# Carbamazepine Lowers Aggression: A Review

**John L. Young, MD and Marc Hillbrand, PhD**

**A small but growing number of reports document the antiaggressive effect of carbamazepine. Although it is supported by a small total number of patients studied with less than ideal rigor, the use of this medication as a means of reducing aggressive behavior is becoming an established clinical practice. The target diagnostic spectrum is broad, and the effect appears within days when it occurs. To promote both wider practice and further study, the authors summarize and briefly evaluate the reported investigations, single case studies, and articles related to the efficacy of carbamazepine for reducing aggression. Conceptual problems in aggression research, the relationships between epilepsy and aggression, possible mechanisms of action for this effect of carbamazepine, and practical clinical considerations are outlined.**

Since its introduction as an anticonvulsant in the 1960s, carbamazepine has found diverse additional uses in clinical psychiatry. These have included the treatment, usually in refractory cases, of bipolar disorder,[1-4] depression,[5] and agitated dementia.[6, 7] A carefully controlled study demonstrating the effectiveness of carbamazepine added to haloperidol for treatment of "excited psychoses"[8] has placed augmentation strategies on a firm footing, and still further psychiatric applications have been explored for this drug.[9, 10]

Dr. Young is service chief at Whiting Forensic Institute, Middletown, Connecticut, and associate clinical professor of psychiatry at Yale University School of Medicine. Dr. Hillbrand is unit director at Whiting Forensic Institute and assistant clinical professor of psychiatry at Yale University School of Medicine. This paper was presented at the 23rd Annual Meeting of the American Academy of Psychiatry and the Law, