REVIEW

Side Effect Profiles and Behavioral Consequences of Antiepileptic Medications

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In 1991, Dodrill carefully reviewed the behavioral effects of antiepileptic drugs (AEDs) and concluded: "The area of behavioral effects of antiepileptic drugs is poorly defined, lacks recognized and validated methods of assessment, and has suffered from a number of methodological limitations, especially including the use of experimental designs which have led to the contamination of drug effects and subject effects" (1). He further observed that the best controlled study showed that the behavioral effects of AEDs were quite limited; the benzodiazepines had the most consistently favorable effect, but were of limited utility in epilepsy, because they were not typically administered on a long-term basis; carbamazepine was associated with a favorable behavior change, but this change was seen most consistently in nonepileptic subjects; relatively few studies of valproic acid had been conducted; phenytoin was not associated with either a consistently positive or consistently negative change; and the barbiturates were clearly associated with the most negative behavior change.

Since Dodrill's review, eight new AEDs have been approved by the Food and Drug Administration (FDA) for use in the United States, thereby dramatically increasing the therapeutic options for patients with epilepsy. These new drugs also increase the complexity of choosing the ideal drug for any given patient. Certainly a critical component of the decision to initiate or continue a specific treatment is the side effect profile of the medication. In clinical practice, behavioral and cognitive side effects of the older AEDs are significant concerns.

This paper reviews the clinically important behavioral and cognitive side effects of the more commonly used, established AEDs as well as the newer AEDs within the limits of currently available published peer-reviewed literature and clinical experience. Particular emphasis is given to subpopulations at risk. © 2000 Academic Press

OVERVIEW OF AED ADVERSE EFFECTS

Adverse effects from AEDs can be categorized as dose/concentration-related effects, inherent side effects, idiosyncratic reactions, and additive effects (when given in combination therapy).

Dose/concentration effects of AEDs are usually straightforward to recognize and usually cause symptoms referable to the central nervous system (CNS).

Specific drugs may result in characteristic patterns of CNS toxicity.

The inherent side effects often include lethargy, decreased attention span, change in sleep patterns, impotency, irritability, ataxia, diplopia, headache, and leukopenia, which may blend into dose/concentration effects for some patients.

Idiosyncratic reactions are of greatest concern because they can be potentially life-threatening. Examples are allergic dermatitis, which can progress in some cases to a Stevens-Johnson syndrome; lupus erythematosus; bone marrow depression or failure;
hepatotoxicity; renal failure; pancreatitis; and encephalopathy (2, 3).

Additive effects are particularly important for AED therapy, since nearly one-half of patients are on polytherapy and experience neurotoxic symptoms (2, 3).

In addition to the above potential side effects, AED therapy can also have behavioral consequences, both directly and indirectly. Occasionally, the direct behavioral and/or cognitive effects of AEDs develop so gradually that the patient is unaware of the changes. Other patients, for example, those patients who are cognitively impaired, very young, or mentally ill, may be unable to express AED-related discomfort except by a change in their behavior. Besides these indirect effects on behavior, these groups are also more vulnerable to direct behavioral effects.

PHENYTOIN

The dose/concentration side effects of phenytoin are well established and include cognitive impairment, ataxia, poor concentration, and dyskinesia. The unique challenge to prescribing phenytoin results from its nonlinear kinetics. Unlike the ideal AED that has linear kinetics (i.e., a change in dose at any point on the curve results in the same change in the serum concentration), phenytoin, for most patients, changes from first order to saturation kinetics at the lower end of the therapeutic range. Consequently, beyond that point a small increase in dose can result in a dramatic increase in the serum concentration (Fig. 1) (4).

Significant drug interactions occur with phenytoin and other drugs, such as psychotropic medications, antibiotics, and other AEDs, because phenytoin is tightly protein bound. Toxicity may manifest as a behavioral change only, especially in the special populations identified above (4).

Non-dose-related effects of phenytoin include significant cosmetic effects (e.g., darkening or increase in body hair, coarsening of facial features, worsening of acne or gingival hyperplasia), which may indirectly cause significant behavioral consequences in patients who are overly concerned with their appearance. Long-term use over years may be associated with osteopenia and folic acid deficiency, which may precipitate fractures, anemia, and CNS manifestations of folate deficiency (5, 6).

The idiosyncratic reactions of phenytoin are allergic dermatitis, hepatic failure, aplastic anemia (extremely rare), a lupus-like reaction, and (uncommonly) a pseudolymphoma state.

