Withdrawal From Controlled Carbamazepine Therapy Followed by Further Carbamazepine Treatment in Patients With Dementia

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Background: The aim of this study was to assess the effects of withdrawal from placebo and carbamazepine administered for agitation associated with dementia and to assess safety, tolerability, and efficacy of subsequent ongoing carbamazepine therapy.

Method: We previously reported the results of a 6-week, randomized, parallel-group study of placebo versus carbamazepine in 51 nursing home patients with dementia who were agitated; 47 subjects completed that study. This report first presents the results of withdrawal from that experimental treatment assessed by (blinded) observations 3 weeks later (N = 45 remaining). The primary outcome measure was the Brief Psychiatric Rating Scale. Secondary outcome measures addressed other aspects of behavior, cognition, function, safety, and tolerability. Patients were then treated with carbamazepine for an additional 6 weeks (N = 32 remaining) or 12 weeks (N = 25 remaining), with the same assessments performed.

Results: Patients who had previously shown behavioral improvement with carbamazepine therapy reverted to their baseline state after washout, whereas there was no change in the patients previously treated with placebo. There were no other significant effects of washout. During subsequent therapy with carbamazepine at a modal dose of 300 mg/day, there were 2 deaths and 4 other adverse events resulting in dropout. Neither of the deaths, and only 1 serious adverse experience, was judged to be related to carbamazepine. There were a variety of nonserious adverse experiences during the trial. Behavior ratings showed ongoing improvement in agitation and aggression, as well as in other aspects of psychopathology.

Conclusion: The washout data provided independent confirmation of efficacy found in the prior placebo-controlled phase of this trial. Ongoing treatment was not associated with unexpected toxicity and was associated with improvement in measures of agitation and aggression that appeared to continue for up to 12 weeks. These findings confirm and extend results from earlier placebo-controlled studies.

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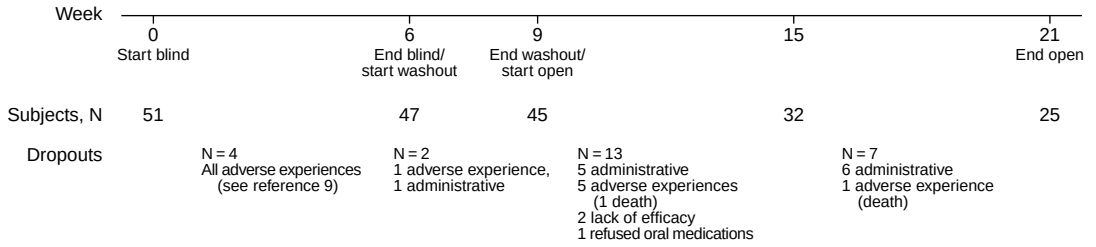
Dementia is accompanied frequently by psychopathologic signs and symptoms including behaviors referred to as "agitation."[1–3] Agitation in the context of dementia is a descriptive term applied to inappropriate verbal, vocal, or motor activity not easily explained by needs or confusion.[4] Since agitation is multidetermined, its management emphasizes careful exploration of potential physical, environmental, social, and psychiatric precipitants and modulators.[5] Use of psychotropic medication ideally is reserved for significant agitation that fails to respond to nonpharmacologic approaches.

Under these circumstances, anticonvulsants can be considered as one of several classes of relevant psychotropics.[5] We have previously reported results from a series of studies addressing the efficacy, safety, and tolerability of carbamazepine for agitation and aggression associated with dementia. These included an open trial[6]; a nonrandomized, placebo-controlled, crossover study in 25 agitated nursing home patients permitted to receive as-needed psychotropics[7,8]; and a 6-week, confirmatory, randomized, multisite, parallel-group study in 51 such patients taking no psychotropics other than chloral hydrate administered on an as-needed basis.[9] Both of our controlled studies showed that short-term therapy with carbamazepine (5–6 weeks) reduced measures of agitation and aggression in comparison with placebo, with generally good safety and tolerability. Neither report, however, ad-

Figure 1. Summary of Design and Dropouts



dressed the issue of duration of benefit or possible late-onset toxicity.

