Three clinical pearls in the treatment of patients with seizures and comorbid psychiatric disorders

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Abstract
A strong association exists between epilepsy and psychiatric comorbidities, especially depression, anxiety, attention deficit disorders, and psychosis. The impact of psychotropic medications in lowering seizure threshold both directly and indirectly, hypersensitivity reactions to antiepileptic and other psychotropic medications, and how antiepileptic drugs affect psychiatric disorders are explored through three patient cases. Ultimately, in selecting an appropriate psychotropic medication for an individual with epilepsy and psychiatric comorbidities, it is important to consider the clinical and quality-of-life impacts that a particular medication will have on that individual.

Keywords: antiepileptic drugs (AEDs), psychiatric comorbidities, proconvulsant, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, psychiatric disorders, suicidal tendencies

Introduction
Epilepsy is a common chronic but complex medical disease that affects approximately 5.1 million adults and children in the United States and 50 million worldwide.1-3 It is characterized by more than 25 syndromes and multiple seizure types, which can vary in both severity and response to treatment.4 Due to the diverse symptomatology of epilepsy, persons with this condition may be challenged with psychiatric symptoms, such as cognitive and behavior changes, that can complicate epilepsy management by mimicking psychiatric disorders.5,6 Likewise, individuals with a psychiatric disorder, such as psychosis, anxiety, mood, and attention deficit disorder, have a higher likelihood of developing seizures and other neurological disorders, such as migraines and stroke, than the general population.6-9 Postmortem hippocampi were compared in individuals with mesial temporal lobe epilepsy, a common intractable seizure type, in the presence or absence of major depression versus interictal psychosis (a schizophrenia mimic).10,11 A closely related pattern of neuroinflammatory chemical abnormalities was seen in the presence of mesial temporal lobe epilepsy and either psychiatric disorder. This neuroinflammatory chemical finding may suggest greater insight into the relationship between the pathophysiology of epilepsy and comorbid psychiatric disorders.

Common psychiatric comorbidities seen with epilepsy (Table 1) are depression, anxiety, attention deficit disorder, and psychosis at a prevalence rate of 20% to 30%.5,12,13 The most common psychiatric comorbidity is depression with a prevalence of 20% to 55%; however, in select populations, the prevalence can reach as high as 80% (Table 1).5,14 The prevalence of anxiety disorders is 19%, but these coexist with depression in up to 66% of...
A 68-year-old patient was brought into the emergency room by family members for increased anxiety, decreased appetite, fatigue, and insomnia over the previous 3 weeks. The family also stated that the patient had seizure-like activity that lasted about 2 minutes. The patient has a past psychiatric history of major depressive disorder with psychotic features with a first hospitalization 4 years earlier. Medical history was significant for focal seizures diagnosed 1 year earlier. The patient graduated from college with a teaching degree and taught high school science until retiring at age 58. The patient lived from college with a teaching degree and taught high school science until retiring at age 58. The patient lived independently until having a focal seizure and now lives with family members. Current medications include olanzapine 15 mg by mouth daily, bupropion hydrochloride extended-release 150 mg by mouth daily (started 3 weeks earlier), and levetiracetam 750 mg by mouth twice daily. Previous antidepressant history includes escitalopram, which caused diarrhea and was discontinued 3 weeks previously. A mental status exam noted that the patient appeared older than stated age with poor grooming, poor eye contact, depressed mood, and auditory hallucinations calling the patient worthless. Vital signs and laboratory results were normal. Height: 5’6”; weight: 60 kg; and body mass index: 26 kg/m².

Several psychotropic medications are associated with a proconvulsant effect or withdrawal syndromes that may be responsible for drug-related seizures (Table 2). The seizure incidence associated with psychotropic medications varies. At therapeutic doses, the incidence ranges from approximately 0.1% to 1.7%, and with either intentional or unintentional overdoses, the incidence ranges from 4% to 58% (Table 2). More recently, however, reports suggest that there are limitations in estimating the likelihood for each psychotropic medication to provoke seizures because many of these epidemiology studies are retrospective, of small sample size, and lack controls. In a small observational study evaluating electroencephalogram (EEG) changes of olanzapine in relationship to total daily dose and plasma concentration of patients diagnosed with paranoid schizophrenia. This study found EEG changes are common, especially when doses of olanzapine 20 mg/d are used although the predictability of future seizures is limited. When applied to this case, the potential for olanzapine to lower the seizure threshold is low because a total daily dose of 15 mg was used. In general, the risk of EEG changes varies between typical and atypical antipsychotics, and the greatest risk is seen with clozapine and olanzapine followed by risperidone and typical antipsychotics. Despite these methodological drawbacks, the proconvulsant concept has prompted the addition of generic warning labeling for most psychotropic medications, such as chlorpromazine and bupropion, yet when warnings are applied equally to all patients with epilepsy and a psychiatric comorbidity, suboptimal or lack of treatment of the psychiatric disorder is frequently the unfortunate out-

