Clinical Use and Monitoring of Antiepileptic Drugs

Claire E. Knezevic1 and Mark A. Marzinke1*

Background: Antiepileptic drugs (AEDs) have been used for the treatment of epilepsy and other neurological disorders since the late 19th century. There are currently several classes of AEDs available for epilepsy management, many of which are also used to treat migraines, bipolar disorder, schizophrenia, depression, and neuropathic pain. Because of their molecular and mechanistic diversity, as well as the potential for drug–drug interactions, AEDs are prescribed and monitored in a highly personalized manner.

Content: This review provides a general overview of the use of AEDs with a focus on the role of therapeutic drug monitoring. Discussed topics include mechanisms of action, guidelines on the clinical applications of AEDs, clinical tests available for AED monitoring, and genetic factors known to affect AED efficacy.

Summary: Implementation of AED therapies is highly individualized, with many patient-specific factors considered for drug and dosage selection. Both therapeutic efficacy and target blood concentrations must be established for each patient to achieve seizure mitigation or cessation. The use of an AED with any additional drug, including other AEDs, requires an evaluation of potential drug–drug interactions. Furthermore, AEDs are commonly used for nonepilepsy indications, often in off-label administration to treat neurological or psychiatric disorders.

IMPACT STATEMENT

Understanding the molecular mechanisms of action of antiepileptic drugs, as well as the role of the clinical laboratory in monitoring drug concentrations, can aid in the successful selection and management of epilepsy, in its myriad presentations.
Epilepsy is a multifactorial neurological disorder that occurs in 1% of the population and is characterized by recurrent and unprovoked seizures. Epilepsies may be generalized (affecting both brain hemispheres) or focal (localized to a single neural network or hemisphere), and these categories vary with respect to their presentation, severity, and response to treatment (1). The clinical definition of epilepsy and diagnostic criteria were updated by the International League Against Epilepsy (ILAE) in 2014 (2). A clinical diagnosis of epilepsy may be made if the following scenarios are met: (a) after 2 unprovoked seizures at least 24 h apart, (b) a single, unprovoked seizure with high risk (>60%) of recurrence, or (c) if an individual has previously been diagnosed with an epilepsy syndrome, such as benign Rolandoic epilepsy or Landau–Kleffner syndrome. Because of the multifactorial etiology of the disease, an important consideration in the clinical diagnosis of epilepsy is the ability to differentiate unprovoked seizures from those triggered by head trauma, metabolic disturbances, or drug effects; only the former are used in disease diagnosis (3).

The use of antiepileptic drugs (AEDs) is the primary modality for the mitigation of symptoms and disease management. AEDs are a diverse group of compounds with a history reaching back to the 1800s. From a historical perspective, potassium bromide was the first compound used therapeutically for recurrent seizures (4). Although potassium bromide is no longer standard of care, many traditional compounds, including phenytoin and phenobarbital, are still used today (2). AEDs may be administered as a monotherapy or combinatorially, with an overall goal of seizure prevention, while minimizing potential side effects on both cognition and mood. Currently, there are 24 AEDs approved by the U.S. Food and Drug Administration (FDA), with the synaptic vesicle 2A (SV2A) ligand brivaracetam most recently approved in 2016. A summary of antiepileptic agents, including their proposed mechanisms of action, is provided in Table 1. Application of AED therapy can be complex, as a delicate balance must be achieved with respect to efficacy, adverse effects, drug–drug interactions, pharmacogenetics, comorbidities, and patient compliance. With AED therapy, approximately 70% of epilepsy patients achieve full seizure control. Seizures that do not respond to AED therapy are considered refractory and are treated with a ketogenic diet, stimulation of the vagus nerve, deep brain stimulation, or surgery.

AED terminology and drug stratification follows a generational pattern. First-generation AEDs refers to those drugs in use or approved for use before 1993; second-generation AEDs are those approved between 1993 and 2007. The most recent AEDs, approved after 2008, are referred to as third-generation agents. While third-generation AEDs elicit their effects via a variety of mechanisms, these compounds exhibit improved bioavailability, lower plasma protein binding (with the exception of clobazam, ezogabine, and perampanel), and fewer drug–drug interactions than first- and second-generation compounds (5).

The physiological underpinning of epilepsy is a misfiring of neurons in the brain. Neuronal signaling is based on the propagation of action potentials down a neuronal axon, ultimately resulting in the release of neurotransmitters from the presynaptic neuron into the synaptic junction (Fig. 1). Once released, neurotransmitters bind to receptors on the postsynaptic neuronal membrane, allowing for signal propagation to the postsynaptic cell. Seizures result from either excess neuronal excitation or amelioration of neural inhibition. AEDs primarily function by modulating neurotransmitter activity to prevent inappropriate signaling. However, these compounds may also cause sedative effects and pain relief, resulting in AED utilization in clinicopathological states other than epilepsy.
Table 1. FDA approval years and molecular mechanisms of antiepileptic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of first FDA approvala</th>
<th>AED generation</th>
<th>Therapeutic range (µg/mL)</th>
<th>Liver enzyme(s) responsible for metabolism</th>
<th>Voltage-gated sodium channel inhibition</th>
<th>GABA-related mechanisms</th>
<th>AMPA receptor antagonist</th>
<th>Other mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Pre-FDA</td>
<td>First</td>
<td>15–40</td>
<td>CYP2C9, CYP2C19</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>1954</td>
<td>First</td>
<td>5–12</td>
<td>CYP2C19</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1953</td>
<td>First</td>
<td>10–20</td>
<td>CYP2C9, CYP2C19</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>1960</td>
<td>First</td>
<td>40–100</td>
<td>CYP3A4</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Carbamazepine</td>
<td>1968</td>
<td>First</td>
<td>4–12</td>
<td>CYP3A4</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1975</td>
<td>First</td>
<td>0.02–0.07</td>
<td>CYP3A</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>1978</td>
<td>First</td>
<td>50–100</td>
<td>CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2E1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1993</td>
<td>Second</td>
<td>12–20</td>
<td>No hepatic metabolism</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>1993</td>
<td>Second</td>
<td>30–60</td>
<td>CYP3A4, CYP2E1</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1994</td>
<td>Second</td>
<td>3–15</td>
<td>Glucuronidation</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>1996</td>
<td>Second</td>
<td>5–20</td>
<td>No significant hepatic metabolism</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>1997</td>
<td>Second</td>
<td>0.005–0.07</td>
<td>CYP3A</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1999</td>
<td>Second</td>
<td>10–60</td>
<td>No hepatic metabolism</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>2000</td>
<td>Second</td>
<td>12–35</td>
<td>ARK1C1, ARK1C2, ARK1C3, ARK1C4</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Zonisamide</td>
<td>2000</td>
<td>Second</td>
<td>10–40</td>
<td>CYP3A4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Pregabalin</td>
<td>2004</td>
<td>Second</td>
<td>2–5</td>
<td>No hepatic metabolism</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Rufinamide</td>
<td>2008</td>
<td>Third</td>
<td>5–30</td>
<td>Human carboxylesterase 1 (hCE1)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lacosamide</td>
<td>2008</td>
<td>Third</td>
<td>1–10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CYP2C19</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vagabatrin</td>
<td>2009</td>
<td>Third</td>
<td>20–160&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No significant hepatic metabolism</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retigabine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2011</td>
<td>Third</td>
<td>NA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Glucuronidated</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clobazam</td>
<td>2011</td>
<td>Third</td>
<td>0.03–0.3</td>
<td>CYP3A4, CYP2C19, CYP2B6</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perampanel</td>
<td>2012</td>
<td>Third</td>
<td>NA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CYP3A4</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>2013</td>
<td>Third</td>
<td>3–35</td>
<td>Glucuronidated</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brivaracetam</td>
<td>2016</td>
<td>Third</td>
<td>NA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>CYP2C19</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Reference for FDA approval dates: Drugs@FDA database.

<sup>b</sup> Discontinued as of June 2017 for commercial reasons.

<sup>c</sup> Therapeutic ranges are not well established; usual levels under normal dosing shown.

<sup>d</sup> No therapeutic range determined.

<sup>Ca</sup><sup>2+</sup> channel inhibitor

<sup>NMDA</sup> signal inhibition

<sup>SV2A</sup> ligand

<sup>K</sup> channel stimulation
Mechanisms of action of AED drug classes

AEDs can be stratified by their molecular mechanisms of action (Table 1). However, there are several AEDs in which the mechanism of action is not established or only partially elucidated. Each drug's mechanism of action can target specific seizure subtypes and other disease states that may benefit from the compound, including the management of pain.

