

The Effects of Antiepileptic Drugs on Pediatric Cognition, Mood, and Behavior

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Abstract

In the past three decades, several new antiepileptic drugs (AEDs) have been marketed across the world, although with a surprisingly modest improvement in overall seizure control. During the same period, the use of AEDs as mood stabilizing or impulse control agents has been trending upwards, due to a notable increase in comorbid mood and behavior disorders in children, and a desire to address these pharmacologically. AEDs have been frequently associated with adverse mood and behavior changes, along with neuropsychiatric effects on attention, memory, and cognition. In this review, we discuss the use and adverse effects of the first- (e.g., barbiturates, carbamazepine, ethosuximide, phenytoin, valproate), second- (e.g., clobazam, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, stiripentol, vigabatrin, zonisamide), and third- (e.g., brivaracetam, eslicarbazepine acetate, lacosamide, perampanel, retigabine, rufinamide) generation AEDs in pediatric mood and behavior disorders. We also address what is currently known about the potential long-term neuropsychiatric consequences of AEDs. The distinction between the U.S. Food and Drug Administration-approved drugs versus off-label use of these drugs in the pediatric population is also examined.

Keywords

- ▶ antiepileptic drugs
- ▶ mood
- ▶ behavior
- ▶ cognition
- ▶ adverse effects

Introduction

Since the description of epileptic phenomenon in Babylonian cuneiform tablets more than 3,000 years ago, human beings have been fascinated with the etiology and treatment of seizures.¹ Hippocrates was arguably the first, in 450 BC, to describe the proposed natural or physical causes underlying the occurrence of seizures and he led the search for physical or medical cures to counter the age-old spiritual healing practices that addressed seizures as reflecting suspected demonic possession.² The dawn of antiepileptic drug (AED) therapy, however, began in 1857 with the mention of potassium bromide as a potential treatment for “hysterical epilepsy connected with the menstrual period,” published in the *Lancet*.^{3,4} In 1912, the use of newly synthesized phenobarbi-

tal as a tranquilizer in epileptic patients was linked to the decrease of their seizure frequency. The following 60 years witnessed the second phase in the evolution of AED use, which included the development of phenytoin, primidone, ethosuximide, benzodiazepines, carbamazepine, and sodium valproate. In the past three decades, considered to be the modern era of AED development, more than 28,000 compounds have been screened as AEDs.³

Unfortunately, as will be further discussed, while this explosion of new AEDs has not fully translated into better seizure control for refractory seizures, there has been important improvements in the management of seizures overall. However, the secondary use of AEDs in mood and behavior disorders has increased manifold.² This article aims to discuss the use and effects of AEDs in pediatric mood and behavior

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disorders, along with the long-term consequence of AEDs on developing cognition and regulatory control.

AEDs and Mood and Behavior Disorders

The Diagnostic and Statistical Manual of Mental Disorder (DSM-5; APA 2013), categorizes mood and behavior disorders as the following⁵:

1. Bipolar and related disorders
 - a. Bipolar I disorder
 - b. Bipolar II disorder
 - c. Cyclothymia
2. Disruptive, impulse-control, and conduct disorders
 - a. Oppositional defiant disorder
 - b. Intermittent explosive disorder
 - c. Conduct disorder

Substance/medication-induced bipolar and related disorders are not included in this article due to their presumed different etiological presentation.

Along with the antipsychotic medications, such as olanzapine, risperidone, and aripiprazole, the U.S. Food and Drug Administration (FDA) has approved several AEDs for medication management of mood and behavior disorders.^{6,7} Perucca and Mula divide AEDs into three generations (see ►Table 1).⁸ The older, or traditional AEDs, were the only medications available to treat epilepsy before 1994.⁹ Since then there has been an explosion of new AEDs coming into the treatment pipeline, although there remains only limited data to suggest that epilepsy control has substantially improved.^{8,9} The mechanism of action of these drugs is suggested, but still uncertain, due to the varying molecular targets in the brain that may facilitate impact; these consist of γ -aminobutyric acid (GABA), glutamate, N-methyl-D-aspartate receptor (NMDA)/ α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, voltage-gated sodium and calcium channels and serotonin neurotransmitters and receptors.¹⁰⁻¹² Furthermore, most of the available AEDs work on more

than one receptor or neurotransmitter system and likely to create either a synergistic or antagonistic complex interaction, or a combination of both, when utilized.¹³

FDA approved indications of AEDs in mood and behavior disorders are limited and listed in ►Table 2.^{6,7} It is of particular note that no AED is currently FDA approved for use in pediatric mood and behavior disorders, although they are indicated in different types of pediatric seizure disorders.⁶ Tran et al, published an interesting account of the national trends of anticonvulsant use in pediatric population in the United States¹⁴ and found that during the period of 1996 through 2009, along with “seizure and convulsive” diagnoses, AEDs were increasingly prescribed in psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorder, conduct disorder, oppositional defiant disorder, bipolar disorder, depression and anxiety disorders. The number of prescriptions for the AEDs essentially doubled during the course of 14 years, regardless of the indication of use, however, there was no statistically significant change in the number of visits related to seizure disorders. Among other possibilities, this finding could suggest that AEDs have been increasingly prescribed to manage conditions other than seizures such as pediatric mood and behavior disorders. The authors also note a statistically significant trend of off-label use of AEDs especially in disruptive behavior disorder. Disruptive behavior disorder (or disruptive behavior disorder not otherwise specified) was a part of the “attention-deficit and disruptive behavior disorders” in the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV-TR; APA 2000); it has now been placed in a separate category of “disruptive, impulse-control and conduct disorders” in DSM-5.^{5,15} Over the course of the studied period, there was a notable decline of divalproex (Depakote, Abbott Laboratories, Lake Bluff, Illinois, United States) use in pediatric psychiatric conditions and a trend of off-label increased use of lamotrigine.¹⁴ A similar trend has been reported in a recent publication from Italy, showing an increasing use of valproic acid and lamotrigine in mood disorders during a period of 2005 to 2011¹⁶ in that country.

