Pharmacokinetics of new anticonvulsants in psychiatry

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Since bromide was used for catamenial seizures and hysteria by Locock in the mid-1800s, antiepileptic drugs (AEDs) have been utilized in the treatment of various psychiatric disorders.[1] Today, valproate and carbamazepine are important therapies for treatment of mania and bipolar disorder. Now, a number of newer anticonvulsant agents—including gabapentin, lamotrigine, topiramate, and tiagabine—with improved pharmacokinetic profiles are being investigated for psychiatric indications as well. In addition, the range of their psychiatric utility has been expanded, and the effect of AEDs is currently being considered not only in bipolar disorder but in panic and social phobia and in the treatment of neuropathic pain and detoxification.

The mechanisms by which these agents influence mental status and pain perception is unclear, but a review of their pharmacologic properties may reveal some potential mechanisms of action. In addition, an outline of their metabolism, drug interactions, and adverse effects will help to establish their most appropriate administration guidelines and most effective application in the psychiatric arena.

IMPROVING THE PHARMACOLOGIC PROFILE

Several pharmacologic features of the older AEDs have complicated their use. A short half-life necessitating multiple daily doses can undermine patient compliance with several of the agents.[2] High protein binding associated with some of the drugs may also result in drug interactions.[3] In addition, active metabolites of carbamazepine, valproic acid, and primidone alter the safety profile of several compounds; hepatic metabolism and clearance complicate the use of most older AEDs. All of the older AEDs are known to interact with other drugs.

The newer AEDs have an improved pharmacologic profile providing greater anticonvulsant activity while improving patient tolerability and safety. The pharmacokinetic properties of the ideal AED have been described by Gram (*Table 1*).[4] Do the newer available anticonvulsant agents used in psychiatry fit this profile of an ideal drug?

TABLE 1
PHARMACOKINETICS OF THE IDEAL AED

High oral bioavailability
No/low protein binding
Long half-life
Linear kinetics
No active metabolites
Renal elimination
No enzyme induction
No/few drug interactions

Adapted with permission from Gram.[4]

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TABLE 2
PHARMACOKINETIC CHARACTERISTICS OF THE NEWER AVAILABLE AEDs

Drug	Peak Absorption (h)	Bioavailability (%)	$T_{1/2}$(h)	Protein Binding (%)
Felbamate	2–6	> 90	15–23	25
Gabapentin	2–3	35–60	6–7	0
Lamotrigine	1–3	98	15–70	55
Topiramate	1–4	> 80	18–23	15
Tiagabine	1–2	100	5–8	96

Adapted from Gram.[4]

CURRENTLY MARKETED AEDS USED IN PSYCHIATRY

The pharmacokinetic characteristics and interactions of the newer AEDs are summarized in *Tables 2* and *3*. The benefit to be gained from these second-generation agents will be evaluated for their pharmacokinetic profiles, reduced incidence of adverse effects, and limited drug-drug interactions. Many of the newer agents do, indeed, have simpler pharmacokinetics and fewer drug interactions than the older AEDs. These parameters will be described in greater detail in the following sections.

Felbamate

Felbamate is a dicarbonate derivative that appears to potentiate the action of γ-aminobutyric acid (GABA) and to elicit postsynaptic blockade of the *N*-methyl-D-aspartate (NMDA) receptor.[5] It is the only one of the newer agents that is approved currently for use as monotherapy in the treatment of epilepsy.

Felbamate is rapidly and completely absorbed in a linear fashion after oral administration, reaching maximum concentrations in 2 to 5 hours; it exhibits a high bioavailability (> 90%).[6–8] The half-life has been estimated at approximately 20 hours,[6,7] which, theoretically, should allow for qd or bid administration. High doses frequently result in gastrointestinal complaints, so patients may tolerate it only when divided into three daily doses. Felbamate is metabolized in the liver. There is no evidence that felbamate induces liver enzymes, but it does inhibit the clearance of some other drugs.

Although protein binding is low (approximately 25%), felbamate is nonetheless associated with substantial drug interactions, particularly when combined with other AEDs. Polytherapy including felbamate has been shown to increase plasma concentrations of phenytoin,[9,10] valproate,[11] and carbamazepine epoxide and to decrease carbamazepine plasma levels.[9,10,12–14] In addition, comedication with phenytoin and carbamazepine reduces the felbamate concentration[15]; valproate may increase it.[11]

Felbamate is nonsedating, but complaints of insomnia, nausea, anorexia, and weight loss are common, and there have been reports of anxiety and psychosis.[16,17] Use of felbamate in the treatment of epilepsy significantly declined when it was reported to cause aplastic anemia and hepatic necrosis.[18,19] Its use will be limited in psychiatry as well because of these same complications.

