Epileptogenic drugs: a systematic review

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A wide range of substances, including drugs and illicit compounds, increase the risk of epileptic seizures. In this systematic review, the authors address the issue of the epileptogenic potential of marketed drugs, with the aims of providing criteria for the assessment of the cause–effect relationship between drug exposure and the risk of seizures; and to identify the compounds better fulfilling the requirements of an epileptogenic drug. Finding a correlation between drug exposure and occurrence of seizures does not necessarily establish a causal association. In light of the available evidence, even with these limitations, some conclusive remarks can be made on the epileptogenic potential of some active principles. Drugs with high epileptogenic potential include meperidine, sevoflurane, clozapine, phenothiazines and cyclosporine. Drugs with intermediate epileptogenic potential include propofol, maprotiline, tricyclic antidepressants and chlorambucil. Drugs with low epileptogenic potential include fluorquinolones, carbapenems, bupropion and iodinated contrast media. Drugs with minimal or inconclusive epileptogenic potential include interferon α.

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A wide range of substances, including drugs and illicit compounds, increase the risk of epileptic seizures. In a study by Porter and Dick in 1977, seizures were recorded in less than 1% of 32,812 consecutive patients prospectively monitored for drug toxicity [1]. As many as 15% of drug-related seizures present as status epilepticus [2]. In 1996, drug overdose was reported in 2% of children and 3% of adults with status epilepticus in a population-based survey [3].

Several factors are implicated in the pathophysiology of drug-induced seizures [4]. They can be schematically subdivided into two major categories: drug- and patient-related. Drug-related factors comprise intrinsic epileptogenicity of the specific agent, factors influencing drug serum levels and CNS levels, including lipid solubility, molecular weight, ionization and protein binding. Patient-related factors include genetic susceptibility to the convulsant action of drugs, drug interactions, natural rate or impairment of the hepatic or renal drug metabolism, presence of blood–brain barrier (BBB) breakdown and intentional overdose. However, the mechanisms of drug-induced seizures are poorly understood and the possibility exists of a chance occurrence of seizures, often in patients with no previous of seizures history.

This systematic review will address the issue of the epileptogenic potential of marketed drugs, with the aim of identifying compounds better fulfilling the requirements of an epileptogenic drug.

Methodological issues in the assessment of the cause–effect relationship between drug exposure & epileptic seizures

Finding a correlation between drug exposure and occurrence of seizures does not necessarily establish a causal association. In order for drug exposure to be considered a risk factor for an epileptic seizure, the association should meet the following conditions [5]:

- Temporal sequence: the exposure must precede the epileptic seizure in time (the smaller the time interval, the greater the probability of a causal link)

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- Strength: individuals exposed to the drug have a greater risk of seizures compared with nonexposed individuals and the larger the difference of exposure the greater the strength of the association
- Consistency: the association should be reproducible in different populations and under different conditions
- Biological gradient: there should be evidence of a dose–response effect
- Biological plausibility: the association between epilepsy and exposure should be consistent with a recognized biological mechanism

As epilepsy has multiple genetic and nongenetic environmental causes, the possibility also exists that seizures among patients exposed to drugs are the result of an environmental factor (drug exposure) acting on a genetically predisposed individual. Several models of gene–environment interaction have been identified that link susceptibility genes, environmental risk factors and the disease [6]. These include the following:

- Genotype increases expression of risk factors (in this case, drug exposure)
- Genotype exacerbates effect of risk factors
- Risk factors exacerbate effects of genotype
- Both genotype and risk factor are required to increase the risk
- Genotype and risk factor influence risks independently; in this context, genetic susceptibility may affect drug metabolism, predisposing an individual to the putative epileptogenic effects of a drug

Procedure for the assessment of the epileptogenic drugs

A Medline search for studies on drugs and epileptic seizures published since 1966 was performed. The keywords used in the search were drug induced, seizures, pharmaceutical agents and epilepsy. If this search led to the identification of a drug or a drug category, then the name of that drug or drug category was used for a further search. Additional articles were identified through the reference lists of the eligible articles. The target population was represented by children, adolescents and adults with one or more epileptic seizures occurring during or after exposure to drugs given at therapeutic dosages. A drug was then selected for review if studies satisfied at least one of the following criteria:

- A Medline search resulting in at least one publication dealing with 30 exposed individuals and providing information on at least one of the conditions required to meet the criteria for causal association (temporal sequence, strength, consistency, biological gradient or biological plausibility);
- At least ten case reports, each of which were required to have information regarding three parameters: time elapsed between drug intake and seizures, drug dosage, presence of risk factors for seizures (family and/or personal history, concurrent epileptogenic conditions, other CNS drugs, impaired liver or renal function; electrolyte imbalance or other relevant metabolic condition).

These limitations were considered to restrict the review of those compounds whose epileptogenicity was supported by greater than minimal evidence-based criteria. Only studies and case reports that dealt with therapeutic doses and/or levels of the drug were taken into consideration. Thus, all cases of overdose were excluded. Publications presented as abstracts, book chapters or meeting proceedings were also excluded. Each eligible article was subjected to systematic review, and data regarding the criteria for causal association were abstracted and tabulated. Furthermore, details on patients' characteristics were taken into consideration, with special reference to risk factors for epilepsy (family and/or personal history of seizures, presence of any epileptogenic condition) or seizures (e.g., renal dysfunction). One of the authors examined all of the publications, performed the systematic review and discussed with the other authors any problem in the interpretation of each article's findings.