Before discussing individual AEDs, it is important to review the concept of “off-label” use. Off-label use is when a medication is prescribed outside the terms of its product license or marketing authorizations, which in the United Kingdom is

Table 1 Antiepileptic drugs currently in market

First generation	Second generation	Third generation
Barbiturates	Clobazam	Brivaracetam
Benzodiazepines	Felbamate	Eslicarbazepine acetate
Carbamazepine	Gabapentin	Lacosamide
Ethosuximide	Lamotrigine	Perampanel
Phenytoin	Levetiracetam	Retigabine
Valproate	Oxcarbazepine	Rufinamide
	Pregabalin	
	Tiagabine	
	Topiramate	
	Stiripentol	
	Vigabatrin	
	Zonisamide	

Table 2 FDA-approved indications of AEDs in mood and behavior disorders

Medications	FDA-approved indications
Carbamazepine	Acute manic and mixed episodes in bipolar I disorder in ≥ 18 y
Lamotrigine	Maintenance treatment of bipolar disorder in ≥ 18 y
Valproate	Mania associated with bipolar disorder in ≥ 18 y

Abbreviations: AEDs, antiepileptic drugs; FDA, Food and Drug Administration.

defined as the terms of a medication use including its indications, recommended doses, contraindications, and special warnings and precautions.¹⁷ In the United States, off-label drug use involves prescribing currently available and marketed medications, but for an indication (e.g., a disease or a symptom) that has never received FDA approval.^{18,19} For example, Leslie et al identified that 60.2% of a total of 279,778 veterans who received antipsychotic medications in the year 2007 had no record of a diagnosis for which these drugs were approved.²⁰ In pediatric populations, off-label use of medication is estimated at 50 to 70%.²¹ Haw and Stubbs argue that although the off-label use of drugs, including mood-stabilizers, has potential benefits for the patients, informed consent and assent of the patients and their parents regarding the off-label use is required, and that more robust clinical monitoring for side effects is warranted in such situations.²²

We have divided our discussion of the AEDs being used with psychiatric conditions into two sections. The first section reviews the current use of AEDs in mood and behavior disorders, and offers guidelines for their consideration while the second section focuses on the psychiatric and neuropsychiatric adverse effects of AEDs on mood, behavior, and cognition.

Use of AEDs in Mood and Behavior Disorders

First-Generation AEDs

Barbiturates

Barbiturates potentiate GABAergic neurotransmission by acting as positive allosteric modulators of GABA_A receptors. Phenobarbital is the most widely used AED in the world. It has a long half-life ($T_{1/2}$) up to 3 to 5 days in adults and 1.5 days in children.²³ Other barbiturates include primidone, butobarbital, pentobarbital, secobarbital, and thiopental, among others. They are divided according to the $T_{1/2}$ into long, medium, short, and very short acting barbiturates. Common indications are seizure disorders, anesthesia, headache, anxiety, insomnia, essential tremors, and delirium tremens associated with alcohol withdrawal.^{8,16} Barbiturates are known inducers of enzymes and can decrease the level of other medications. They are not primarily used in mood and behavior disorders, however, exert significant effects, including depression, suicidal ideation, paradoxical aggression, etc., as discussed in the next section.

Carbamazepine

Carbamazepine blocks sodium-channel and is approved by the FDA for its use in manic and mixed episodes of bipolar I disorder in ≥ 18 years (**Table 2**). Findling and Ginsberg demonstrated the efficacy of carbamazepine extended-release formulation in an open-label pediatric trial of bipolar I disorder in a manic or mixed episode.²⁴ Around 57% of the subjects, including 58 children and 97 adolescents showed a reduction of more than 50% in young mania rating scale. Schneider et al, reported a normalization of activation of right Brodmann area 10 in 11 manic youths when compared with 10 age-matched controls in their recent study.²⁵ There is no evidence of the use of carbamazepine in schizophrenia or other psychotic disorders.²⁶

Ethosuximide

Ethosuximide blocks thalamic "T" type calcium channels, an effect possessed by drugs that are effective against absence seizures.²⁷ It is not indicated for its use in mood and behavior disorders.

Phenytoin

Phenytoin blocks frequency and use and voltage-dependent neuronal sodium channels, thus limiting the repetitive firing of action potentials. Bersudsky demonstrated its efficacy as an antimanic agent in adults' bipolar disorder that was comparable to other anticonvulsants.²⁸ Another proposed mechanism of its antimanic action was through the inhibition of p-glycoprotein pump that in turn increases the concentration of cortisol in brain tissue and thereby the availability of cortisol at the central glucocorticoid receptor. Interestingly, it is reported that phenytoin can block the hypomanic effects of prescription corticosteroids in patients with allergies or pulmonary or rheumatological illnesses.²⁹ Phenytoin is a P450 enzyme inducer and can affect the concentrations of concomitant medications such as carbamazepine.

Valproate (Divalproex)

Multiple mechanisms have been reported for the proposed action of valproate. They include increased brain GABAergic inhibitory activity, reduction of cortical excitability, and potentiation of high-frequency repetitive firing of Na⁺-dependent action potentials through blockade of Na⁺ channels.^{13,27,30} Masuch et al, recently described its role in microglial neuroprotection by a novel mechanism involving tumor necrosis factor- α release.³¹ It is FDA approved for the treatment of mania with bipolar disorder in ≥ 18 years. Liu et al, discuss eight open-label and three double-blind studies of Depakote in pediatric bipolar disorder.³² Pavuluri et al demonstrated a differential engagement of fronto-striato-temporal circuitry in pediatric mania in the functional magnetic resonance imaging study.³³ Total subjects of 36 were divided into healthy control, risperidone, and Depakote groups. Under emotional duress, divalproex group enhanced activation in a frontotemporal striatum circuit while risperidone increased activation in the dopamine (D₂) receptor rich ventral striatum. In general, open-label studies had a range of response from 53 to 74% of participants, although 65% of completers of the trial required rescue medication such as a second-generation antipsychotic or lithium. Double-blind studies did not show a superior range of response as compared with quetiapine. Furthermore, both Depakote and lithium were not found to be effective in the maintenance of bipolar disorder. Common side effects included sedation, gastrointestinal disturbance, headaches, dizziness, weight gain, tremor, and decrease platelet count.³⁴

Padhy et al assessed the role of Depakote in conduct disorder and found that of reactive/adaptive/defensive/impulsive aggression (RADI) ($n = 68$) showed a more favorable response to Depakote treatment than those with the subtype characterized by predatory/instrumental/premeditated aggression.³⁵ As RADI is displayed commonly in the

conduct disorder population, Depakote is likely to have a role in the treatment without gender or environmental bias.³⁵

Second-Generation AEDs

Clobazam

Clobazam is a long-acting benzodiazepine acting on GABA_A receptors. It is available as an anxiolytic since the 1970s and received FDA approval as an adjunct for use in partial complex seizures associated with Lennox–Gastaut syndrome.³⁶ It has not been used in pediatric bipolar and behavior disorders.

