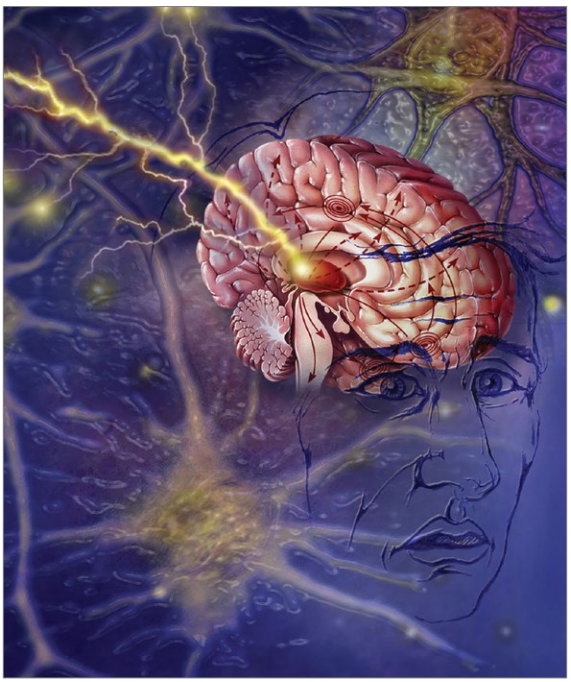
Current PSYCHIATRY

Antipsychotics and seizures: What are the risks?

Some agents may lower the seizure threshold, but higher-quality evidence is needed

Antipsychotics, especially second-generation antipsychotics (SGAs), have been proven effective for treating psychosis as well as mood disorders.[1,2] Because antipsychotics can lower the epileptogenic threshold, seizures are a serious potential adverse effect. Antipsychotics can cause isolated EEG abnormalities in 7% of patients with no history of epilepsy, and clinical seizures in .5% to 1.2% of such patients.[3] Additionally, the neuropathophysiology underlying epilepsy can predispose patients to psychiatric disorders[4]; the estimated prevalence of psychosis in patients with epilepsy is approximately 7%.[5] This review will shed light on the risk of clinical seizures related to antipsychotics.



KEVIN SOMERVILLE

Rita Khoury, MD
Geriatric Psychiatry Fellow

Elias Ghossoub, MD
Clinical Fellow, Forensic Psychiatry

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Department of Psychiatry and Behavioral Neuroscience
Saint Louis University School of Medicine
St. Louis, Missouri

Comparing seizure risk among antipsychotics

In a review of the World Health Organization's adverse drug reactions database, Kumlien and Lundberg[6] calculated the ratio of the number of reports of seizures to the total number of reports for each drug. They found that approximately 9% of all adverse drug reaction reports involving clozapine were due to seizures. Equivalent ratios were 5.90% for quetiapine, 4.91% for olanzapine, 3.68% for risperidone, 3.27% for haloperidol, and 2.59% for aripiprazole. Using the database of the Pharmacovigilance Unit of the Basque Country, Lertxundi et al[7] reported a 3.2-fold increased risk of seizure with SGAs in comparison with first-generation antipsychotics (FGAs) (95% confidence interval [CI], 2.21 to 4.63), which went down to 2.08 (CI, 1.39 to 3.12) once clozapine was excluded. However, as the authors of both studies noted,

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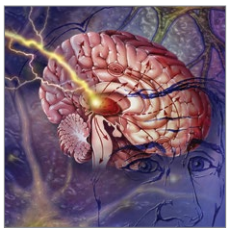

Antipsychotics and seizures

Clinical Point

Most of the evidence on antipsychotics and seizure risk is low quality and relies on case reports or expert opinions

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the quality and relevance of this data are limited because it relies on spontaneous reporting.

Overall, the evidence regarding the seizure risk associated with antipsychotics is scarce. To the best of our knowledge, only 2 large observational studies have compared the seizure risks associated with different antipsychotics.

