Do Psychotropic Drugs Cause Epileptic Seizures? A Review of the Available Evidence

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Contents

Abstract Psychiatric comorbidities in patients with epilepsy are common. A bidirectional relationship has been well described where not only patients with epilepsy have a higher prevalence of psychiatric comorbidities but also patients with primary psychiatric disorders are at an increased risk of developing seizures. The aim of this review is to highlight the complex relationship between epilepsy and common psychiatric disorders and to answer the question whether psychotropic medications are proconvulsant by reviewing the preclinical and clinical literature. The evidence shows that the majority of psychotropic medications are not proconvulsant when used in therapeutic doses with the exception of a subset of medications, mainly bupropion IR and certain antipsychotic drugs such as clozapine. An effective treatment of psychiatric comorbidities in patients with epilepsy must consider not only the potential therapeutic effect of the drug, but also its potential iatrogenic effects on the seizure disorder.

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1 Introduction

Psychiatric comorbidities are common in patients with epilepsy, the most common being anxiety, depressive disorders, and suicidality (Tellez-Zenteno et al. 2007). In population-based studies of patients with active epilepsy the rate of depression has been reported to range between 20 and 55% (Gilliam et al. 2004) and that of anxiety between 12 and 22% (Brandt and Mula 2016). In the pediatric population, ADHD is a very common comorbidity as it has been reported in up to 25% of children with epilepsy (Dunn 2019). The actual prevalence of ADHD in adults with epilepsy is yet to be established; however, since more than half of children with ADHD continue to be symptomatic in adulthood, it is expected to be high as well.

These prevalent psychiatric comorbidities are known to have a significant impact in the quality of life of people with epilepsy. Together with toxicity to antiepileptic drugs (AEDs), comorbid depression and/or anxiety disorders have been found to predict a poor quality of life in patients with treatment-resistant focal epilepsy to a greater extent than seizure frequency (Boylan et al. 2004; Gilliam 2003). If left undiagnosed and untreated, depression and anxiety would limit the ability of our patients to fulfill their life goals, even when seizures are under control. In addition, untreated ADHD can have an impact on the cognitive development and affect school performance in children with epilepsy (Hermann et al. 2008).

The relationship between the onset of these psychiatric comorbidities and epilepsy is complex as in some cases the psychiatric symptoms precede the onset of epilepsy and in others they become evident after the seizures began. A bidirectional relationship between epilepsy and psychiatric disorders has been well-described in the literature where not only people with epilepsy are at an increased risk of developing psychiatric comorbidities, but patients with a primary psychiatric disorders are at increased risk of developing epilepsy (Hesdorffer et al. 2000, 2006, 2012; Josephson et al. 2017). For example, patients with a primary psychotic disorder have an increased risk for seizures up to sixfold higher than the general population (Chang et al. 2011; Adelöw et al. 2012). Several population-based studies indicate that depression may be associated with a three to sevenfold increased risk of seizures irrespective of the use of antidepressants with the risk being higher in patients with suicidality (Davidson 1989; Forsgren and Nyström 1990; Hesdorffer et al. 2000, 2006). To establish whether antidepressant and antipsychotic drugs increase the risk of seizures, Alper et al. compared the incidence of seizures between patients randomly assigned to a psychotropic drug and placebo in phase II and III, multicenter-randomized placebo-controlled trials submitted to the United States Food and Drug Administration (FDA) for regulatory purposes between 1985 and 2004 (Alper et al. 2007). The authors found that the rate of seizures in patients

treated with placebo in clinical trials for antidepressants was 19 times higher compared to that of the general population, supporting the existence of an association between primary depression and the development of seizures and epilepsy.

A bidirectional relationship between primary psychiatric disorders and epilepsy was also found for ADHD, where population-based studies showed that children with ADHD have a 2–2.5 higher risk for developing seizures (Wiggs et al. 2018; Hesdorffer et al. 2004).