Felbamate

The proposed mechanism of felbamate is the inhibition of NMDA receptor-related sodium currents, the potentiation of GABAergic activity and the inhibition of voltage-gated sodium channels.³⁷ It is FDA approved for partial seizures since 1992. There have been no studies for its use in mood or behavior disorder.^{38,39}

Gabapentin/Pregabalin

Both gabapentin and pregabalin are structural analogues of GABA. As opposed to gabapentin that has shown no role as a mood stabilizing agent in several trials, pregabalin has shown some promise in the maintenance phase of bipolar disorder both as antimanic and antidepressant agent.^{8,40,41} The subjects included adults and older adolescents. Out of the total of 58, at the end of 2-month acute trial, 41% were considered as responders to adjunctive pregabalin. The participants were taking on an average of three additional psychotropic medications. Gabapentin has been involved in several lawsuits related to its off-label use and associated adverse consequences.⁴¹

Lamotrigine

Putative mechanisms of action of lamotrigine include sodium channel blockade and having an additional antiglutaminergic action that is believed to block the completed kindled seizures.⁴² Lamotrigine is FDA approved for its use in the maintenance treatment of bipolar disorder in ≥ 18 years. It is more specifically indicated in bipolar disorder depressed type. Peruzzolo et al, in a recent review of open-label trials, in pediatric population found that lamotrigine was effective in depressive phase of bipolar disorder. Lamotrigine was also associated with improvement in depressive, ADHD, and psychotic symptoms.^{42,43} There was a 25% discontinuation rate in these trials mostly related to the dermatological side effects of lamotrigine. Lamotrigine is associated with a reduction of interleukin 1 β and interleukin 2, as well, which purportedly relate to the inflammatory processes in the pathophysiology of neurological disorders and diseases.⁴⁴ The significance of this finding is under investigation due to the newly discovered immunomodulatory role of GABA and other anticonvulsants, including primidone, carbamazepine, levetiracetam, valproate, topiramate, phenobarbital, and lithium affecting the cytokines system, as well.^{45,46} Öncü et al published a case series on the potential use of lamotrigine in ADHD comorbid with mood disorders.⁴⁷

Levetiracetam

Levetiracetam block high voltage-activated calcium channels and is approved for partial seizures.³⁹ There have been several negative trials for its use in bipolar disorder in both pediatric population and adults.^{48,49} Its negative behavioral effects are discussed in the next section.

Oxcarbazepine

The chemical structure and mechanisms of action are similar to carbamazepine.⁵⁰ It blocks voltage-gated sodium channels. In the past decade, there have been several open-label and double-blind studies published in the literature showing no difference between oxcarbazepine and placebo in different phases of bipolar disorder such as manic, depressed, mixed, or maintenance.^{51–53}

Tiagabine

Tiagabine is a potent inhibitor of GABA uptake into neurons and glial cells.⁵⁴ After its approval as an antiepileptic, it showed some promise in the treatment of bipolar disorder with severe anxiety, however, in the following decade, its efficacy in mood and behavior is inconclusive at best.^{38,55,56} There is no evidence for its use in pediatric mood and behavior disorders to date.

Topiramate

Topiramate is considered to be a unique anticonvulsant and exerts its antiepileptic effect by several mechanisms, including modification of sodium and/or calcium-dependent action potentials, enhancement of GABA activity, and inhibition of kainate (KA)-mediated conductance at glutamate receptors of the KA type.⁵⁴ There have been used in several trials of topiramate in pediatric mood disorders.^{38,54,57} The exact mechanism of weight loss with topiramate is unclear, but this side effect has successfully been used in a recent open-label trial. Topiramate was used as an adjunct with olanzapine in pediatric bipolar disorder to counter the side effect of weight gain.⁵⁸ The weight gain in the olanzapine group was 5.3 ± 2.1 kg and the weight gain in the olanzapine + topiramate group was statistically significantly lower, 2.6 ± 3.6 kg. Topiramate augmentation, however, did not lead to a greater reduction in symptoms of mania.⁵⁸

Stiripentol

Stiripentol is a GABA modulator.⁵⁹ There are no current pediatric mood and behavior disorder trials.³⁸

Vigabatrin

Vigabatrin is the only selective, irreversible GABA-transaminase (GABA-T) inhibitor that greatly increases whole-brain levels of GABA, presumably making it more available to its receptor site.⁵⁴ Vigabatrin use in pediatric mood disorders is not recommended due to potential adverse effect. Details are given in the next section.

Zonisamide

Zonisamide is a novel AED that has a broad combination of complementary mechanisms of action. It alters the fast

inactivation threshold of voltage-dependent sodium channels and also inhibits low-threshold T-type calcium channels in neurons.⁶⁰ Like topiramate, it is also shown to decrease appetite and increase weight loss.⁶⁰ No double-blind randomized controlled trial (RCT) is available for its use in bipolar depression.³⁸ The serious psychiatric adverse such as mania, psychosis, and suicidal ideation associated with zonisamide are discussed later.⁶¹

Third-Generation AEDs

Brivaracetam, Eslicarbazepine Acetate, Lacosamide, Retigabine, and Rufinamide

Third-generation AEDs have novel mechanisms of action. No pediatric psychiatric uses have been published as of yet. Due to its relationship with carbamazepine and oxcarbazepine, eslicarbazepine acetate was used in a recent trial of double-blind bipolar disorder in adults. The outcome was not statistically significant from placebo in treating manic symptoms.⁶²

–Table 3 summarizes the AEDs effect on comorbid psychiatric disorders.

Psychiatric Adverse Effects of AEDs

First-Generation AEDs

Barbiturates

Phenobarbital and primidone have been long associated with behavioral and affective adverse effects, particularly depression.⁶³ In an open-label study, adverse effects occurred in 61% (60/99) of children receiving primidone, most commonly irritability, sleep disturbance, and hyperactivity. Severe hyperactivity has been associated with phenobarbital leading to discontinuation.^{64–68} Rates of depression were elevated in two trials comparing phenobarbital to carbamazepine (40 vs. 4%, and 38 vs. 0%, respectively).^{69,70} In the former study, suicidal ideation was also more prevalent (47 vs. 4%). In contrast, other studies have found no significant behavioral differences between phenobarbital compared with phenytoin, and carbamazepine.^{71,72}

Phenytoin

Phenytoin has demonstrated favorable mood and behavioral adverse effect profiles in comparison to other antiepileptic medications; this underlies its continued choice as a starting first-generation medication. Four studies comparing phenytoin to phenobarbital found significantly lower rates of depression and behavioral adverse effects with phenytoin.^{63,69,73–76} In a double-blind RCT of children receiving phenytoin, clobazam, or carbamazepine, phenytoin was associated with fewer behavioral effects than clobazam.⁷⁷ Though a long-term follow-up study of 392 children, demonstrated that phenytoin was associated with depression,⁷³ phenytoin has rarely been associated with adverse mood effects.⁸ It should be noted that phenytoin toxicity can cause delirium, agitated psychosis, visual hallucinations, mania, and a syndrome consisting of lethargy, ataxia, ophthalmoplegia, involuntary movements, and paradoxical seizures.^{78–81}

Valproate (Divalproex)

The beneficial affective and behavioral effects of valproate are utilized for treatment of numerous divergent psychiatric diagnoses in children and adolescents, as well as its continued emphasis in the treatment of epilepsy. Despite its known positive effects when treating seizures, the use of valproate in pediatric epilepsy has been linked to adverse cognitive effects, minor behavioral effects, and severe adverse psychiatric symptoms.^{72,82–85} A double-blind, RCT of 453 children comparing ethosuximide, valproic acid, and lamotrigine determined that the valproic acid cohort, 42% of the 115 subjects, experienced a high rate of adverse events, often leading to drug discontinuation.⁸⁶ Hyperactivity, attention problems, hostility, decreased concentration, personality change, and sleep problems were reported more frequently in the valproic acid group. In addition, a significant number of subjects in the valproic acid cohort experienced negative effects on attentional measures, in contrast to ethosuximide or lamotrigine cohort. Valproate demonstrated a more favorable behavioral symptom profile when compared with phenobarbital and had fewer adverse effects in comparison to phenytoin, or carbamazepine.^{67,72,87}

Table 3 AEDs effect on comorbid psychiatric disorders

Mood lability/bipolar disorder		Anxiety		Depression		Psychosis	
Consider	Avoid	Consider	Avoid	Consider	Avoid	Consider	Avoid
Carbamazepine Oxcarbazepine Phenytoin Valproate Lamotrigine		Benzodiazepines Gabapentin Pregabalin	Felbamate Lamotrigine Levetiracetam Tiagabine	Lamotrigine	Barbiturates Levetiracetam Pregabalin Tiagabine Topiramate Vigabatrin Zonisamide		Ethosuximide Felbamate Levetiracetam Phenytoin Tiagabine Topiramate Vigabatrin Zonisamide

Abbreviation: AEDs, antiepileptic drugs.

Source: Adapted from Zaccara and Perucca.¹³

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Carbamazepine

The affective, behavioral, and cognitive profile of carbamazepine has been extensively examined, as described above. Overall, psychiatric adverse effects are not common in children and adults treated with carbamazepine.^{24,76,88} Behavioral changes described in 7/200 children with diverse seizure types included irritability, developmental regression, agitation, obsessive thinking, auditory hallucinations, delirium, psychosis, combativeness, being “spaced out,” insomnia, aggression, hyperactivity, and paranoia. The same study reported hallucinations or psychosis in one patient and delirium in a second patient.⁸⁹ In an RCT of 108 children treated with carbamazepine, 6 of 54 children developed restlessness and hyperactivity, though behavioral improvement in young children has also been reported.³⁰ In comparisons to topiramate, phenobarbital, primidone, and phenytoin, carbamazepine demonstrated less adverse psychiatric effects, including more favorable attention and motor performance, and less behavioral problems, anxiety, depression, and aggression.^{72,73,75,86,89} However, when compared with vigabatrin, clobazam, and valproate, carbamazepine was more likely to elicit sleep disturbance, cognitive, and mood and behavioral adverse effects.^{73,90,91} One double-blind study in partial epilepsy reported evidence of agitation (6%), depression (3%), and insomnia (2%), whereas a controlled study in generalized epilepsy found no evidence of increased depression, aggression, or neurosis with treatment.^{92,93} The use of carbamazepine has been linked to improvements in obsessive compulsive and paranoid symptom profiles, and has demonstrated both positive and negative effects on cognitive performance in patients with Rolandic epilepsy.^{94,95}

Ethosuximide

Ethosuximide is relatively well tolerated by pediatric epilepsy patients with few psychiatric adverse effects. A double-blind RCT of 453 children comparing ethosuximide, valproic acid, and lamotrigine determined a higher rate of adverse events (42% of the 115 subjects), in the valproic acid cohort, unlike the subjects in the ethosuximide cohort.^{63,96} Transient, mild attentional problems were demonstrated in children treated with ethosuximide when compared with baseline.^{97,98} “Forced normalization” resulting in psychosis has been reported in both children and adults treated with ethosuximide.^{79,99} Case reports also describe the onset of psychosis, mania, suicidal ideation, “autism, anxiety, and weeping fits” in children and adolescents with ethosuximide initiation.^{79,100}

► **Table 4** summarizes the first-generation AEDs and their pertinent adverse effects.