Using data from the UK-based Clinical Practice Research Datalink between 1998 and 2013, Bloechlinger et al[8] examined the incidence rates of seizures among patients newly diagnosed with schizophrenia, affective disorders, or dementia who were prescribed antipsychotics. They excluded patients with a history of seizures or antiepileptic use. In the cohort of 60,121 patients, the incidence rates of seizures per 10,000 person-years were 11.7 (CI, 10.0 to 13.4) for those who did not use antipsychotics, 12.4 (CI, 10.9 to 13.8) for past users, 115.4 (CI, 50.1 to 180.7) for current users of haloperidol, 48.8 (CI, 30.7 to 66.9) for current users of quetiapine, 25.9 (CI, 11.8 to 40.0) for current users of risperidone, and 19.0 (CI, 8.7 to 29.3) for current users of olanzapine. No data were available about clozapine use.

In subsequent analyses, the authors found that among patients with affective disorders, only current use of medium- to high-potency FGAs (haloperidol, prochlorperazine, and trifluoperazine) was associated with a significantly increased risk of seizures (adjusted odds ratio: 2.51, CI, 1.51 to 4.18) compared with non-users.[8] Among patients with dementia, current use of olanzapine or quetiapine and current use of any FGAs were associated with significantly increased odds of seizures. This study suggests that the underlying mental illness might modulate the seizure risk associated with antipsychotics.[8]

Wu et al[9] conducted a study based on the National Health Insurance Research Database in Taiwan. They examined the 1-year incidence of new-onset seizures among patients diagnosed with schizophrenia or mood disorders who were new to antipsychotic treatment, and calculated the risk of seizure associated with each antipsychotic in reference to risperidone. They found that those receiving clozapine, thioridazine, and haloperidol were 2 to 3 times more likely to develop seizures than those treated with risperidone; risks associated with the rest of the FGAs were similar to that of risperidone.

The results of these 2 large cohort studies are somewhat concurrent in indicating that, other than clozapine, SGAs incur similar risks of seizures; furthermore, they specify that, contrary to earlier studies,[10] haloperidol is associated with significantly higher odds of seizures. While both of these cohort studies controlled for several sociodemographic and clinical confounders, they have several limitations. First, diagnoses of seizures were based on information available in databases, which might be subject to inaccuracies. Second, neither study evaluated the effect of drug dosage and duration of exposure on new-onset seizures.

Most evidence is from case reports

Other than these 2 large studies, most of the evidence addressing the relationship between the use of antipsychotics and incidence of seizures is low quality and relies on case reports or expert opinions. Older studies found that, among FGAs, seizure risk is highest with chlorpromazine and promazine, and lowest with thioridazine and haloperidol.[10] As for SGAs, case reports have described seizures associated with the use of quetiapine, aripiprazole, risperidone, paliperidone, and olanzapine.

Quetiapine. Three case reports published between 2002 and 2010 describe generalized tonic-clonic seizures secondary to quetiapine use.[11-13] In placebo-controlled trials, seizures were reported to have occurred in 1 of 951 patients receiving quetiapine compared with 3 of 319 patients receiving placebo.[14]

Aripiprazole. Five case reports described staring spells and tonic-clonic seizures in patients receiving 10 to 15 mg of aripiprazole.[15-19] In the New Drug Application (NDA) for aripiprazole, the incidence of seizures was estimated to be .11% (1 of 926 patients) in placebo-controlled trials and .46% (3 of 859 patients) in haloperidol-controlled trials.[20]

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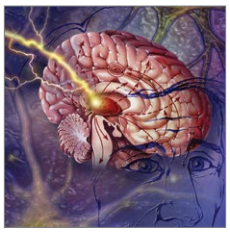

Clinical Point

Use caution when prescribing risperidone or paliperidone to a patient with a history of seizures

