Zonisamide discontinuation due to psychiatric and cognitive adverse events

A case-control study

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ABSTRACT

Objectives: Zonisamide (ZNS) is an antiepileptic drug (AED) that has been associated with psychiatric adverse events (PAE) and cognitive adverse events (CAE); controlled studies evaluating these adverse events are limited. Our objectives were to 1) determine the incidence of PAE and CAE leading to the discontinuation of ZNS and 2) identify risk factors for PAE and CAE associated with the discontinuation of ZNS.

Methods: All patients exposed to ZNS at MINCEP Epilepsy Care between March 2000 and September 2008 were identified. Reasons for discontinuing ZNS were documented. Separate case-control studies were performed to identify risk factors associated with the discontinuation of ZNS due to PAE or CAE via multivariate binary logistic regression.

Results: A total of 544 patients were exposed to ZNS during the study period. PAE and CAE were the most frequently identified reasons for terminating ZNS therapy. The incidence of PAE severe enough to be associated with the discontinuation of ZNS was 6.9%; the incidence of CAE was 5.8%. Factors associated with termination of ZNS therapy due to PAE were past psychiatric history ($p = 0.005$), symptomatic generalized epilepsy ($p = 0.027$), and lower maximum ZNS serum concentration (mean = 17.9 mg/L vs 34.7 mg/L, $p < 0.001$). Independent variables associated with discontinuing ZNS due to CAE were greater number of concomitant AEDs ($p = 0.011$) and lower maximum ZNS serum concentration (mean = 16.6 mg/L vs 30.6 mg/L, $p = 0.002$).

Conclusions: We have identified clinically relevant risk factors associated with the discontinuation of ZNS. Our findings support the concept that selected patients are relatively more vulnerable to CNS adverse events when exposed to ZNS. *Neurology*® 2010;75:513–518

GLOSSARY

AED = antiepileptic drug; **CAE** = cognitive adverse event; **CI** = confidence interval; **FDA** = Food and Drug Administration; **LEV** = levetiracetam; **LOQ** = limit of quantification; **OR** = odds ratio; **PAE** = psychiatric adverse event; **PD** = Parkinson disease; **TPM** = topiramate; **ZNS** = zonisamide.

Zonisamide (ZNS) is an antiepileptic drug (AED) approved for adjunct treatment of partial seizures in adults.[1] Its mechanisms of action include inhibition of voltage-dependent sodium and T-type calcium channels.[2] In addition to the treatment of several generalized epilepsy syndromes, it may also play a role in managing obesity, migraine, and motor dysfunction in Parkinson disease (PD).[3]

More than 2 million patient-years of experience provides evidence that ZNS is generally well-tolerated.[4] However, since the first report of ZNS-induced mania,[5] severe psychiatric adverse events (PAE) and cognitive adverse events (CAE) have been associated with its use.[1,6–8] ZNS use has been correlated with a number of PAE including suicidal ideation and psychosis.[7,9] PAE are of particular concern because of the controversial Food and Drug Administration (FDA) decision in December 2008 requiring warnings of potential suicidality for all AEDs.[10,11] CAE associated with ZNS use include cognitive slowing, memory deficits, and language dysfunction in a manner comparable to topiramate (TPM).[1,12–14]

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In spite of multiple reports linking PAE and CAE to treatment with ZNS, little information has been published regarding risk factors for these adverse events.[9] The objectives of this study were to 1) determine the incidence of PAE and CAE severe enough to result in the discontinuation of ZNS in a large clinical practice and 2) identify risk factors for PAE and CAE associated with the discontinuation of ZNS.

METHODS

Study population. A tertiary epilepsy clinic database was used to identify all patients exposed to ZNS from March 2000 (FDA approval date) through September 2008 at MINCEP Epilepsy Care. Each patient chart was reviewed to confirm information in the database and to record additional data (see Data Analysis). The study population included patients of all ages and included those who initiated ZNS at the study clinic and patients who started ZNS prior to being followed at the study clinic.

After identifying all patients exposed to ZNS during the study period, patients were categorized into 1 of 2 groups: 1) discontinued ZNS or 2) continuing ZNS at the most recent clinic visit. Although patients may have experienced more than one adverse event while on ZNS, each subject who stopped ZNS was categorized by the primary reason that the drug was discontinued as indicated in the clinic notes. In order to attribute an adverse event to ZNS, the adverse event had to 1) be due to ZNS exposure, in the opinion of the treating physician; and 2) resolve after ZNS was stopped.