The evaluation of the epileptogenicity of alcohol and illicit drug abuse (e.g., cocaine, phencyclidine and amphetamines) is beyond the scope of the present review.

Results

Only 13 drugs or drug categories met the inclusion criteria, and these include (listed in alphabetical order): analgesics (meperidine), anesthetic agents (propofol, sevoflurane), antibacterial agents (carbapenems, fluorquinolones), antidepressant drugs (bupropion, maprotiline, tricyclic antidepressants [TCAs]), antineoplastic agents (chlorambucil), antipsychotic agents (clozapine, phenothiazines), contrast media, immunosuppressants and immunomodulators (cyclosporin, interferon [IFN]-α).

Meperidine, first synthesized as an anticholinergic agent, is a widely used opioid analgesic for the treatment of acute painful conditions. The suggested safe therapeutic dose is 600 mg/day with a 1200 mg/day upper limit [7]. The association between seizures and meperidine use was investigated in two published reports: a large retrospective series of 510 children with sickle cell disease [8] and a prospective survey of 67 patients receiving the drug for postoperative pain or chronic pain from cancer [9]. Meperidine was administered at therapeutic doses and patients had no risk factors for epilepsy. Detailed neurological evaluation of the ten patients with seizures in the prospective study demonstrated agitated delirium, and the electroencephalogram (EEG) was characterized by diffuse slow-wave and intermittent paroxysmal activity. When combining the data from the two studies, seizures were recorded in 12 out of 577 (2.1%) patients. However, the incidence of seizure was significantly higher in cancer patients than in anemic children (14.9 vs 0.4%), possibly because of renal dysfunction, which was mostly present in cancer patients and contributed to the accumulation of normeperidine. The latter is a potent metabolite of meperidine and has CNS toxicity.

Anesthetic agents

Propofol

Propofol is an intravenous short-acting anesthetic agent acting on γ-aminobutyric acid (GABA) A receptors [10]. The drug has been successfully used in the treatment of status epilepticus [11]. The

Table 1. Sevoflurane.

N (with seizures)	Dose and biological gradient	Temporal sequence	Risk factors for seizures (family and/or personal history of seizures, presence of other epileptogenic conditions)	Study design	Ref.
30 (22, 18 of whom only had EEG seizures)	Induction of anesthesia with 8% sevoflurane inspired in air, for 6 min	60–120 sec	None	Double-blind, controlled, randomized	[12]
30 (22, 20 of whom only had EEG seizures)	As above	267 ± 44 sec	None	Randomized	[13]
31 (17, all of whom with only EEG seizures)	As above	Not specified	None	Randomized	[14]
30 (0)	Sevoflurane 2%	Not specified	None	Not specified	[15]
8 (one case with clinically manifesting seizures)	Induction with 8%; end-tidal concentration maintained at 2% for 30 min, then 3% for 30 min, and 4% for another 30 min (during which the seizure occurred)	<90 min	None	Prospective, systematic	[16]

EEG: Electroencephalogram.

large majority of data on the correlation between propofol and seizures was found in a recent systematic review of 55 reports, with data on 70 patients that had no history of epilepsy [11]. In these cases, propofol induction dose was 0.5–5.2 mg/kg. Seizure-like phenomena were recorded during the induction period in 24 cases (34%), during emergence in 28 (40%), and after 33 min, 6 days after anesthesia in 16 (23%). An EEG was performed in 24 patients (34%), five of whom had an abnormal tracing. The strength of evidence of a causal relationship was based on the occurrence of the majority of seizures during the induction or the emergence period (during which variations in drug concentration and in cortical activation could have triggered epileptic activity) and the absence of concurrent treatments.

Sevoflurane

Sevoflurane is a methyl ether used for mask induction and maintenance of anesthesia in children and adults (TABLE 1). Most of the published information on the association between sevoflurane and seizures has been obtained from prospective and randomized clinical trials [12–16]. A total of 129 individuals were investigated, including women undergoing elective gynecological surgery (60), children undergoing elective otolaryngological surgery (61) and healthy subjects (eight). None of them had risk factors for epilepsy. Where specified, seizures occurred within 90 min. The incidence of seizures ranged from 0 to 12%. Except for one study demonstrating no seizures or EEG abnormalities in the entire sample [15], epileptiform EEG activity was seen in 70–100% of cases. Nieminen and colleagues attributed the absence of seizures and epileptiform potentials either to the use of lower sevoflurane doses or to the concurrent administration of thiopental and midazolam [15]. In another study, epileptiform discharges occurred in all healthy subjects, one of whom (receiving the highest dose) also had clinical seizures [16]. The drug has a strong suppressive effect on the inhibitory activity of GABA.

Antibacterial agents

Fluoroquinolones

Fluoroquinolones are a commonly prescribed class of antibacterial agents used to treat infections of the urinary and respiratory tract, sexually transmitted diseases, gastrointestinal infections, and skin and soft tissue infections [17,18]. Seizures during treatment with these antibiotics were reported for ofloxacin, ciprofloxacin, levofloxacin, norfloxacin and alatrofloxacin, mostly as case reports. Only two studies examined the incidence of seizures in large samples of patients. One was a review of the most frequently reported adverse reactions occurring in 2197 patients receiving 3–10 days of ofloxacin in clinical trials [19]. In this study there were no seizure reports. The second study was a randomized trial comparing intravenous ciprofloxacin (400 mg three-times daily) with imipenem/cilastatin [20]. Seizures occurred in three of 202 (1%) patients in the ciprofloxacin treatment group. In two of these patients, seizures occurred more than a week after drug discontinuation. Risk factors for epilepsy and seizures were not reported or absent. The CNS stimulation induced by fluoroquinolones occurs as a result of the antibiotic binding to the GABA receptors in the brain. In addition, animal studies suggested an agonistic effect on the glutamate receptor *N*-methyl-D-aspartate [21].

Carbapenem antibiotics

Carbapenem antibiotics are synthetic β-lactam agents that are active against a wide range of pathogens and are used primarily to treat serious infections in the hospital setting (TABLE 2) [22].

Table 2. Carbapenems.

N (with seizures)	Dose and biological gradient	Temporal sequence	Risk factors for seizures (family and/or personal history of seizures, presence of other epileptogenic conditions)	Study design	Ref.
21 (7)*	Imipenem/cilastatine 25 mg/kg intravenous 30–40 min, every 6 h	3 patients: 1 day 3 patients: 3 days 1 patient: 4 days	Bacterial meningitis	Prospective	[23]
75 (1)	<2 g/day imipenem/cilastatine	13 days	None	Retrospective	[24]
22 (5)	Imipenem/cilastatine Patients 1,2, and 3: 500 mg/6 h Patient 4: 500 mg/12 h Patient 5: 1 g/6 h	Patient 1: 8 days Patient 2: not specified Patient 3: 42 h Patient 4: 2 h Patient 5: 18 h	4/5 with diminished renal function	Population study	[25]
1754 (16)	Imipenem/cilastatine 54% of enrolled patients: 2 g 22%: <2 g 24%: ≥3 g	Mean: 7 days	Not specified	Retrospective	[26]
28 (0)	Meropenem 6 g/day	Mean duration of treatment: 11 days	Not specified (patients with diminished renal function were excluded)	Prospective, randomized	[27]
1951 (4)	Imipenem/cilastatine 2 patients: 1,6–2 g/day 1 patient: 2,1–3 g/day 1 patient: >3 g/day	2 patients: 5 days 2 patients: 6 days	1/4 with history of seizures	Prospective	[28]
200 (11)	Imipenem/cilastatine 1 g/8h intravenous, administered in 40–60 min	Not specified	Dose adjusted according to renal function	Multicenter, randomized	[29]
132 (1)	Imipenem/cilastatine 500 mg/8 h intravenous, administered in 30 min	Not specified	Not specified (patients with lowered renal function were excluded)	Prospective	[30]
117 (0)	Meropenem 500 mg/8 h intravenous in 30 min	Not specified	Not specified	Prospective	[31]
129 (0)‡	Meropenem 40 mg/kg/8 h	Duration of treatment: 7–14 days, according to pathogenic agent	None	Prospective	[32]

*5/7 were partial seizures (one with secary generalization), two tonic–clonic seizures.
‡15 seizures considered secary to underlying medical condition (bacterial meningitis).

Among these are imipenem (given with cilastatin, a dehydropeptidase inhibitor, to prevent nephrotoxicity and metabolic breakdown) and meropenem. The therapeutic daily dose for imipenem/cilastatin is 100 mg/kg or 1500–4000 mg, while for meropenem it is 1500–3000 mg. The occurrence of seizures was investigated in four prospective studies on patients receiving imipenem/cilastatin and in three prospective studies on those treated with meropenem [23–31]. In these studies, the daily dose varied according to the renal function. In one of the largest series including patients in noncomparative trials [25], 3% of patients had seizures during treatment with imipenem/cilastatin. Of these, only 0.9% were deemed to be correlated with the drug. The remaining patients with seizures either had relapses after stopping the drug (nine), while taking other antibiotics (17) or while untreated (six). Patients with drug-related seizures had lower creatinine clearance, lower body weight, were older and more severely ill. The average time between treatment start and seizure onset was 7 days (1–29 days). In the other large study, a much lower incidence of seizures was detected (0.2%) [27]. The seizures occurred within 6 days of the treatment starting. Investigators speculated that the β-lactams might exert CNS stimulatory effects by binding GABA receptors [32]. This postulated mechanism of action is the basis for the epileptogenic effects of cephalosporins, fluoroquinolones, aztreonam and penicillins [30].

Neurotoxic reactions may occur frequently with other β-lactam antibiotics (semisynthetic penicillins and cephalosporines, such as cefepime) [33,34]. Penicillins probably

Table 3. Bupropion and tricyclics.