Many of the traditional AEDs, including carbamazepine and phenytoin, elicit their mechanisms of action through the inhibition of voltage-gated sodium channels. These channels serve as critical components for the initiation and propagation of action potentials, facilitating neurotransmitter release and signal transmission to postsynaptic neurons. Voltage-gated channel inhibitors may exert their effects through stabilization of the channel in the inactive state via transient interactions with the core or membrane-bound portions of the channel. Certain AEDs are postulated to function solely through this mechanism, while several combine this activity with other molecular mechanisms to modulate neurotransmission.

Compounds like lamotrigine and valproic acid elicit their antiepileptic activity through several mechanisms, all related to the action of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). GABA serves to prevent the generation of action potentials at the postsynaptic neuron and is regulated by transporter protein GABA-transporter-1, or GAT-1 (6). GAT-1 facilitates GABA reuptake into the presynaptic neuron for degradation. The GABA_A receptor is a ligand-gated chloride channel that, when activated by GABA or another small molecule, hyperpolarizes the membrane, thereby suppressing action potentials in the postsynaptic neuron. Several AEDs, including phenobarbital, clonazepam, felbamate, and topiramate, are known to activate the GABA_A receptor. Others, such as tiagabine and vigabatrin, inhibit GABA reuptake or degradation, thus prolonging GABA’s inhibitory effect on neurotransmission. Additionally, gabapentin is structurally similar to GABA, and stimulates GABA release through multiple interactions, one of which may be inhibition of voltage-gated calcium channels (7).

Several other molecular mechanisms are used by AEDs that target a diverse set of proteins and processes. Levetiracetam and its recently
approved chemical analog brivaracetam are thought to exert their effects through binding to SV2A, a neurotransmitter reporter found in synaptic vesicles and endocrine granules. SV2A was shown to regulate the exocytotic release of GABA (8). Thus, these drugs may be similar to those with GABA-related mechanisms. Notably, both levetiracetam and brivaracetam have improved toxicity profiles compared with earlier generation AEDs. Phenobarbital, topiramate, and zonisamide partially elicit their antiepileptic functions by operating as competitive antagonists of the glutamate-gated α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. AMPA receptors are ligand-gated ion channels that mediate fast excitatory neurotransmission. Further, the primary mechanism of action of third-generation AED perampanel is through the noncompetitive antagonism of the AMPA receptor. Valproic acid and felbamate are both thought to combine a GABA-related mechanism and N-methyl-D-aspartate (NMDA) signal inhibition. NMDA is an agonist of the NMDA receptor, which is a postsynaptic glutamate receptor involved in the regulation of synaptic plasticity. NMDA receptor hypofunction and overstimulation have been implicated in a wide range of neurological disorders, including dementia, neuropathic pain, schizophrenia, and epilepsy (9).

Epilepsy treatment guidelines

Major epilepsy groups have published and continue to update clinical guidelines for the diagnosis and treatment of epilepsy. These include the American Academy of Neurology, the American Epilepsy Society, and the ILAE. In 2015, the American Academy of Neurology and American Epilepsy Society published a joint guidance based on a systematic review of 47 qualifying studies on the treatment of adults with a first unprovoked seizure (10). This meta-analysis revealed that the overall risk for seizure recurrence within 2 years was 21%–45% and that certain clinical characteristics were linked with an increased risk of seizure recurrence, including electroencephalogram with epileptiform abnormalities, abnormal brain imaging, prior brain insult, and nocturnal seizure. Immediate initiation of AED therapy reduced the risk of recurrence by 35% within the first 2 years when compared with delaying AED therapy until a second seizure event. In these studies, the first-generation AEDs carbamazepine, phenytoin, and phenobarbital were most often used. However, no difference in quality of life or rate of long-term (2–5 years) seizure remission was found between immediate and delayed AED therapy initiation. While the rate of adverse events from AEDs, including depression, dizziness, GI symptoms, fatigue, and headache, was as high as 31%, most adverse events were mild and reversible through dose reductions. These findings suggest that therapeutic drug monitoring (TDM) may be beneficial to ensure sufficient exposure and minimize toxicities, thereby increasing efficacy and quality of life regardless of when pharmacotherapy is initiated.

