

Newer Anticonvulsants: Dosing Strategies and Cognition in Treating Patients With Mood Disorders and Epilepsy

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Background: Anticonvulsants are employed to treat a variety of disorders. The most common adverse side effects of anticonvulsants are mediated via the central nervous system. Examples include sedation, dizziness, psychomotor slowing, and impairment of attention, memory, and other cognitive functions. Since multiple new anticonvulsants have been introduced in recent years, the question arises as to the frequency and magnitude of their cognitive side effects. **Method:** Experimental design flaws in assessing the cognitive effects of anticonvulsants were reviewed. A MEDLINE search of the medical literature was conducted, cross-referencing terms related to cognition and anticonvulsants. Research articles were selected based on their relevance to the topic and adherence to methodological criteria. **Results:** Incomplete information is available on the new anticonvulsants, but the present data suggest that some of the newer anticonvulsants possess favorable cognitive profiles. Also, the importance of dosing regimens and titration speed at drug initiation is discussed. **Conclusion:** All anticonvulsants possess some cognitive side effects, but differential effects can be seen. The cognitive effects of several newer anticonvulsants have been examined, but additional studies are needed to fully establish the cognitive effects of these agents. Dosage, titration rate at initiation, comedications, individual sensitivity, and underlying disease processes may influence cognitive side effects. Understanding these factors is important to maximize the benefits of anticonvulsant therapy. Cognitive side effects are one of the factors that physicians should consider in drug choice and monitoring of their patients.

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Paracelsus, who lived in the early Renaissance, has been called the “father of pharmacology.”¹ His real name was Phillipus Aureolus Theophrastus Bombastus Von Hohenheim (1493–1591), and he became famous through a series of remarkable cures after local physicians had failed. Paracelsus was one of the first to recognize the importance of dosing in medicinal therapy. He noted that “the right dose differentiates a poison and a remedy.”²

Dose, titration, and both pharmacodynamic and pharmacokinetic interactions are important to consider in clinical pharmacology. They can dramatically influence efficacy and tolerability of medications. These factors vary widely across medications, and when a new medication is introduced, it takes time to understand it and apply the

knowledge to optimize the utility of the medicine. Further, these factors vary across individual patients, which creates an additional challenge for the physician.

ANTIEPILEPTIC DRUGS/ANTICONVULSANTS

The term *antiepileptic drugs* is an ironic title for a class of drugs that has not been proven to be truly “antiepileptic” in the sense of preventing epilepsy. Antiepileptic drugs are actually anticonvulsant or antiseizure drugs. Further, antiepileptics are not used solely for epilepsy. In fact, the number of antiepileptic drug prescriptions written in the United States over the last several years for treating epilepsy or seizures is less than half of the total number of prescriptions. The majority of the other prescriptions are written for pain or psychiatric indications. Despite these caveats, the term *anticonvulsant* will be used here.

Irrespective of the disorder, physicians and patients are concerned about the side effects of a medication. Anticonvulsants produce a variety of side effects, but the most common are central nervous system effects such as sedation, dizziness, and cognitive impairment.³ Since anticonvulsants were developed to reduce neuronal irritability, it should not be surprising that they also reduce neuronal excitability and affect cognition.

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Despite the common use of anticonvulsants in treating patients with pain and psychiatric disorders, formal investigations of the cognitive side effects of anticonvulsants have not been conducted in these patients, except for in patients receiving benzodiazepines. Numerous studies on the cognitive effects have been conducted in patients with epilepsy. These studies may or may not be generalizable to psychiatric patients depending on design flaws and whether substantial reductions in seizures may have improved cognition and offset any anticonvulsant-induced adverse cognitive effects. However, anticonvulsant cognitive studies have also been conducted in healthy volunteers, which may be more pertinent to psychiatric populations. Nevertheless, the overall magnitude and differential effects found in these studies have been similar to those in well-controlled studies in patients with epilepsy.³

METHODOLOGICAL ISSUES

The magnitude of anticonvulsant effects on standard neuropsychological measures is modest and is generally about the size of test-retest effects. Thus, the effects of anticonvulsants may be missed if appropriate study designs are not employed.⁴ In contrast, flaws in the experimental design may lead to apparent drug differences, which may actually be attributed to other factors. The literature on the cognitive effects of anticonvulsants must be viewed cautiously because of frequent problems in experimental design, analysis, and interpretation.^{3,4} Experimental design errors include subject-selection bias, nonequivalence on clinical variables, and nonequivalence on dependent variables. Subject-selection bias occurs when subjects are not randomly assigned to treatment groups, when subjects are not adequately matched, or when the sample size is inadequate for a parallel-group design. Nonequivalence on clinical variables may occur when there is a failure to control for dose, anticonvulsant blood levels, or titration. Nonequivalence of the dependent measures may occur if the treatment groups are not similar on the dependent measures prior to treatment.

