Increased Seizure Frequency Associated With Felbamate Withdrawal in Adults

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Objective: To characterize changes in seizure frequency following felbamate withdrawal.

Design: Nonrandomized, retrospective chart review of a case series.

Setting: Epilepsy program specializing in adults with uncontrolled epilepsy.

Patient Population: Forty-five ambulatory patients withdrawn from felbamate use. Patients were included if they had received felbamate for at least 1 month, were 18 years or older, had accurate seizure frequency documentation, had accurate documentation of all antiepileptic drugs, and received the same concomitant antiepileptic drugs before and after felbamate therapy, except for the possible addition of gabapentin. Patients were excluded if they had hematologic or hepatic toxic effects with felbamate, were unable to withdraw from felbamate treatment, had a progressive neurologic disorder, or participated in another drug trial.

Methods: When information became available on aplastic anemia and hepatotoxicity associated with felbamate, all patients were advised to taper their felbamate dosage over approximately 2 weeks. They received written instructions for tapering felbamate and adjusting concomitant antiepileptic drugs and kept calendars to note the number of seizures. The charts of all patients who received felbamate were evaluated for adherence to inclusion and exclusion criteria. Statistical analysis was performed using a log-linear model for count data.

Main Outcome Measures: Seizure frequency during the 6 months before initiating felbamate therapy served as the baseline. Changes in seizure frequency were evaluated by comparing the number of seizures in the month felbamate was tapered and the 3 months after felbamate discontinuation with the baseline frequency. Comparisons were made between patients who started gabapentin therapy and those who did not and between felbamate responders and nonresponders.

Results: Felbamate withdrawal resulted in a significant ($P=0.02$) increase in seizure frequency. Patients receiving gabapentin had a smaller increase in seizure frequency, but the difference was not statistically significant. There was no statistically significant difference in seizure frequency between felbamate responders and nonresponders.

Conclusions: Felbamate withdrawal caused a significant increase in seizure frequency over the subsequent 3 months. These findings are important for clinical trial design and clinical practice.


Withdrawing an antiepileptic drug (AED), either to discontinue medication or to change to another medication, may lead to increased seizure frequency. At least 3 mechanisms have been proposed for this phenomenon. An AED may cause a true withdrawal effect, producing increased seizures while the AED serum concentrations is decreasing. This has been observed during barbiturate withdrawal.1 Increased seizures may also occur because of a lack of therapeutic effect. Schmidt2 reported that 17% of patients who converted from AED polytherapy to monotherapy had an increased seizure frequency. Bromfield and colleagues3 provided additional support for this mechanism when they showed that seizures increased only when phenytoin serum concentrations became subtherapeutic or undetectable. Finally, the removal of a drug-drug interaction may result in increased seizures. For example, when an AED that inhibits the metabolism of another AED is discontinued, an unwanted decrease in the serum concentrations of the remaining AEDs will result and breakthrough seizures will occur. In many cases, more than 1 mechanism may be responsible.
PATIENTS AND METHODS

All patients treated with felbamate in our clinic were identified for review. This outpatient practice consists primarily of adults referred for treatment of epilepsy uncontrollably by standard AED therapy. When we were informed of the Food and Drug Administration action, we instructed our patients to taper the felbamate dosage over approximately 2 weeks. Each individual was given a written schedule for tapering felbamate and adjusting concomitant AED therapy. Seizure frequency from patient calendars had been recorded in the charts for each month reviewed. All charts were reviewed by a research nurse, who is familiar with AED studies; a clinical pharmacist (T.E.W.), who specializes in AED pharmacotherapy; or an epileptologist (M.P.).

Patients were included if they (1) had received felbamate for at least 1 month; (2) were at least 18 years old; (3) had accurate documentation by seizure calendars of total monthly seizure frequency for 6 months before felbamate use, during felbamate use, and at least 4 months after felbamate discontinuation; (4) had documentation in the chart of all AED doses and the rate of dosage change (including any intermittent use of benzodiazepines), both before and after felbamate discontinuation; and (5) received the same AED at similar doses during the first 4 months after felbamate was discontinued as during the 6 months before felbamate was started, except for the possible addition of gabapentin.