Although most clinical trials and guidelines focus on epilepsy in adult populations, children account for roughly one-quarter of all epilepsy cases. The guidelines published in 2003 by the American Academy of Neurology and the Practice Committee of the Child Neurology Society provide similar recommendations for children as those provided for adults (11). An important consideration in the initiation of daily pharmacotherapy in a pediatric population is the potential impact of drug administration on the child’s psychosocial development. Although fewer trials have been conducted in pediatric populations, the effects of AED therapy are similar in children as in adults. AED therapy likely reduces the risk of a second seizure, but it does not necessarily improve long-term remission success.

A survey of clinical trials evaluating the efficacy of AEDs for various types of epilepsy was first published by the ILAE in 2006 (12) and updated in 2013 (13). Notably, data were enriched and recommen-


AED therapy

The goals for AED therapy postdiagnosis are to prevent further seizures while minimizing adverse and off-target drug effects. Generally, AED monotherapy is initiated and patient response is monitored. If seizure control is not achieved initially, monotherapy is attempted with a different AED. Transitioning between monotherapies requires vigilant monitoring for efficacy and potential toxicity. Approximately 50% of patients achieve seizure control with monotherapy (14). Once monotherapy options have been exhausted, combination therapy with an adjunctive AED is commonly pursued for disease management. Of note, many of the second- and third-generation AEDs were initially approved as adjunctive therapies; however, recent data suggest that many of the third-generation AEDs are also effective as first-line monotherapies (15, 16). While these drugs may be preferred by patients due to a lower incidence of side effects, most are not currently approved as first-line therapies for epilepsy.

Given the large number of drugs and overlapping mechanisms of action within drug classes, AED selection can be a significant challenge. Current guidelines in the US and Europe provide multiple options for first-line, second-line, and adjunctive therapeutic options for each type of seizure, as outlined in Table 2 (17). There are many key factors that must be considered when selecting a therapy, either for initial or combination therapy, all of which are specific to the patient (18). These include (a) the demonstrated efficacy of each drug toward the specific type of seizure; (b) potential side effects of the drugs, especially with regard to the patient’s preferences; (c) hepatic and renal function; (d) use of concurrent medications, including oral contraceptives; (e) reproductive plans, as some drugs may adversely affect fertility and/or fetal development; and (f) the cost of the therapeutic agent, with respect to insurance coverage as older therapies are available as lower cost generics, while newer drugs are still on patent and may be significantly more expensive.

Addition of an adjunctive AED, or incorporation of an AED into an existing drug regimen, requires an assessment of potential drug–drug interactions. This topic is beyond the scope of this review, and reference texts are available that enumerate the many AED drug–drug interactions that have been established and observed (19, 20). In brief, most AEDs are at least partially metabolized by liver enzymes, and many AEDs either inhibit or induce hepatic cytochrome P450 enzyme activity. Drug doses must be carefully selected and adjusted to achieve desired therapeutic concentrations.

Therapeutic drug monitoring for AEDs

The importance of monitoring AED concentrations in blood has been recognized for several decades. AEDs have a narrow therapeutic window and display wide interindividual variability with regard to pharmacokinetics. One challenging aspect of AED therapy is that their clinical efficacy is variable, even among patients with the same serum drug concentrations. Given these considerations and the common use of multiple AEDs, TDM is an important aspect of pharmacological epilepsy treatment. Guidelines concerning the use of TDM for AEDs were first published by the ILAE in 1993 (21) and updated in 2008 (22). The ILAE emphasized the thoughtful application of TDM and use of TDM results within the larger clinical context.


dations made primarily for focal seizures and pediatric absence seizures. For other epilepsy types, such as generalized onset tonic-clonic and juvenile myoclonic epilepsy, only low levels of evidence were available. Overall, well-designed randomized controlled trials are lacking in epilepsy, and this makes it difficult to determine which AEDs are the most effective for each type of epilepsy. As such, empirical use of AEDs is necessary when recommended first-line drugs are not effective and literature data are limited.