N (with seizures)	Dose and biological gradient	Temporal sequence	Risk factors for seizures (family and/or personal history of seizures, presence of other epileptogenic conditions)	Study design	Ref.
Buproprion					
3100 (3)	1 patient:100 mg/day 2 patients: 300 mg/day	3, 46, 66 days	None	Prospective	[35]
3395 (15)	≤450 mg/day	1–1026 days (median: 19 days)	7/15 (3 with history of seizures, 1 with cerebral metastasis, 1 with alcohol withdrawal, 1 with concurrent intake of alprazolam and 1 with concurrent intake of amitriptyline 450 mg/day	Retrospective	[36]
1372 (0)	Approximately 420 patients: 300 mg/day approximately 410 patients: <300 mg/day approximately 120 patients: 400 mg/day	8 weeks	None	Multicenter randomized, double-blind, parallel-group, placebo-controlled trial	[37]
2708 (10)	300–450 mg/day	9–48 days	None	Prospective	[38]
Tricyclics					
107 (2)	Patient 1: imipramine 250 mg/day Patient 2: imipramine 150 mg/day	Patient 1: 7 months Patient 2: 11 months	None	Prospective	[43]
400 (4)	2 patients: 50 mg/day 1 patient: 150 mg/day 1 patient: 200 mg/day of unspecified tricyclic	2 and 6 weeks with 50 mg/day 3 days with 150 mg/day 1 week with 200 mg/day	2 patients (50 mg/day) with history of seizures 2 patients with family history of seizures	Retrospective	[44]
45 (1)	75 mg/day	2 weeks	None	Retrospective	[41]

increase CNS excitability by antagonizing GABA. There is considerable variability in the neurotoxic potential of the various agents. Benzylpenicillin and cefazolin have the higher neurotoxic potential. Factors increasing the risk of seizures include excessive dose, decreased renal function, damage of the BBB, preexisting CNS disorders and concurrent use of nephrotoxic agents or drugs lowering the seizure threshold.

Antidepressant drugs

Bupropion

Bupropion hydrochloride is an amino ketone approved for the treatment of depression at a dose range of 100–600 mg daily (TABLE 3). Four large retrospective or prospective case series involving 10,575 patients are available [35–38]. Seizures were recorded in 0.3% of cases in up to 1026 days after the treatment started. The incidence of seizures was 0.2% in prospective studies and 0.4% in the retrospective study. In this report, risk factors for seizures and epilepsy were present in seven of the 15 affected cases [36]. When combining the results of the randomized trials, among the 4262 patients receiving bupropion, 34 had seizures associated with drug treatment (0.8%). However, approximately half of these patients had predisposing or other contributing factors. Although there are no specific mechanisms for the purported proconvulsant activity of bupropion, other antidepressant agents are accompanied by a high risk of seizures, including clomipramine and second-generation antidepressants amoxapine and maprotiline [39].

Maprotiline

Maprotiline hydrochloride is a second-generation tetracyclic antidepressant with relatively fewer anticholinergic effects and a better cardiovascular profile. The daily dose range in clinical practice is 75–450 mg. Although seizures were recorded in 25 of 6100 patients (0.4%) exposed to maprotiline in clinical trials, with a dose-dependant relationship, no additional details were available from the manufacturer [40]. As part of postmarketing surveillance, a total of 229 seizures have been reported among 920,000 drug prescriptions in the UK (0.025%/month's exposure) [40]. This risk approximates the

0.1% incidence of seizures reported in the USA by Ciba-Geigy for the years 1981–1982. Since then, two additional retrospective reports have been published, the first with data on 98 patients developing seizures mostly within 1 week [40] and the second with data from 32 patients with an unremarkable history for seizure susceptibility (all of them developing seizures within 6 days after an increase in dose) [41]. The putative proconvulsant activity of maprotiline was explained by its strong lipophilic activity, leading to high brain concentrations, or the selective blockade of norepinephrine reuptake with little or no effect on serotonin metabolism [42]. Suggestions were also made for high plasma levels of a hypothetical convulsant metabolite [40].

Tricyclic antidepressants

Imipramine and other TCAs agents are still commonly used at differing doses for the treatment of depression and other mood disorders (TABLE 3). The accepted daily dose of these compounds is 150–300 mg [43]. Several reports of early clinical trials of imipramine demonstrated seizures occurring in up to 4% of the exposed individuals [44]. Despite the abundancy of case reports, only three studies (one with a prospective design) were found that fulfilled the authors inclusion criteria [41,44,45]. The incidence of seizures in these studies was 1–2%. Time-to-seizure ranged from 3 days to 12 months. In the largest series [44], patients with seizures either had a family history of epilepsy (two) or a personal history of seizures (two). The potential of tricyclic and other antidepressants for triggering seizures has been extensively investigated in *in vitro* studies and animal models [46]. These studies indicate that some antidepressants may display both convulsant and anticonvulsant effects. A clear biphasic effect on brain excitability was detected for several compounds, with anticonvulsant effects occurring at lower dosages and convulsant effects at higher dosages.

Among the antidepressant drugs, selective serotonin reuptake inhibitors (fluoxetine, sertraline and paroxetine), monoamine oxidase inhibitors and trazodone are accompanied by a low risk of seizures.

The mechanisms through which antidepressant drugs alter neuroexcitability and modify seizure threshold are still largely unknown [47]. Like other TCAs, imipramine increases the concentration of biogenic amines (noradrenaline and serotonin) in the synaptic cleft [48]. Buproprion affects noradrenergic and/or dopaminergic, but not serotonergic function and is chemically unrelated to imipramine [49]. Maprotiline selectively increases noradrenergic activity and has little or no effect on serotonergic activity [42]. Thus, as far as the epileptogenicity of these agents is concerned, one cannot identify clear-cut groups according to their mechanism of action. However, a dose-dependent increase in the incidence of seizures is undeniable for these drugs [45].

