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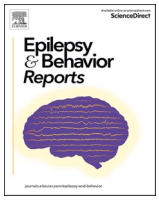

Do psychotropic drugs cause seizures?

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ABSTRACT

Patients with epilepsy often present with concurrent psychiatric disorders, posing unique challenges for healthcare providers. This review explores the intricate relationship between psychiatric comorbidities, epilepsy, and psychotropic medications to inform clinical decision-making. The bidirectional association between epilepsy and psychiatric conditions complicates treatment, with psychiatric symptoms preceding or following seizure onset. The review discusses the seizure risks associated with antidepressants, CNS stimulants, and antipsychotics, shedding light on both historical perspectives and recent empirical evidence. Antidepressants, particularly tricyclic antidepressants (TCAs), are known to pose seizure risks, while newer agents like selective serotonin reuptake inhibitors (SSRIs) exhibit lower incidences and even potential anticonvulsant effects. Contrary to common beliefs, CNS stimulants used in attention-deficit/hyperactivity disorder (ADHD) treatment show efficacy without significantly increasing seizure risk. However, the association between ADHD and seizures warrants careful consideration. Among antipsychotics, clozapine stands out for its heightened seizure risks, especially during titration and at high doses, necessitating close monitoring and individualized approaches. Understanding the nuanced seizure risks associated with different psychotropic medications is crucial for optimizing patient care and minimizing iatrogenic seizures in this vulnerable population. By recognizing the complexities of psychiatric comorbidities in epilepsy and considering the unique challenges they pose, healthcare providers can make informed decisions to enhance patient safety and treatment outcomes. This review offers practical insights to guide clinicians in navigating the intricate landscape of managing psychiatric comorbidities in patients with epilepsy.

Introduction

Patients with epilepsy (PWE) often have concurrent psychiatric disorders, such as depression (20–55 %) [1], anxiety (12–22 %) [2], and suicidality (25 %) [3], which may require treatment with psychotropic medications [4,5]. Comorbidity in PWE and attention-deficit/hyperactivity disorder (ADHD) is also common, with a prevalence that varies from 12 to 39 % in patients with newly diagnosed epilepsy, 70 % in patients with drug-resistant epilepsy [6], and 25 % for children with epilepsy (CWE) [7,8]. It has been widely reported in the pediatric epilepsy literature that CWEs exhibit higher levels of behavioral and psychiatric disorders compared to matched control groups [9].

There is an intricate connection between psychiatric comorbidities and epilepsy, whereby psychiatric symptoms can precede or follow seizure onset. Literature extensively establishes a bidirectional relationship whereby epilepsy increases the risk of psychiatric disorders and vice versa [10–12]. Similarly, studies in childhood ADHD have confirmed a bidirectional relationship between primary psychiatric disorders and epilepsy, whereby children with ADHD were more susceptible to developing seizures [13–16].

The bidirectional relationship between epilepsy and psychiatric disorders is increasingly recognized. Research suggests that a history of psychiatric conditions before the onset of seizures may elevate the risk of developing epilepsy and experiencing uncontrolled seizures [10,12,50,51]. Therefore, this relational relationship could lead to the misinterpretation of seizure occurrence, attributing it to psychotropic drugs rather than the natural progression of the primary psychiatric disorder. This trend is observed across various conditions, including major depressive disorder (MDD), bipolar disorder (BIP), schizophrenia (SCZ), and autism spectrum disorder (ASD) [12,52]. Therefore, it is essential to recognize psychiatric comorbidities [21] not only as complications of epilepsy but also as significant factors that may potentially lower the seizure threshold.

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Psychiatric comorbidities and seizure Risk: Bidirectional insights (Hesdorfer et al.'s) [33]

- Depression: Significant hazard ratio increases for seizures in depression.
- Suicidality: Elevated seizure risk associated with suicidality.
- Anxiety Disorders: Statistical evidence of heightened seizure risk in anxiety disorders.
- ADHD: Empirical support for increased hazard ratio in ADHD.
- Psychosis: Complex bidirectional relationship with an augmented hazard ratio.