Subjects in our recent study[9] underwent a 3-week washout from controlled experimental treatment followed by further treatment with carbamazepine. This extension had several aims. The first was to investigate whether clinical benefits observed with carbamazepine therapy in the initial 6-week phase of the study would diminish significantly during washout as assessed by raters blinded to the original treatment condition. A finding of this nature would separately confirm the results previously reported, and this represented our primary hypothesis. Further, we wished to ascertain whether washout from carbamazepine versus placebo was associated with changes in function or side effects. Next, we wished to explore the tolerability and safety of open carbamazepine therapy lasting up to 3 months. Finally, we wished to obtain preliminary data regarding efficacy of longer term carbamazepine therapy and examine possible patterns of behavioral response.

METHOD

Subjects

The subjects reported on here were described in our earlier report.[9] In brief, we studied 51 well-characterized patients with probable or possible Alzheimer's disease (N = 33) by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[10] vascular dementia (N = 13) by DSM-IV criteria, or mixed dementias (N = 5). The mean ± SD age of the patients was 86 ± 6.4 years, and the mean ± SD Mini-Mental State Examination (MMSE)[11] score was 6 ± 7. To be eligible, patients had to exhibit disturbed behaviors for at least 2 weeks of sufficient intensity to result in Brief Psychiatric Rating Scale (BPRS)[12] scores ≥ 3 on items rating tension, hostility, uncooperativeness, or excitement. All subjects were medically stable at the time of enrollment. Written informed consent was obtained from each subject's legally authorized caregiver. Assent was obtained for subjects who were unable to provide written informed consent. Subjects were free of all other psychotropics for at least 2 weeks prior to randomization with the exception of use of as-needed chloral hydrate, 250 mg p.o., up to a maximum of 2 g in 24 hours. On average, subjects received 1 to 2 doses of chloral hydrate, 250 mg per week, during the sixth week of controlled treatment, without a drug-placebo difference.[9] Four subjects dropped out during the initial 6 weeks of placebo-controlled treatment.[9]

Design

In our previous report,[9] an interim analysis of efficacy was conducted using intent-to-treat principles and retrieved dropout data (N = 50), excluding 1 subject who was included in secondary analyses only (N = 51). The study was terminated prematurely according to predetermined stopping rules invoked because efficacy of carbamazepine had been established. The design of that study had also included a washout phase followed by further treatment, summarized in Figure 1. Specifically, after the initial 6-week blinded phase, experimental therapy was stopped for 3 weeks ("washout"), at the end of which (week 9) ratings were performed by clinicians who had performed the ratings in the placebo-controlled phase and remained blinded to the original treatment condition. Subsequent treatment occurred in 2 ways because of a design change that occurred during the trial. The original design of the next phase of the study had been a crossover to the opposite treatment condition, with blinded ratings performed for 6 additional weeks. The design was changed for administrative reasons after several subjects were enrolled, when we received funding to perform a larger, simpler, parallel-group study. Beginning at that juncture, all subjects completing 6 weeks of placebo-controlled treatment (weeks 0–6) underwent a 3-week washout (week 9) and then received open treatment with carbamazepine for 12 weeks (to week 21). In this version of the trial, different raters joined the week 9 rating session and then performed all subsequent open ratings independently (to preserve the blindedness of the original raters). The present report provides data from all subjects completing week 6 (N = 47; we do not include retrieved dropout data in this report); all available at week 9 (N = 45 remaining); all

available at week 15 (N = 32 remaining), including those who had received placebo in the initial crossover design and then received carbamazepine after washout (with blinded ratings in the second phase) as well as all those enrolled in the parallel-group design (who were treated and rated openly after washout); and all available at week 21 (N = 25 remaining), consisting of those enrolled in the later parallel-group design (see Figure 1). Data from blinded and open ratings are combined for the sake of simplicity.

Outcome Variables

Behavioral, functional, and cognitive ratings were performed at weeks 6, 9, 15, and 21. These included the BPRS[12] (total scores), Clinical Global Impressions scale (CGI),[13] the Overt Aggression Scale,[14] the Consortium to Establish a Registry for Alzheimer's Disease Behavior Rating Scale for Dementia (BRSD),[1] the Physical Self Maintenance Scale (PSMS),[15] and the MMSE.[11] The rationale for each of these measures and descriptions of them were presented previously.[9] Laboratory tests, described previously, were performed approximately every other week, and serum carbamazepine levels were determined at weeks 15 and 21. Adverse events were rated continuously throughout the study.