Second-Generation AEDs

Clobazam

The FDA approved clobazam as an adjunctive treatment for Lennox–Gastaut syndrome in adults and children 2 years of age and older in 2011, though it was originally synthesized in the 1970s as an anxiolytic. Data regarding efficacy and tolerability of Clobazam is available due to longstanding international clinical use. In a multicenter, double-blinded RCT of 235 children, aged 2 to 16 years, clobazam was associated with an increased likelihood of adverse psychiatric effects in comparison to carbamazepine and phenytoin.⁷⁷ Conversely, in another randomized double-blind trial, Bawden et al demonstrated no difference in

Table 4 Psychiatric adverse effects of first generation AEDs

AEDs	Effects			Comments
	Mood	Behavior	Cognition	
Barbiturates (Phenobarbital and Primidone)	Depression Irritability Suicidal Ideation Self –injurious behavior	Hyperactivity Aggression Agitation Sleep disturbance	Impaired cognition Inattention	May be more common in children, patients with intellectual disability
Carbamazepine	Irritability Depression Psychosis	Agitation Aggression Sleep disturbance Somnolence Hyperactivity Behavioral disturbance	Impaired attention	Generally uncommon Less AE compared with topiramate, more compared with vigabatrin, valproate Improvement in OCD and paranoia
Ethosuximide	Anxiety Psychosis Mania		Mild attention	Few psychiatric AE
Phenytoin	Depression Irritability Psychosis	Somnolence	Mild cognitive impairment	Toxicity associated with agitated, psychosis, mania, visual hallucinations
Valproate (Divalproex)	Irritability Mood lability	Hyperactivity Aggression Behavioral disturbance Hostility Somnolence Sleep problems	Attention problems Decreased concentration Improved alertness	Conflicting data on cognitive and mood effects

Abbreviations: AE, aeromedical evacuation; AEDs, antiepileptic drugs.

psychiatric effects between clobazam and carbamazepine, at 6-week and 12-month follow-up.¹⁰¹ Severe behavioral adverse effects have been associated with clobazam. These symptoms include severe aggression, and severe depression associated with suicidal ideation, self-injurious behavior, incessant motor activity, and aggressive agitation, in developmentally delayed and developmentally disabled pediatric patients with epilepsy. Notably, the behavioral dysregulation occurred within a short period of clobazam initiation, and remitted within 3 weeks of discontinuation of the medication.^{102,103} Despite these behavioral effects, clobazam is considered among the safest AEDs for the children.¹⁰⁴

Felbamate

Felbamate has been associated with both beneficial and adverse psychiatric effects in epilepsy patients, though data in children are limited. Positive cognitive outcomes include improvements in alertness, attention, concentration, as well as in social, intellectual, and motor functioning.^{105,106} However, in one retrospective study of 38 children, nearly a quarter of patients experienced psychiatric adverse effects, including insomnia, anorexia, irritability, and motor or vocal tics. One patient's vocal and motor tics were severe and disruptive, and prompted discontinuation therapy.¹⁰⁷ During an RCT evaluating felbamate monotherapy, 6 of the 21 treated patients discontinued felbamate due to treatment-emergent psychiatric adverse effects, including psychosis, anxiety, sleeping difficulties, abdominal discomfort, and orobuccal dyskinesia.¹⁰⁸ Felbamate has also been linked to milder adverse effects such as decreased appetite, insomnia, and fatigue.¹⁰⁹⁻¹¹¹

Gabapentin

Gabapentin has been associated with behavioral dysregulation, though this is most commonly seen in children and adolescents with intellectual disability or developmental delay.^{105,112-115} Reported psychiatric adverse effects typically include hyperactivity, irritability, and agitation or aggression. Risk factors increasing the likelihood of behavioral symptoms include a history of ADHD, learning disorder, or previous behavior disorder and are reversible.

Lamotrigine

Lamotrigine is generally well tolerated both as an adjunctive medication and as monotherapy in children and adolescents.^{116,117} Two open-label studies in children and adolescent reported limited occurrence of overall adverse effects, including psychiatric effects. Hyperactivity, agitation, aggression, self-injurious behaviors, violence, insomnia, and hallucinations have also been reported.¹¹⁸ In contrast, another open-label study demonstrated improved behavior and alertness in 33% of children and adolescents using lamotrigine as adjunctive therapy.¹¹⁹ Two RCTs demonstrated the increased occurrence of behavioral changes, aggression, depression, anxiety, agitation, and confusion in adults with epilepsy,¹²⁰ and case reports describe potential exacerbation of behavioral problems in intellectually disabled patients.¹²¹ The positive effects of lamotrigine on cognitive function in pediatric and adult epilepsy patients include improved alertness, attention, and learning.¹²²⁻¹²⁵

Levetiracetam

Levetiracetam has well-established negative and positive behavioral and affective adverse effects in both pediatric and adult epilepsy patients. The most common adverse effects in children and adults with partial or mixed epilepsy are irritability, somnolence, aggression, and hyperactivity.¹¹² Behavioral and emotional adverse effects are common, occurring in 5 to 34% of children and adolescents taking levetiracetam.¹²⁶⁻¹³⁰ A small study of children found irritability in nearly half of the sample, followed by somnolence, irritability, and aggression.¹³¹ A recent case report details the onset of obsessive-compulsive symptoms after initiation of levetiracetam in an adolescent with no psychiatric history or intellectual disability, with resolution of the symptoms after discontinuation.¹³² Another case report details a reversible autistic regressive episode in a biologically vulnerable young girl, which resolved after the discontinuation of levetiracetam.¹³³ When used in young children, nearly 16% of the patients in one trial discontinued levetiracetam due to behavioral effects.¹³⁴ While there may be an elevated risk of adverse psychiatric symptoms in patients with intellectual disabilities with prior behavior problems, psychiatric history, or history of status epilepticus, improved alertness and behavior in patients with learning disabilities has also been described.^{135,136} The use of levetiracetam was linked to improvements in cognition and/or behavior in children with partial epilepsy.^{137,138} A RCT of children with partial epilepsy demonstrated positive effects on activities and competence scores on the child-behavior checklist scale.¹³⁹