The co-occurrence of seizures in patients with primary psychiatric disorders raises the question whether psychotropic medications may be proconvulsant. This concern has been one of the main reasons why psychiatric comorbidities in epilepsy are often left untreated. Is this concern based on real evidence or could it be that seizures may occur as an expression of the natural course of the psychiatric disease? A review of preclinical and clinical data will aim to answer this question.

2 Antidepressants

2.1 Experimental/Pre-clinical Data

There is good preclinical data showing that antidepressant drugs of the selective serotonin reuptake inhibitor (SSRI) family do not only lack proconvulsant effects at therapeutic doses but may also have protective properties against seizures. In several animal models of epilepsy, the administration of SSRIs such as sertraline (Yan et al. 1994, 1995) or fluoxetine (Prendiville and Gale 1993) has shown anticonvulsant effects. For example, experiments with a generalized epilepsy model-genetically epilepsy-prone rats (GEPRs) in which certain acoustic stimuli induces generalized tonic-clonic seizures showed that incremental increases in serotonin levels with the SSRI sertraline or fluoxetine resulted in a dose-dependent seizure frequency reduction. This anticonvulsant effect correlated with increased extracellular thalamic concentration of serotonin (Yan et al. 1995). A dose-dependent protective effect on seizures of the SSRI fluoxetine was seen in other epilepsy models including a focal limbic seizure model in rats (Prendiville and Gale 1993) and in the maximal electroshock stimulation model (Buterbaugh 1978).

Studies with serotonin receptor agonists confirmed the role of serotonin in seizure generation. Lopez-Meraz et al. studied the effect of two serotoninergic receptor agonists (8-OH-DPAT and indorenate) in three epilepsy models (clonic-tonic convulsions induced by pentylenetetrazol (PTZ), status epilepticus (SE) of limbic seizures produced by kainic acid (KA), and tonic-clonic seizures by amygdala kindling (López-Meraz et al. 2005). 8-OH-DPAT not only reduced the tonic seizures induced by PTZ but also decreased the mortality rate. Indorenate increased the latency and reduced the severity of the PTZ-induced seizures and also decreased mortality. Both serotonin receptor agonists increased the latency and reduced the frequency of seizures in the KA model. Both agents delayed the establishment of status epilepticus in this seizure model. 8-OH-DPAT and Indorenate did not alter the

expression of kindled seizures. Furthermore, mutant mice lacking serotonin 5-HT 2c receptors are extremely susceptible to audiogenic seizures (Brennan et al. 1997).

Experiments using microdialysis techniques have revealed that increased extracellular serotonin concentration may enhance anticonvulsant properties of antiepileptic drugs (Hamid and Kanner 2013). For example, Yan et al. showed that the addition of serotonin depleting drugs decreases the anticonvulsant effectiveness of carbamazepine in genetically epilepsy-prone rats (Yan et al. 1992).

Similarly Clinckers et al. (2005) showed that the anticonvulsant effect of oxcarbazepine and its metabolite was accompanied by significant increases in dopamine and serotonin levels in the hippocampus (Clinckers et al. 2005).

2.2 Human Data

Proconvulsant effects of antidepressant drugs have been reported in the literature mostly from overdoses of tricyclic antidepressants (Lipper et al. 1994; Baselt 1982). Seizures have also been observed in patients undergoing treatment for depression with therapeutic doses of certain tricyclic antidepressants (TCA), such as clomipramine, maprotiline, and monoamine oxidase inhibitors and bupropion) (Pisani et al. 2002; Trimble 1978) (Davidson 1989; Pesola and Avasarala 2002; Preskorn and Fast 1992; Rosenstein et al. 1993) (Table 1). Yet, given the bidirectional relation between depression and anxiety disorders and epilepsy, the actual proconvulsant risk of antidepressant drugs can only be objectively established by comparing the seizure incidence following their exposure to that of placebo. As indicated above, Alper et al. studied the incidence of seizures in the course of multicenter-randomized, placebo-controlled trials of SSRIs and SNRIs for the treatment of primary major depressive disorder and obsessive-compulsive disorder (Alper et al. 2007). The authors found that the incidence of seizures was much lower among patients who received antidepressants than among those receiving placebo (standardized incidence ratio = 0.48; 95% CI 0.36–0.61) strengthening the experimental data suggesting these drugs may have anticonvulsant effects. On the other hand, the incidence of seizures was higher in subjects randomized to bupropion (in its immediate-release formulation) and clomipramine than placebo.