Statistical Analysis

In order to assess the effects of washout from controlled treatment with carbamazepine versus placebo, a 2-sample t test of within-subject change in rating scale scores (week 9 observation – week 6 observation) was performed, using a version that does not assume equal variance. This addressed our primary hypothesis. We also performed a similar analysis with week 15 minus week 9 data in order to explore whether there was a difference in response to ongoing carbamazepine therapy based on prior exposure to carbamazepine or placebo. There was not, hence these data are not presented. Subsequent single-sample t tests were performed in order to address the statistical significance of changes occurring with treatment starting at week 9 (week 15 – week 9, week 21 – week 9). Ordinal data were analyzed using the Mann-Whitney test since these represented ordered, categorical variables. A significance level of .05 was used for all analyses. Adjustments were not made for multiple comparisons, since the only controlled data were obtained at week 9, for which our primary outcome variable was the total BPRS,[12] and since the remainder of the study was exploratory in nature.

RESULTS

Treatment

The modal carbamazepine dose at weeks 15 and 21 was 300 mg/day, with mean ± SD serum levels of 4.7 ± 1.8 μg/mL at week 13 and 5.0 ± 1.4 μg/mL at week 21. No psychotropics other than chloral hydrate were permitted or used; chloral hydrate use at a dose of 250 mg averaged 1 to 4 doses/week/subject for those receiving it (N = 19 for week 6, N = 15 for week 9, N = 11 for week 15, and N = 1 for week 21).

Adverse Experiences

Figure 1 summarizes the adverse experiences that resulted in dropouts, described further here. One subject was withdrawn during washout because the placebo-controlled study had been terminated after the interim analysis, and that subject had not responded to carbamazepine in the blind phase. Another developed a urinary tract infection associated with increased agitation resulting in use of multiple psychotropics starting at week 8. At the end of the washout period (week 9), 2 subjects were withdrawn from the study and treated with other psychotropics for severe agitation at the request of their primary physicians: 1 had previously received placebo, the other had received carbamazepine. One subject died at the end of week 10, with sepsis related to pneumonia and a refractory urinary tract infection, having a total white blood cell count of over 10,000/mm^3 and severe congestive heart failure. The subject had been maintained on carbamazepine, 100 mg/day, at the request of her physician, as it was affording some behavioral relief. The death was judged to be unrelated to carbamazepine. A subject who had previously received carbamazepine developed a deep venous thrombosis at week 10. A subject who had not previously received carbamazepine developed sinus bradycardia associated with falls resulting in injury at week 10. Five subjects received placebo in the subsequent 6 weeks and were not included after week 9 ("administrative"). One subject developed ataxia at week 11 while taking carbamazepine, 200 mg/day, which reversed after the medication was discontinued. Another subject developed a urinary tract infection while receiving carbamazepine, 200 mg/day, became mildly sedated, and was dropped from the study per family request. The sedation did not improve after discontinuation of carbamazepine. One subject died at week 15, after experiencing fever and a persistent urinary tract infection despite multiple courses of antibiotics, having a total white blood cell count of 10,000–12,000/mm^3 prior to death and serum carbamazepine levels ranging from 4.5 to 7.8 μg/mL. Carbamazepine was continued despite her illnesses because its use had been associated with improved behavior and permitted discontinuation of antipsychotics. The death was judged to be unrelated to carbamazepine. Finally, 6 subjects finished blinded carbamazepine therapy at week 15 ("administrative"); no adverse experiences occurred in any subject during weeks 16 through 21. Upon close scrutiny of all of these cases, it appeared that only 1 serious adverse experience was likely to have been attributable to carbamazepine therapy (ataxia at week 11).