Other design issues to consider include sample size, test-retest effects, and the characteristics of the cognitive tests. Because the cognitive effects of anticonvulsants are modest and actually about the size of test-retest effects, it is important to control for test-retest effects as well for individual variation. One effective method is the use of randomized, double-blind, crossover designs. However, their application in patient populations can be problematic owing to practical and ethical concerns.

The statistical analyses should employ appropriate contrasts and instruments. When multiple comparisons are made, there is a risk of type I error (i.e., a statistical difference owing to chance fluctuation, which is not a real difference). If a difference is found, a consistent pattern of deficits across similar cognitive tests should be apparent.

Control of type I error should be balanced with the risk of type II error (i.e., finding no difference when a real difference is actually present). Finally, the magnitude and impact of the statistical findings must be interpreted in terms of clinical significance taking into account the overall risks:benefits ratio of the anticonvulsant and the severity of the underlying disorder.

COGNITIVE EFFECTS OF THE OLDER ANTICONVULSANT DRUGS

The risk of adverse cognitive effects from anticonvulsants is increased with polytherapy.³ Higher dosages and blood levels are also associated with an increased risk, but this relationship is modest within standard therapeutic ranges.³ For example, very high dosages of some anticonvulsants can induce coma. However, some patients may tolerate and respond best at levels above the standard ranges. Of note, the anticonvulsant doses employed in psychiatric disorders are frequently lower than the dosages employed in epilepsy.

Cognitive side effects are more prominent on initiation of an anticonvulsant, and slower titration rates reduce these effects. Over approximately 3 weeks at steady dose, patients habituate somewhat to the cognitive effects of anticonvulsants. The habituation to the perceived subjective side effects is greater than the habituation to objective cognitive side effects. Patients' perception of cognitive side effects from anticonvulsants are better correlated with mood than with objective cognitive performance.⁵

Healthy volunteer studies⁴ avoid the effects of seizures or premorbid brain abnormalities on cognition. Further, such studies allow ready application of double-blind, randomized, crossover designs, which control for test-retest effects and variance in performance across individuals. Although differences in the behavioral effects of carbamazepine, phenytoin, and valproate exist, healthy volunteer studies³ have shown that these 3 anticonvulsants have similar cognitive side effects. However, phenobarbital has significantly more adverse side effects. In one study comparing carbamazepine and phenytoin, only 2 variables (10%) of the neuropsychological variables were significantly different (1 variable in favor of each anticonvulsant).^{6,7} Thus, no overall difference between carbamazepine and phenytoin was noted. In contrast, performances on 52% of the neuropsychological measures were significantly worse for the 2 anticonvulsants compared with the nondrug average. In a separate healthy volunteer study,⁸ performance was worse with phenobarbital for 32% of the measures compared with phenytoin or valproate. Phenytoin and valproate differed on only a single measure, which was considered to be a chance finding (i.e., type I error). Again, significant differences were found between the average nondrug condition and the anticonvulsants. Compared with the 3 anticonvulsants, nondrug performance was better on 55% of the variables.

All of the older anticonvulsants produce cognitive side effects. However, the magnitude of the effect for carbamazepine, phenytoin, and valproate is modest and appears to be less than that of the acute dose of over-the-counter antihistamines.^{3,9} In contrast, phenobarbital has a more adverse cognitive profile. The major cognitive effects of the anticonvulsants include psychomotor slowing and reduced attention/vigilance and, secondarily, impairment of other cognitive functions such as memory.³

COGNITIVE EFFECTS OF THE NEWER ANTICONVULSANT DRUGS

Multiple new anticonvulsant drugs have been brought to market in recent years, although none of these new anticonvulsants are approved for psychiatric indications. The data on the cognitive profiles of the new anticonvulsants are still being developed. In particular, direct comparisons with older anticonvulsants and between the new anticonvulsants are limited. A review of cognitive studies involving the newer anticonvulsants follows.

Felbamate

Felbamate has been noted anecdotally to be alerting in contrast to the older standard anticonvulsants. However, the bone marrow and liver toxicity of felbamate severely limits its clinical utility in epilepsy and eliminates its use for off-label indications, such as psychiatric disorders.