### Take Home Points:

1. Individuals with seizure disorders and comorbid psychiatric conditions are frequently undertreated with psychotropic medications due to a misconception that all psychotropic medications are proconvulsant. Only a subset of psychotropic medications, such as chlorpromazine and bupropion, have the highest likelihood to provoke seizures.

2. Aromatic antiepileptic drugs (AEDs) and tricyclic antidepressants are associated with idiosyncratic cutaneous reactions that can cross-react whereas other aromatic antidepressants rarely cross-react and can be used safely.

3. Seizure disorders are associated with behavioral disturbances while taking AEDs, especially in children and individuals with developmental delay. The causes of these behavioral manifestations are multifactorial and include, for example, suppression of seizure activity, seizure complexity, AED pharmacology, polypharmacy, drug interactions, genetics, and environmental influences.

### Psychotropic Proconvulsants

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### Table 1: Prevalence rate comparing epilepsy and psychiatric comorbidities 5

| Psychiatric Comorbidity | General Population, % | Epilepsy Population, % |
|-------------------------|-----------------------|------------------------|
| Anxiety                 | 1.5 to 19             | 19 to 66               |
| Attention deficit disorder | 15                  | 30 to 40               |
| Depression              | 10.7                  | 17.4 to 80             |
| Psychosis               | 1 to 7                | 6 to 10                |
| Suicide                 | 1.4 to 6.9            | 13 to 25               |

5% of patients with epilepsy. The prevalence of attention deficit disorder and psychosis with epilepsy is lower—up to 40% and 10%, respectively. In this article, three cases explore the impact of psychotropic medications in lowering seizure threshold both directly and indirectly, antiepileptic and other psychotropic hypersensitivity reaction considerations, and how antiepileptic drugs (AEDs) affect psychiatric disorders and suicidality.

**Take Home Points:**

1. Individuals with seizure disorders and comorbid psychiatric conditions are frequently undertreated with psychotropic medications due to a misconception that all psychotropic medications are proconvulsant. Only a subset of psychotropic medications, such as chlorpromazine and bupropion, have the highest likelihood to provoke seizures.

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Other factors that can promote seizures include the addition of psychotropic medications in vulnerable patient populations (eg, preexisting seizures, traumatic brain injury, eating disorders), polypharmacy (especially with AEDs, which are associated with pharmacokinetic, pharmacodynamic, or a combination of interactions), rapid downward titrations, and very high dosages or overdoses.26,40,41

This patient case illustrates the potential consequence of using bupropion to treat depression in an individual with a preexisting seizure disorder. Bupropion and its primary active metabolite (hydroxybupropion) have been associated with an increased risk of seizures, in part, due to their sympathomimetic amine structures (similar to amphetamine) and proposed mechanism of increased noradrenergic and dopaminergic activity.27,42 It is contraindicated in epilepsy or certain comorbid conditions, including a history of eating disorders or abrupt discontinuation of AEDs, barbiturates, benzodiazepines, and ethanol.38 This phenomenon is dose-related and associated with the immediate-release product where a 10-fold increase in seizure risk is seen when the dose of bupropion is increased from 450 mg/d to 600 mg/d or greater.43 Typically, seizures present within 6 hours of ingestion of the immediate-release product.44,45 In contrast, the time to seizure onset with bupropion overdose is delayed with other formulations occurring at 10 hours (sustained-
release) or 12 hours (extended-release), respectively, but can occur up to 24 hours. For sustained-release or extended-release products, the labeling is the same, but the seizure rate is lower based on a reduced peak plasma concentration associated with the longer-acting products. One could argue, however, that the risk of using either long-acting product within the therapeutic dose is comparable to the general population. Nevertheless, the contraindication labeling should dissuade a clinician from recommending any bupropion formulation from both a medical-legal perspective and clinical experience.