Table 1. Adverse Events Not Resulting in Dropout: Number of Subjects With Any Event During Weeks 6 Through 21

System/Event	Total	At Week 9
Central nervous system		
Fall		
With injury	11	1
Without injury	6	2
Postural instability	10	4
Fatigue/drowsiness	7	3
Light-headedness	4	2
Ataxia	4	1
Fainting	2	1
Disorientation	2	0
Gastrointestinal		
Loss of appetite	5	1
Diarrhea	4	2
Vomiting	2	0
Drooling	2	1
Cardiorespiratory		
Hypotension	2	0
Pallor	2	1
Cough	2	1
Rhinitis	2	1
Musculoskeletal		
Joint/limb pain	4	1
Other		
Fever	5	2
Rash	4	1
Injury not related to fall	3	1
Itching	2	1

Table 1 summarizes other adverse experiences, not resulting in dropout, encountered during weeks 6 through 21. The major events of concern pertained to the central nervous system, especially falls. The data in Table 1 are offered primarily for descriptive purposes: since they were obtained in an uncontrolled fashion, causality is difficult to determine. There was no pattern in adverse experiences suggesting a difference at week 9 between subjects who previously received carbamazepine versus those who previously received placebo.

Laboratory Data

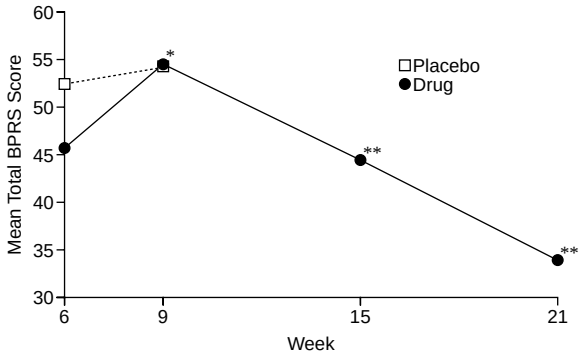
There were no clinically significant changes in any laboratory values (grouped or individual) at the end of the washout period, nor in the period of ongoing treatment from weeks 9 through 21.

Washout Effects

Figure 2 shows mean total BPRS scores for the drug and placebo groups for the entire study, including washout, clearly showing a convergence of the 2 groups at the end of washout.

Table 2 presents the behavioral, cognitive, and functional data at weeks 6 and 9, assessing the effects of washout from prior controlled treatment. Essentially all behavior rating scales showed that subjects previously treated with carbamazepine returned to their untreated baseline with respect to measures of agitation and aggression. On the other hand, BPRS factors[16] assessing anxiety/depression, psychosis, and cognitive dysfunction did not show significant change from week 6 to week 9 in these subjects. Likewise, change in BRSD scores in these subjects did not reach statistical significance. In subjects previously treated with placebo, there were no significant changes in any ratings. CGI data at week 6 showed a significant drug-placebo difference in favor of drug ($p < .001$) that disappeared by week 9 ($p = .4$). Neither treatment group showed significant changes in measures of functional status or cognition from week 6 to week 9.

Figure 2. Change in Mean Total Brief Psychiatric Rating Scale (BPRS) Score Over Time



*p < .001 for drug vs. placebo for change during washout (week 9 – week 6).
**p < .001 for change vs. week 9.

Ongoing Treatment Effects

Figure 2 shows mean total BPRS scores for weeks 9 through 21. Table 3 summarizes data obtained during this ongoing treatment phase. These data showed a consistent decline in measures of agitation and aggression over time. Other measures of psychopathology as captured by BPRS factors showed some decrease as well, suggesting an effect that transcended an "antiagitation" effect. The BPRS factor assessing cognitive dysfunction did not show similar changes. Other cognitive and functional ratings showed a gradual decline over time.

DISCUSSION

Interpretation of data obtained from this study is complicated by the design change, number of dropouts, and relatively small sample size. Nonetheless, certain conclusions are possible. After washout, patients previously treated with carbamazepine but not those treated with placebo showed recurrence of agitated and aggressive behaviors as assessed by blinded raters using a variety of rating scales. This finding separately confirms results from the 6-week placebo-controlled phase of the study.[9] Further, this reemergence of agitation was not associated with improved cognition or functional status, nor disappearance of side effects, indicating that removal of carbamaz-

Table 2. Washout Data (by original treatment assignment)[a]