Case-control studies. Two separate case-control studies were performed to identify risk factors associated with the discontinuation of ZNS due to PAE or CAE. For the case-control studies, all patients exposed to ZNS during the study period were considered for inclusion regardless of where ZNS was initiated. Index and control patients were matched by ZNS initiation date according to the following procedure: 1) all patients exposed to ZNS and meeting inclusion criteria were listed by date of starting ZNS; 2) from this list, patients who had discontinued ZNS due to PAE or CAE were selected as index cases; 3) 2 control patients were selected for each index case by choosing the next 2 patients on the database list and included only patients who were continuing to use ZNS at the last follow-up visit. ZNS initiation date was used for matching in order to control for changes in prescribing practice over time.

Data analysis. The following variables were included for the PAE and CAE case-control studies: age at the time ZNS was started, age at onset of epilepsy, duration of epilepsy, number of previous AED trials, number of concomitant AEDs at the time ZNS was started, initial ZNS dose (mg/kg), titration rates (mg/kg/day) at 30 and 90 days, maximum ZNS concentration (mg/L), apparent clearance (CL/F, L/kg/day), gender, past history of psychiatric diagnosis, epilepsy syndrome, cognitive status (intellectually disabled or not intellectually disabled), etiology of epilepsy, seizure lateralization, years of education, history of special education, use of a psychotropic medication, use of levetiracetam (LEV) at the time of ZNS initiation, and treating physician.

Two titration rates were calculated: 1) 30-day titration rate (mg/kg/day) = maximum dose of ZNS (mg/kg) at 30 days divided by the number of days to reach this maximum dose; 2) 90-day titration rate (mg/kg/day) = maximum dose of ZNS (mg/kg) at 90 days divided by the number of days to reach this maximum dose. Serum concentrations were convenience samples taken at routine clinic visits and were not taken at fixed times after the administration of the last dose. The maximum ZNS concentration (mg/L) was identified for each patient and was determined by reviewing all available concentrations. The limit of quantification (LOQ) for ZNS was <5 mg/L. For analysis purposes, levels that were reported as <5 mg/L were entered as half the LOQ, which equals 2.5 mg/L.[15] CL/F of ZNS was calculated by the following formula:

CL/F (L/kg/day) = ZNS dose (mg/kg/day)/ZNS concentration (mg/L).

Only steady-state ZNS concentrations were included for the CL/F analysis. Patients were categorized as intellectually disabled if the full-scale Wechsler Intelligence Scale quotient was ≤70 or if the patient was considered untestable because of severe cognitive impairment. Cognitive testing was performed as part of the evaluation of the patient's epilepsy, and was not performed specifically for this study. Etiology was categorized as etiology known or unknown. In order to evaluate if treatment of mood affected the rate of adverse events, patients were categorized as being "on" or "off" psychotropic medications at the time ZNS was initiated. For each patient, 2 methods of defining psychotropic medications were assessed: 1) psychotropics included antidepressants, antipsychotics, anxiolytics, and mood stabilizers other than AEDs; and 2) psychotropics included AEDs known to stabilize mood (carbamazepine, oxcarbazepine, lamotrigine, and valproic acid),[16] plus antidepressants, antipsychotics, anxiolytics, and mood stabilizers. Because there are reports that LEV is associated with PAE,[17,18] patients were categorized as being "on" or "off" LEV at the time ZNS was initiated (only analyzed for PAE case-control study). The treating physician was entered for each patient to determine if differences in individual physician practices were associated with PAE or CAE.