Table 1

Case reports of seizures attributed to aripiprazole

Case report	Summary	Dose of antipsychotic/ serum levels	EEG result	Notes
Thabet et al[19] (2013)	Child, age 3, with accidental ingestion Two staring spells (absence seizures), one of which was followed by a generalized seizure	30 mg/d	Mild, generalized slowing	History of a single unprovoked generalized tonic-clonic seizure at the age of 18 months with normal EEG. Was not maintained on antiepileptic medications
Yueh et al[18] (2009)	Man, age 54 Two tonic-clonic seizures	15 mg/d	Normal	Seizures concomitant with abrupt discontinuation of benzodiazepines
Arora and Arndorfer[17] (2007)	Boy, age 13 Four weeks of treatment Staring spells and hand twitching. No full-blown tonic-clonic seizures or loss of consciousness	10 mg/d	Generalized epilepsy	
Tsai[16] (2006)	Patient with schizophrenia Six weeks of treatment Generalized tonic-clonic seizures Resolution of seizures after switch to olanzapine	10 mg/d	Normal	Maintained on flunitrazepam 2 mg/d
Malik and Ravasia[15] (2005)	Man, age 31, with delusional disorder Two seizures (1 complex partial) 3 weeks after treatment initiation	15 mg /d		

Risperidone's product labeling suggests the drug should be used with caution in patients with a history of seizures or conditions that could result in a lower seizure threshold. In Phase III placebo-controlled trials, seizures occurred in .3% of patients treated with risperidone, although in some cases, the seizures were induced by electrolyte disturbances such as hyponatremia.[21] Gonzalez-Heydrich et al[22] and Holzhausen et al[23] found no increase in seizure activity among patients with epilepsy who were receiving risperidone. Lane et al[24] published a case report of a geriatric woman who presented with a generalized tonic-clonic seizure related to rapid titration of risperidone; however, with slower titration and lower doses, she stopped having seizures without adding any antiepileptic drugs. Komossa et al[25] found that risperidone is less epileptogenic than clozapine, with a relative risk of .22.

Paliperidone is the active metabolite of risperidone and does not have pharmacokinetic interactions with drugs metabolized by the cytochrome P450 (CYP) enzymes. Its labeling indicates that the drug should be used with caution in patients with a history of seizures.[26] In Phase III placebo-controlled trials of paliperidone, the rate of seizures was .22%.[27] Two case reports suggest close monitoring of seizure risk in patients receiving paliperidone.[28,29] Liang et al[29] reported that co-administration of valproic acid could mask an underlying decrease of the seizure threshold caused by antipsychotics such as paliperidone.

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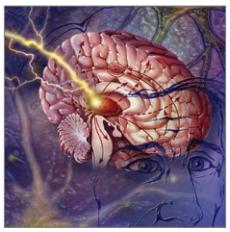


Antipsychotics and seizures

Clinical Point

Clearance of olanzapine is lower in women, and most case reports of olanzapine-related seizures occurred in women

Table 2

Case reports of seizures attributed to olanzapine

Case report	Summary	Dose of antipsychotic/ serum levels	EEG result
Anzellotti et al[32] (2016)	Man, age 47 Lingual dystonia, repetitive episodes of right mouth deviation and eyelid myoclonia	10 to 15 mg/d	Left fronto-temporal focus with recruiting polyspikes, followed by generalized spikewave complexes at 4 to 5 Hz
Rosen et al[37] (2011)	Woman, age 67 Seven years of treatment Generalized myoclonus	2.5 mg/d (no recent dose changes)	Initially: generalized slowing + spikes and sharp waves Normalization 2 days after discontinuation
Behere et al[35] (2009)	Man, age 25 Three months of treatment with adjunctive sertraline Two tonic-clonic seizures Resolution of seizures after switch to haloperidol	Gradual increase to 20 mg/d	Generalized spikes + sharp and slow wave discharges Normalization 1 month after discontinuation
Spyridi et al[39] (2009)	Woman, age 48 Treatment for 2 days status epilepticus	Rapid titration to 30 mg/d	Status epilepticus
Camacho et al[36] 2005)	Woman, age 54 Treatment for 2 days Myoclonic status	5 mg/d	High-amplitude generalized spikes, and spike/wave and polyspike/wave complexes Normalization 36 hours after discontinuation
Wooley and Smith[34] (2001)	Man, age 30, with schizophrenia Three months of treatment Generalized tonic-clonic seizures	10 mg/d	Multifocal and generalized epileptiform discharges Resolved with discontinuation
Lee et al[33] (1999)	Woman, age 31 Thirteen days of treatment Three generalized tonic-clonic seizures	10 mg/d	Resolution of seizures with discontinuation of olanzapine and initiation of phenytoin
Wyderski et al[38] (1999)	Woman, age 41, with alcohol use disorder Five months of treatment Status epilepticus	Unknown	