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<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Presentation</th>
<th>First-line drug options</th>
<th>Adjuvant drug options</th>
<th>Further drug options</th>
<th>Drugs that may worsen seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized tonic-clonic</td>
<td>Initial general muscle stiffening, then jerking of limbs in a rhythmic pattern.</td>
<td>Carbamazepine, lamotrigine, oxcarbazepine, valproic acid</td>
<td>Clobazam, lamotrigine, levetiracetam, valproic acid, topiramate</td>
<td>NA</td>
<td>Gabapentin, phenytoin, pregabalin, tiagabine, vigabatrin</td>
</tr>
<tr>
<td>Tonic or atonic</td>
<td>Tonic: sudden and general stiffening of muscles, usually for about a minute. Atonic: sudden loss of muscle tone.</td>
<td>Valproic Acid</td>
<td>Lamotrigine</td>
<td>Rufinamide, topiramate</td>
<td>Carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, vigabatrin</td>
</tr>
<tr>
<td>Absence</td>
<td>Seizure with arrest of current behavior with EEG showing generalized spike wave activity.</td>
<td>Ethosuximide, lamotrigine, valproic acid</td>
<td>Ethosuximide, lamotrigine, valproic acid</td>
<td>Clobazam, clonazepam, levetiracetam, topiramate, zonisamide</td>
<td>Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Very short and sudden jerking movements.</td>
<td>Levetiracetam, valproic acid, topiramate</td>
<td>Levetiracetam, valproic acid, topiramate</td>
<td>Clobazam, clonazepam, piracetam, zonisamide</td>
<td>Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin</td>
</tr>
<tr>
<td>Focal</td>
<td>Seizure is limited to one hemisphere, can be localized or widely distributed.</td>
<td>Carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, valproic acid</td>
<td>Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproic acid</td>
<td>Eslicarbazepine, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, zonisamide</td>
<td>NA</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>Myoclonic seizures after waking, with onset between 5-20 years of age. May also have absence and generalized tonic-clonic seizures.</td>
<td>Lamotrigine, levetiracetam, topiramate, valproic acid</td>
<td>Lamotrigine, levetiracetam, topiramate, valproic acid</td>
<td>Clobazam, clonazepam, zonisamide</td>
<td>Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin</td>
</tr>
</tbody>
</table>
to guide dosage changes. In particular, they recommended establishing a patient-specific effective range, termed the therapeutic range, after AED therapy is initiated, and assessing drug concentrations every 6–12 months or when changes to the clinical situation warranted. In contrast to the individualized therapeutic range, the commission defined the term “reference range” as a population-based effective range established by each laboratory. Lamotrigine is a widely used AED and serves as a good example for how TDM for AEDs is practiced in the clinic. As with many AEDs, there is no established target range, but a general suggested reference range of 3–15 μg/mL is widely used. While a higher rate of mild to moderate toxicities is observed at concentrations above 15 μg/mL, some patients achieve effective seizure prevention without adverse effects at these levels, demonstrating the need to establish individual therapeutic target concentrations (23).

To date, only 2 published randomized trials have compared epilepsy patients with and without routine TDM for guiding AED dosing. Neither trial found an improvement in overall outcome with routine TDM (24, 25). These results do not, however, address the utility of TDM in selected clinical situations, such as during medication modifications, in which the information provided is likely more impactful. Further, the need for TDM of third-generation AEDs has not been definitively established and may thus be used in a different context than for first- or second-generation AEDs.

Due to short half-lives, many AEDs are associated with a high pill burden to sustain therapeutic concentrations. For some second-generation AEDs, extended-release formulations have been approved and marketed for epilepsy and other indications. These include gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate. Reviews of available pharmacokinetic data suggest that the overall PK data for extended-release formulations compares favorably to immediate-release formulations, with reductions in peak-to-trough fluctuations (26). Although small studies have shown that patients rate tolerability and quality of life higher when switched to extended-release formulations, there is no large-scale evidence of increased safety (26, 27). The potential advantages of once-daily administration include increased compliance, more stable blood concentrations, and patient preference for more convenient dosing.