FIG. 1. (A) Phenytoin saturation kinetics. (B) First-order kinetics. D2 = D1 = D3 = D2 for (A), but C2 > C2 = C1 for phenytoin.

Overall, at doses that are nontoxic, phenytoin appears essentially devoid of any significant direct behavioral effects, as noted by Dodrill (1).

CARBAMAZEPINE

The principal dose-related effects of carbamazepine include diplopia (usually correlating with peak serum concentrations), cognitive viscosity, lethargy, and movement disorders.

Non-dose-related side effects include hyponatremia, which when pronounced can cause an exacerbation of seizures or confusional states. White blood cell (WBC) suppression is observed but is rarely clinically significant unless the total WBC count drops below 3000 and/or the absolute neutrophil count is below 1000 (2).

Idiosyncratic reactions include aplastic anemia (approx 1/5000), allergic dermatitis (approx 1/20), as well as hepatic and renal failure (rare) (7, 8).

Carbamazepine is associated with a variety of favorable behavioral effects, including decreased anxi-
Valproic Acid

Valproic acid has demonstrated efficacy in bipolar disorder (12). There is additional suggestive evidence that valproic acid is useful in treating impulsive-aggressive behavior in patients with personality disorders (13, 14). These effects have to be carefully weighed against the side effect profile of the drug and require a detailed knowledge of the drug's unique features.

Dose-related side effects of valproic acid include gastrointestinal upset (much less in enteric-coated formulations), tremor, elevation of whole blood ammonia concentrations, somnolence, cognitive viscosity, and thrombocytopenia. The hyperammonemia may occur without apparent liver dysfunction and yet result in a confusional-irritable state, especially in vulnerable populations (15). However, Murphy and Marquard observed hyperammonemia without apparent consequence in a large group of cognitively impaired patients (16). Carnitine supplementation can ameliorate this effect in many patients. Cognitive impairment is mostly associated with very high blood levels (>100 μg/ml in polypharmacy, >150 μg/ml in monotherapy).

Dose-related thrombocytopenia is a concern particularly for patients who fall from seizures, who, therefore, are at increased risk for significant intracranial bleeding, including subdural or intracerebral hematomas, with resultant behavioral and cognitive consequences (15).

The non-dose-related effects of valproic acid include weight gain, nausea, and a change in hair texture and/or hair loss. Cosmetic effects can have indirect but significant effects on behavior, as may occur with phenytoin (15).

Idiosyncratic reactions to valproic acid include hepatic failure, a confusional syndrome that can progress to coma or stupor, and pancreatitis. The risk of hepatic failure from valproic acid in a polypharmacy regimen is 1 in 500 patients under the age of 2, as compared with <1 in 12,000 in older patients treated with polypharmacy (17, 18). The confusional syndrome, which can progress to coma, may occur in the absence of elevated ammonia or other liver functions, and is supported by the presence of high-voltage, frontally predominant delta activity on the EEG (19). A variant of this presentation is seen at the Minnesota Epilepsy Group, in St. Paul, Minnesota, at least once quarterly, and consists of patient who is diagnosed with a confusional state or pseudodementia who on closer evaluation is determined to have valproic acid-induced encephalopathy. The ammonia level is usually not elevated and the diagnosis is confirmed by normalization of behavior with discontinuation of valproic acid. A variant of this syndrome was reported by Papazian et al. in which there was evidence of brain atrophy in two cases, with reversal on brain imaging after 1 year off the valproate (20).

Phenobarbital

The barbiturates are the drugs most clearly associated with negative behavioral changes. Several studies have demonstrated phenobarbital-related depression, irritability, unhappiness, inattentiveness, argumentativeness, stubbornness, or aggression. The barbiturates are also associated with the most negative cognitive effects among the AEDs (1).

The most convincing studies on the adverse effects of phenobarbital have been conducted with children. In Italy, Domizio et al. studied children aged 3.1 to 15.9 years (21). Of 300 children, 197 were treated with phenobarbital and 103 were treated with other AEDs. From questionnaires completed by parents, it was determined that 76% of the phenobarbital-treated children showed one or more behavioral disturbances including hyperactivity, irritability, disturbances of sleep, and drowsiness. Only 31% of the children treated with the other AEDs experienced these side effects. The most frequently observed behavioral disturbance was hyperactivity.

