

Should you use an anticonvulsant to treat impulsivity and aggression?

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Mr. V, age 29, is a US Army veteran who presents to the psychiatric emergency department because of increasing aggression. He recently returned from deployment overseas and lives with his parents. Mr. V's mother reports that he has been increasingly "unstable" and describes an incident during which he punched a hole in his bedroom window after a temporary slowdown in the home's Internet connection.

The workup and review of the history rules out substance abuse, posttraumatic stress disorder, bipolar disorder, seizure disorder, and personality disorders. He is currently taking only omeprazole, 40 mg/d, for acid reflux. The psychiatrist considers prescribing an antiepileptic medication to treat the agitation. Why this choice of agent?

According to DSM-5, patients who have repeated episodes of aggression can be given a diagnosis of intermittent explosive disorder, but such behavior can occur secondary to other psychiatric diagnoses (*Table 1, page 50*). No medications are FDA approved for aggression.¹

Aggression and associated verbal and physical acts fall into 2 subtypes: impulsive type and premeditated (predatory) type. *Impulsive aggression* generally is described as an emotionally charged aggressive response characterized by a loss of behavioral control.

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Premeditated aggression, on the other hand, is characterized as purposeful, goal-oriented, and requiring forethought or planning.

Pharmacotherapy is directed primarily at treating impulsive aggression because this subtype is thought to be caused by neurologic deficits that can affect a person's ability to process, and react appropriately to, external stimuli. Agitation can result from neuronal hyperactivity.² Agents such as antiepileptic drugs (AEDs) have the potential to reduce the intensity and frequency of such behaviors.²

In this article, we focus on the use of AEDs for treating impulsive aggression in adults.

Reviewing the evidence for AEDs

The neurobiology of aggression involves multiple neurotransmitters, intracellular pathways, and ion channels.³ AEDs have several mechanisms of action, however; primary mechanisms include action on sodium and calcium channels and modulation of



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Practice Points

- All AEDs have some documented efficacy for treating aggression.
- Oxcarbazepine might have the strongest evidence in favor of its use; more research is needed.
- Because all AEDs have evidence of efficacy, choosing the appropriate agent depends, in part, on other patient-specific variables.
- Consider nondrug therapies, such as cognitive-behavioral therapy, which might produce a synergistic effect with pharmacotherapy—as is the case in other psychiatric disorders.

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Several trials have found a statistically significant difference between phenytoin and placebo for treating impulsive aggression

Table 1

Aggressive behavior: The differential diagnosis

Antisocial personality disorder
Attention-deficit/hyperactivity disorder
Bipolar disorder
Borderline personality disorder
Conduct disorder
Dementia
Generalized anxiety disorder
Intermittent explosive disorder
Major depressive disorder
Mental retardation
Obsessive-compulsive personality disorder
Oppositional defiant disorder
Posttraumatic stress disorder
Psychotic disorder
Seizure disorder
Substance abuse disorder
Traumatic brain injury

γ -aminobutyric acid (GABA), glutamate, and carbonic anhydrase.^{2,3} Agent-specific mechanisms of actions are listed in *Table 2*.

Phenytoin. Several double-blind, placebo-controlled trials have found a statistically significant difference between phenytoin and placebo for treating impulsive aggression, as measured by the Overt Aggression Scale (OAS)³ or a modified version (MOAS/OAS-M).^{1,2,4} Researchers found that phenytoin, 300 mg/d, but not 100 mg/d, decreased impulsive aggression.⁴

Valproate. Trials of valproate for decreasing aggressive behaviors have produced mixed results with regard to primary outcome when used at standard dosages and within the therapeutic range measured by serum concentration.^{2,3} In a pooled analysis of studies that met stringent criteria (randomized, controlled trial, aggressive behavior as primary outcome, patients free of organic illness or neurologic

illness), Jones and colleagues¹ reported that valproate/divalproex did not produce statistically significant results compared with placebo for treating impulsive aggression.