Olanzapine is a thienobenzodiazepine derivative and is chemically related to clozapine.[30] The olanzapine NDA[31] shows that 23 of 3,139 patients developed seizures, mainly tonic-clonic, with evidence suggesting that the seizures may have been due to confounding factors such as a history of seizures or metabolic abnormalities. There were no statistically significant differences in the rate of seizures associated with olanzapine compared with placebo or haloperidol (P = .252 and .168, respectively).

A literature review for olanzapine yielded 1 case report of repetitive focal seizures and lingual dystonia,[32] 5 case reports of generalized tonic-clonic seizures and myoclonus,[33-37] and 2 case reports of status epilepticus.[38,39] Olanzapine's clearance is 25% to 30% lower in women, and most of these case reports occurred women.[40]

Details of the above case reports are summarized in ***Table 1*** (***page 24***) (aripiprazole[15-19]), ***Table 2*** (olanzapine[32-39]), and ***Table 3***, (***page 28***) (paliperidone,[28,29] quetiapine,[11-13] and risperidone[22-24]).

	Notes
	History of epilepsy treated with phenobarbital 150 mg/d, and topiramate, 300 mg/d
	History of Alzheimer's disease, hypertension, dyslipidemia, hypothyroidism. Maintained on a stable dose of gabapentin
	Maintained on sertraline, 150 mg/d, procyclidine, 5 mg/d, and propranolol, 20 mg/d
	Hospitalized for management of anorexia nervosa. Switch from quetiapine to olanzapine. Mirtazapine was increased from 30 to 60 mg/d concomitantly with switch
	History of Alzheimer's disease. Maintained on citalopram, 20 mg/d, and donepezil, 5 mg/d
	History of seizure disorder, maintained on valproic acid
	History of organic brain disease, anemia, and generalized seizure disorder. Maintained on multiple medications, including lithium, valproic acid, bethanechol, nitrofurantoin, benztropine. Seizures concomitant with abrupt discontinuation of haloperidol, 80 mg/d

Ziprasidone. According to the NDA safety database, the seizure rate attributed to ziprasidone was 1.8 per 100 subject-years or 0.54% of participants (12 of 2,588).[41] No additional studies have been published regarding its seizure risk.

Clozapine has a black-box warning

To the best of our knowledge, clozapine is the only antipsychotic that carries an FDA "black-box" warning regarding its risk of inducing seizures.[42] Devinsky and Pacia[43] reported a cumulative risk of 10% after 3.8 years of treatment. The literature has described clozapine-induced generalized tonic-clonic, myoclonic, simple and complex partial, and absence seizures.[44] ***Table 4***[45] (***page 29***) lists the estimated frequency of each seizure type based on 101 cases of clozapine-induced seizures. Myoclonic seizures and drop attacks could be precursors/warning signs of grand mal tonic-clonic seizures.[46,47] Seizures have been observed at all stages of treatment, but were more common during initiation of clozapine, which emphasizes the importance of a progressive and slow titration.[43,48] The incidence of seizures was estimated to be 6% in a sample of 216 patients with schizophrenia with no history of epilepsy who were prescribed clozapine.[49]