Hesdorfer et al.'s data-driven insights emphasize the intricate link between psychiatric comorbidities and seizure risk [33]. These findings underscore the need for tailored interventions and heightened clinical awareness in managing individuals with diverse psychiatric challenges.

Studies have established that comorbid psychiatric disorders have a negative impact on the quality of life (QOL) of PWE, and subsequently, the use of psychotropic medications is often necessary for PWE [17,19]. However, the co-occurrence of seizures in patients with primary psychiatric disorders raises the question of whether psychotropic medications may be epileptogenic agents. There has been substantial debate and safety apprehensions regarding psychotropic drugs and the ensuing undertreatment of psychiatric comorbidities in PWE [17–19]. Among the medications that have raised questions regarding their association with seizures are Wellbutrin (immediate release), clozapine, and tramadol. Understanding the seizure risk, clinical indications, and regulatory considerations associated with these medications is critical for healthcare practitioners to ensure patient safety and optimal therapeutic outcomes.

Pragmatic review: psychotropic drugs and iatrogenic seizures

This review synthesizes empirical evidence and clinical insights to investigate the risk of iatrogenic seizures associated with various classes of psychotropic drugs, mainly antidepressants, CNS stimulants, and antipsychotics. Of note, before considering the risk of iatrogenic seizures, clinicians should be reminded that the point prevalence of epilepsy across populations ranges from 5 to 8 per 1000 people (0.5–0.8 % of the population. Therefore, a relative risk ratio of seizure incidence should include the baseline risk of seizures/epilepsy in the population [53]. Aimed at healthcare practitioners, this review offers practical insights for informed decision-making in patient management (Table 1).

Table 1
Psychotropic drugs and its effects on seizures.

Psychotropic Class	Safest Drugs	Drugs: Worse Seizure Risk	Drugs: High Risk
Antidepressant	SSRIs (e.g., Sertraline, Fluoxetine)		Bupropion (IR formulation) TCAs (e.g., Clomipramine): Higher incidence of seizures at clomipramine doses greater than 300 mg/day (2.1 %) than with doses less than 250 mg/day (0.48 %)
CNS Stimulants	Atomoxetine (non-stimulant)	Amphetamines	Methylphenidate (Stimulants)
Antipsychotic (2nd generation)	Aripiprazole (low risk)	Olanzapine (Low to Moderate Risk)	Clozapine (consider long-lasting formulation for reduced risk)
	Ziprasidone (low risk)	Quetiapine (Low to Moderate Risk)	−Very rapid titration and the use of high doses of clozapine are the triggers of the occurrence of seizures which increase by 0.7 % for each 100 mg of the drug. −Up to 300 mg/day, the risk of seizures is comparable to other antipsychotic drugs.
	Risperidone (low risk)	Lurasidone (low to moderate)	−Between 600 and 900 mg/day, this risk reaches 5 %
First-Generation Antipsychotics (1st generation)		Haloperidol (low risk)	Chlorpromazine: Logothetis et al. observed [64]:
		Fluphenazine (low risk)	−High dosages of antipsychotic drugs and the timing of dose initiation or escalation.
		Perphenazine (low risk)	−9% of patients treated with high doses (1,000 mg/day chlorpromazine equivalent) −0.7 % of patients with moderate doses −0.3 % of patients with low doses (200 mg/day chlorpromazine equivalent)

TCA tricyclic antidepressant, *SSRI* selective serotonin reuptake inhibit or, *CNS* central nervous system.

Antidepressants

Proconvulsant Effects of Antidepressant Overdoses: Seizures are primarily associated with tricyclic antidepressant (TCA) overdoses, as documented by Lipper et al. [22] and Baselt [23].

Seizures with Therapeutic Doses of TCAs and Other Antidepressants: Therapeutic doses of TCAs, including clomipramine, maprotiline, monoamine oxidase inhibitors, and bupropion, have been linked to seizures in depressed patients [23–29]. The risk of seizures with TCA at effective therapeutic doses is relatively high (0.4 % to 1–2 %) [30].