Measure	Placebo Week 6 (N = 23)	Placebo Week 9 (N = 23)	Drug Week 6 (N = 23)	Drug Week 9 (N = 22)	Δ Week 6 – Δ Week 9 (N = 22)[b] Placebo	Δ Week 6 – Δ Week 9 (N = 22)[b] Drug	Week 9 – Week 6 Drug vs. Placebo t	Week 9 – Week 6 Drug vs. Placebo p Value
Total BPRS score	52.4 (9.8)	54.3 (8.8)	45.6 (9.4)	54.9 (10.1)	1.9 (6.2)	9.8 (5.8)	–4.4	.0001
BPRS agitation factor score	11.9 (3.1)	12.0 (3.3)	8.9 (3.1)	11.7 (4.0)	0.0 (2.4)	3.0 (3.1)	–3.5	.0008
BPRS hostility factor score	7.8 (2.4)	8.7 (1.9)	4.9 (1.9)	7.8 (2.2)	1.0 (2.3)	3.1 (2.2)	–3.2	.0030
Total aggression score[c]	11.3 (7.3)	12.3 (5.8)	6.5 (5.7)	12.4 (5.6)	1.0 (7.7)	6.1 (5.9)	–2.5	.0154
Total BRSD score[d]	44.9 (20.5)	47.8 (19.8)	40.8 (21.7)	53.0 (21.8)	3.2 (11.7)	12.6 (20.0)	–1.9	.0707
PSMS score	13.9 (4.5)	14.2 (4.6)	16.1 (4.8)	15.9 (4.7)	0.7 (1.6)	–0.1 (1.2)	1.6	.1168
MMSE score	8.1 (7.7)	7.2 (7.5)	3.9 (5.7)	2.7 (5.4)	–0.7 (4.2)	–1.4 (3.5)	0.6	.5593

[a]All values shown as mean (SD) except statistical data. Abbreviations: BPRS = Brief Psychiatric Rating Scale, BRSD = Behavior Rating Scale for Dementia, MMSE = Mini-Mental State Examination, PSMS = Physical Self Maintenance Scale.
[b]Change from week 6 to week 9 with placebo vs. change from week 6 to week 9 with carbamazepine.
[c]Total aggression score derived from the Overt Aggression Scale.
[d]The sum of all item scores is used.

Table 3. Open Treatment Data (all subjects combined)[a]

Measure	Week 9 (N = 45)	Week 15 (N = 32)	Week 15 – Week 9	Week 15 vs. Week 9 t	Week 15 vs. Week 9 p Value	Week 21 (N = 25)	Week 21 – Week 9 (N = 25)	Week 21 vs. Week 9 t	Week 21 vs. Week 9 p Value
Total BPRS score	54.5 (9.4)	44.3 (12.9)	–10.2 (9.4)	–6.1	.0001	33.8 (9.3)	–18.3 (8.7)	–10.6	.0001
BPRS agitation factor score	11.8 (3.6)	8.2 (4.3)	–3.7 (3.2)	–6.5	.0001	5.3 (2.5)	–5.6 (2.8)	–10.2	.0001
BPRS hostility factor score	8.3 (2.1)	5.9 (2.0)	–2.2 (2.1)	–6.2	.0001	4.3 (1.8)	–3.6 (2.0)	–9.0	.0001
BPRS anxiety/depression factor score	9.5 (3.7)	8.4 (3.2)	–0.9 (2.7)	–1.9	.0585	6.2 (2.2)	–2.7 (2.7)	–5.0	.0001
BPRS psychosis factor score	9.0 (2.2)	7.8 (2.9)	–1.2 (1.7)	–3.8	.0006	6.4 (2.1)	–2.3 (1.7)	–6.7	.0001
Total aggression score[b]	12.4 (5.6)	8.5 (6.1)	–3.8 (5.7)	–3.8	.0007	5.7 (4.9)	–6.8 (5.5)	–6.1	.0001
Total BRSD score	50.2 (20.7)	39.6 (25.0)	–12.5 (13.9)	–5.1	.0001	27.9 (19.4)	–21.5 (17.1)	–6.3	.0001
PSMS score	15.0 (4.7)	15.0 (3.7)	0.1 (1.8)	0.2	.8436	14.0 (4.0)	–0.3 (2.2)	–0.6	.5250
MMSE score	5.1 (6.9)	15.0 (3.7)	–1.3 (2.4)	–3.1	.0044	3.7 (7.2)	–2.6 (4.7)	–2.7	.0116

[a]All values shown as mean (SD) except statistical data.
[b]Total aggression score derived from the Overt Aggression Scale.

epine therapy did not result in improvement in domains other than behavior. This suggests that prior behavioral improvement was not perforce associated with impaired cognition or function or easily measurable toxicity.