Oxcarbazepine

Unlike its analog, carbamazepine, oxcarbazepine has demonstrated few psychiatric adverse effects. Among the limited studies performed on the pediatric population with partial epilepsy, one blinded, randomized, study of infants and young children with partial seizures and another unblinded (open label), RCT of patients demonstrated mild somnolence as the most frequent behavioral adverse effect.^{120,140} Aggression has been linked to oxcarbazepine monotherapy in a small number of children.¹⁴¹

Oxcarbazepine demonstrated mild beneficial effects on cognitive function in a pediatric retrospective study.¹⁴² In a prospective, multicenter, open-label trial of 168 children with partial epilepsy, oxcarbazepine monotherapy demonstrated improvements in perceptual organization, attention and concentration, and picture completion subtests after treatment in the intellectually normal group. The same study indicated improvement of the social problem parameter in intellectually impaired children.¹⁴³ Oxcarbazepine was not associated with decreased cognitive function when compared with carbamazepine and valproate.¹⁴⁴

Pregabalin

Few adverse mood or behavior effects have been associated with pregabalin treatment.¹⁴⁵ In one open-label add-on trial of children and adolescents, behavioral changes were reported by 32% of patients.¹⁴⁶ Adults treated with pregabalin in an open trial reported some memory difficulties, but no

mood symptoms. In this trial, patients with partial epilepsy treated with pregabalin demonstrated higher anxiety and variability in hostility scores than those treated with levetiracetam. Overactivation leading to discontinuation has also been reported.⁴²

Stiripentol

Stiripentol is not currently FDA approved in the United States. Stiripentol has been linked to adverse behavioral effects, such as hyperactivity, irritability, aggressiveness, and insomnia. In a randomized, double-blind, placebo-controlled trial, drowsiness, hyperactivity, aggressiveness, and insomnia were reported in 91% of the patients taking stiripentol versus 25% of those on placebo.¹⁴⁷

Tiagabine

There are conflicting data regarding the psychotropic profile of tiagabine. In a recent study of 231 adults and children with diverse seizure types, psychiatric adverse effects included psychomotor slowing (13%), ataxia (8%), and insomnia (5%). The majority (12/19) of the serious adverse effects reported were behavioral.¹⁴⁸ An earlier study examining tiagabine in children with epilepsy determined that the psychiatric adverse effects in children were reported in 83% of the children studied, and paralleled those of their adult counterparts, namely, asthenia, nervousness, dizziness, and somnolence.¹⁴⁹ While five clinical trials have found a greater incidence of mood disorders and nervousness in patients taking tiagabine compared with those who received placebo,¹⁵⁰ several case series and open-label studies have found that tiagabine may have beneficial or no effects on mood and anxiety.^{151–153}

Topiramate

Though generally well tolerated, topiramate has been associated with a wide range of mood, behavior, and cognitive side effects in children and adults with epilepsy. Two RCTs of children treated with topiramate reported depression, anxiety/agitation, and aggression as the most common psychiatric adverse effects, especially in patients with partial epilepsy. Other frequent adverse effects include cognitive slowing, dysphasia, and agitation, memory effects, anxiety, appetite changes, somnolence, and poor concentration.^{87,154,155} The cognitive effects of topiramate are well studied in both adults and children; however, data on the nature and duration of topiramate effects are divergent. Persistence of mild-to-moderate cognitive or behavioral impairment has been reported at 6-, 12-month, and long-term follow-up.^{89,156} However, positive behavioral and cognitive effects and increased alertness in children have also been reported.^{157–159} A double-blind RCT of topiramate monotherapy in children found high-dose topiramate was associated with slowing in psychomotor reaction times, though learning, memory, and executive function were not affected.¹⁶⁰ A retrospective, cross-sectional study found use of topiramate increased the risk of cognitive impairment by the factor 1.3 to 2.0 and negatively affected executive function.¹⁶¹

Vigabatrin

Psychiatric adverse effects of vigabatrin in children and adults are well described, both beneficial and detrimental.^{162,163} The most common behavioral presentations include hyperkinesia or hyperactivity, irritability, aggression, agitation, and insomnia, and rarely severe aggressive agitation.⁷⁸ Reported risk factors for developing adverse psychiatric effects during vigabatrin therapy include high starting and maintenance doses, severe form of epilepsy, and psychiatric history—though other studies refute the association of psychiatric adverse effects with psychiatric history.^{164–166} Though more common in adults, a case report describes the occurrence of psychosis in an adolescent with the use of vigabatrin, with a potential occurrence of “forced normalization.”¹⁶⁷ Severe psychiatric adverse effects requiring psychiatric hospitalization has been described.¹⁶⁸ Vigabatrin has fewer psychiatric effects when compared with lamotrigine and gabapentin.¹⁶⁹ The beneficial effects of vigabatrin on psychiatric symptoms include improved mood and alertness in children with partial epilepsy,¹⁶² and some reduction in aggression and stereotypies.¹⁷⁰ One outlying study reported cognitive impairments in children with vigabatrin treatment.¹⁷¹

Zonisamide

Zonisamide has been subject to discontinuation due to adverse mood and behavior effects. In a single-center study of 544 patients, 6.9% discontinued therapy due to adverse psychiatric effects, most commonly depression, aggression, psychosis, and irritability.¹⁷² A retrospective chart review of adults and adolescents treated with zonisamide reported incidence of aggression, agitation, irritability, poor attention, and hyperactivity in 23.5% of the patients.¹⁷³ Diverging from these findings, a double-blind RCT in adults and adolescents reported no discontinuation of zonisamide due to adverse effects, but noted evidence of somnolence, anorexia, and ataxia.¹⁷⁴ Two retrospective studies of adult and pediatric patients found low rates of psychiatric adverse effects.^{175,176}

► **Table 5** summarizes the second-generation AEDs and their pertinent adverse effects.