Antineoplastic agents

Chlorambucil

Chrorambucil is a nitrogen mustard derivative used primarily for the treatment of chronic lymphocytic leukemia, Hodgkin and non-Hodgkin lymphoma, Waldenstrom macroglobulinemia and some malignant neoplasms. The daily dose of the drug is 0.2 mg/kg for 4–8 weeks. There is only one retrospective study demonstrating seven seizures in 91 children receiving 99 courses of chlorambucil (1.5–36.7 mg/kg) for the treatment of nephrotic syndrome [50]. Seizures occurred after 6–90 days. None of the patients had risk factors for seizures. The neurotoxicity of

Table 4. Clozapine and phenothiazines.

N (with seizures)	Dose and biological gradient	Temporal sequence	Risk factors for seizures (family and/or personal history of seizures, presence of other epileptogenic conditions)	Study design	Ref.
Clozapine					
50 (1)	900 mg/day (plasma levels: 320 ng/ml)	8 weeks (56 days)	None	Prospective in cohort	[52]
148 (11)	Daily doses (mg/day): 200, 250, 500 (3 patients), 600 (2 patients), 625, 700, 900	Mean: 34 days Range: 13–101 days	No history of seizures; family history not specified	Prospective, systematic	[53]
5629 (71)	Group 1 (n = 21): 0–299 mg/day (1.6%) Group 2 (n = 29): 300–600 mg/day (0,9%) Group 3 (n = 21): ≥600 mg/day (1.9%)	Mean: 42 days	44/71 were taking other drugs active on CNS 16/71 had a history of seizures	Retrospective	[54]
10 (2)	1 patient: 400 mg/day 1 patient: 275 mg/day	1 patient: end of fourth week (circa 28 days) 1 patient: fifth week (circa 35 days	None	Double-blind, randomized	[55]

Table 4. Clozapine and phenothiazines. (cont.)

N (with seizures)	Dose and biological gradient	Temporal sequence	Risk factors for seizures (family and/or personal history of seizures, presence of other epileptogenic conditions)	Study design	Ref.
Clozapine					
1418 (41)	≥600 mg/day (4.4%) 300–599 mg/day (2.7%) <300 mg/day (1.0%)	Median time between onset of clozapine treatment and first seizure: 75 days	19/41 were taking other medications with CNS activity	Retrospective	[56]
Phenothiazines					
859 (10)	7/78 high doses 3/781 medium-low doses	Median total time on phenotiazines: 37.5 days. Median time after initial or modified daily dosage to seizure: 9.5 days	4/10 with organic cerebral disorders (3 presenile psychoses, 1 posttraumatic dementia), 2 of whom had a remote history of seizures	Retrospective	[58]
400 (14)	Chlorpromazine 75–200 mg	Not specified	Not specified	Not specified	[59]
120 (3)	Chlorpromazine 100–300 mg	Not specified	Not specified	Not specified	[60]
800 (10)	Chlorpromazine 150–300 mg	Not specified	Not specified	Not specified	[61]
364 (1)	Chlorpromazine up to 600 mg	Not specified	Not specified	Not specified	[62]
300 (3)	Chlorpromazine ≥30 mg	Not specified	Not specified	Not specified	[63]
750 (11)	Chlorpromazine 50–900 mg	Not specified	Not specified	Not specified	[64]
21 (11)	Chlorpromazine 200–4000 mg	Not specified	Not specified	Not specified	[65]
19 (6)	Promazine 900–1800 mg	Not specified	Not specified	Not specified	[66]

chlorambucil is suggested by the neurotoxic potential of the hydrolysis products of the parent compound and its alkylating metabolite, for their structural similarity to the metabolites of ethanol and chloral hydrate and by data showing lethal seizures in experimental animals [51].

Antipsychotic agents

Clozapine

Clozapine, a dibenzodiazepine derivative, is a powerful neuroleptic drug, with high affinity for the dopamine D_4 receptors and low affinity for D_2 receptors (it blocks cortical D_2 receptors but not D_2 receptors in the striatum) (TABLE 4) [48]. A report on 1418 USA patients, exposed to clozapine before marketing found an incidence of seizures in 2.8% of cases and a cumulative 10% risk of seizures after 10 years of treatment. The risk seemed dose-dependent, with the highest seizure risk in patients taking a daily dose of 600 mg or higher [52]. Among studies fulfilling the authors inclusion criteria, the incidence ranged from 1.3 to 20% [52–56]. The largest retrospective investigation of the correlation between clozapine and seizures is that of Pacia and Devinsky [54]. The authors reviewed all the epileptic seizures recorded in the Clozaril Patient Management System. A total of 71 patients out of 5629 had a generalized tonic–clonic seizure (1.3%) and 24 had recurrent seizures. Of these, 44 were concurrently taking other drugs active on the CNS and 16 had a history of antecedent seizures. Seizures occurred after a mean treatment duration of 42 days. No correlation was found between drug–daily dose and the risk of seizures. Most patients who were rechallenged with clozapine after the seizures had no recurrences, after dose reduction and gradual dose titration. Two prospective studies in patients without apparent risk factors for seizures found a seizure risk of 2 and 7.4%, respectively [52,53]. High occurrence of seizures (67%) and EEG abnormalities were found in 12 patients seen at a neurophysiology unit while treated with clozapine [57]. The EEGs revealed interictal epileptiform abnormalities in eight patients, two of whom were seizure-free.

The reduced affinity of clozapine for the striatal dopaminergic receptors and its significant anticholinergic profile may account for the extrapyramidal effects and the epileptogenic

Table 5. Contrast media.