Gabapentin

Gabapentin was developed by integrating GABA into a lipophilic cyclohexane moiety, in order to transport GABA across the blood-brain barrier. The goal was for this analogue molecule to inhibit seizures by binding to the GABA receptor. Gabapentin does have anticonvulsant activity but, in fact, does not adhere to the GABA receptor; instead, it is believed to bind to a novel site that has not been well characterized.[20]

The starting dose of gabapentin is 300 mg qd, increasing to 300 mg bid on day 2 and to 300 mg tid on day 3, with subsequent increases as needed. Gabapentin is rapidly absorbed (2 to 3 hours) following oral single-dose administration. Food has no effect on absorption. The bioavailability, estimated at 60%, can be variable due to the drug's dose-dependent absorption kinetics over the dose range 100 to 900 mg.[21] This dose dependence is probably related to the mechanism of absorption from the gut, which functions via a saturable L-system transporter for neutral amino acids.[22] The

TABLE 3
INTERACTIONS OF THE NEWER AEDS

Parent	Induces Metabolism of These Drugs	Inhibits Metabolism of These Drugs	Induces Parent Drug Metabolism	Inhibits Parent Drug Metabolism
Felbamate	CBZ	CBZ-E, PHT, PB, VPA	PHT, PB, CBZ	None
Gabapentin	None	None	None	None
Lamotrigine	None	None	PHT, PB, CBZ	VPA
Topiramate	Oral contraceptives	None	PHT, PB, CBZ	None
Tiagabine	None	None	PHT, PB, CBZ	None

CBZ=carbamazepine, CBZ-E=carbamazepine epoxide, PB=phenobarbital, PHT=phenytoin, VPA=valproic acid.
Adapted from Gram.[4]

nonlinear absorption profile is unique among the AEDs. This saturable transport mechanism may reduce the symptoms from overdose because the maximum drug absorption results in a lower plasma level.

The serum half-life of gabapentin is relatively short, at 6 to 7 hours. In the central nervous system (CNS), however, the effect of the drug appears to be longer than the serum half-life would suggest. Thus, the CNS efficacy is sustained beyond the duration of peak serum levels,[23] probably because of accumulation of gabapentin in the neurons. Gabapentin does not undergo hepatic metabolism in man and is excreted unchanged in the urine. Dose adjustments may be necessary in renally impaired patients.[24] Hemodialysis does increase clearance in anuric patients.[25] The absence of hepatic metabolism and zero protein binding prevents significant drug interactions, although alterations in gabapentin renal clearance have been observed with cimetidine,[21] and reduced absorption has been related to use of aluminum/magnesium hydroxide antacids.[26] There are no interactions with oral contraceptives.[21]

The most common adverse effects of gabapentin are somnolence, ataxia, dizziness, and fatigue. Significant side effects, however, are uncommon and rarely necessitate withdrawal of the drug.

Pregabalin, which is currently in clinical trials, is structurally similar to gabapentin, binds to the gabapentin-specific receptor, and may prove to be a more potent and longer-lasting analogue of gabapentin.[27] This compound will likely prove to have a role in neurology, psychiatry, and pain management as future research unfolds.[28]

Lamotrigine

Lamotrigine is a phenyltriazine derivative that inhibits voltage-gated sodium channels and reduces the release of glutamate. The anticonvulsant spectrum of this drug, however, is far broader than that of phenytoin and carbamazepine, which also work at the sodium channels. In addition, its psychiatric activity suggests additional mechanisms play a role in its clinical activity.

Lamotrigine is rapidly (1 to 3 hours) and completely absorbed, with almost 100% bioavailability.[29–31] It has moderate protein binding (56%) that is unaffected by other AEDs.[32] In monotherapy it has a half-life of 25 hours, but when administered with metabolism-inducing agents such as phenytoin or carbamazepine, the half-life drops to ≤ 15 hours.[30,33] When combined with a drug that inhibits its metabolism, such as valproic acid, the half-life can reach 60 hours.[33] This potential for drug interaction complicates its titration schedule (*Table 4*). Lamotrigine has no significant effect on plasma concentrations of other AEDs or on oral contraceptive efficacy.

Lamotrigine is conjugated in the liver. It follows linear kinetics, but to some extent has been shown to induce its own metabolism[34]; thus, with higher doses, where autoinduction is greater, the plasma concentration would appear to fall off somewhat on a kinetic curve.