We excluded patients from this study if they had (1) hepatotoxic effects or severe hematologic adverse effects during felbamate treatment; (2) an inability to successfully withdraw from felbamate treatment (ie, felbamate was discontinued or reduced, but seizure frequency increased dramatically and the benefits of continuing felbamate outweighed the potential risks); (3) any progressive neurologic problem with a propensity to increase during felbamate; or (4) participated in an investigational drug trial.

Seizure frequency (all seizure types combined) during the 6 months before starting felbamate therapy (prefelbamate) was compared with the frequency during the month felbamate was tapered and 3 months after felbamate discontinuation (postfelbamate). In this type of longitudinal study design, repeated observations of seizure frequency in individual patients enable a direct study of change in frequency. However, the set of observations in an individual patient may be interdependent, requiring special statistical methods that account for this correlation before drawing valid scientific inferences. We chose the GENMOD procedure with repeated statements using SAS/STAT software (release 6.12, SAS Institute, Cary, NC) as a statistical method that considers this type of correlation. This statistical analysis is based on using each patient’s seizure history individually. It provides the optimal solution to model parameters. Details of this approach can be reviewed elsewhere.\(^5\)

A log-linear model with \(\pi(\mu) = \mu\) (the Poisson variance function) and the following formula was used:

\[
\log[E(Y_{ij})] = \beta_0 + X_1i + \beta_1 + X_2i + X_3i + \beta_3 + \log(t_{ij}),
\]

where \(Y_{ij}\) indicates the number of seizures in interval \(j\); \(t_{ij}\) indicates the length of interval \(j\) (prefelbamate \(j=6\), post-felbamate \(j=1\)) (to be used in \(\log[E(Y_{ij})]/t_{ij}\)); \(X_1i\) is 0 prefelbamate and 1 postfelbamate; and \(X_0i\) is 0 for no gabapentin, female sex, and felbamate nonresponders and 1 for gabapentin, male sex, and felbamate responders (patients with a 50% or greater reduction in seizure frequency while receiving felbamate).

For example, the difference between the log seizure rates in the baseline period and the posttreatment period is \(\beta_3\) for the no-gabapentin group and \(\beta_3 + \beta_4\) for the gabapentin group. A value of \(\beta_3 < 0\) indicates a reduction in the seizure rate. The correlations between the counts were modeled as \(rij = \alphaij\) (exchangeable correlations). Statistical significance was \(\alpha < 0.05\). Because there was a relatively small number of subjects, we examined each variable one at a time. Interactions were assessed first and when found not to be significant \((P>0.05)\), each interaction was dropped and the model reassessed.

### Table 1. Demographic Data*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (N = 45)</th>
<th>No Gabapentin (n = 18)</th>
<th>Gabapentin (n = 27)</th>
<th>Felbamate Responders (n = 14)</th>
<th>Felbamate Nonresponders (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>35 ± 11</td>
<td>34 ± 12</td>
<td>36 ± 10</td>
<td>35 ± 13</td>
<td>35 ± 10</td>
</tr>
<tr>
<td>Felbamate dose, mg/d</td>
<td>3028 ± 783</td>
<td>2578 ± 826</td>
<td>3181 ± 839</td>
<td>2807 ± 845</td>
<td>3129 ± 746</td>
</tr>
<tr>
<td>Felbamate use duration, mo</td>
<td>8 ± 3</td>
<td>7 ± 3</td>
<td>9 ± 3</td>
<td>9 ± 3</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Felbamate taper duration, wk</td>
<td>2.0 ± 0.6</td>
<td>2.0 ± 0.8</td>
<td>2.0 ± 0.5</td>
<td>2.0 ± 0.9</td>
<td>2.0 ± 0.4</td>
</tr>
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* Data are given as mean ± SD.