Small open-label studies in epilepsy patients, with and without depression, have suggested a clinically significant anticonvulsant effect of the SSRI's citalopram (Favale et al. 2003; Specchio et al. 2004) and fluoxetine (Favale et al. 1995). In an open, multicentered, uncontrolled study conducted in Italy, 42 patients with epilepsy received 20 mg of citalopram for 4 months for the treatment of depression. A significant improvement in their depressive symptoms and a reduction in seizure frequency were observed (Specchio et al. 2004). In another study, 17 patients with focal epilepsy were given fluoxetine. Their seizure frequency was assessed (mean follow-up 14 months +/− 1 month). Six patients became seizure free and in the others the seizure frequency was reduced by 30% (Favale et al. 1995). Ribot et al. conducted a retrospective observational study of 100 consecutive patients with

Table 1 Psychotropic drugs and its effects on seizures

Indication category	Group	Drug name	Seizure risk
Antidepressant	TCA	Clomipramine Imipramine	Low (high with overdose)
	Aminoketone	Bupropion	Moderate (IR formulation)
	SSRI	Sertraline Fluoxetine Citalopram, Escitalopram Paroxetine	Low (potentially anti-convulsant effects)
	SNRI	Venlafaxine Duloxetine	Low
	NaSSA	Mirtazapine	Low
ADHD medication	Stimulants	Methylphenidate Amphetamines	Low (potential anticonvulsant effect)
	Non-stimulant	Atomoxetine	Low
Antipsychotic	1st generation (typical): Phenothiazines	Chlorpromazine Thioridazine	Moderate
	1st generation (typical): Phenothiazines	Fluphenazine Perphenazine	Low
	1st generation (typical): Butyrophenones	Haloperidol	Low
	2nd generation	Clozapine	Moderate to high
		Olanzapine Quetiapine	Low to moderate
		Ziprasidone, Aripiprazole and Risperidone	Low

TCA tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin-norepinephrine reuptake inhibitor, *NaSSA* noradrenergic and specific serotoninergic antidepressant, *ADHD* attention deficit hyperactivity disorder

epilepsy who were started on an SSRI or an SNRI for the treatment of depressive and or anxiety disorder (Ribot et al. 2017). The authors found that overall SSRIs or SNRIs did not worsen seizure frequency and there was a positive effect with seizure reduction in patients with >1 seizure/month (48% had >50% reduction in seizure frequency). A small ($N = 10$) double-blind crossover study of the tricyclic antidepressant imipramine showed a significant decrease in absence and myoclonic seizures (Fromm et al. 1978).

PET studies suggest that the serotonin system is affected in patients with epilepsy. Studies in patients with temporal lobe epilepsy have shown reduced serotonin (5HT1) receptor binding ipsilateral to the seizure onset zone (Toczek et al. 2003; Savic et al. 2004; Merlet et al. 2004; Theodore et al. 2006; Hasler et al. 2007) and in

one study with juvenile myoclonic epilepsy (JME) patients, reduced serotonin receptor binding was seen in different brain regions (Meschaks et al. 2005).

3 Central Nervous System (CNS) Stimulants

3.1 Experimental/Pre-clinical Data

The literature of preclinical studies on a proconvulsant effect of amphetamines shows contradictory results. In some epilepsy models, amphetamines can decrease the seizure risk, while in other it shows proconvulsant effects (Yehuda and Carasso 1977; King and Burnham 1980; Ellinwood Jr. et al. 1973; Greer and Alpern 1980). For example, in a study using a rat model of absence epilepsy, a dose-response suppression of flash evoked after discharges (FAED) was seen with d-amphetamine (King and Burnham 1980). In another experimental study, methylphenidate showed weak evidence of seizure promoting effects, by slightly increasing the duration of seizures in kindled rats (Babington and Wedeking 1973). At therapeutic doses, atomoxetine was not associated with an increased risk of seizures. In animal models, however, atomoxetine was proconvulsant only at very high doses (Torres et al. 2008).