Although AEDs elicit their mechanisms of action in the non-protein bound, or free, form, laboratory assays typically report total drug concentrations in serum or plasma. Free drug measurements are not indicated or clinically useful for non-highly bound molecules, such as phenobarbital. However, when a molecule is highly protein bound, such as is the case with phenytoin, measurement of free drug concentrations can provide additional information regarding therapeutic efficacy or toxicity. Anemia, hypoalbuminemia, and uremia can all displace drug–protein interactions, thereby increasing free drug concentrations. Thus, for highly protein-bound AEDs, when plasma protein concentrations are altered, such as during pregnancy, or low, such as in elderly patients, free drug measurements can be clinically useful for drug monitoring (28, 29). Non-protein bound drug may be separated using methodologies such as ultrafiltration before analysis with downstream laboratory methods.

Analytical methodologies

Immunoassays. Immunoassays are commonly employed in the measurement of many first-generation AEDs. While many vendors have automated antibody-based assays available for canonical AEDs like phenytoin and carbamazepine, immunoassay offerings for many second- and third-generation compounds are more limited. Of note, QMS™ Therapeutic Drug Monitoring via Thermo Fisher Scientific and ARK Diagnostics offer microparticle or enzyme-
based immunoassays for AED quantification, respectively. Homogeneous immunoassays are available for second-generation AEDs, including lamotrigine (30), levetiracetam (31), gabapentin (32), topiramate (33), and zonisamide (34). Offerings via third-party vendors, such as the aforementioned assays available through ARK Diagnostics, may be integrated into automated laboratory platforms to streamline laboratory workflows. Important considerations, however, include potential increased cost per assay and decreased efficiency due to limited reagent stability and laboratory needs. Further, like all immunoassays, they can be subject to interferences and cross-reactivity with similar compounds.

Mass spectrometry

In the absence of commercially available methods for all AEDs, mass spectrometry is an alternative approach for AED quantification. Notably, the use of liquid chromatography-mass spectrometry (LC-MS/MS) provides an additional level of analyte identification and can differentiate similar compounds based on fragmentation of the analyte and detection of the resulting product ions. Such laboratory tests may be targeted for a single AED or may be multiplexed in design. In the literature, there are a plethora of methods described for the quantification of individual AEDs in biological matrices, with the majority of these methods utilizing mass spectrometry. Of note are several publications describing multiplexed LC-MS/MS methods for the identification and quantification of 10 or more AEDs within a single analytical run (35–39). Simultaneous quantification of analytes is challenging due to the potential for similar retention times, variable ionization efficiency, and overlapping precursor and product ions. Nonetheless, published methods demonstrate that 10–12 AEDs, generally including first- and second-generation drugs, can be successfully quantified using as little as 10 μL of plasma or serum (35, 38, 39). Chromatographic times varied from 6–12 min (35, 38, 39). Up to 22 AEDs can be successfully quantified with 100 μL of material, including many newer AEDs. With an increased number of drugs to separate, analytical run times may exceed 17 min per sample (36, 37). Most patients on multi-AED therapy are prescribed 2 or 3 AEDs at a time, and these combinations are tailored to the individual patient. If developed for clinical use, a multiplexed assay covering most AEDs could be applied to nearly all patients and reduce the number of separate tests ordered. Further, specialized laboratories may provide quantitative tests for AED TDM utilizing immunoassay, gas chromatography (GC), high-performance liquid chromatography (HPLC), or LC-MS/MS technologies, with multiple methods potentially available for the same AED. When potential interferences with an immunoassay are of concern, methodologies that utilize chromatography could be used, as these provide physical separation of serum components.

Use of AEDs in nonepileptic disease states

While AEDs are developed and studied for their ability to address epilepsy, they are also commonly used for other indications. In fact, the majority of AEDs are prescribed to patients without an epilepsy diagnosis, mostly for the treatment of psychiatric disorders (40, 41). While the use of AEDs in psychiatric disorders is widespread, only 4 AEDs are approved by the FDA for psychiatric indications (pregabalin for generalized anxiety disorder and carbamazepine, lamotrigine, and valproic acid for bipolar disorder). Beyond this small number of drugs and limited indications, the use of AEDs in psychiatric disorders is considered off-label. Support and guidance for how AEDs can be used is derived mainly from open-label studies, small uncontrolled trials, and case reports (42). Additionally, the incidence of psychiatric disorders, particularly depression, among patients with epilepsy is higher than that of the general population and thus appropriate AED therapy may be used to treat both conditions (43).
Other common indications for AED use are neuropathic pain and headaches. Gabapentin and pregabalin are approved for postherpetic neuralgia (lingering pain from complications of shingles), while pregabalin is also approved for the treatment of peripheral diabetic neuralgia. Gabapentin and pregabalin generally provide a 30%–50% reduction in pain, although side effects of dizziness, somnolence, and weight gain are common (44). Carbamazepine is the first-line treatment for trigeminal neuralgia (severe episodic facial pain); however, the progressive nature of the disease decreases carbamazepine’s effectiveness over time (45). The Canadian Pain Society recently recommended gabapentin, pregabalin, and carbamazepine as first-line therapies and other anticonvulsants as fourth-line therapies for neuropathic pain (46).