### AED Hypersensitivity Reactions and Cross-Reactivity

A 32-year-old Asian American female of Chinese descent with a history of depression and no seizure disorder intentionally overdosed on approximately 60 bupropion sustained-release 150 mg tablets and was found down after about 3 hours in her apartment by her roommate. She was transported by paramedics to the emergency room and during transport suffered what appeared to be a generalized tonic-clonic seizure lasting 30 seconds, which self-terminated. She was alert and oriented to place and person as well as able to follow commands. Her vital signs, laboratory, urine toxicology, and physical exam were normal except the electrocardiogram showed a sinus tachycardia of 110 beats per minute. A prolactin level was drawn 15 minutes after the ictal event and was abnormal with a measured level of 45 mcg/L, indicating a seizure took place. In the emergency room, she complained of nausea and had another generalized tonic-clonic seizure lasting 30 minutes despite treatment with 2 doses of lorazepam 4 mg intravenous (IV) via slow push. She was then loaded with phenytoin 1000 mg IV and started on phenytoin 300 mg by mouth daily, escitalopram 10 mg by mouth daily for depression, and trazodone 100 mg by mouth at bedtime for sleep.

#### TABLE 2: Psychotropic medications known to lower seizure threshold (continued)

| Reference | Psychotropic Medication | Estimated Seizure Risk |
|-----------|-------------------------|------------------------|
| 16,18,24,26,30-32 | Atypical antipsychotics | Therapeutic to overdose |
| 16,18,24,26,30-32 | Atypical antipsychotics | Therapeutic to overdose |

...
By day 6 of the admission, her mental status exam was unremarkable. She was noticeably less depressed, participating in groups, goal oriented, eating 100% of her meals, and was sleeping about 8 hours per night. During medication group, she complained of a rash on her back, legs, and arms, which she said started early that morning. Upon physical exam, her pulse was 87 beats per minute, blood pressure 135/77 mmHg, respirations 17 breaths per minute, and temperature 39°C (102.2°F). She appeared moderately uncomfortable. Her skin revealed a scattered, erythematous, maculopapular rash along with painful, moderately uncomfortable. Her skin revealed a scattered, erythematous, maculopapular rash along with painful, moderately uncomfortable. Her skin revealed a scattered, erythematous, maculopapular rash along with painful.

The patient was diagnosed with presumptive drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome based on clinical and laboratory findings. Phenytoin was immediately discontinued, and her seizures were managed with an alternative AED while escitalopram was continued. She was treated symptomatically with both systemic and topical corticosteroids, hydroxyzine, and IV fluids. By hospital day 10, all symptoms and laboratory findings were normalized, and she was discharged with a plan to assess the appropriateness of continuing the AED at her first outpatient appointment.

Aromatic AEDs (including carbamazepine, eslicarbazepine, ethosuximide, lamotrigine, lacosamide, oxcarbazepine, phenobarbital, phenytoin, primidone, and zonisamide) are associated with idiosyncratic cutaneous eruptions, which are diverse and range from common, nonsevere drug reactions known as AED hypersensitivity syndromes to rare life-threatening reactions, such as DRESS, Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Both SJS and TEN occur acutely and progress quickly. Painful skin lesions and mucosal membrane blisters develop and erode, leading to skin detachment and large areas of body surface area (BSA) necrosis. Frequently, the liver or other organs are involved. The amount of BSA detachment, however, is the distinguishing feature between SJS (BSA: 10% or less) and TEN (BSA: above 30%).

DRESS syndrome is life-threatening with a mortality risk primarily from liver failure in up to 10% to 20% of patients. It is characterized by cutaneous skin eruptions (87%), fever >38°C (90% to 100%), lymphadenopathy (70% to 75%), hematologic abnormalities (especially eosinophilia; 52%), and mild-to-severe involvement of internal organs (eg, liver: 50% to 80%, kidneys: 40%, lung: 33%, heart: 15%, or pancreas: 5%). The symptoms of DRESS commonly manifest after approximately 2 to 6 weeks of treatment but can appear up to 3 months after exposure to the offending agent with an estimated incidence of 1 to 10 per 10,000 drug exposures.

