4BA	1968	633	17	2.69
Trihexyphenidyl	NO4AA	1968	178	24	2.04
Biperidine	*NO4BA*	*1969*	*742*	*39*	*5.26*
Levodopa[a]	NO4BA	1970	5297	6	0.11
Bromocriptine	*NO4BC*	*1977*	*3798*	*208*	*5.48*
Selegiline	NO4BD	1980	1298	34	2.62
Carbegoline	NO4BC	1990	701	9	1.28
Tolcapone	NO4BX	1996	674	7	0.73
Ropinerole	NO4BC	1995	1017	25	2.46
Pramipexole	NO4BC	1998	1001	12	1.20
Entacapone	NO4BX	1999	545	4	0.73

Drugs with reports of convulsions expressed as percentage of total number of adverse drugs exceeding 5% are given in italic.
[a] Levodopa + decarboxylase inhibitors.

Table 6
Anxiolytic drugs. Reports of suspected drug-related seizures in WHO Vigibase 1968–2006.

Drug name	ATC-code	Year of first report	Total no. ADRs	Total no. convulsions	Percentage convulsions of total no. of ADRs
Diazepam	NO5BA	1968	8236	206	2.50
Chlormethiazole	NO5CM	1986	327	4	1.22
Nitrazepam	NO5CD	1968	105	14	1.33
Oxazepam	NO5BA	1969	1775	63	3.55
Propiomazine	NO5CM	1971	476	5	3.50
Lorazepam	NO5BA	1973	5885	291	4.94
Flunitrazepam	NO5CD	1976	1054	43	2.58
Triazolam	NO5CD	1978	1668	65	1.63
Alprazolam	*NO5BA*	*1983*	*7261*	*403*	*5.55*
Midazolam	*NO5CD*	*1984*	*3966*	*260*	*5.27*
Buspirone	NO5BE	1987	4691	113	2.41
Zolpiclone	NO5CF	1987	4936	45	1.58
Zolpidem	NO5CF	1988	4908	139	2.83
Zaleplon	NO5CF	2000	2854	9	1.89

Drugs with reports of convulsions expressed as percentage of total number of adverse drugs exceeding 5% are given in italic.

convulsive reactions. This means that many of the case reports included more than one ADR. Convulsions constituted 0.97% of all ADRs and were recorded in 1.99% of the case reports. For individual drugs, the number of reports of convulsions is expressed as a percentage of the total number of ADR reports for that particular drug. The results are presented in Tables 1–7 according to the drug's proposed mechanism of action and year of the first ADR report.

Table 7
Miscellaneous neurotropic drugs. Reports of suspected drug-related seizures in WHO Vigibase 1968–2006.

Drug name	ATC-code	Year of drug introduction	Total no. ADRs	Total no. convulsions	Percentage convulsions of total no. of ADRs
Methylphenidate	NO6BA	1969	4496	175	3.89
Modafinil	NO6BA	1997	816	38	4.66
Piracetam	NO6BX	1975	739	23	3.11
Donepezil	*NO6DA*	*1997*	*4226*	*355*	*8.40*
Rivastigmin	*NO6DA*	*1998*	*2092*	*134*	*6.41*
Galantamine	*NO6DA*	*1976*	*1100*	*59*	*5.36*
Memantine	NO6DX	1984	2132	87	4.08
Neostigmine	NO7AA	1968	222	6	2.70
Pyridostigmine	NO7AA	1972	247	4	1.62
Pilocarpine	NO7AX	1969	749	5	0.67
Naltrexone	NO7BB	1985	681	17	2.50
Buprenorphine	NO7BC	1978	3493	39	1.12
Methadone	NO7BC	1968	3096	52	1.68

Drugs with reports of convulsions expressed as percentage of total number of adverse drugs exceeding 5% are given in italic.

Among the neuroleptic agents, the number of reports including convulsions varied from 1.4 to 8.89% of the total number of ADRs for a particular drug. In this group chlorprothiexene had the highest figure (8.89%), followed by alimemazine (5.05%). The atypical neuroleptics had a range of 2.59–9.0%. Clozapine had the largest proportion of convulsive reports (9.0%). Antidepressants ranged from 1.3 to 14.43%. In this group maprotilene had 14.43%, escitaloprame 9.78%, amoxapine 8.74%, trimipramine 5.69% and clomipramine 5.6%.