The therapeutic effects of CNS stimulants and atomoxetine are mediated by dopaminergic and adrenergic effects in the brain. Clinckers et al. investigated the effects of extracellular dopamine on the seizure propensity in rats. In a microdialysis study, dopamine perfused into the hippocampus, protected freely moving rats from seizures induced by pilocarpine. This effect was only seen within a certain concentration range (between 70 and 400% relative to baseline levels). On the other hand, high extracellular dopamine (>1,000% of baseline) concentrations worsened the seizure frequency, mediated by increases of extracellular glutamate and monoamines (Clinckers et al. 2004). These studies suggest a possible explanation for the anticonvulsant effect seen with CNS stimulants and atomoxetine at certain doses and the proconvulsant effect seen mostly with overdoses.

3.2 Human Data

There is a long-held belief that the therapeutic use of stimulants is associated with seizures. This misconception is further perpetuated by the information included in the package insert of most CNS stimulants. The increased risk for seizures in patients treated with CNS stimulants likely reflects the natural course of ADHD. In fact, several population-based studies have shown that children with ADHD have an increased risk for seizures independently of the treatment. For example, a population-based study from Iceland demonstrated that children with ADHD of the inattentive type have a 2.5 higher risk of developing seizures and epilepsy

compared to controls (Hesdorffer et al. 2004). In another study, non-epileptic children with ADHD were found to have a significantly higher frequency of Rolandic spikes in their EEG compared to a historical control of normal school-aged children (Holtmann et al. 2003).

Several case report studies have shown that the treatment of ADHD in patients with epilepsy, in particular with methylphenidate is effective and is not associated with an increase in seizures (Torres et al. 2008) (Table 1). In two separate small prospective studies of children with well-controlled epilepsy and ADHD, methylphenidate was found to be effective and there was no evidence for recurrence of their seizures (Gross-Tsur et al. 1997; Feldman et al. 1989). A study with children with active epilepsy and ADHD found no change in their baseline seizure frequency after adding methylphenidate and there were improvements seen in the EEG (Gucuyener et al. 2003). Wroblewski et al. found no worsening of seizures after adding methylphenidate to patients with post-traumatic epilepsy (Wroblewski et al. 1992).

More recent larger studies reaffirmed that children with ADHD are at increased risk for seizures and that CNS stimulants are not only safe but may be associated with a protective effect against seizures. A Swedish population-based study found that patients with epilepsy (N = 995) had a lower rate of seizures when they initiated treatment with CNS stimulants compared to periods without ADHD treatment (Brikell et al. 2019). Another large population-based study of ADHD patients, with and without a history of seizures, confirmed that patients with ADHD were at higher risk for any seizure compared with non-ADHD controls. In addition treatment with ADHD medication was associated with lower risk of seizures in individuals with and without a prior history of seizures (Wiggs et al. 2018).

The incidence of seizures during randomized placebo-controlled trials of atomoxetine, a commonly used noradrenergic non-stimulant drug to treat ADHD, was found to range between 0.1% and 0.2%, which was not significantly different compared to the rate of seizures in subjects randomized to placebo or methylphenidate (Wernicke et al. 2007). Atomoxetine was only studied in one prospective open-label study in patients with epilepsy (Hernandez 2005). The authors found the drug to be effective for treating ADHD and only one out of 17 patients showed worsening of seizures in the first 2 weeks of treatment.

4 Antipsychotic Drugs

4.1 Experimental/Pre-clinical Data

Clozapine has been shown to cause seizures in animal seizure models in a dose-dependent manner (Citraro et al. 2015; Minabe et al. 1998). Rats receiving repeated administrations of a fixed low dose of clozapine showed a progressive increase of brain excitability consistent with a kindling effect (Stevens et al. 1996). In an animal model of hippocampal seizures, clozapine had a greater proconvulsant action than haloperidol (Minabe et al. 1998). The same group studied the effect of six

antipsychotic drugs on seizure susceptibility in a different seizure model (genetically epilepsy-prone rats). They found that clozapine had the most proconvulsant effect followed by olanzapine and risperidone. Quetiapine showed modest proconvulsant properties and haloperidol had only a mild proconvulsant effect. In this model the investigators found that aripiprazole had anticonvulsant properties (Citraro et al. 2015) and it was found to be effective at reducing the duration and frequency of seizures in a rat model of absence epilepsy (Russo et al. 2013).