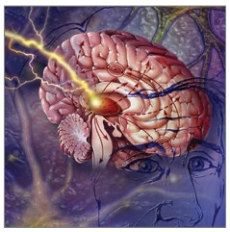
Regarding a possible association between clozapine dose or clozapine plasma levels and seizure risk, there is a positive linear relationship between the dose of clozapine and its serum concentration over a dosing range of 25 to 800 mg/d.[50] However, the plasma concentration is also significantly affected by factors such as smoking, gender, age, drug interactions, and CYP genotypes. Therefore, the same clozapine dose will yield a lower serum concentration in an older male who smokes compared with a younger, non-smoking female.[51] Perry et al[52] suggested a dosing nomogram to calculate the influence of gender and smoking. Seizure risk, especially for tonic-clonic seizures, has been reported to increase with clozapine doses >600 mg/d,[53] and with plasma concentrations exceeding 1,000 to 1,300 mg/L.[54] However, in a 2011 regression analysis, Varma et al[55] found no statistically significant relationship between seizure risk and clozapine oral dose; there was not enough data to test a correlation between clozapine plasma levels and the incidence of seizures.

How antipsychotics might lower the seizure threshold

Researchers have suggested several possible mechanisms to explain how antipsychotics might lower the seizure threshold. Antagonism of dopamine D4, histamine H1, and acetylcholine-muscarinic receptors

Clinical Point

With clozapine, seizures have been observed at all stages of treatment but are more common during initiation of therapy



Clinical Point

Many antipsychotics and antiepileptics are metabolized by CYP enzymes, and interactions may impair seizure control

Table 3

Case reports of seizures attributed to paliperidone, quetiapine, and risperidone

Case report	Summary	Dose of antipsychotic/ serum levels	EEG result	Notes
Paliperidone				
Liang et al[29] (2011)	Man, age 41 Three months of treatment	9 mg/d for 1 month		Maintained on valproic acid for management of irritability and aggression; discontinued prior to seizure
Schneider and Lizer[28] (2008)	Man, age 46 Four days of treatment	3 mg/d on Day 1 6 mg/d on Days 2, 3, and 4		History of diabetes mellitus, hypertension, and dyslipidemia. Maintained on metformin, insulin, simvastatin, enalapril, escitalopram, lamotrigine, and clonazepam. First episode of atrial fibrillation simultaneous with seizure
Quetiapine				
Young et al[13] (2009)	Woman, age 27 24 hours after intoxication Late onset of 2 seizures	Overdose with 30 g. Blood levels 8.67 mg/L on Day 1 (normal range: 0.1 to 1 mg/L)	No epileptiform activity	
Dogu et al[12] (2003)	Woman, age 75, with visual hallucinations and delusions Eighteen months of treatment Two generalized tonic-clonic seizures	500 mg/d	Non-specific generalized slowing at 6 to 7 Hz	History of Alzheimer's disease. Maintained on carbamazepine for aggression; serum level 6.7 mEq/L
Hedges and Jeppson[11] (2002)	Woman, age 27 One day after initiation of treatment Generalized tonic-clonic seizure	100 mg/d		Maintained on olanzapine, 15 mg/d, and sertraline, 100 mg/d. Concomitant slow taper of clonazepam
Risperidone				
Holzhausen et al[23] (2007)	54 children, age 2 to 18 (mean age: 10) No exacerbation of seizures in 94.5% of cases	.01 to .14 mg/kg/d		History of comorbid epilepsy
Gonzalez-Heydrich et al[22] (2004)	21 youths, age 4 to 19 No exacerbation of seizure in all cases	2.4 to 3.5 mg/d		History of comorbid epilepsy
Lane et al[24] (1998)	Woman, age 64 Two days of treatment Generalized tonic-clonic seizure There were no seizures after risperidone was stopped, then re-initiated 15 days later at a lower dose and with a slower titration schedule	2 mg/d on Day 1 4 mg/d on Day 2	Normal before and after treatment	Was being treated with sulfamethoxazole-trimethoprim and astemizole