Experimental Data on Antidepressant Seizure Risks (Alper et al.): Multicenter-randomized, placebo-controlled trials on SSRIs and SNRIs for major depressive disorder and obsessive–compulsive disorder revealed a lower seizure incidence with antidepressants compared to placebo (Standardized Incidence Ratio (SIR) = 0.48; 95 % CI, 0.36-0.61) [31]. However, seizure incidence increased with bupropion IR relative to placebo (SIR = 1.58; 95 % CI, 1.03–2.32) and Clomipramine (SIR = 4.08; 95 % CI, 2.64–6.02), highlighting the nuanced relationship. Across studies, the risk estimates vary depending on the study, data source, and patient population, whether predisposed vs. nonpredisposed [50]. Newer antidepressants, including SSRIs, bupropion, and mirtazapine, are generally associated with a low risk of seizures (0.0 %–0.4 %), similar to the incidence of first seizures in the general population (0.07 %–0.09 %) [58]. Additionally, among PWE with a baseline seizure frequency ≥ 1 seizure/month, 48 % exhibited a > 50 % reduction in seizure frequency after starting treatment with SSRIs or SNRIs [32].

Antidepressants and Anticonvulsant Effects: Alper et al.'s study suggests potential anticonvulsant effects of antidepressants, demonstrating a significantly lower incidence of seizures compared to placebo (standardized incidence ratio = 0.48; 95 % CI 0.36–0.61) [31]. Furthermore, SSRIs have demonstrated safety in open trials involving people with epilepsy (PWE), with some studies suggesting a potential reduction in seizure frequency [43]. Notably, sertraline was observed to worsen seizures in only 1 out of 100 consecutive patients with pharmacoresistant epilepsy [44]. These findings underscore the complex interplay between antidepressants and seizure susceptibility [31].

Bidirectional Relation Between Depression, Anxiety Disorders, and Epilepsy: A comprehensive assessment of the bidirectional relationship

underscores the importance of accurately comparing seizure incidence with antidepressants to that of placebo. This nuanced evaluation becomes imperative, especially in the context of comorbid mental health conditions.

Specific Antidepressants and Seizure Incidence: Bupropion (immediate-release formulation) and clomipramine were associated with a higher seizure incidence than placebo, shedding light on specific drugs that may warrant closer monitoring.

Statistics: The standardized incidence ratio with antidepressants was 0.48 (95 % CI 0.36–0.61), indicating a significantly lower seizure incidence compared to placebo [31].

Central nervous system (CNS) stimulants

There is a pervasive belief regarding the association between stimulant use and seizures, perpetuated by CNS stimulant package inserts. However, emerging evidence challenges this notion, suggesting that the increased seizure risk in CNS stimulant-treated patients may align with the natural course of ADHD [33].

Population Studies on ADHD and Seizures (Hesdorffer et al.; Holtmann et al.): Several population-based studies indicate that children with ADHD, regardless of treatment, have an elevated risk of seizures. An Icelandic study found a 2.5-fold higher risk of seizures and epilepsy in children with inattentive-type ADHD (95 % CI, 1.1–5.5). EEG analysis in non-epileptic ADHD children revealed a significantly higher frequency of Rolandic spikes [33,34].

Case Reports on ADHD and Epilepsy Treatment (Torres et al.; Gross-Tsur et al.; Koneski et al.): Case reports and small prospective studies on ADHD in epilepsy patients, particularly with methylphenidate, demonstrate treatment efficacy without increased seizure risk. Studies on well-controlled epilepsy cases using methylphenidate show effectiveness and no evidence of seizure recurrence [35,36]. A Brazilian sample (n = 24) study found an overall improvement in ADHD symptoms in 70.8 % of patients, and there was no increase in the frequency of epileptic seizures in 22 patients (91.6 %). Conversely, Mann et al. found that among 269 individuals with incident seizures, there was a significantly increased risk of recurrent seizures during the first 30 days of methylphenidate treatment (IRR 5.00, 95 % CI 1.09–22.96). However, the overall risk during methylphenidate treatment remained low (incidence of 4.4 per 10,000 patient-years) [37].