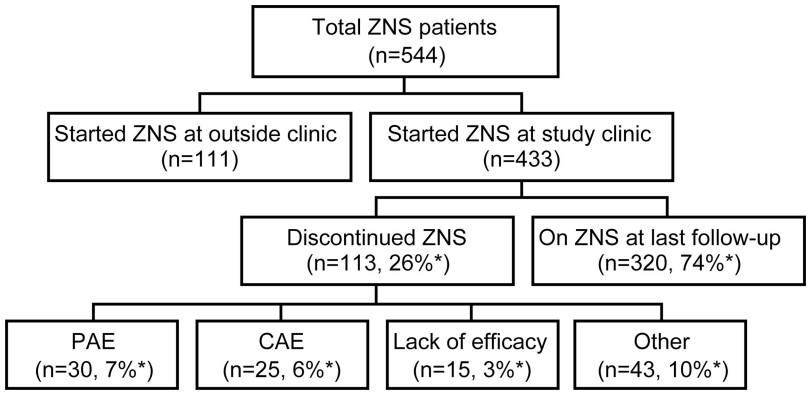
Statistical analysis. Duration of therapy was analyzed for those who discontinued ZNS due to 1) PAE; 2) CAE; 3) lack of efficacy; and 4) other reasons (listed in table 1). The log-rank test was used to compare differences in time to discontinuation of ZNS among the 4 groups. The number of days to the first dose reduction of the drug due to PAE or CAE was also evaluated.

Table 1 Reasons for the discontinuation of ZNS

Reason ZNS discontinued	All patients taking ZNS (n = 544), n (%)	Started ZNS at study clinic (n = 433), n (%)
Psychiatric adverse event	30 (5.5)	30 (6.9)
Cognitive adverse event	29 (5.3)	25 (5.8)
Lack of efficacy	27 (5.0)	15 (3.5)
Other		
Lethargy	18 (3.3)	14 (3.2)
Anorexia	14 (2.6)	12 (2.8)
Dizziness/ataxia	7 (1.3)	7 (1.6)
Renal stone	5 (0.9)	3 (0.7)
Miscellaneous[a]	9 (1.7)	7 (1.6)
Total	139 (26)	113 (26)

Abbreviation: ZNS = zonisamide.
[a] Discontinued ZNS due to paresthesias (n = 2), seizure-free after epilepsy surgery (n = 2), prolonged period of being seizure-free (no surgery) (n = 1), patient stopped on own (n = 1), rash (n = 1), nonepileptic events only (n = 1), pregnancy (n = 1).

Figure Categories of patients



CAE = cognitive adverse event; PAE = psychiatric adverse event; ZNS = zonisamide.

In order to determine which factors may be associated with the discontinuation of ZNS due to either PAE or CAE, univariate analysis was performed initially. See Data Analysis for a list of the variables analyzed. Univariate tests to evaluate categorical data included χ^2 analysis or Fisher exact test when expected values were <5; continuous data were assessed using paired *t* test. Variables that demonstrated a degree of significance of $p < 0.05$ on univariate testing were entered into a multivariate binary logistic regression analysis. Significance was set at $p < 0.05$ in the multivariate analysis. Statistical analysis was performed with SPSS version 13.0 statistical software (SPSS Inc., Chicago, IL).

Standard protocol approvals, registrations, and patient consents. The institutional review board deemed that the protocol met criteria for a limited data set and waived requirements for individual consent.

RESULTS **Demographic data.** A total of 544 patients were exposed to ZNS during the study period and met inclusion criteria (figure). PAE and CAE were the most common reasons for discontinuing ZNS (figure, table 1). When considering only those patients started on ZNS at the study clinic (n = 433), the incidence of PAE severe enough to be associated with the discontinuation of ZNS was 6.9%; the incidence of CAE was 5.8%. Demographic information for PAE, CAE, and control patients is summarized in table 2. In the PAE group, depressed mood was the most common reason to discontinue ZNS (table 3). For the CAE group, language impairment and cognitive slowing were the most common adverse events (table 4). Word-finding difficulties and dysfluent speech were the most common language problems reported. Some patients reported both PAE and CAE. In the PAE group, 6 patients (20%) also reported CAE. In the CAE group, 11 patients (38%) also reported PAE.

Four patients in the PAE group were hospitalized for being a danger to themselves or others (0.92% of 433 patients who started ZNS at the study clinic). One patient attempted suicide by overdose with pain medications. Another patient expressed suicidal thoughts. Two patients became psychotic. All 4 hospitalized patients had a history of psychiatric disorder. In each case, the patient's psychiatric symptoms improved when ZNS was discontinued. In addition to stopping ZNS, these patients were treated with

Table 2 Demographic data for patients included in PAE and CAE case-control studies