Third-Generation AEDs

Brivaracetam

Limited data are available regarding the safety and tolerability of brivaracetam. In one RCT, the most common reason for discontinuation was psychiatric adverse effects, unrelated to dose. Though the study found elevated rates of behavioral adverse events such as irritability and aggression, the numbers reported appeared to be less than in prior published reports of levetiracetam.¹⁷⁷ Clinical trials evaluating the use of brivaracetam in pediatric populations are ongoing.¹⁷⁸

Eslicarbazepine Acetate

Cognitive and psychiatric side effects associated with eslicarbazepine acetate have occasionally included anxiety, depression, insomnia, and irritability. However, in a 1-year follow-up of adults enrolled in clinical trials of eslicarbazepine, mood or cognitive effects were not reported.¹⁷⁹ Limited data are

Table 5 Psychiatric adverse effects of second generation AEDs

AEDs	Effects			Comments
	Mood	Behavior	Cognition	
Clobazam	Depression Irritability Suicidal ideation Self-injury	Hyperactivity Aggression Agitation		May be more common in children, patients with intellectual disability
Felbamate	Irritability Anxiety Psychosis	Sleep disturbance Orobuccal dyskinesia	Improved in alertness, attention, concentration, social functioning	Both beneficial and detrimental effects
Gabapentin	Irritability Mood lability Anxiety Depression	Aggression Hyperactivity Somnolence	Confusion	More common in patients with developmental delay, ADHD
Oxcarbazepine		Aggression Somnolence	Improved attention and concentration Improved social problem parameter	Few psychiatric AE No "forced normalization"
Pregabalin	Anxiety	Hyperactivity Somnolence Behavioral disturbance	Memory impairment	Few psychiatric AE
Lamotrigine	Self-injury Anxiety Irritability Psychosis	Hyperactivity Agitation Aggression Sleep disturbance Somnolence	Improved behavior, alertness, attention, learning Confusion	May be more common in patients with intellectual disability
Levetiracetam	Irritability Nervousness Depression Mood Lability Anxiety Psychosis Improved mood	Hyperactivity Aggression Behavioral disturbance Somnolence	Improved cognition and behavior Improvement on CBCL	Both beneficial and detrimental effects. May be more common in patients with intellectual disability
Stiripentol	Irritability	Hyperactivity Aggression Sleep Disturbance		
Tiagabine	Anxiety Mood disturbance Irritability Depression	Sleep disturbance Orobuccal dyskinesia	Slowing	Conflicting data. Serious behavioral effects reported
Topiramate	Depression Nervousness Anxiety Psychosis Irritability Mood lability	Aggression Agitation Behavioral disturbance Somnolence	Cognitive impairment of attention and memory Word finding difficulty Psychomotor reaction slowing Inattention Confusion Somnolence	
Vigabatrin	Irritability Depression Psychosis	Hyperactivity Aggression Agitation Sleep disturbance Behavioral disturbance	Improved alertness	Both beneficial and detrimental effects. AE more common with initiation, severe epilepsy
Zonisamide	Depression Irritability Psychosis	Hyperactivity Aggression Agitation Somnolence	Inattention	Wide range of AE

Abbreviations: AE, aeromedical evacuation; ADHD, attention-deficit/hyperactivity disorder; CBCL, child-behavior checklist.

available regarding mood, behavioral, or cognitive effects of eslicarbazine acetate in children, though in one open-label study of 31 children two patients developed moderate psychomotor agitation and behavioral adverse effects.¹⁸⁰

Ezogabine/Retigabine

Retigabine, known as ezogabine in the United States, has demonstrated some neuropsychiatric adverse effects in clinical trials. Elevated rates of confusion, psychosis, and auditory and visual hallucinations were reported in three pivotal double-blinded, RCTs of greater than 1,200 patients, though less than 5% of the studied population was affected.^{3,181,182} The factors conferring greater risk of neuropsychiatric symptoms included dosage, initial exposure to the medication, and rapid titration. Other dose-related symptoms in adults included dizziness and somnolence.⁸ The adverse effects were generally mild or moderate in severity, mostly emerged during initial titration phase, and diminished with continued use.¹⁸³

Lacosamide

In a prospective open-label study of adjunctive lacosamide for 70 children with refractory epilepsy, 50.6% (40/70) experienced psychiatric adverse effects, most commonly drowsiness, hyperactivity, sleep disturbance, and giddiness. Most adverse effects observed were mild-to-moderate in severity, though one patient withdrew due to aggressive behavior.¹⁸⁴ In a separate case report, the authors describe severe hyperactivity, aggression, and inattention within 1 week of initiating lacosamide, which abated on discontinuation.¹⁸⁵ In a retrospective study of 16 children treated with lacosamide as adjunctive therapy, Guilhoto et al reported that one patient developed oral tics while a second developed depression associated with suicidal ideation. Both patients' symptoms subsided after lacosamide was withdrawn. A third patient developed behavioral outbursts causing discontinuation of lacosamide treatment.¹⁸⁶ Lacosamide use in children has been associated with the irritability and personality change.¹⁸⁷⁻¹⁸⁹ Dizziness, headache, ataxia, motor incoordination, and visual disturbances were commonly described in pediatric studies and case series.¹⁹⁰⁻¹⁹² The cognitive effects of lacosamide in children have not been described.

Perampanel

In a multicenter, double-blind, randomized, placebo-controlled trial of 388 adults and adolescents dizziness (38%), somnolence (18%), and irritability (7.5%) were the most common psychiatric adverse effects.¹⁹³ A pooled analysis of phase III data from 1,478 patients indicated that dose-related psychiatric and behavioral effects were observed at a greater rate in the perampanel groups compared with the placebo group. Significant psychiatric adverse effects affected 12 patients (1.2%) receiving perampanel, including three cases of aggression and one case of suicidal ideation.¹⁹⁴ Serious psychiatric and behavioral adverse events were also reported in other studies of perampanel.¹⁹⁵