The report from the Committee on Drugs (1995), published in Pediatrics, examined the behavioral and cognitive effects of AEDs. The report noted a study involving 39 children with epilepsy who underwent psychiatric interviews that found a high rate of major depressive disorders following the initiation of phenobarbital in children with a family history of affective disorders. In another study, phenobarbital was discontinued in 14% of the study group due to the development of severe behavior problems.
Observations of cognitively impaired patients receiving barbiturates made by clinicians at the Minnesota Epilepsy Group were published in the Report on the Behavioral Side Effects of Barbiturate Antiepileptic Drugs for the State of Minnesota (22). This monograph identified profiles of behavior that may result from barbiturates when used in this population to treat behaviors such as irritability, aggression, self-injuries, depression, disruptive vocalizations, sleep disturbance, and temper tantrums. While all of these behaviors can occur in cognitively challenged individuals independent of barbiturates, or for social-environmental reasons (23), the report underscores the possibility that they may be iatrogenic in this population.

Hyperactivity can be a non-dose-related phenomenon, as can depression and decreased attention span (24).

As with other AEDs, idiosyncratic reactions may occur and include allergic dermatitis, Stevens-Johnson syndrome, hepatic failure, and Dupuytren contractures (24).

FELBAMATE

The epilepsy community enthusiastically received felbamate on its approval in 1993, the first of the so-called second-generation AEDs. However, after approximately 100,000 patients were exposed, felbamate was associated with an irreversible idiosyncratic side effect—aplastic anemia, with an incidence of approximately 1 in 5,000 (25)—that, together with an additional risk of hepatic failure, significantly limited its subsequent use. However, many patients who had been on felbamate for more than a year have continued, and a small number of refractory patients, especially children with Lennox-Gastaut syndrome, are started on the drug de novo each year. In the United States, approximately 12,000 patients are currently using felbamate. To date, no patient on the drug for more than a year has developed aplastic anemia.

Dose-related effects include insomnia, as well as weight loss and nausea, which for many patients result in a regression to their ideal body weight and the need for less sleep, rather than the 10 to 11 hours required in connection with more sedating AEDs. The net effect for some patients is an overall sense of well-being they have never experienced before.

Adverse behavioral effects may be observed in cognitively impaired patients. The Minnesota Epilepsy Group reported an 8% incidence of adverse behavior exacerbation in this population, especially in those patients with a previous history of medication-induced behavior deterioration (26). Due to the risks of aplastic anemia and hepatic failure, further research on the behavioral effects of felbamate is unlikely.

GABAPENTIN

Gabapentin was approved by the FDA in 1993 after felbamate. The usual non-dose-related and dose-related side effects of gabapentin are somnolence, dizziness, ataxia, fatigue, and nystagmus, with incidences ranging from 8 to 20% (27). No significant idiosyncratic effects have been reported to date.

In 1995, a study by the Minnesota Epilepsy Group (28) in a group of 119 patients with refractory epilepsy who were treated with adjunctive gabapentin demonstrated dose-related irritability or aggressive behavior in 15 patients (13%). The mean dose was 3136 mg/day for a mean duration of 8.25 months. Nine patients had a full-scale IQ under 70 and seven patients had a prior history of irritability or behavior problems with other AEDs. When gabapentin was discontinued in 11 patients, the irritability or behavior problems resolved.

Other investigators have observed the negative behavioral effects of gabapentin. Tallian et al. (29) described two children who developed intolerable aggressive behavior requiring dose reduction or drug discontinuation. In another case by Short and Cooke (30), hypomania was apparently induced by gabapentin.

LAMOTRIGINE

The FDA cleared lamotrigine for marketing in 1994. The principal side effects of lamotrigine are rash (8%), intolerable movement disorder (4%), ataxia (2%), and decreased appetite (2%) (31). Dose-related somnolence (or insomnia in some patients) can usually be ameliorated with slow titration.

Adverse behavioral consequences were observed in a study by Beran et al. (32), who reported a series of 19 cognitively impaired patients 9 of whom demonstrated aggression that dictated medication discontinuation or reduction. In the 5 patients in whom lamotrigine was discontinued, aggressive behavior resolved. In contrast, some other studies have suggested an efficacy in mood stabilization.

The primary idiosyncratic reaction is allergic dermatitis, which can progress to Stevens-Johnson syndrome, with an apparent incidence of 3 in 1000 adults.
and 1 in 100 children. This appears to be related to an antigen-loading phenomenon that is unique to the drug (i.e., the more rapidly the drug is titrated up, the more likely the Stevens-Johnson syndrome is likely to occur) (33). Consequently, meticulous adherence to the dosing regimen described in the package insert is very important, with particular attention to coadministered medications.