	Psychiatric adverse event (PAE)			Cognitive adverse event (CAE)		
Variable	PAE index (n = 30)	PAE control (n = 60)	*p* Value univar (multivar)	CAE index (n = 29)	CAE control (n = 58)	*p* Value univar (multivar)
Age started ZNS, average (SD)	33.2 (11.6)	34.0 (15.8)	0.764	33.9 (11.6)	31.1 (13.0)	0.214
M/F	16/14	22/38	0.131	16/13	24/34	0.224
Duration of epilepsy, average (SD)	22.3 (13.3)	21.2 (14.9)	0.674	22.7 (12.3)	18.5 (18.5)	0.073
No. of previous AED trials, average (SD)	6.6 (3.1)	6.1 (3.1)	0.388	7.2 (2.5)	6.2 (3.2)	0.047 (0.807)
No. of concomitant AEDs, average (SD)	2.4 (0.7)	2.3 (1.1)	0.685	2.7 (0.67)	2.1 (0.87)	<0.001 (0.011)
Maximum ZNS concentration (mg/L), average (SD)	17.9 (11.8)	34.7 (19.0)	<0.001 (<0.001)	16.6 (14.5)	30.6 (16.5)	<0.001 (0.002)
Apparent clearance (L/kg/day), average (SD)	0.37 (0.22)	0.39 (0.19)	0.726	0.38 (0.14)	0.39 (0.25)	0.711
History of psychiatric diagnosis, Y/N	21/9	25/35	0.011 (0.005)	17/12	24/34	0.129
Epilepsy syndrome, LRE/SGE/IGE	14/16/0	42/14/4	0.010 (0.027)	22/4/3	31/12/15	0.085
Intellectually disabled, Y/N	13/17	23/37	0.648	9/20	22/36	0.527

Abbreviations: IGE = idiopathic generalized epilepsy; LRE = localization-related epilepsy; multivar = multivariate analysis; SGE = symptomatic generalized epilepsy; univar = univariate analysis.

Table 3 Categories of psychiatric adverse events

Psychiatric adverse event	No. of patients	Median days to dose reduction[a] (range)	Median days on ZNS[b] (range)
Depression	11	87.5 (38–295)	242.0 (38–573)
Aggressive behavior	8	93.5 (48–576)	189.0 (83–700)
Psychosis	6	53.0 (4–550)	101.0 (4–958)
Irritability	5	69.0 (28–93)	93.0 (79–140)
Total	30	76.5 (4–576)	147.0 (4–958)

Abbreviation: ZNS = zonisamide.
[a] Number of days from the initial ZNS dose to the first dose reduction of ZNS due to psychiatric adverse events.
[b] Number of days from the initial ZNS dose to the last ZNS dose.

psychotropic medications as inpatients. The incidence of suicidality in this study was 0.46% (2 patients out of a total of 433).

Duration of therapy. No significant differences in the time to discontinue ZNS were identified among PAE, CAE, lack of efficacy, and other groups (log-rank test = 4.56, $p = 0.207$). Median number of days to the first dose reduction in ZNS was 76.5 for PAE and 61.0 for CAE (tables 3 and 4). In the PAE group, 5/30 patients (17%) reduced ZNS due to PAE in <6 weeks of therapy. In the CAE group, 8/25 patients (32%) reduced ZNS due to CAE in <6 weeks. The majority of patients developed PAE or CAE in the first 3 months of exposure to ZNS and discontinued the drug within 5 months. Some patients developed PAE or CAE after many months of therapy, in association with late dose increases of ZNS. Another pattern observed was that some patients developed PAE or CAE soon after initiating ZNS, had difficulty achieving a therapeutic ZNS dose, and remained on the drug at a relatively low dose for many months until it was ultimately discontinued.

PAE case-control study. PAE index patients (n = 30) were compared with controls (n = 60). Three variables were associated with discontinuing ZNS on univariate analysis: past psychiatric history ($p = 0.011$), symptomatic generalized epilepsy ($p = 0.010$), and lower maximum ZNS concentration (mg/L) ($p < 0.001$). All 3 of these variables remained significant on multivariate analysis: past psychiatric history (odds ratio [OR] [95% confidence interval (CI)] 5.9 [1.7–20.1], $p = 0.005$), symptomatic generalized epilepsy (OR [95% CI] 3.8 [1.2–12.2], $p = 0.027$) and lower maximum ZNS concentration (mg/L) (OR [95% CI] 1.1 [1.0–1.2], $p < 0.001$).