seems to induce EEG alterations and increase the risk of seizures.[56] Additionally, modulation of the *N*-methyl-D-aspartate and the gamma-aminobutyric acid pathways might also be implicated.[57,58] Certain brain regions upon which antipsychotics act (eg, the hippocampus and the amygdala) might be associated with a higher susceptibility to convulsions compared with cortical regions.[59,60] Another mechanism described in epilepsy is "kindling," which consists of a progressive increase in brain excitability after repeated administration of a fixed subconvulsive dose of an excitatory agent; clozapine is believed to have a higher "kindling" activity compared with other antipsychotics.[59,60] Overall, these proposed mechanisms remain speculative.[57]

Watch for pharmacokinetic interactions

The CYP enzymes involved in drug metabolism include CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Most commonly used antiepileptics and antipsychotics are metabolized by CYP enzymes, and may also act as inhibitors or inducers of these enzymes.[61] Drug interactions may impair seizure control, which is why monotherapy is preferable to combination treatment in patients with epilepsy.[62] Carbamazepine and phenytoin are inducers of both CYP1A2 (which metabolizes olanzapine and clozapine), and CYP3A4 (which metabolizes haloperidol, risperidone, quetiapine, ziprasidone and clozapine). Paliperidone is not metabolized by CYP enzymes.[62] Discontinuing an enzyme-inducing agent may result in increased antipsychotic plasma concentrations, which might lead to an increased risk of seizures.

Valproic acid, which is often used to prevent or treat clozapine-induced seizures, has an unclear effect on clozapine plasma concentrations.[63] Although valproic acid is known to inhibit clozapine metabolism, 2 reports have suggested that the plasma concentrations of clozapine and its metabolites may decrease after adding valproic acid.[64,65] Other studies have found that valproic acid increases plasma concentrations of clozapine while it decreases plasma concentrations of norclozapine; norclozapine is the main clozapine metabolite responsible for inducing seizures.[66,67]

Table 4

Frequency of clozapine-induced seizures, by type

Seizure type	Frequency[a]
Generalized	
Tonic-clonic	54%
Myoclonic and/or atonic	28%
Tonic-clonic with other seizure types	12%
Partial	
Simple	3%
Complex	3%

[a]Among 101 cases of clozapine-induced seizure

Source: Adapted from reference 45

Steps for minimizing seizure risk

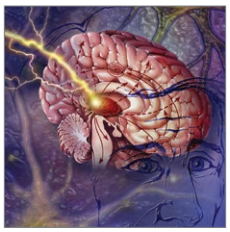
Determining the seizure risk for a patient taking an antipsychotic is challenging because doing so depends not only on the seizurogenic potential of each drug but also on individualized predisposing factors.[11,57,68] Choosing the "best" antipsychotic therefore largely depends on each patient's profile. The predisposing factors consist mainly of the individually inherited seizure threshold (personal history of febrile convulsions or a family history of seizures) and other comorbid seizurogenic conditions, such as a history of head trauma, brain injury, intellectual disability, cerebral arteriosclerosis, neurodegenerative diseases, encephalopathy, chronic renal insufficiency, and hyponatremia. Furthermore, seizure risk depends on the antipsychotic dose administered and the rate of titration.[11]

There is not enough evidence to recommend performing an EEG in all patients taking antipsychotics. Such testing is recommended only for patients who have predisposing factors for seizures. If an EEG shows any abnormality in a patient taking clozapine, consider decreasing the clozapine dose[69,70] or adding an antiepileptic drug such as valproic acid or lamotrigine.[44,70]

continued

Clinical Point

Determining seizure risk depends on the seizurogenic potential of the antipsychotic and on the patient's individualized predisposing factors