4.2 Human Data

There is evidence of proconvulsant effects in a subset of antipsychotic drugs, which has often led to some clinicians' hesitance to use these drugs in patients with epilepsy for fear of worsening seizures.

First generation antipsychotic drugs with lower potency of dopamine D_2 neuroreceptor blockade including chlorpromazine and thioridazine have been associated with an increased risk for seizures in a dose-dependent manner (Muench and Hamer 2010). On the other hand, other commonly used older antipsychotic drugs including haloperidol, perphenazine, fluphenazine, and molindone have been found to have the lowest incidence of seizures (Kanner 2016).

The occurrence of seizures with atypical antipsychotic drugs is mostly described with clozapine (Devinsky et al. 1991; Landry 2001; Littrell et al. 1995; Pacia and Devinsky 1994; Varma et al. 2011). The clozapine-related seizures can occur in patients without risk factors for epilepsy and tend to occur during the titration period and at high doses (>600 mg/day). Patients with epilepsy can have an exacerbation of their seizures at low doses (Pacia and Devinsky 1994). Based on these concerns the FDA issued a black box warning regarding the risk seizures with clozapine. Alper et al. found that (non-epileptic) patients receiving clozapine in clinical trials had an increased incidence of seizures compared to patients receiving placebo. This study also found a higher incidence of seizures with the second-generation antipsychotic drugs olanzapine and quetiapine, but to a lesser degree than clozapine. The incidence of seizures in patients randomized to other atypical antipsychotic drugs including ziprasidone, aripiprazole, and risperidone was comparable to that of patients randomized to placebo (Alper et al. 2007).

Information about the seizure risk with the newer atypical antipsychotics including asenapine (Saphris), iloperidone (Fanapt), and lurasidone (Latuda) is lacking.

EEG changes have been reported with a higher prevalence than seizures in approximately 7% patients taking antipsychotic drugs (Koch-Stoecker 2002). Most common EEG changes reported are diffuse slowing but some of these drugs, particularly clozapine, can cause interictal sharp waves and spikes (Kanner and Rivas-Grajales 2016).

As reviewed in this section the risk for seizures in not equal among all antipsychotic drugs (Table 1). In addition to the type of medication, the presence of any of following factors can increase the risk: (1) a history of epilepsy, (2) abnormal EEG

recordings, (3) history of CNS disorder, (4) rapid titration of the antipsychotic dose, (5) high doses of antipsychotic drug, and (6) the presence of other drugs that lower the seizure threshold (Kanner and Rivas-Grajales 2016).

5 Conclusion

Although there is a widespread belief that all psychotropic drugs cause seizures, the evidence for it is lacking. With the exception of a subset of medications, mainly bupropion IR and certain antipsychotic drugs such as clozapine, the evidence shows that the majority of psychotropic medications are not proconvulsant when used in therapeutic doses (Table 1). A bidirectional relationship between epilepsy and certain psychiatric comorbidities has been demonstrated and backed by experimental studies (Kanner 2011). The more robust literature exists for depressive disorders where population studies show that people with epilepsy are at higher risk of developing a depressive disorder and patients with major depression have up to a twofold to sixfold increased risk for unprovoked seizures (Hesdorffer et al. 2000, 2006).

Treating psychiatric comorbidities of people with epilepsy improves the patient's quality of life and leads to better seizure outcomes. As access to psychiatrist can be limited in certain parts of the USA, neurologists need to become familiar with the use of psychotropic drugs. The goals of treatment in epilepsy should not only be "no seizures and no side effects," but rather freedom of seizures without psychiatric comorbidities and no side effects.

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