Table 4 Categories of cognitive adverse events

Cognitive adverse event	No. of patients	Median days to dose reduction[a] (range)	Median days on ZNS[b] (range)
Language impairment	10	77.0 (18–1162)	194.0 (41–1197)
Cognitive slowing	10	62.0 (24–428)	130.5 (37–685)
Memory impairment	5	14.0 (7–86)	27.5 (7–86)
Mental concentration	4	70.0 (60–91)	483.0 (100–531)
Total	29	61.0 (7–1162)	129.5 (7–1197)

Abbreviation: ZNS = zonisamide.
[a] Number of days from the initial ZNS dose to the first dose reduction of ZNS due to cognitive adverse events.
[b] Number of days from the initial ZNS dose to the last ZNS dose.

CAE case-control study. CAE index patients (n = 29) were compared with controls (n = 58). Three variables were associated with discontinuing ZNS on univariate analysis: greater number of concomitant AEDs ($p < 0.001$), lower maximum ZNS concentration (mg/L) ($p < 0.001$), and greater number of previous AED trials ($p = 0.047$). On multivariate analysis, 2 of these variables remained significant: greater number of concomitant AEDs (OR [95% CI] 2.7 [1.3–5.8], $p = 0.011$) and lower maximum ZNS concentration (mg/L) (OR [95% CI] 1.1 [1.0–1.1], $p = 0.002$). Greater number of previous AED trials was not found to be significant on multivariate analysis ($p = 0.807$).

The majority of patients in the case-control studies were on concomitant AEDs in addition to ZNS: no PAE or CAE index patients were on monotherapy; only 2 PAE control patients and 2 CAE control patients were on monotherapy. Considering all ZNS concentrations included in the case-control studies (n = 1,096), 55 concentrations (5.0%) were reported as <5 mg/L (LOQ). Patients started on ZNS at an outside clinic (PAE patients n = 0; PAE controls n = 8; CAE patients n = 4; CAE controls n = 9) had incomplete data for the following variables: number of concomitant AEDs, initial ZNS dose, titration rate, use of psychotropic medication, and use of LEV.

Our study included few pediatric patients: 2 patients in the PAE group and 1 patient in the CAE group were <16 years old when ZNS was initiated. When the case-control study data were reanalyzed excluding PAE and CAE patients <16 years old, the same significant variables were identified on univariate and multivariate analyses as those that included patients of all ages.

Post hoc analysis. Our results included the finding that past psychiatric history was associated with PAE. Because of the possibility that psychotropic medication use may cause PAE, we compared the use of concomitant psychotropic medications in PAE patients at the time ZNS was first lowered due to PAE to the use of psychotropic medications in control patients; no significant difference was found ($p = 0.405$). The association of polypharmacy and stopping ZNS due to CAE identified in our results also

prompted further evaluation. We explored whether a particular type of AED would be associated with CAE by comparing the types of concomitant AEDs used in CAE patients vs controls (a total of 15 AEDs were compared); no significant differences were found.

DISCUSSION PAE and CAE were the most common adverse events in our study. Patients with a history of psychiatric disorder and symptomatic generalized epilepsy were at significantly greater risk of developing PAE leading to the discontinuation of ZNS. In addition, polypharmacy was associated with the discontinuation of ZNS due to CAE. Perhaps our most interesting finding was that the average maximum ZNS concentration in those patients who discontinued ZNS due to PAE or CAE was significantly lower than the control's maximum ZNS concentration. The magnitude of this difference was surprisingly large, with the PAE and CAE patients achieving only approximately 50% of the maximum ZNS levels of control patients. Thus, toxic levels are clearly not required to develop significant PAE or CAE.

Several studies have reported that previous psychiatric history is a risk factor for developing PAE associated with AED use.[8,17,18] There is little information available about risk factors for PAE or CAE in patients specifically taking ZNS.[9] One study evaluated factors associated with psychotic episodes in 14 of 74 (18.9%) ZNS users.[9] Male gender, history of neurotic symptoms, younger age, shorter duration of epilepsy, and shorter duration of ZNS treatment were associated with the development of psychosis.[9] This study has been criticized because of concerns that ZNS was not clearly the cause of the psychosis in the study patients.[19] It has been suggested that some patients may be inherently vulnerable to CNS adverse events due to AED exposure.[16] Our data support this concept and suggest that patients with the risk factors we identified may be predisposed to psychopathology triggered by ZNS.