AEDs are used for pain relief from headaches, particularly migraine headaches. While both topiramate and valproic acid are approved for the treatment of migraines, several other AEDs, such as carbamazepine, clonazepam, levetiracetam, vigabatrin, and zonisamide, are commonly prescribed off-label for this purpose (47). Unfortunately, clinical data for most AEDs for the prevention of migraines are limited. The best clinical evidence is available for topiramate and valproic acid, both of which reduce migraine frequency when compared with placebo in multiple clinical trials (48).

Genetic variables in drug metabolism

Several polymorphisms are known to have pharmacogenetic effects for one or more AEDs. These effects include alterations to pharmacokinetic parameters and increased risk of serious adverse effects. Within the HLA-B15 serotype, one polymorphism has been identified that increases the risk of certain severe adverse effects of some AEDs. HLA-B*1502 has been demonstrated to increase risk for Stevens-Johnson syndrome, a condition of blistering and peeling of the skin, due to treatment with carbamazepine, oxcarbazepine, phenytoin, and lamotrigine. The link between HLA-B*1502 and increased risk of Stevens-Johnson syndrome has been most strongly observed among the Han Chinese and Thai populations and occurs to a lesser extent in Caucasian populations, suggesting that other factors modulate the penetrance of this polymorphism (49).

Cytochrome P450 (CYP) enzymes are responsible for the oxidation processes of phase I metabolism. CYP2C9 polymorphisms have been demonstrated to decrease the rate of metabolism of phenobarbital, phenytoin, and valproic acid (49). This effect is most pronounced for phenytoin, where CYP2C9 is responsible for 90% of metabolism. Despite high-quality evidence, prospective CYP2C9 genotyping is not commonly performed, with clinical practice generally relying on monitoring serum drug concentrations and clinical presentation (50). CYP2C19 variants can also impact AED metabolism, with a substantial effect on phenobarbital and to a lesser extent on phenytoin. Initial studies also suggest that CYP2C19 variants may decrease the rate of zonisamide metabolism (49).

UDP glucuronosyltransferase (UGT) enzymes catalyze the glucuronidation of xenobiotics as part of phase II drug metabolism. Polymorphisms of UGT2B7 significantly decrease serum valproic acid levels in epilepsy patients (51). UGT1A4 is the main enzyme responsible for the glucuronidation of lamotrigine. The UGT1A4 L48V variant decreases serum lamotrigine concentrations and affects its overall efficacy in both pediatric and adult patients (49, 51). Overall, the translation of genotypes of relevant genes to dose adjustments for individual patients remains challenging, partly due to lack of conclusive evidence as well as clear guidelines.

CONCLUSIONS

Due to their range of neurotransmission-modulating mechanisms, AEDs have been
successfully used not only for the treatment of epilepsy but also for various psychiatric conditions and certain types of pain. AED therapy, either as mono- or polytherapy, successfully prevents seizures in approximately 70% of epilepsy patients. Identifying an effective AED for an individual patient involves empirical testing of different drugs, often guided by TDM. Multiple assay modalities are available for determining serum concentrations of AEDs. Furthermore, pharmacogenetics testing can be applied during consideration of AED therapy or when investigating unexpected clearance kinetics. Overall, AEDs are an important drug type that must be carefully prescribed and monitored to achieve successful treatment in a variety of conditions.

Additional Content on this Topic

**Antiepileptic Drugs: Therapeutic Drug Monitoring of the Newer Generation Drugs**
Matthew D. Krasowski, CLN, June 2013.

**REFERENCES**

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