Clinical Point

There is no consensus on co-prescribing an antiepileptic agent for patients receiving clozapine

Table 5

Prevention of clozapine-induced seizures

Primary prevention[42,51,57]

- 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), including cimetidine, caffeine, ciprofloxacin, erythromycin, citalopram, and fluvoxamine
- Educate the patient about the risk of smoking cessation abruptly increasing clozapine blood levels and reducing seizure threshold
- Screen for drop attacks, myoclonic jerks, or partial seizures that may precede generalized tonic-clonic seizures. If present, measure clozapine plasma levels and decrease the dose of clozapine

Secondary prevention, first seizure[45,51,74]

- If a seizure occurs independent of a dose increase, investigate possible causes that might have increased clozapine plasma levels (eg, co-administration of drugs that lower seizure threshold or inhibit CYP enzymes 1A2, 2D6, or 3A4, or smoking cessation)
- Measuring clozapine plasma levels can be helpful in monitoring drug exposure
- Post-seizure, hold clozapine for 24 hours and then resume at a lower dose; last dose prior to the seizure-inducing dose or half of the seizure-inducing dose are suggested options

Secondary prevention, second seizure: Consider adding valproic acid or another anticonvulsant in selected patients (eg, if valproic acid is contraindicated[44])

First choice: **Valproic acid**[45,51,55,74]

- Due to the risks associated with valproic acid treatment (eg, neutropenia, thrombocytopenia, weight gain, and hyperammonemia), and the low incidence of clozapine-related seizures even at higher plasma clozapine levels, routine prophylactic therapy is not recommended
- If a second seizure occurs, or if high clozapine doses (above that which induced the seizure) are required, valproic acid is the anticonvulsant of choice for clozapine-related tonic-clonic, myoclonic, or atonic seizures
- Particularly recommended in schizoaffective disorder

Other anticonvulsants:

- **Lamotrigine.** Slow titration of lamotrigine is necessary in order to reach the anticonvulsant dose of 200 mg/d; this might conflict with the immediate need to control seizures[69]

Avoid:

- **Phenytoin.** Drug–drug interactions lead to a potential decrease in clozapine plasma levels and an increased risk of phenytoin toxicity[75]
- **Carbamazepine.** Drug–drug interactions lead to a potential decrease clozapine plasma levels. Carbamazepine increases the risk of agranulocytosis and of myoclonic seizures[51]

CYP: cytochrome P450

Although clozapine carries a black-box warning of increased risk of causing seizures, there is no consensus regarding the efficacy of co-prescribing an antiepileptic. Some studies have suggested prescribing valproic acid prophylactically,[71] after the occurrence of 1 seizure,[59] or after 2 seizures.[54,72] Others have recommended prescribing prophylactic valproic acid for patients taking ≥600 mg/d of clozapine or whose clozapine plasma levels are >500 mg/L.[73] Varma et al[55] recommended starting an antiepileptic medication if there are clear epileptiform discharges on EEG, if the patient develops stuttering or speech difficulties, or if seizures occur. Liukkonen et al[72] advised initiating an antiepileptic at the start of clozapine treatment in patients who are taking other epileptogenic medications, patients with pre-existing seizure disorder, and patients with neurologic abnormalities. On the other hand, Caetano[51] argued against primary prevention of seizures for patients receiving >600 mg/d of clozapine, suggesting that "the risk of seizures would be better managed by close clinical monitoring and measures of clozapine serum concentration rather than adding an anticonvulsant drug."

Current recommendations for primary and secondary prevention of clozapine-induced

seizures are detailed in ***Table 5***[42,44,45,51,55,57,69,74,75] (***page 30***).