We report that the incidence of PAE severe enough to be associated with the discontinuation of ZNS was 6.9%; the incidence of CAE was 5.8%. Previous investigators have suggested that PAE and CAE are common in patients exposed to ZNS.[8,6] A recent study of the relative rates of PAE in the newer AEDs indicated that ZNS was associated with the third highest rate of PAE (LEV and tiagabine demonstrated higher rates of PAE).[8] A separate analysis of the relative rates of CAE[6] among the newer AEDs indicated that TPM was associated with the highest rate of CAE followed by ZNS. Our report adds to the literature that PAE and CAE are important reasons for patient intolerance of ZNS.

The FDA recently performed a meta-analysis on 199 placebo-controlled studies involving 11 AEDs and found that treated patients experience more suicidal thoughts or behaviors than patients on placebo (0.43% vs 0.22%).[10] In our study, we found that 2 patients (0.46%) exposed to ZNS demonstrated suicidality, similar to the FDA meta-analysis.[10] It should be stressed that we did not provide definitive proof that ZNS caused the severe PAE observed. It was the opinion of the treating physician that ZNS resulted in the suicidal behavior and the PAE did improve when ZNS was stopped. However, it should be noted that all patients who were hospitalized had a past psychiatric history and received treatment in addition to stopping ZNS. Such factors complicate the determination of a cause and effect relationship between ZNS and the most severe PAE. Proposed mechanisms for ZNS-induced PAE include alterations in brain serotonin and dopamine levels.[20,21]

The most common CAEs in our study were language impairment and cognitive slowing. Language disruption has been noted with ZNS use since the earliest pilot studies.[13,22] Reports have suggested that ZNS impairs language in a manner similar to TPM.[14] ZNS and TPM have several properties in common; proposed mechanisms for ZNS-induced language impairment include GABAergic dysfunction in the prefrontal cortex or an adverse effect of the sulfa moiety.[12,14]

Although our study focused on adverse events associated with ZNS, we also report a 74% retention rate, which suggests that ZNS is a well-tolerated AED. Previous long-term studies have described that 50%–60% of patients taking ZNS will continue the drug for more than 1 year.[23] Our retention rate may be artificially high because some patients who were taking ZNS at the last available clinic visit were lost to follow-up; the percentage of those patients who were lost to follow-up and eventually discontinued ZNS is unknown.

Limitations of our report included the retrospective study design and lack of definitive proof that PAE and CAE were caused by ZNS. Several variables examined in this study, including cognitive function, seizure lateralization, and the use of psychotropic medications, may have proven to be predictive if we had a larger number of patients in the study. Moreover, nearly all the patients in the study were on multiple AEDs. We also did not analyze seizure frequency and thus did not address issues related to forced normalization.[24] We did attempt to provide evidence supporting that adverse events reported in this study were due to ZNS exposure by requiring that it was the treating physician's opinion that

ZNS caused the adverse event and that the PAE or CAE resolved when ZNS was discontinued. Although our study design has drawbacks, the methodology used has advantages, since it permits the examination of a wide range of mood disorders, different epilepsy syndromes, and flexible AED dosing regimens. The results obtained from our study may be representative of real-life tertiary level patient care and thus have the potential to be directly applicable to clinical practice.[25]

PAE and CAE are important adverse events associated with ZNS intolerance. Our report provides a profile of patients who may be relatively more vulnerable to PAE and CAE when exposed to ZNS.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. White with assistance from Dr. Marino and Dr. Birnbaum.

DISCLOSURE

Dr. White and Dr. Walczak report no disclosures. Dr. Marino is as an inventor on a patent filed by the University of Minnesota re: Injectable topiramate for seizures; receives research support from the NIH (NINDS K01 NS050309 [PI] and 3K01NS050309-05W1 [PI]) and the University of Minnesota (AHC Faculty Research Development Grant); and receives royalties from CyDex Pharmaceuticals, Inc. for a patent re: IV topiramate. Dr. Beniak reports no disclosures. Dr. Leppik has received funding for travel and speaker honoraria from Eisai Inc. and Sanofi-Aventis (Zentiva). Dr. Birnbaum has a patent pending re: Novel parenteral carbamazepine formulation; has served as a consultant for Lundbeck Inc. (formerly Ovation Pharmaceuticals); and receives research support from GlaxoSmithKline and the NIH (5R01AG026390 [PI]).

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