Rash, similar to that observed with phenytoin and carbamazepine, can be a significant problem during lamotrigine therapy. In early clinical trials, roughly 8% of adults and 16% of children experienced a rash.[35] Serious rashes requiring hospitalization occur in < 0.5% of patients, but because they may lead to

TABLE 4
LAMOTRIGINE TITRATION SCHEDULE FOR ADULTS*

Without VPA but with enzyme-inducing AEDs
Add-on:
Begin 50 mg/d
Increase to 50 mg bid after 2 weeks
Increase by 100 mg every 1 to 2 weeks to maximum of 500 mg

With VPA and enzyme-inducing AEDs
Add-on:
Begin 25 mg every other day
Increase to 25 mg/d after 2 weeks
Increase by 25 to 50 mg/d every 1–2 weeks to 100 to 150 mg/d

*Note: New titration schedules for adults and children are under consideration by the manufacturer and the FDA. VPA = valproate.

Stevens-Johnson syndrome, toxic epidermal necrolysis, and angioedema, all rashes should be regarded as serious. Early studies of lamotrigine were performed prior to the clarification of its interaction with valproate, and before slow titration was known to be a necessity.[35] Low starting doses and slow dose titration are important and markedly reduce the occurrence of rash in adults and children.

Topiramate

Topiramate is a sulfamate-substituted monosaccharide with influence at several neurologic sites. It inhibits rapid firing at voltage-dependent sodium channels, increases the effect of GABA at the $GABA_A$ receptor, and antagonizes kainate at the α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor.[36]

Topiramate therapy is initiated at a dose of 25–50 mg/day and titrated with weekly 25-to 50-mg increases to an effective dose (usually 200–400 mg). It is well absorbed following oral administration,[36] although absorption may be slowed by food.[37] It has a half-life of approximately 20 hours, allowing bid dosing. The bioavailability exceeds 80%. It is largely unbound to plasma proteins and predominantly (80%) excreted unchanged in the urine in a linear manner, undergoing 20% hepatic oxidation (when given as monotherapy).[37]

Topiramate does not affect liver enzymes and has no effect on plasma levels of carbamazepine or valproate[38]; it can reduce clearance of phenytoin, however, by as much as 20% in some patients.[38–41] In the presence of metabolism-inducing drugs, topiramate becomes more extensively metabolized in the liver, and its plasma concentration and half-life fall by as much as 50%.[38–41] In addition, topiramate can interfere with the efficacy of oral contraceptive agents; women taking these drugs should be advised of this interaction and should consult with their gynecologist.

The main adverse effects of topiramate therapy[42] include somnolence, dizziness, ataxia, speech and cognitive disorders, and fatigue. Weight loss occurs in about 20% of patients. Cognitive symptoms—including difficulty with speech, memory, and language processing—are insidious and affect roughly 25% of patients. The cognitive side effects are the principal reasons why patients discontinue therapy with this drug.

Tiagabine

Tiagabine is a nipecotic acid derivative that blocks glial and neuronal reuptake of GABA, resulting in elevated extracellular GABA concentrations. Its mechanism is thought to be via intensification of inhibitory GABA-ergic transmission.[43]

Tiagabine is rapidly and well absorbed after oral administration,[44] reaching peak concentrations within 1 hour (food intake may slow absorption).[45,46] It is approximately 95% protein bound and extensively metabolized, probably in the liver by the P450 enzyme system.[47–49] The half-life during monotherapy is 8 hours.[48] Tiagabine is not itself an enzyme-inducing agent, but when added to enzyme-inducing medications, its clearance is increased and half-life reduced to 4 to 6 hours. It exhibits a linear excretion profile.[50]

Tiagabine does not appear to interfere with the metabolism of other AEDs,[51] but there is theoretic potential for pharmacodynamic interaction with other GABA-enhancing compounds. Tiagabine does not interfere with the efficacy of oral contraceptives,[52] but little is known about other drug-drug interactions. It is often prescribed with food to delay the extremely rapid absorption and thereby minimize side effects. The most common side effects of tiagabine are dizziness, somnolence, and tremor. It

may also cause confusion, as well as speech and language problems.

SUMMARY

The newer AEDs have potential in the treatment of psychiatric disorders. In light of this expanding spectrum of activity, it is necessary to refine and focus the safety and efficacy of the use of these agents among a wider population. The classic AEDs had numerous problems, ranging from inconvenient dosing schedules to frequent side effects due to active metabolites and common drug interactions; newer agents have been developed to avoid some of these pitfalls. Indeed, a generation of drugs that appears to have relatively simple pharmacokinetics and limited drug interactions—making them safer and easier to administer—is now available.

The use of these agents in psychiatry will necessitate additional investigation into their dosing and administration guidelines, as well as their interactions with other common psychiatric or concomitant drugs. Certainly, over time, they will be evaluated for these parameters in the newer indications. In the meantime, a review of the established pharmacokinetic and pharmacodynamic activities of these agents is the first step in defining their optimal uses and limitations in the psychiatric setting.

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