The pathogenesis of DRESS syndrome is not fully understood. Three mechanisms have been proposed. Aromatic AEDs are preferentially metabolized via cytochrome P450 to an arene oxide intermediate. This intermediate can be detoxified enzymatically to a nontoxic metabolite by epoxide hydrolase or glutathione transferase. It is postulated that individuals with a defect in 1 of these enzymes will accumulate the arene oxide intermediate, which either triggers an immune response or covalently binds to macromolecules leading to cell death. Another proposed mechanism is the reactivation of several human herpesviruses including human herpesvirus 6 and 7, Epstein-Barr virus, and cytomegalovirus, which may trigger the DRESS syndrome. However, it remains unclear whether the reactivation of human herpesviruses is a trigger or is a complication of the syndrome. Last, there is a genetic relationship between the human leukocyte antigen (HLA) haplotypes that predispose an individual to a drug hypersensitivity reaction, such as with SJS/TEN. For example, individuals of Asian descent, particularly Han Chinese, Malaysian, South Chinese, and Thai individuals, are more likely to have the HLA-B*1502 allele, which leads to a tenfold increased risk of developing carbamazepine-induced SJS/TEN. In contrast, there is a strong association between the HLA-A*3101 allele and carbamazepine-induced SJS/TENS, and this allele is found more frequently in individuals from Korea, Japan, or Northern Europe compared to other genetic backgrounds. In at-risk populations, genetic testing should be conducted. When patients test positive for either HLA allele, carbamazepine should be avoided along with other aromatic AEDs known to cross-react with carbamazepine, including oxcarbazepine or phenytoin, unless the benefit clearly outweighs the risk.

This case demonstrates the importance of recognizing the symptoms of DRESS early. It also emphasizes the need to immediately discontinue any medication(s) that may have caused DRESS as well as to avoid any medications that may cause it in the future. It is difficult in the early stages to predict whether the rash will remain benign or progress to a severe skin reaction. Moreover, the high rate of cross-reactivity (70%) among the aromatic AEDs is also a concern when selecting an alternative AED as there are limited genetic tools to assist in this decision. As seen with this case, however, the patient’s seizures were provoked by a bupropion overdose. These seizures often can be managed by acute benzodiazepine treatment alone. In selecting alternative AEDs for unresolved or
Agitation, Irritability, Hyperactivity, and Suicide Related to AED Use

A patient was brought in by the police with suicidal thoughts and irritability after being found standing on a 200-foot bridge. The patient had no precipitant or past suicide attempts or hospitalizations. Past medical history includes status-posttraumatic brain injury secondary to a car accident (including an intracranial hemorrhage, burr hole, and 3-month coma), and a history of 2 recent complex partial seizures within the last year. The patient lives at home with family. Current medications include escitalopram 20 mg by mouth daily, levetiracetam 1000 mg by mouth twice daily (started 2 weeks earlier), lithium carbonate 300 mg by mouth twice daily, ferrous fumarate 1 tablet by mouth daily, and norethindrone acetate and ethinyl estradiol 1 tablet by mouth daily. Previous AEDs include phenytoin, which caused hirsutism, and topiramate, which caused cognitive impairment and reduced effectiveness of oral contraceptive. The mental status exam was unremarkable except the patient appeared poorly groomed with minimal eye contact and depressed, irritable mood. Vital signs and laboratory results were normal. Lithium level was 0.7 mmol/L.

Antiepileptic drugs can be associated with both positive and negative psychiatric effects in individuals with seizures. These types of behaviors associated with seizures, including agitation, hyperactivity, irritability, psychosis, and restlessness, are more common in children and individuals with developmental delay (Table 3). In a large, single-center chart review, 16% of adults with epilepsy experienced psychiatric/behavioral side effects (PSE); more than 60% of these side-effects were attributed to the addition of new AEDs. The study also found that fewer PSEs were associated with gabapentin (0.6%, P < .001) and lamotrigine (4.8%, P < .001) when compared to other, newer AEDs. Levetiracetam, however, was associated with the highest incidence of PSEs at 15.7% (P < .001). In fact, individuals treated with AEDs who have a previous psychiatric history are prone to PSEs. In some individuals with epilepsy, suppression of seizure activity can result in psychotic episodes or behavioral/mood disturbances. This phenomenon is known as forced normalization and is most common in patients with temporal lobe and generalized epilepsies. Other factors that have been shown to predispose individuals to PSEs while taking AEDs include pharmacology, polypharmacy, drug interactions, genetics, and environmental influences.