N (with seizures)	Dose and biological gradient	Temporal sequence	Risk factors for seizures (family and/or personal history of seizures, presence of other epileptogenic conditions)	Study design	Ref.
1418 (7)	Vascoray 100 ml	5 patients: 2–5 min after injection 2 patients: within 30 min	5/7: None 2/7: History of seizures	Retrospective	[68]
15226 (29)	Variable doses: 50 or 100 ml of iodinated or noniodinated contrast media, administered iintravenously in 2–3 min	2 patients: during injection 22 patients: <10 min 5 patients: between 11 and 30 min	22 patients. with a history of seizures	Retrospective	[69]
1000 (5)	4 patients: iothalamate sodium 66% 100 ml intravenous 1 patients: 30% diatrizoate meglumine 300 ml	1 patient: during injection 1 patient: after 5 min. 1 patient: after 15 min. 2 patients: immediately following injection	Cerebral metastasis; no history of seizures	Retrospective	[70]

potential of the drug. The specific affinity of the drug may also explain the EEG abnormalities arising from the temporal lobe. The increase in rapid eye movement (REM) at the expense of non-REM sleep seen in patients taking clozapine may also explain this drug's epileptogenicity. This could lead to a dose-dependent compensatory activation of non-REM sleep mechanisms during wakefulness causing altered states of vigilance [57].

Phenothiazines

Other antipsychotic drugs lower seizure threshold and may precipitate seizures even in people without a history of seizure disorders (TABLE 4). Factors implicated in the occurrence of seizures include high daily dose, rapid titration and concomitant brain pathology.

The risk of seizures differs according to drug class. The aliphatic phenothiazines (e.g., chlorpromazine, promazine and trifluperazine) have the highest epileptogenic potential [58–66]. Logothetis prospectively followed 859 psychiatric patients taking aliphatic phenothiazines for 4 years [58]. Ten of these patients, none of whom had concurrent risk factors for convulsions, developed seizures in a median time of 37.5 days and a median time from upward dose modification of 9.5 days. Seven patients were on high doses of phenothiazines (mainly chlorpromazine), while three patients were taking low to moderate doses. Logothetis also pooled available data on phenothiazine treatment and convulsions from other studies, demonstrating a large variability in seizure incidence during phenothiazine therapy: from 0.3% in patients taking low to moderate doses (maximum: 900 mg/day) to as high as 50% in patients on high doses (maximum: 4000 mg/day). The biochemical basis of the epileptogenic effect of antipsychotics has been attributed to the dopamine-blocking properties of these drugs [67]. The piperazine phenothiazines (acetophenazine, fluphenazine, perphenazine, prochloperazine and trifluoperazine) have a less potent epileptogenic activity. Other antipsychotic agents, including haloperidol, pimozide, thioridazine and risperidone exhibit the lowest epileptogenic effects [68]. Patients with epilepsy are at higher risk of seizures induced by antipsychotic agents. In patients with epilepsy, a drug interaction leading to an enhanced metabolism of the antiepileptic drugs may also be implicated.

Contrast media

Iodinated and noniodinated intravenous contrast media are commonly used to refine the radiological diagnosis in several clinical conditions (TABLE 5). Seizures are a rare complication of iodinated contrast media given for excretory urography [68] but are more common in patients undergoing computed tomography. Three large retrospective surveys found seizures in 0.2–0.5% of cases [69–71]. Seizures occurred within 30 min of contrast infusion. However, the majority of patients seen in these and other reports had a history of seizures or an underlying epileptogenic condition. Seizures have been reported after administration of intravenous contrast media in as many as 15% of patients with brain metastases [69]. Factors possibly correlated to the occurrence of seizures with intravenous contrast include the chemical composition of the contrast agent, iodine concentration, osmolarity, dose and speed of injection [68]. Animal studies showed that seizures can be triggered by iodinated contrast administered by intravenous, intra-arterial, intracerebral and subarachnoid routes. The mechanisms of neurotoxicity are based on alteration of the BBB permeability [69].

Immunosuppressants & immunomodulators

Cyclosporine

Cyclosporine is a routinely used immunosuppressive agent after allogenic bone marrow transplantation due to its efficacy in the prophylaxis of acute graft-versus-host disease (TABLE 6). The treatment consists of a starting daily dose of 15 mg/kg and a maintenance dose of 2–6 mg/kg. The correlation between cyclosporine

Table 6. Cyclosporine.

N (with seizures)	Dose and biological gradient	Temporal sequence	Risk factors for seizures (family and/or personal history of seizures, presence of other epileptogenic conditions)	Study design	Ref.
367 (3)	Not specified	Mean time to seizure: 6 days	Not specified	Retrospective	[72]
630 (3)	Sudden increase in dosage (within therapeutic index)	2–14 days	Not specified	Retrospective	[73]
463 (11)	Not specified	1 week–6 months	None	Retrospective	[74]
231 (24)	5 mg/kg intravenous, starting 2 days prior to transplant, until 6 days following transplant; then 3 mg/kg for the following 2 months, after which drug was gradually tapered	Not specified	Concurrent therapy with corticosteroids; patients with thalassemia and diminished liver function	Retrospective	[75]
182 (5)	5 mg/kg intravenous, starting on day of transplant, cyclosporine serum levels (ng/ml): 103, 170, 320, 351, 384	Median time to seizure: 31 days (range: 22–61)	Concurrent therapy with methylprednisolone	Retrospective	[76]
129 (5)	Serum levels (ng/ml): 216, 245, 274, 382, 597	3–37 days	Concurrent therapy with methylprednisolone	Retrospective	[77]