Gabapentin

Gabapentin is generally well tolerated, and several studies¹⁰⁻¹² have reported positive psychotropic effects in patients with epilepsy. However, irritability, hyperactivity, and agitation have occurred in children with epilepsy.^{13,14}

Gabapentin versus placebo in patients with epilepsy. Different doses of gabapentin were compared with placebo in an adjunctive, crossover study¹⁵ of 27 adult patients with partial seizures. Each treatment arm was 3 months. No significant differences were noted on 37 neuropsychological variables. However, subjective drowsiness was higher in patients during treatment with gabapentin at 2400 mg/day.

Gabapentin versus carbamazepine in healthy volunteers. The cognitive effects of gabapentin and carbamazepine were compared in a double-blind, randomized, crossover study¹⁶ in 35 healthy adult volunteers. Each treatment period was 5 weeks. The neuropsychological battery included 31 variables and was performed during nondrug periods and at the end of each anticonvulsant treatment period. Carbamazepine was titrated to blood levels in the mid-therapeutic range (6–12 µg/mL); the mean dose was 731 mg/day, and mean blood level was 8.3 µg/mL on the day of testing. Gabapentin was titrated to 2400 mg/day in all subjects. Gabapentin-treated patients scored significantly better on 26% of the variables when compared with carbamazepine-treated patients. Compared with

carbamazepine, performance in the nondrug conditions was significantly better on 48% of the variables. Carbamazepine was superior to the nondrug condition on 3% of the variables. Gabapentin was significantly worse compared with nondrug conditions on 19% of the variables and was better on 3%. Thus, both carbamazepine and gabapentin produce some cognitive side effects, but gabapentin has fewer cognitive side effects.

Lamotrigine

In several studies,¹⁷⁻¹⁹ quality of life measures have demonstrated beneficial effects on perception of psychological well-being in patients with epilepsy. These positive effects were seen in direct comparisons with placebo, carbamazepine, and phenytoin. Such observations suggested possible positive psychotropic effects and led to ongoing trials for lamotrigine in psychiatric disorders. In the above placebo-controlled study,¹⁷ a brief neuropsychological battery found no cognitive differences between lamotrigine and placebo as adjunctive therapy in epilepsy patients.

Lamotrigine versus carbamazepine in healthy volunteers. The cognitive effects of lamotrigine and carbamazepine were compared in healthy volunteers using a double-blind, randomized, crossover study.²⁰ Lamotrigine was titrated to 150 mg/day, and carbamazepine was titrated to the mid-standard therapeutic range. The mean dose of carbamazepine was 696 mg/day, and mean blood level was 7.6 µg/mL on the day of testing. The neuropsychological battery included 40 variables and was performed at 2 nondrug baselines and at the end of each 10-week anticonvulsant treatment period. Comparison of the 2 anticonvulsants revealed significantly better performance on 48% variables for lamotrigine, but none for carbamazepine. The nondrug average was significantly better than carbamazepine on 62% variables, but no variable was significantly better for carbamazepine. The nondrug average was significantly better than lamotrigine on 2.5% of the variables, and lamotrigine was better on 2.5%. Thus, lamotrigine produced significantly fewer cognitive side effects than carbamazepine at the dosages employed in this study.

Levetiracetam

Approved recently for the adjunctive treatment of partial epilepsy, levetiracetam has a favorable efficacy-to-side-effect ratio; however, no formal studies of its cognitive effects have been reported.

Oxcarbazepine

In clinical epilepsy trials, oxcarbazepine has been reported to be better tolerated than carbamazepine or phenytoin, but few studies with formal cognitive assessments are available. Oxcarbazepine did not differ from phenytoin on cognitive tests in a small parallel-design study²¹ of patients with new onset epilepsy. One small, healthy volunteer study²² found that subjects improved on

a cancellation task with oxcarbazepine but had slowing of reaction time.

Tiagabine

Tiagabine versus placebo in patients with epilepsy. Tiagabine at doses of 16, 32, or 56 mg/day was compared with placebo in a double-blind, add-on, parallel, dose-response study²³ of patients with complex partial seizures. Maintenance treatment was 12 weeks after a 4-week dose-titration phase. No significant differences were found on any of the 11 variables; however, the results may have been biased by a greater dropout rate for tiagabine than for placebo.

Tiagabine versus carbamazepine and phenytoin in patients with epilepsy. Tiagabine was compared with carbamazepine and phenytoin in adjunctive therapy for patients with partial epilepsy.²⁴ Patients were tested on 11 neuropsychological tests at baseline and after 16 weeks of add-on therapy. No significant differences were found between tiagabine and phenytoin. Compared with carbamazepine-treated patients, tiagabine-treated patients had better verbal fluency and faster psychomotor speed but had less positive mood and increased financial concerns.