Large Studies on ADHD, Seizures, and CNS Stimulants (Brikell et al.; Wiggs et al.): Also, recent larger studies challenge the perceived risk associated with ADHD and CNS stimulant therapy. A Swedish population-based study revealed a lower seizure rate in epilepsy patients initiating CNS stimulant treatment. It was noted that the ADHD medication periods were associated with a reduced rate of acute seizures (hazard ratio [HR] 0.73, 95 % CI 0.57–0.94) compared to non-medication periods within the same individuals. Likewise, ADHD medication was associated with lower odds of seizures among patients with (OR = 0.71, 95 % CI = 0.60–0.85) and without (OR = 0.71, 95 % CI = 0.62–0.82) prior seizures [38]. Another large study (n = 801, 838) confirmed a higher seizure risk in ADHD patients but noted a lower risk with ADHD medication (OR = 0.71, 95 % CI = 0.60–0.85), suggesting a potential protective effect [15].

Atomoxetine Trials and Seizure Incidence (Wernicke et al.; Hernandez): In randomized placebo-controlled trials, atomoxetine, a non-stimulant ADHD medication, demonstrated a low incidence of seizures comparable to placebo or methylphenidate [39]. The comprehensive atomoxetine database, including controlled and uncontrolled trials (n = 5,083 pediatric patients, n = 748 adult patients), revealed 13 individuals (n = 12 pediatric, n = 1 adult) with at least one seizure event. This resulted in a crude incidence of 0.2 % (n = 12 events among 5,083 pediatric patients) or 2.3 per 1000 patient-years for pediatric patients and 0.1 % (n = 1 event among 748 adult patients) or 1.7 per 1000 patient-years for adults [73]. Additionally, a prospective open-label study in epilepsy patients (n = 17) demonstrated atomoxetine's efficacy for ADHD treatment, with minimal seizure worsening observed in only one patient during the initial two weeks [40].

Amphetamine-associated seizures in PWE (Brown et al) [56]: The incidence of amphetamine-associated seizures (AAS) remains uncertain, with studies suggesting their rarity. For example, out of 49 cases of recreational drug-induced seizures, only 11 were attributed to amphetamine usage, indicating that amphetamines may contribute to around 22 % of such cases [53]. Over an 8-year period, only 44 cases of AAS were identified, suggesting they constitute a small proportion of overall seizures. Studies examining patients with new-onset seizures have reported amphetamine use in approximately 3.9 % of cases, a figure similar to controls without seizures [54]. However, documentation of amphetamine use within 24 h of seizures was often lacking. Overall, AAS appears to have a lower recurrence rate compared to seizures provoked by other factors, based on data from studies such as that by Hesdorffer et al. [55].

Statistics: Standardized incidence ratio with antidepressants: 0.48 (95 % CI 0.36–0.61) – lower seizure incidence compared to placebo [31]. Incidence of seizures during randomized placebo-controlled trials of atomoxetine: 0.1 % to 0.2 %, not significantly different from placebo or methylphenidate [39].

Antipsychotic drugs

First-Generation Antipsychotics: First-generation antipsychotics present a more complex pharmacodynamic picture. Agents like chlorpromazine and thioridazine, characterized by lower dopamine D2 neuroreceptor blockade potency, demonstrate a dose-dependent escalation in seizure risk (Table 2) [41,46,49]. In a study spanning over four years, Logothetis et al. observed that 1.2 % of patients treated with phenothiazines experienced seizures, compared to none among those receiving other treatments. 106 The study identified two key factors contributing to the likelihood of seizures: high dosages of antipsychotic drugs and the timing of dose initiation or escalation. Specifically, seizures occurred 9 % of patients treated with high doses (1,000 mg/day chlorpromazine equivalent); 0.7 % of patients with moderate doses and 0.3 % of patients with low doses (200 mg/day chlorpromazine) equivalent) [64]. Also, first-generation antipsychotic medications such as haloperidol, perphenazine, fluphenazine, and molindone are recognized for their low proconvulsant properties. [4].

Atypical Antipsychotics: The atypical antipsychotic domain introduces nuance, with notable variations in seizure risk among specific drugs. Clozapine (Table 2) [47–49], notorious for its association with seizures, particularly during titration and at high doses, prompts a black box warning from the FDA [15,36–39]. A recent 2023 study utilizing the Japanese Adverse Drug Event Report (JADER) database investigated trends in clozapine-induced seizures [86]. The analysis (n = 1,784) revealed that medium (200–400 mg) and high (>400 mg) clozapine doses had significantly higher reporting rates of seizures compared to low doses (<200 mg), (adjusted reporting odds ratio [aROR] = 3.05, 95

Table 2
From Effects of Psychotropic Drugs on Seizure Threshold: Seizure incidence with antipsychotics [24].