and seizures was investigated retrospectively in several studies, six of which have been reported here [72–77]. Seizures occurred in 0.5–3.9% of cases over a wide interval (2–180 days), mostly in patients with no risk factors for seizures. The study reporting the higher risk for seizures found plasma cyclosporin levels above the upper limit of 250 mcg/ml in four of the five cases [77]. In another study including 367 children and adults, abnormal EEG findings were detected in 13 out of 21 patients undergoing electrophysiological assessment [72]. A direct neurotoxic potential of cyclosporine was documented by the occurrence of symptoms of acute psychosis and of tremors and by the results of imaging studies, demonstrating typical findings (lesions in the white and/or gray matter of the cerebral hemispheres disappearing upon drug withdrawal) [75–77].

Interferon-α

IFN-α is an established antiviral, antiproliferative and immunomodulatory agent used for the treatment of chronic viral hepatitis and neoplasms of the hematopoietic and lymphatic organs. The average maintenance dose is 3 million international units three-times weekly. Only two studies (carried out in 11,241 and 311 patients) calculated the risk of seizures among exposed individuals. In the largest study only four patients reported seizures (incidence 0.07%) [78]. Seizures occurred with a wide range of doses and intervals and with no correlation with dose. IFN increases the excitability of neural cells, stimulating their spontaneous and evoked electrical activity [79].

Other drugs

The epileptogenic potential of theophylline is well known. Seizures and status epilepticus have been repeatedly reported with theophylline, most often attributable to inadvertent or intentional overdosing [80]. However, some patients may develop seizures with therapeutic or mildly toxic drug concentrations [81]. The exact mechanism of theophylline-induced seizures is unknown, although it may be related to antagonism of adenosine [82]. β-blockers and other antiarrhythmic agents have been reported to precipitate seizures as well, particularly in overdose [83].

Levodopa, insulin, thiazide diuretics, lidocaine, tramadol, lithium, cimetidine, isoniazid, salicylates, chemotherapeutic agents, L-asparaginase and baclofen have been reported to cause seizures on several occasions, mostly in seizure-prone individuals or when given at toxic dosages [80,84,85]. Seizures have also been reported in elderly patients receiving aminoglycosides, metronidazole, quinolones and amantadine. Isoniazide-induced seizures have been reported, mostly in patients with a history of epilepsy [37]. Isoniazide probably provokes seizures by antagonizing pyridoxal phosphate (the active form of pyridoxine), which is involved in GABA biosynthesis [37]. The drugs most commonly reported to be correlated with seizures are listed in TABLE 7 [4,86,87].

Expert commentary

Despite the large number of observations, the heterogeneity of the target populations and the flaws in the study designs prevent firm conclusions on the epileptogenicity of any of the investigated compounds. The majority of the studies were based on case reports and small patient series. The former did not provide data on the number of exposed individuals from which the cases in question were derived. The latter were mostly recruited from referral populations, which might lead to an overestimation of the risk of seizures. This selection bias is greater in retrospective studies but cannot be completely eliminated, even in prospective studies. The small sample size leads

Table 7. Substances reported to cause seizures*.

Drug type	Agent
Psychotropic	
Antidepressant	Fluoxetine••
	Maprotiline•••
	Bupropion ••
	Amitriptyline•••
	Imipramine•••
	Nortriptyline•••
	Desipramine•••
	Doxepin••
	Protriptyline•••
	Monoamine oxidase inhibitors†••
Antipsychotic	Clozapine••••
	Phenothiazines•••
	Haloperidol••
Hypnolic and Tranquilizers	Meprobamate (withdrawal)••
Antiepileptic drugs	
	Phenytoin •
	Carbamazepine•
	Vigabatrin•
	Ethosuximide•
	Gabapentin•
	Benzodiazepines (withdrawal)••••
	Barbiturates (withdrawal)••••
Analgesics & anesthetics	
	Meperidine••••
	Propofol•••
	Lidocaine••
	Etomidate•
	Enflurane•
	Naloxon•
	Iodine contrast media••
Antibacterial	
	Penicillins••••
	Isoniazid•••
	Mefloquine•••

*Modified from Garcia and Allredge (1994).
Epileptogenic potential: high (••••), intermediate (•••), low (••), minimal (•).

Table 7. Substances reported to cause seizures*. (cont.)

Drug type	Agent
	Nalidixic acid••
	Norfloxacine••
	Cyprofloxacine••
Antiviral agents	
	Zidovudine•••
	Acyclovir••
	Gancyclovir••
	Foscarnet ••
Antineoplastic & immunosuppressant agents	
	Cyclosporine••••
	Iphosphamide•••
	Chlorambucil•••
	Busulphan•••
Respiratory agents	
	Theophylline••••
	Phenylpropanolamine•••
Cardiovascular agents	
	β-blockers•
	Mexiletine•
	Alcohol•••
Illicit drugs	
	Cocaine••••
	Amphetamines••••
	Phencyclidine•••
	Heroin••

*Modified from Garcia and Allredge (1994).
Epileptogenic potential: high (••••), intermediate (•••), low (••), minimal (•).