### Table 2. Doses and Concentrations of Concomitant Antiepileptic Drugs*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>First Postfelbamate Month</th>
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<tbody>
<tr>
<td></td>
<td>PHT</td>
<td>CBZ</td>
</tr>
<tr>
<td>Mean dose, mg/d</td>
<td>398 ± 132 (16)</td>
<td>1192 ± 385 (26)</td>
</tr>
<tr>
<td>Mean concentration, µg/mL</td>
<td>14.8 ± 7.2 (13)</td>
<td>10.0 ± 2.3 (22)</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD (number of patients). Postfelbamate month indicates month after felbamate withdrawal; PHT, phenytoin sodium; CBZ, carbamazepine; and VPA, valproate sodium.
In August 1994, the Food and Drug Administration issued 2 letters to physicians recommending extreme caution when using felbamate, because of a possible association between this AED and aplastic anemia or hepatic failure. The actual risk of a potentially fatal complication was unknown at that time, so we advised most patients in our center to discontinue felbamate therapy. Soon after initiating a uniform withdrawal regimen in our patients, we began to see dramatic and prolonged increases in seizure frequency. In addition, at least 1 report of status epilepticus during the tapering of felbamate appeared in the literature. We performed a retrospective chart review to better characterize the nature and magnitude of seizure increases in our patients after felbamate withdrawal.

RESULTS

A total of 95 patient charts were reviewed, with data from 45 charts included in the analysis. Eight patients were excluded due to participation in investigational drug trials, 1 because of felbamate-related hepatotoxic effects, 25 due to a postfelbamate drug regimen that differed entirely from the prefelbamate regimen (1 patient experienced status epilepticus during felbamate withdrawal), 3 because they received felbamate for less than 1 month, 5 due to an inability to discontinue felbamate, and 8 because of incomplete seizure calendars. Demographic data for patients included in the study are presented in Table 1. Doses and serum concentrations of the concomitant AED were slightly lower after felbamate withdrawal compared with baseline doses and concentrations (Table 2).

Seizure frequency increased significantly (P = .02) with felbamate withdrawal (Table 3). This effect peaked at 106% above the mean baseline seizure rate during the month of felbamate tapering. The effect persisted for 3 months after felbamate withdrawal with increased seizure rates ranging from 24% to 56% above the mean baseline seizure frequency. The increase was independent of age, sex, or maximum felbamate dose.

Patients who received gabapentin had a smaller seizure increase than those who did not receive gabapentin, when prefelbamate seizure frequency was compared with postfelbamate seizure frequency (Table 3). This difference did not reach statistical significance (P = .56). Specific parameter estimates for this comparison are shown in Table 4. These estimates allow solution of the log-linear statistical equation and demonstrate a strong trend toward gabapentin reducing the seizure increase seen with felbamate withdrawal. In addition, patients who eventually received gabapentin had significantly more seizures during the prefelbamate period (P = .03).

There was no difference in seizure frequency in the prefelbamate and postfelbamate periods between felbamate responders and nonresponders (P = .82).

Most previous studies of AED drug discontinuation have examined short-term seizure frequency changes during inpatient presurgical evaluation. Several investigators found seizure rates were increased as much as 163% when AEDs were withdrawn over periods of 10 days or less. A few studies have evaluated seizure frequency beyond the immediate withdrawal phase. Duncan et al found that the frequency of seizures remained 66% above baseline 4 weeks after discontinuation of carbamazepine (rate of decrease, 200 mg every 2 days), but withdrawal of phenytoin sodium and valproate sodium did not result in increased seizures. In a long-term study of barbiturate and benzodiazepine withdrawal, Theodore et al reported “transient increases” for some patients in weekly seizure frequency during drug withdrawal, and only 1 of 78 patients had more than a 50% increase in seizures at long-term follow-up (mean follow-up of 17 months for outpatients, 24 months for inpatients). In addition, Doyle and colleagues, using standard AEDs, observed a 45% decrease in seizure frequency when the previous AED regimen was reestablished in patients who had medication withdrawn as part of a presurgical evaluation of their seizures. The increase in seizure frequency noted in the first month after felbamate withdrawal is similar to that seen with rapid withdrawal of other AEDs. In contrast, our patients had greater increases in seizure frequency beyond the immediate withdrawal phase than that reported in other studies.