Reports of convulsions in the triptans varied from 1.11 to 2.76% Drugs used in Parkinson's disease had a range of 0.11–5.48%. In this group the greatest proportions was attributed to the dopamine agonist, bromocriptine (5.48%). Among miscellaneous neurotropic drugs, convulsions were noted for the acetylcholinesterase inhibitors: donepezil (8.40%) and rivastigmine (6.41%).

4. Discussion

We used the spontaneous ADR database to identify epileptic events that occurred in relation to the reported drug treatment. Despite the limitations of spontaneous reporting, most notably underreporting, no clear link to drug exposure data, lack of control group, potential biases in reporting, missing and incomplete data, and unknown causality, uneven quality of information provided, and influences by media and publicity, a high number of reports of a similar nature may identify important ADRs.

Unfortunately, from our study, it is not appropriate to compare a drug with another concerning the number of convulsive reports, since the total number of patients who were treated with a particular drug is not known and it is impossible to calculate the true prevalence of ADRs. For each drug, the reported numbers of convulsive ADRs were assessed relative to the total number of ADR reports. Previous studies have used the ratio expressed as: specific ADR/total ADR.[4,5] In the present study, we found that this ratio was 1.99% for convulsions. We built up this discussion on the assumption that for any given drug, a high ADR/total ADR ratio indicates a high risk for inducing seizures. Additionally, tentative mechanisms are discussed.

Incidence studies have suggested that the risk for psychosis may be 6–12-fold greater in patients with epilepsy than in the general population.[6] Therefore, it is expected that the usage of antipsychotic drugs is more frequent in a population with high seizure susceptibility which contributes to an increased number of reported convulsions.

The major antipsychotic drugs are the neuroleptics, which act mainly by blocking dopamine receptors. These drugs have been associated traditionally with a high risk of seizures. Different dopamine receptors mediate opposing influences on neuronal excitability and seizure susceptibility. Blocking the D2 receptor is associated with seizure precipitation,[7] while D1 antagonists are known to protect against seizures[8]. The neuroleptics have variable net effects on seizure threshold, probably because each drug has a different affinity for each of the dopamine receptors. Among the first-generation antipsychotic medications (typical antipsychotics), chlorprothiexene, which exerts its effects on D1, D2, D3, serotoninergic and cholinergic receptors, had a relatively large proportion (8.89%) of reported convulsions. Shortly after becoming available clinically, chlorpromazine was noticed to be associated with generalised seizures consistent with the incidence found in this study. Later publications however have shown an incidence of seizures of $<2\%$.[9] Other typical neuroleptics in this study had a relatively low potential for convulsive adverse events in accordance with the estimates in previous literature.[10] Alimemazine, although structurally related to chlorpromazine, is a sedating antihistamine used for allergic skin reactions and sedation. Five percent of the ADRs reported for alimemazine were convulsions. However, it may be hazardous to draw any firm conclusion about the relationship between alimemazine and seizure induction because it is often used to treat alcoholism.

Both typical and atypical antipsychotic medication may cause seizures. In the present study, clozapine was the atypical antipsychotic that was most frequently associated with seizures. Our data are in agreement in previous studies in which clozapine-induced seizures were estimated to occur in 3.5% of patients in pre-marketing trials and showed a predicted 5% cumulative risk at 1 year.[11] The mechanism by which clozapine lowers the seizure threshold is not fully understood. Clozapine displays strong affinity to several subtypes of dopamine receptors. It has been proposed that clozapine and clozapine-related drugs (olanzapine and quetiapine) have selectivity for mesolimbic dopamine receptors, which may account for their proconvulsive effects.[12] According to VigiBase data, risperidone, which has a low affinity for D2 receptors, caused less convulsive ADRs than clozapine did. This concurs with the results of pre-marketing monitoring.[13]