Topiramate

The early clinical trials revealed that topiramate could produce somnolence, psychomotor slowing, memory problems, and language deficits including word-finding difficulties. However, in a clinical trial²⁵ conducted prior to marketing, cognitive side effects were reduced by a slower titration at the initiation of topiramate therapy.

Topiramate versus gabapentin and lamotrigine in healthy adults. The cognitive effects of these 3 anticonvulsants were compared in a randomized, single-blind, parallel-group study in a small number (N = 17) of healthy adults.²⁶ Subjects were tested at baseline and then after an acute single dose (gabapentin, 1200 mg; lamotrigine, 250 mg; or topiramate, 200 mg). Subjects were then restarted at lower doses, which were titrated upward over 4 weeks (end dosages: gabapentin, 2500 mg; lamotrigine, 500 mg; topiramate, 400 mg). It is important to note that the rate of titration for topiramate exceeded recommendations, which biased the study against topiramate. Gabapentin and lamotrigine showed no significant effects after the acute dose, but topiramate produced significant declines on several measures. Only topiramate displayed adverse cognitive effects at week 4.

Topiramate in patients with epilepsy. A retrospective, nonrandomized sample of epilepsy patients treated with topiramate was evaluated with formal neuropsychological testing.²⁷ Marked cognitive deficits were demonstrated; however, the retrospective, nonrandomized nature of the study may have exaggerated the usual magnitude of effects and thus may not have been representative of the risk for most patients.

Topiramate versus valproate in patients with epilepsy.

Two randomized, double-blind, parallel group, multicenter, adjunctive-therapy studies^{28,29} in patients with epilepsy have compared the cognitive effects of topiramate and valproate. In both studies, patients received topiramate or valproate in add-on treatment to carbamazepine monotherapy. In the multicenter European study,²⁸ topiramate was titrated slowly over the first 8 weeks at a rate of 25 mg/day. Additional increases were then made at 25 or 50 mg/day over the next 4 weeks to 400 mg/day or maximum tolerated dose. Subsequently, patients were maintained at a constant dosage for the remaining 8 weeks of the study. The mean dose for topiramate was 251 mg/day and for valproate, 1384 mg/day. Overall, topiramate effects were comparable to those of valproate. Only 1 statistically significant difference was found across the 17 neuropsychological variables at the end of the maintenance phase: performance on a verbal memory task was better for valproate. The cognitive effects produced by topiramate were less than those found in clinical trials using faster titration and higher dosage.

Preliminary results from a similar multicenter study²⁹ conducted in the United States found comparable results. Topiramate, valproate, or placebo were added on to carbamazepine monotherapy. Only a small group received placebo. In contrast to the European study, topiramate was titrated at 50 mg/day. Dosages were titrated over 8 weeks and maintained over 12 weeks. Target dosages were 400 mg/day for topiramate and 2250 mg/day for valproate. The neuropsychological battery included 24 variables. At the end of the maintenance phase, only 2 tests showed significantly greater negative effects for topiramate compared with valproate (i.e., symbol-digit modalities and controlled word association). Compared with the placebo group, the topiramate group performed worse on 6 variables, and the valproate group performed worse on 1 variable at the end of maintenance. The statistical effect appeared to be driven by a subset of patients who were particularly affected by topiramate.

Zonisamide

The only formal investigation of zonisamide's cognitive effects is a small preliminary study³⁰ involving add-on therapy in epilepsy patients. Zonisamide was reported to impair cognition (e.g., learning), but some tolerance appeared to develop over 24 weeks.

CONCLUSIONS

The major cognitive effects of the anticonvulsants include psychomotor slowing and reduced attention/vigilance and, secondarily, impairment of other cognitive functions such as memory. Differential effects are seen across some anticonvulsants, but additional studies are needed to further delineate the cognitive side effects of the newer anticonvulsants. Cognitive side effects from anticonvulsants

are influenced by dosage, titration rate at drug initiation, comedICATIONS, individual sensitivity, and underlying disease processes. Understanding these factors is important in maximizing the benefits of anticonvulsant therapy. Cognitive side effects are one factor that physicians should consider in anticonvulsant selection; however, the ultimate goal is to select the drug that has the greatest efficacy to alleviate the underlying disease while producing the fewest side effects.

Drug names: carbamazepine (Tegretol and others), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Kepra), oxcarbazepine (Trileptal), phenobarbital (Donnatal and others), phenytoin (Dilantin and others), tiagabine (Gabitril), topiramate (Topamax), zonisamide (Zonegran).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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