TOPIRAMATE

The FDA approved topiramate in 1996. In the original clinical trials, inherent and dose-related side effects related to CNS toxicity were reported as predominating, with a small but significant increased risk of renal calculi as well. Among patients treated with 200 to 1600 mg/day who discontinued for CNS effects, the most common adverse effects were psychomotor slowing (4.1%), memory difficulty (3.3%), fatigue (3.3%), confusion (3.2%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.9%), dizziness (2.6%), weight decrease (2.5%), nervousness (2.2%), ataxia (2.2%), paresthesia (2.0%), and language problems (2.0%) (34).

In 1999, neuropsychological testing was performed in a group of adult patients before and after initiation of topiramate (35). Eighteen of twenty-two patients (82%) had significantly reduced verbal fluency, and notably, only 56% of the affected patients were aware of the difficulty. Similar problems with verbal fluency were reported from other centers (36). However, a study by the Minnesota Epilepsy Group of topiramate-treated patients with cognitive impairment showed no evidence of behavior exacerbation or cognitive decline (37).

TIAGABINE

The FDA cleared tiagabine for marketing in 1997. Data on the behavioral and cognitive effects of tiagabine are limited. The most common adverse events in a postmarketing clinical trial were fatigue (19%), nausea and GI upset (9%), dizziness (7%), and insomnia (7%) (38). In 1998, Dodrill et al. performed neuropsychological testing on 82 patients on tiagabine and concluded that there were few differences between adjunctive tiagabine, phenytoin, and carbamazepine, except that motor speed was slightly faster in patients using tiagabine. Verbal fluency was also slightly better.

There have been several reports of prolonged nonconvulsive seizures in patients treated with tiagabine associated with generalized, irregular epileptiform EEG patterns. This twilight nonconvulsive status epilepticus could be misinterpreted as stupor or an involutional behavioral disturbance (39).

LEVETIRACETAM

At the time of FDA approval of levetiracetam in December 1999, fewer than 3000 patients had been exposed to the drug. In the clinical trials, asthenia (15%), somnolence (15%), and dizziness (9%) were reported and appeared to occur predominantly during the first 4 weeks of therapy. No rash cases were reported and pharmacokinetic data suggest that little interaction between levetiracetam and the other AEDs is to be expected, with <10% protein binding and no hepatic cytochrome P450 dependence for metabolism. The efficacy profile is promising (40). No reports of behavioral or cognitive effects have been published to date.

OXCARBAZEPINE

Oxcarbazepine was approved by the FDA in early 2000. In clinical trials of oxcarbazepine, dizziness, nausea, and headache were the principal side effects, both inherent and dose-related. Unlike carbamazepine, oxcarbazepine is not metabolized to an epoxide, with the attendant side effects. Hyponatremia occurred in 2.5% of patients in clinical trials, 79% of whom were receiving sodium-depleting medication. Treatment with oxcarbazepine in conjunction with phenytoin may result in significant elevations of phenytoin serum concentrations, with behavioral consequences. Despite its worldwide use, including approximately 125,000 patient-years exposure (based on drug sales and an assumed average daily dose of 1200 mg), very little has been published on the behavioral effects of oxcarbazepine (41–44).

ZONISAMIDE

Zonisamide was the last drug approved for partial seizures by the FDA. However, it became commercially available in 1989 in Japan, and 3 years later in Korea; therefore, there has been extensive exposure to this drug.

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In the U.S. and European adjunctive studies of zonisamide (n = 499), somnolence was seen in 17%, dizziness in 13%, anorexia in 13%, headache in 10%, nausea in 9%, and agitation/irritability in 9%. Only 12% of patients in controlled clinical trials discontinued use due to an adverse event. Zonisamide is a sulphonamide; not surprisingly, therefore, 2.2% discontinued treatment due to rash and 4% of patients developed clinically or possibly confirmed kidney stones. Of these, 12 (1.2%) were symptomatic, with greatest risk within 12 months of initiating treatment. As is the case with oxcarbazepine, there have been few reports of zonisamide-induced behavioral or cognitive effects (45, 46).

CONCLUSION

The side effect profiles and behavioral effects of the older AEDs are better known than those that may be related to the second-generation AEDs. Further studies are needed to inform clinicians of the relative incidences of functionally impairing side effects for the new AEDs as compared with the old AEDs. The hope is that with so many AEDs to choose from, the choice of treatment for each patient will allow for a maximal beneficial effect with minimal adverse consequences.

REFERENCES

Side Effects/Behavioral Consequences of AEDs