Antidepressant drugs are known to have a proconvulsive effect. Mood and affect disorders occur more frequently in persons with epilepsy as compared with the general population; this necessitates the use of antidepressant drugs in this group.[14] Depression in itself may cause seizures thereby contributing to an increased number of ADRs.[15] The incidence of seizure adverse events range from 0.1 to 4.0% in the literature in patients treated with antidepressants.[16] We found high numbers for convulsive ADRs in the antidepressant group, most frequently for maprotilene, amoxapine, imipramine, buproprion and escitalopram. Differences in sampling size may explain the higher frequency. However, maprotilene, buproprione, and amoxapine have been associated previously with a greater seizure risk than other antidepressants.[17,18] The mechanisms through which antidepressants alter neuronal excitability and modify seizure threshold are still largely unknown. Antidepressants act mainly by blocking the re-uptake of monoamines. Both animal and human data have shown that blocking the re-uptake of norepinephrine and/or serotonin has an anticonvulsant effect[19]. The convulsive properties of antidepressants have been suggested to be the result of their possible local anaesthetic or anticholinergic effect.[20] It has been proposed that selective serotonin re-uptake inhibitors (SSRIs) are less likely to cause seizures than cyclic antidepressants.[21] On the other hand, seizures have been associated with SSRIs in previous studies of adverse events as in the case of escitaloprame.[22]

Although distinct in their pathogenesis, migraine headaches and epilepsy may coexist and interrelate in a number of ways. Patients with migraine aura may sometimes progress to have clear epileptic events.[23] In the literature, however, there are very few reports on seizures provoked by migraine medications. This is not surprising considering the fact that the ergot derivatives and triptanes exert their effect by direct stimulation of serotonin-receptors outside the brain in extra-cranial vessels. In VigiBase, it was a low number of reports of convulsions in response to migraine treatment.

Historically, dopamine is known to have an anticonvulsant effect. However, there are many examples of dopamine agonists with proconvulsive properties. This is attributable to the different effect of dopamine and its receptor subtypes; D_1 being proconvulsive and D_2 anticonvulsive.[24] The majority of anti-Parkinson drugs act by increasing dopaminergic transmission directly or indirectly. Levodopa has been reported to lower, exacerbate or not alter seizure threshold.[24] Few reports in VigiBase of convulsions and dopamine stimulation favour the view that levodopa has little influence on seizure threshold. With the exception of bromocriptine, stimulation of dopamine receptors directly by agonists also seems to have little effect on seizure threshold. In VigiBase the

frequency of convulsive ADRs for bromocriptine was over 5%. An explanation for this may be related to the use of bromocriptine for suppression of lactation in postpartum women who are at risk for developing hypertension and encephalopathy, in whom seizures are part of the symptomatology. In addition, bromocriptine is used for treatment of prolactinomas, which may extend into the temporal lobes and cause seizures.

In the anxiolytic drugs, there were few reports of seizures in relation to treatment with different benzodiazepines or chlomethiazole. The pharmacological effect of these drugs is mediated mainly by increasing GABA, the major inhibitory neurotransmitter in the brain. The fact that there have been some reports of convulsions with benzodiazepines and chlomethiazole might be related to drug withdrawal or use of the drugs in the treatment of epilepsy.

Seizures can be induced or exacerbated by cholinomimetic drugs. Seizure activity may also be a manifestation of Alzheimer's disease, which is the primary use of cholinomimetics. Cholinomimetics act by reversible inhibition of the enzyme acetylcholinesterase and exert their therapeutic action by enhancing neuronal cholinergic transmission. Cholinergic dysfunction[25] and alteration of nicotinic cholinergic mechanisms contribute to various forms of central nervous system dysfunction such as seizures.[26] In the present study, donepezil and rivastigmine were associated with relatively high numbers of convulsive adverse events. To the best of our knowledge, there have so far been occasional but no systematic reports of convulsive adverse events from donepezil or rivastigmine in the literature.

Our analysis of the ADRs in VigiBase indicates that treatment with neuroleptics, antidepressants and cholinomimetic drugs can lower the seizure threshold and provoke seizures. Nonetheless, it should be noted that these conclusions are based on uncontrolled, retrospective case reports in patients who may have other risk factors for epileptic seizures. Furthermore, the total number of treated patients is not known. To properly evaluate different drugs and their propensity to cause adverse events, such as seizures, evidence-based medicine, with randomised, controlled trials are needed. Unfortunately, these studies are not likely to appear in the literature. Comprehensive spontaneous ADRs registries can be used to give warning about safety issues and generate important safety hypotheses that can be investigated and corroborated with other knowledge.

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