to an imprecise estimate of the risk of seizures, as demonstrated by the wide confidence intervals (where measured). As opposed to prospective studies, large retrospective series of patients can only lead to a rough assessment of the patients with seizures, because the available databases comprise only general and uncontrolled information, and it is virtually impossible to separate cases with and without other risk factors for epilepsy and seizures. Only few reports were found to fulfill most of the criteria for causal relations between drug exposure and occurrence of seizures. With few exceptions, the incidence of seizures among the exposed individuals was only slightly higher than that of the general population. Furthermore, the risk was often necessarily calculated in the absence of accurate 'time-frames' in which the incidence of seizures following the use of a certain drug was analyzed. The resulting seizure incidences were thus timeless, making it difficult to compare the seizure risk between classes of drugs that are usually employed for differing periods of time (e.g., antidepressants vs antibiotics) [88]. The prevalence of epilepsy ranges from less than three to more than 40 cases per 1000 population [89], depending on the nature and socioeconomic status of the populations, the extent of case ascertainment and the study design and methods. In industrialized countries, the incidence of epilepsy ranges from 24 to 53 cases per 100,000 people per year and the cumulative incidence by age 80 is approximately 8% [89]. Seizures are also commonly encountered in people who do not have epilepsy. Factors other

than drugs that can provoke seizures in nonepileptic individuals include organ failure, ischemia/hypoxia, electrolyte and endocrine disturbance and cancer or systemic disease affecting the CNS [90]. The underlying cause may be reversible, although provoked seizures do heighten the risk of later (spontaneous) seizures. In a study carried out in a well-defined population, the age-adjusted incidence rate of symptomatic seizures was approximately 40 per 100,000 person-years [91]. In the absence of control samples (unexposed individuals) it is difficult to know the proportion of patients experiencing spontaneous seizures even in the presence of a seizure precipitant. The possibility of a chance association between seizures and a given drug exposure is more likely, as the time elapsed after drug discontinuation increases. In this context, only compounds where the exposed individuals have a tenfold or greater risk of seizures compared with the general population should be considered epileptogenic. When a drug is a putative cause of seizures, one might expect that the risk of seizures tends to increase with the increasing dosage. However, this was true only for a minority of compounds, and even in these cases a linear relationship could not be detected. The biological plausibility was also weak for the majority of the examined drugs. With the exception of those active principles for which an epileptogenic potential was determined *in vitro* or in the experimental animal, the postulated mechanisms were only conjectural.

In this review, the authors did not include compounds whose epileptogenic potential was supposedly strong but based only on the results of case reports, which did not include all the required elements. Given our fairly selective inclusion criteria, the authors might have left out some drugs, purely due to the lack of evidence-based findings in the published literature. However, absence of evidence does not exclude the epileptogenicity of these compounds, which need to be further explored with properly designed studies.

Even with these limitations, some conclusive remarks can be made in the light of the available evidence. Drugs with high epileptogenic potential include meperidine, sevoflurane, clozapine and cyclosporine. Drugs with intermediate epileptogenic potential include propofol, maprotiline, TCAs and chlorambucil. Drugs with low epileptogenic potential include fluoroquinolones, carbapenems, bupropion and iodinated contrast media. Drugs with minimal or inconclusive epileptogenic potential include IFN-α.

Five-year view

The medical communitys' knowledge on the epileptogenicity of pharmaceutical agents appears to be progressing on different tracks. Experimental data are accumulating on the biochemical mechanisms underlying epileptic discharges; meanwhile observation and reporting of adverse events are leading to the selection of a group of compounds more frequently involved in epileptic manifestations; furthermore, reviews that summarize information from the aforementioned tracks are being constructively criticized, with a better insight on true cause–effect relationships. Hopefully, the convergence of these three tracks will lead to the creation of evidence-based guidelines for the identification and the management of potentially epileptogenic compounds.

Key issues

- The occurrence of seizures following the intake of a wide variety of pharmaceutical agents calls for the investigation of the actual epileptogenicity of these substances. The necessity arises from the serious damage, both immediate and longlasting, that epileptic seizures can cause.
- A causal relationship between drug intake and seizures is not easily demonstrated, as several factors are involved in the occurrence of seizures, among which are the time elapsed between drug exposure and seizure manifestation, amount of drug taken, and other factors potentially increasing the risk of seizures. Many drugs that have been linked to the occurrence of epileptic seizures have not been investigated with studies that take all the aforementioned factors into consideration.
- Conversely, there is sufficient knowledge of the epileptogenicity of certain drugs and of the factors that contribute to the occurrence of seizures when these drugs are administered; more definite operational guidelines could be defined for the use of these substances. For example, it is important to modify doses of antibacterial agents, such as fluorquinolones or carbapenems, according to patient kidney function, since diminished renal clearance increases the risk of seizures. Kidney function must also be monitored in patients taking meperidine, for it is a crucial factor in avoiding the accumulation of normeperidine, a metabolite with neurotoxic properties.
- The pathogenic mechanisms that may lead to epileptic manifestations differ among different drugs and are mostly hypothetical. Among these are antagonism of γ-aminobutyric acid receptors (mainly antibacterial agents), increasing levels of toxic metabolites (e.g., meperidine) and chemical structure of the drug (e.g., maprotiline).
- New studies are needed to investigate the epileptogenicity of drugs that have been associated with the occurrence of seizures, in order to either demonstrate an unequivocal epileptogenic potential or understand the relevant risk factors associated with the use of these substances.

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