Why was there a dramatic increase in seizure frequency following felbamate withdrawal? The time course of increased seizure frequency in our patients is beyond that expected for true withdrawal seizures produced when AED plasma concentrations are declining. The reasons for increased seizure frequency with felbamate withdrawal are unclear and future investigation into the mechanism behind this phenomenon is indicated.

Patients whose postfelbamate AED regimen differed substantially from that received before felbamate were carefully eliminated from our study. However, the mean doses of concomitant AED were lower during the postfelbamate period compared with the prefelbamate period.
patients were not randomized in respect to receiving gabapentin, and that patients receiving the same baseline dosage regimens, and that patients undergoing surgical evaluation or were discontinued from ineffective medications.

Gabapentin appeared to reduce the magnitude of the felbamate withdrawal effect. This effect did not reach statistical significance, although the negative log of mean seizure rates ($\beta_3$) and the confidence interval range (Table 4) indicate a strong trend. Our small sample size and the large variations among patients in seizure frequency differences may have contributed to the lack of statistical significance. Patients who received gabapentin had a significantly higher prefelbamate seizure frequency. We believe that this bias, introduced into the study by lack of randomization, was due to clinicians choosing to use gabapentin, a new drug, in patients who appeared most refractory. A larger sample size and randomization would allow a more thorough evaluation of this observation.

By selecting patients who had more frequent seizures to receive gabapentin, it could be argued that it was easier for patients not receiving gabapentin to experience a doubling of their seizure frequency. However, during the first month of felbamate withdrawal, while gabapentin doses were being increased, the patients receiving gabapentin also experienced a doubling of their seizure frequency. Subsequently, patients receiving gabapentin had a decline in their seizure rates while those not receiving gabapentin maintained a doubling of their baseline seizure rate. This effect may have led clinicians to underestimate the efficacy of gabapentin. Gabapentin may have had a positive therapeutic effect on seizure frequency, but, because the clinician was unaware of the underlying withdrawal phenomenon, gabapentin may have been thought to be responsible for increasing seizures. Without a prolonged trial of gabapentin, the patient may have been denied the use of a potentially effective drug.

These results also need to be considered in the design of AED trials. If, as observed with felbamate, an increase in seizure frequency can continue for 3 or more months after AED discontinuation, a longer time may be needed to assess seizure changes in studies using a crossover design. Second, in clinical trials comparing 2 or more AEDs after titration to monotherapy, the AED being withdrawn may have an important influence on subsequent seizure frequency and the probability of the patient meeting exit criteria while receiving monotherapy.

Limitations of this study include the retrospective trial design, the fact that patients were not routinely receiving the same baseline dosage regimens, and that patients were not randomized in respect to receiving gabapentin. Nevertheless, in many patients the effect on seizure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Log Mean Seizure Rate</th>
<th>95% Confidence Interval</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>$\beta_0$</td>
<td>1.54</td>
<td>1.01 to 2.07</td>
<td>NA*</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.69</td>
<td>-0.36 to 1.73</td>
<td>.20</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.91</td>
<td>0.14 to 1.68</td>
<td>.02</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>-0.32</td>
<td>-1.42 to 0.78</td>
<td>.57</td>
</tr>
</tbody>
</table>

* Not applicable.
frequency of discontinuing felbamate may be more in tense and last longer than generally appreciated. Clinicians and investigators should be aware that discontinuation of an AED can have an important influence on the perceived efficacy of any new treatment, whether a standard or new AED.

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REFERENCES


Announcement

Free Patient Record Forms Available
Patient record forms are available free of charge to ARCHIVES readers by calling or writing FORMEDIC, 12D Worlds Fair Dr, Somerset, NJ 08873-9863, telephone (908) 469-7031.