Carbamazepine and oxcarbazepine.

Double-blind, placebo-controlled trials and case studies of carbamazepine have shown mixed results. In contrast, oxcarbazepine has been found to significantly decrease aggressive behavior, measured by OAS/MOAS/OAS-M scores.^{2,3} Total daily dosages of oxcarbazepine ranged from 1,500 to 2,400 mg.^{2,4} It has been speculated that oxcarbazepine might be a useful option for treating impulsive aggression because of its therapeutic value in temporal lobe seizures—a subtype of seizure disorder that involves the limbic system, which also modulates aggressiveness.⁵

Additionally, when compared with carbamazepine, oxcarbazepine has a lower risk of cardiotoxicity, neurotoxicity, and blood dyscrasia. Oxcarbazepine has fewer drug-drug interactions because of a lower degree of hepatic enzyme induction.

Topiramate. Several studies have confirmed the efficacy of topiramate for aggressive behavior.^{2,3} However, there have been reports that topiramate can induce or exacerbate aggression in some patients, an effect that might be dose-related. Aggression might respond better to a higher, short-term dosage (eg, 400 mg/d) than to lower (100 to 300 mg/d) dosages, which might exacerbate aggression.³

Gabapentin. Research on using gabapentin for aggression is limited. Speculation is that the combined activity of gabapentin on GABA and glutamate give the drug its anti-aggressive effect.³ No randomized, double-blind, placebo-controlled trials are underway comparing gabapentin and placebo or other active medication for impulsive aggression.

Some case reports and small-scale, open-label studies report a decrease in aggression with gabapentin. As is the case with topiramate, a lower dosage (200 mg to 400 mg) has



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⁴Studies generally used the OAS, or one of its modifications, to evaluate aggressive behavior.^{2,4}

Table 2

How do antiepileptic drugs work, to treat aggression?

Drug	Mechanism
Carbamazepine	Inhibits voltage-dependent sodium channels; γ -aminobutyric acid (GABA) agonist
Gabapentin	Increases release of GABA Decreases release of glutamate Modulates voltage-dependent calcium channels
Lamotrigine	Decreases release of glutamate Modulates sodium, potassium, and calcium channels
Oxcarbazepine	Inhibits voltage-dependent sodium channels; GABA agonist
Phenytoin	Inhibits voltage-dependent sodium channels; GABA agonist
Topiramate	Increases release of GABA Decreases release of glutamate Precise mechanism of action is unknown
Valproate	Increases GABA activity Inhibits N-methyl-D-aspartate activity Modulates voltage-dependent sodium channels

been reported to result in increased aggression—whereas a higher dosage (800 mg) decreases aggressive behavior.^{2,3}

Lamotrigine. The results of several studies, including double-blind, placebo-controlled trials, support the use of lamotrigine for aggressive behavior. A number of these studies, however, used scales other than OAS (or its modifications) to determine this outcome. One trial showed increased aggression in several patients on lower-dosage lamotrigine (100 mg/d) that resolved when the dosage was increased.^{2,3}

Treatment recommendations

Although all AEDs have some documented efficacy against aggression, choosing the appropriate agent depends on patient-specific variables. Avoiding divalproex in patients with liver dysfunction, for example, or carbamazepine in those with a preexisting cardiac conduction abnormality will improve outcomes by avoiding complications.

It is important to rule out all other causes of aggression before selecting a treatment. The presence of one or more of the diagnoses listed in *Table 1* could lead to selection of an

Related Resources

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Drug Brand Names

Carbamazepine • Tegretol	Phenytoin • Dilantin
Gabapentin • Neurontin	Topiramate • Topamax
Lamotrigine • Lamictal	Valproate/Divalproex • Depakote
Omeprazole • Prilosec	
Oxcarbazepine • Trileptal	

alternate class of medication. Nondrug therapies, such as cognitive-behavioral therapy, also should be considered.

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