Proposed mechanisms of action for AEDs that influence psychiatric pharmacotherapy include reduction of glutamate excitation or enhanced gamma amino butyric acid inhibition. For example, benzodiazepines, felbamate, lamotrigine, phenobarbital, primidone, tiagabine, top-
iramate, valproic acid, vigabatrin, and zonisamide are associated with increased inhibitory gamma amino butyric acid neurotransmission. This form of neurotransmission can cause weight gain, sedation, fatigue, and cognitive impairment along with antianxiety and mood stabilization properties.

Excitatory glutamate neurotransmission is inhibited by lamotrigine, perampanel, phenytoin, pregabalin (2%), rufinamide (3%), tiagabine, topiramate (4% to 6% in adolescents and adults), valproate (>1% to <5%), vigabatrin (4%), and zonisamide (3%).

Decreased memory, attention
Brivaracetam, carbamazepine, clonazepam (4% to 5%), gabapentin, lamotrigine, levetiracetam, oxcarbazepine (2%), perampanel (2%), pregabalin (4% to 6%), tiagabine (4%), topiramate (7%), valproate, vigabatrin (7% to 10%), zonisamide (6%)

Depression
Acetazolamide, benzodiazepines, brivaracetam, carbamazepine, clonazepam (6% to 8%), ethosuximide, felbamate (5%), gabapentin, lacosamide (2%), lamotrigine (1% to 5%), levetiracetam (3% to 5%), oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine (3% to 7%), topiramate (≤9%), valproate (>1% to 5%), vigabatrin (4% to 7%), and zonisamide (6%)

Emotional liability
Brivaracetam, carbamazepine, clonazepam (2%), felbamate (3% in children), gabapentin (4% to 6% in children), lamotrigine (1% to 5%), levetiracetam (2% to 5%), oxcarbazepine (4%), phenytoin, tiagabine (3%), topiramate (3% to 5% in children, 5% to 11% in adolescents and adults), valproate (>1% to 6%)

Inomnia
Carbamazepine, felbamate, lamotrigine (5% to 10%), levetiracetam (5% in children and adolescents), oxcarbazepine (2% to 4%), phenobarbital, phenytoin, pregabalin (4%), primidone, tiagabine, topiramate (6% to 9%), valproate (>1% to 5%), vigabatrin (10% to 12% in infants), and zonisamide (6%)

Psychosis
Acetazolamide, benzodiazepines, brivaracetam, carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam (17% in infants and children; 1% in adults), oxcarbazepine, perampanel, phenytoin (toxic levels), pregabalin, primidone, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide

Somnolence
Acetazolamide, benzodiazepines, brivaracetam (20% to 27%), carbamazepine, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproate, and zonisamide
anxiety, nervousness, emotional ability, unmanageable anger, rage, aggression, agitation, hostility, paranoia, somnolence, and insomnia. In determining the cause of PSEs, it is prudent to conduct a thorough medication review and determine which medications, if any, may be contributing to the observed PSEs along with other risk factors of suicidal tendencies. By removing the offending agent, the symptoms typically resolve back to baseline. For this patient, once leviteracetam was discontinued, the symptoms of suicidal ideation and depression improved without de-escalation of current medications.

**Conclusion**

Epilepsy is associated with several psychiatric comorbidities, especially depression, but these are often undiagnosed. If recognized, psychiatric comorbidities may be inadequately treated as a result of efforts to minimize the risk of precipitating a seizure. As was discussed, only a few psychotropic medications, namely bupropion and chlorpromazine, will substantially lower the seizure threshold, especially in vulnerable individuals, but only bupropion carries a contraindication. Besides specific medications, inherent drug properties, medication combinations, rapid titrations, very high dosages or overdoses, and/or an inherent drug property carries a contraindication. Besides specific medications, inherent drug properties, medication combinations, rapid titrations, very high dosages or overdoses, and/or an individual’s response to these factors all play a role in whether an individual will be at risk for a breakthrough seizure or not. Antiepileptic drugs can both positively and negatively influence psychiatric behaviors and suicidality in a select patient population. Antiepileptic drugs can also cause predictable side effects or idiosyncratic cutaneous reactions that can cross-react with other structurally similar psychotropic agents or AEDs, which can lead to life-threatening complications. Ultimately, in choosing an appropriate psychotropic medication for an individual with epilepsy and psychiatric comorbidities, it is important to consider the clinical impact and quality of life aspects that a particular medication will have on that individual.

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