Studies addressing the seizurogenic potential of SGAs other than clozapine have a low level of evidence and include patients who had comorbid conditions and were taking other medications that could cause seizures. Additionally, clinical trials of SGAs rarely include patients with seizure disorders; this might underestimate the risk of seizures.[4]

The effect of the mental illness itself on the seizure threshold needs to be considered.[43] Bloechlinger et al[8] found that dementia might be inherently associated with a higher risk of antipsychotic-related seizures. Moreover, numerous qualitative EEG studies have found abnormalities in 20% to 60% of patients with schizophrenia.[56] Other quantitative studies have reported mild and nonspecific EEG abnormalities, such as increased delta and/or theta activity, in many non-medicated patients with schizophrenia.[10,76] Additionally, brain tissue analysis of deceased patients who had schizophrenia has shown a significant increase in dopamine concentrations in the left amygdala compared with controls, and this might be responsible for enhanced electrical activity in this region.[10] Some studies have described EEG slowing in the frontal brain regions of patients with schizophrenia,[77] and was selectively normalized in these areas with antipsychotics.[78]

As always, start low, go slow

Mounting evidence suggests that antipsychotic medications decrease the seizure threshold. Practitioners should thus be cautious in prescribing antipsychotics and should target reaching the minimal effective dose with slow titration, especially in patients with predisposing factors for epilepsy.

Related Resources

- Druschky K, Bleich S, Grohmann R, et al. Seizure rates under treatment with antipsychotic drugs: Data from the AMSP project. World J Biol Psychiatry. 2018;15:1-10.
- Epilepsy Foundation. For professionals: Antipsychotics. https://www.epilepsy.com/learn/professionals/diagnosis-treatment/psychotropic-drugs-developmental-disabilities/comorbid-5.

Drug Brand Names

Aripiprazole • Abilify
Benztropine • Cogentin
Bethanechol • Duvoid
Carbamazepine • Carbatrol, Tegretol
Chlorpromazine • Thorazine
Cimetidine • Tagamet
Ciprofloxacin • Cipro
Citalopram • Celexa
Clonazepam • Klonopin
Clozapine • Clozaril
Donepezil • Aricept
Enalapril • Vasotec
Erythromycin • Erythrocin
Escitalopram • Lexapro
Flunitrazepam • Rohypnol
Fluvoxamine • Luvox
Gabapentin • Neurontin
Haloperidol • Haldol
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid
Metformin • Fortamet, Glucophage
Mirtazapine • Remeron
Nitrofurantoin • Furadantin
Olanzapine • Zyprexa
Paliperidone • Invega
Phenobarbital • Luminal
Phenytoin • Dilantin
Prochlorperazine • Compazine
Procyclidine • Kemadrin
Propranolol • Inderal
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Simvastatin • Zocor
Sulfamethoxazole/trimethoprim • Bactrim, Sulfatrim
Topiramate • Topamax
Trifluoperazine • Stelazine
Valproic acid • Depakene, Depakote
Ziprasidone • Geodon

Although evidence suggests antipsychotics can induce different types of epileptic seizures, the quality of this evidence is low. Randomized controlled trials are needed to determine which antipsychotics increase seizure risk and whether there is a dose-effect relationship.

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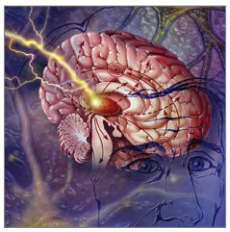
Clinical Point

The effect of the mental illness itself on seizure threshold needs to be considered

Bottom Line

Among second-generation antipsychotics, clozapine appears to increase the risk of clinical seizure the most. Correlations with dosage and/or plasma levels have not been proven. Psychiatrists should be vigilant for pharmacokinetic interactions between antipsychotics and antiepileptics, notably via CYP1A2 and CYP3A4.



Antipsychotics and seizures

Clinical Point

Slow titration of antipsychotics is particularly important in patients with predisposing factors for epilepsy

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Clinical Point

RCTs are needed to determine which antipsychotics increase seizure risk and if there is a dose-effect relationship