Rufinamide

Rufinamide is generally well tolerated by children. Both a pooled analysis of seven studies (including 212 rufinamide

treated and 197 placebo-treated children) examining the safety and tolerability of rufinamide, and a double-blind, RCT of rufinamide in pediatric patients with Lennox-Gastaut syndrome did not find an association with psychiatric adverse effects.¹⁹⁶⁻¹⁹⁸ However, adverse psychiatric effects with rufinamide have been described. In a prospective, open-label study of pediatric patients ($n = 70$) with focal refractory epilepsy found, 5.7% of patients reported agitation and irritability, leading to rufinamide discontinuation.¹⁹⁹ Adverse side effects mainly occurred during the initial titration. In a similar study of children and young adults with Lennox-Gastaut syndrome the most common side effects (6/70 patients) were somnolence and aggressive behavior, though these were transient and mild.²⁰⁰ In a retrospective, open-label study reviewing use of rufinamide in 40 children less than 4 years of age, adverse effects occurred in 37.5% of the children and were most commonly vomiting, drowsiness, irritability, and anorexia.²⁰¹ In two patients with psychiatric history, rufinamide use was linked to suicidal ideation.²⁰² Neurocognitive side effects associated with rufinamide include irritability, shift in mood, sleep disturbance, and attentional disturbances.²⁰³ Overall, rufinamide appears to have a favorable cognitive profile compared with other AEDs.²⁰¹ Clinical observation and parent report indicated positive behavioral effects, including improved attention, school performance, and social interaction in children taking rufinamide.²⁰³ A divergent finding was reported in a study examining cognitive effects of rufinamide in adolescents and adults, where no significant difference was noted between the pre- and posttreatment formal cognitive assessments.²⁰⁴

► **Table 6** summarizes the third-generation AEDs and their pertinent adverse effects.

AEDs and Suicide

Since the FDA issued an alert about an increased risk of suicide ideation and suicide behavior in people treated with AEDs in 2008, several retrospective cohort and case-control studies have attempted to clarify this issue, but gathered results have been contradictory. One retrospective analysis indicates that a subgroup of people with epilepsy, rather than specific mechanism of action of the drug, confers greater risk of developing psychiatric adverse effects of antiepileptic medications.²⁰² Another analysis revealed that the data are not supportive of the presence of a "class effect" on suicide-related behavior; on the contrary there are some data suggesting such an effect concerning treatment with topiramate, lamotrigine, and levetiracetam for which further research is needed.²⁰³ One study initially indicated elevated risk of suicidal behavior with phenobarbital, primidone, phenytoin, lamotrigine, but increased risk diminished or disappeared when psychiatric comorbidity and other well established risk factors for suicidality were analyzed.²⁰⁴ An observational nested case-control study including 453 patients with epilepsy displaying self-harm or suicidal behavior reported AEDs identified as having a high frequency of causing depression, levetiracetam, tiagabine, topiramate, vigabatrin, may increase risk of self-harm or suicidal

Table 6 Psychiatric adverse effects of third-generation AEDs

AEDs	Effects			Comments
	Mood	Behavior	Cognition	
Brivaracetam	Irritability	Aggression		
Eslicarbazepine acetate	Anxiety, depression	Insomnia Irritability	Psychomotor agitation and aggression	
Lacosamide	Depression Personality change Irritability Nervousness	Hyperactivity Sleep disturbance Somnolence Aggression Orobuccal tics Behavioral disturbance	Inattention	
Perampanel	Irritability Suicidal ideation	Aggression Somnolence		
Retigabine/ezogabine	Psychosis	Somnolence	Confusion Cognitive impairment	
Rufinamide	Irritability	Somnolence Agitation Behavioral disturbance Aggression		Common reason for discontinuation

Abbreviation: AEDs, antiepileptic drugs.

behavior.²⁰⁵ Although some AEDs can be associated with treatment-emergent psychiatric problems that can lead to suicidal ideation and behavior, the actual suicidal risk is yet to be established, but it seems to be very low.²⁰² Given the FDA's warning regarding the potential connection between suicidal behavior and epilepsy medications, elevated suicidal risk in the pediatric population with chronic illness, comorbidity of epilepsy and psychopathology,²⁰⁶⁻²⁰⁸ the paucity of data investigating the relationship between AEDs and suicidality in children, further investigation is warranted to clarify the actual potential risk of suicidality with use of AEDs in children and adolescents. Close monitoring and screening of self-injurious behavior and suicidal ideation is recommended, especially in the presence of comorbid psychiatric disorders.^{12,209,210}

Summary and Recommendations

An increased availability of second- and third-generation AEDs for refractory seizures in the past three decades has not translated into a significantly better seizure control in the big picture. As with the older generation AEDs (benzodiazepines, carbamazepine, phenobarbital, phenytoin, ethosuximide, valproate), newer AEDs (clobazam, felbamate, gabapentin/pregabalin, oxcarbazepine, lamotrigine, levetiracetam, stiripentol, tiagabine, topiramate, vigabatrin, zonisamide, brivaracetam, eslicarbazepine, lacosamide, perampanel, retigabine, rufinamide) are associated with mood and behavior effects including mood irritability, anxiety, depression, psychosis, and even suicidal ideation. The bidirectional relationship of epilepsy with psychiatric conditions such as mood, anxiety, psychosis, ADHD, dis-

ruptive behavior disorders, and suicidal ideation is well established¹² and cautions clinicians to monitor for these side effects, as the long-term safety profile of newer AEDs is still emerging in pediatric population. Authors suggest the following: (1) baseline psychiatric assessment of all epileptic patients with the use of standardized tools, (2) referral for neuropsychological evaluation in case of refractory seizures to establish cognitive function profile and periodic follow-ups to monitor progression, (3) in addition to the medication management, interdisciplinary approach to the care of patients including psychosocial interventions such as family psychoeducational and supportive interventions, individual therapy, and school accommodations, (4) early recognition of evolving safety concerns such as suicidal ideation or aggression, behavioral dyscontrol, mood dysregulation, and cognitive effects, and (5) prompt referral to psychiatry for further assessment and possible psychopharmacological interventions.

In conclusion, the jury is still out to establish the long-term safety profile of newer AEDs. A multidisciplinary coordinated team approach that includes neurologists, mental health professionals, and school-based services is warranted to provide the current evidence-based care to the pediatric population suffering from this highly complex neurobiological condition. Collaboration between the child psychiatrist, the clinicians treating the child's medical concerns, and a neuropsychologist, to monitor behavioral and cognitive impact, is well advised. This will allow for identification of potential challenges, and promote appropriate referrals and accommodation planning, to support the child in developing more effectively toward best management of mood and behavior symptoms, and educational goals.

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