Antipsychotic Drug	Seizure Incidence (%)	Patient Population	Drug Does (mg/day)	Reference
Chlorpromazine	0.50	859[b]	<1000	79
	9.00	859[b]	>1000	79
Clozapine	1.00	1418	<300	80
	4.40	1418	>600	80
	1.30	5629	Wide range	81

[a] Incidence of the first unprovoked seizure in the general population = 0.07 to 0.09 % [90].
[b] Patients were receiving phenothiazine compounds, mostly chlorpromazine.
Seizure incidence with antipsychotics[a] as reported by some of the largest/most representative studies.

% confidence interval [CI]: 1.86–4.99 and aROR = 9.81, 95 % CI: 6.06–15.89, respectively) 86. Also, additional associations were found for younger age, antipsychotic polypharmacy, and concomitant use of lithium [45]. The time-to-onset analysis indicated a median time of 134 days, emphasizing the dose-dependent nature of clozapine-induced seizures, warranting monitoring, especially considering age and concomitant medications [45]. On the other hand, second-generation antipsychotics, including olanzapine, quetiapine, ziprasidone, aripiprazole, and risperidone, exhibit seizure incidence comparable to placebo, albeit with some differences [31].

In a systematic review on mortality and serious adverse events with antipsychotics, including all randomized controlled trials comparing second-generation antipsychotics with placebo, the absolute seizure frequencies on the drug ranged from 0 % to 0.15 %, with olanzapine at 11.8 per 1000 person-years (py) [4]. No strong evidence for increased or decreased risk was found for any specific antipsychotic, as all relative risks (RRs) had wide 95 % confidence intervals (CIs) encompassing the possibility of no difference. The analysis showed no significant differences between antipsychotics (test for subgroup differences: $p = 1.00$). While the point estimates for quetiapine (4 vs. 1 event) and brexpiprazole (2 vs. 1) suggested an increased risk, these were very uncertain [4]. Newer atypical antipsychotics like asenapine, iloperidone, and lurasidone lack sufficient data to determine seizure risk.

Electroencephalogram (EEG) Changes: Beyond overt seizures, approximately 7 % of individuals undergoing antipsychotic treatment experience non-specific EEG changes, with diffuse slowing being the prevalent alteration [40]. Notably, certain drugs, especially clozapine, may induce interictal sharp waves and spikes, warranting vigilance in clinical monitoring [42].

Contributing Factors to Seizure Risk: Several factors intersect to influence the overall risk of seizures. A history of epilepsy, abnormal EEG recordings, pre-existing CNS disorders, rapid titration of antipsychotic doses, administration of high drug doses, and concurrent usage of seizure-threshold lowering drugs collectively contribute to an augmented risk [42]. For the two most high-risk anti-psychotic drugs (chlorpromazine and clozapine), there is clearly a strong correlation between dose and seizure risk (Table 2).

Insights: Second-generation antipsychotics, including olanzapine and quetiapine, demonstrated a heightened seizure incidence, albeit less than clozapine [31]. Contrastingly, ziprasidone, aripiprazole, and risperidone demonstrated seizure incidence akin to placebo [31].

Practical tips

Individualized Treatment: Our clinical practice is to reserve the use of antipsychotic medications for psychosis and mood stabilization for patients with mania. Prevention of clozapine-induced seizures involves both primary and secondary approaches, aimed at reducing the risk of seizure occurrence and managing seizures if they occur.

Primary prevention [57–59]

- Screen for risk factors predisposing to seizures.
- Titrate clozapine dose slowly and gradually.
- Avoid concomitant use of drugs that lower the seizure threshold.
- Avoid concomitant use of drug inhibitors of CYP enzymes that metabolize clozapine (1A2, 2D6, and 3A4), such as cimetidine, caffeine, ciprofloxacin, erythromycin, citalopram, and fluvoxamine.
- Educate the patient about the risk of abruptly quitting smoking, which can increase clozapine blood levels and reduce seizure threshold.
- Screen for specific seizure types (drop attacks, myoclonic jerks, or partial seizures) that may precede generalized tonic-clonic seizures. If present, measure clozapine plasma levels and adjust the dose accordingly.