Ongoing treatment with carbamazepine in the extension phase was not associated with undue toxicity. Neither of the deaths that occurred during ongoing treatment could clearly be ascribed to carbamazepine therapy. Only 1 serious adverse experience (ataxia) was judged to be related to carbamazepine, while the other adverse experiences that may have been related to carbamazepine were rated only as mild or moderate. No obvious toxicity was evident in routine measures of cognition or function or in laboratory tests. It is perhaps noteworthy that many of the adverse experiences encountered were similar to those encountered in our prior, shorter, controlled studies,[7–9] where no statistically significant drug/placebo difference was found with respect to specific adverse experiences. The data from our studies collectively highlight the fact that the target patient population is medically frail and susceptible to untoward events with or without anticonvulsant therapy. From a qualitative perspective, sedation and ataxia appeared to be the adverse experiences most likely to result from carbamazepine therapy in this population and might be expected to occur at a statistically significant level in a larger study. It is also relevant to note the decline in cognitive status and functional status over time, which was likely multidetermined, possibly including effects of carbamazepine. Caution is required in interpreting these adverse experiences and dropout data because of the uncontrolled nature of the study.

The behavioral ratings data indicated that improvement in agitation after washout from carbamazepine could be regained with resumption of therapy. The behavioral data also indicated that ongoing therapy was associated with sustainable improvement in agitation. Indeed, for those patients still receiving open therapy at week 21 (i.e., 12 weeks of therapy), behavior was continuing to improve. Finally, the behavioral data suggest that psychotropic effects emerged with prolonged therapy that went beyond "antiagitation" effects, as evidenced by improvement in scores for BPRS factors assessing anxiety/depression and even psychosis. The apparent change in anxious/depressed features might relate to the known antidepressant properties of carbamazepine. The effect on items addressing psychotic features is less easily related to carbamazepine's known clinical effects, but was consistent with occasional clinical observations of reduced paranoia.

Several qualifications must be considered in examining the behavioral data. First, ratings were performed in an open fashion, raising the issue of potential observer bias. This potential was less for the washout phenomena observed (since raters were blinded to prior treatment). Next,

it is possible that behavioral improvement occurred spontaneously, unrelated to therapy. Data from observational studies indicated that psychopathology can be intermittent in patients with dementia.[1] We doubt this is an important issue here, given the persistence of the signs and symptoms during the first 9 weeks of the study. It is possible that the subset of subjects able to continue with open therapy for an extended period were less agitated to begin with. Inspection of data from these subjects did not support this interpretation: for example, the within-subject change data indicated that week 9 mean scores for outcome measures for subjects reaching weeks 15 and 21 were not substantially different from those in the rest of the cohort. Lastly, it is possible that subjects reaching weeks 15 and 21 were so medically ill that they appeared less agitated. Our data do not address this issue definitively, but functional performance data do not support this hypothesis (since functional change was relatively limited), nor do data regarding treatment-emergent medical problems or laboratory tests. The point remains that uncontrolled data regarding behavioral ratings must be viewed with caution.

CONCLUSION

These findings confirm and extend results from our prior controlled studies that showed that short-term carbamazepine therapy can result in decreased measures of psychopathology in comparison with placebo, chiefly agitation and aggression. Ongoing therapy was generally well tolerated in these extremely frail subjects. The data suggest that behavioral efficacy observed in the short run can be maintained for up to 12 weeks and, in fact, may increase during this time period.

As indicated in our prior report,[9] data such as these are not sufficient to define new clinical practice, but they do serve as a useful guide during an era in which there are relatively few studies available to clinicians. While we are increasingly convinced that certain anticonvulsants show efficacy and can be well tolerated in this situation, we are exploring other, potentially safer, alternatives to carbamazepine.[17]

Drug name: carbamazepine (Tegretol and others).

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