Secondary prevention (first seizure) [58,60,62]

- Investigate possible causes that might have increased clozapine plasma levels.
- Measure clozapine plasma levels for monitoring drug exposure.
- Post-seizure, hold clozapine for 24 h and then resume at a lower dose, either the last dose prior to the seizure-inducing dose or half of the seizure-inducing dose.

Secondary prevention (second seizure) [58,60,61,63]

- Consider adding valproic acid or another anticonvulsant in selected patients, particularly if valproic acid is contraindicated.
- Valproic acid is the first-choice anticonvulsant for clozapine-related tonic-clonic, myoclonic, or atonic seizures, especially recommended in schizoaffective disorder.

Other psychotropic medications

- Lamotrigine may be considered, but slow titration is necessary to reach the anticonvulsant dose of 200 mg/d, which may conflict with the immediate need to control seizures.

Avoid

- Phenytoin and carbamazepine due to potential drug interactions leading to a decrease in clozapine plasma levels or increased risk of toxicity or agranulocytosis, respectively [63].

Overall, while routine prophylactic therapy with anticonvulsants is not recommended due to the low incidence of clozapine-related seizures, prompt management strategies should be employed if seizures occur, including adjusting clozapine dosage and considering adjunctive anticonvulsant therapy in selected cases. Close monitoring and collaboration between healthcare providers are essential for optimizing patient safety and treatment outcomes.

We suggest that each neurologist should learn about three SSRI/SNRI with slightly different mechanism of action to start prescribing comfortably. SSRI/SNRI are safe for epilepsy. Welbutrin IR is more associated with seizures and ER or XL; however, there is so much negative press about welbutrin that if considering ER or XL (IR should not be given to PWE) should be used with caution.

High-potency benzodiazepines such as alprazolam, lorazepam, and diazepam are increasingly used as rescue medications for seizure clusters and aborting seizures. However, when used frequently, which may be a high risk in patients with anxiety disorders, there is a high risk of dependence and withdrawal seizures. Epileptologists are accustomed to prescribing the low-potency benzodiazepines clobazam (Onfi) and are generally aware of its interactions with other medications, especially cannabinoids. Neurologists should discourage the use of high-potency benzos and should be comfortable recommending clobazam for the dual purpose of managing anxiety disorders and epilepsy.

Consider Safety: Prioritize medications with a lower risk of increasing seizure frequency, especially for patients with epilepsy [20]. Medications such as clozapine and welbutrin IR can cause seizures; however, if they are the last resort medication for the patient, then they can be considered.

Monitor Side Effects: Vigilantly monitor for adverse effects, with open communication between healthcare providers and patients. The most common side effects of SSRI are stomach upset, sexual side effects, paradoxical agitation, and irritability; if bipolar diagnosis is missed, then it can cause mania.

Potential for Combination Therapy: When treating complex cases, consider the potential for combined psychotropic and antiseizure medications [57].

Psychotherapy as an Adjunct: Explore the benefits of psychotherapy as

an adjunct to pharmacological treatment, particularly for mood and anxiety disorders [58,59]. CBT is a well-established and highly effective psychological treatment for a wide range of issues, with numerous studies supporting its ability to improve functioning and quality of life, often performing as well as or better than other therapies and medications.

Psychiatrist Referral: When symptoms are severe, treatment is ineffective, or new symptoms emerge, do not hesitate to involve a psychiatrist for specialized care [60].

In conclusion, the management of psychiatric comorbidities in PWE presents a complex challenge. By addressing the nuances of psychiatric symptomatology, guiding medication choices, and considering potential interactions it empowers neurologists to make informed decisions and enhance patient care. Therefore, by adhering to these recommendations and considering the unique challenges of patients with epilepsy and psychiatric comorbidities, neurologists can provide effective and safe care.

CRediT authorship contribution statement

Margaret Gopaul: Writing – review & editing, Writing – original draft, Conceptualization. **Hamada Altalib:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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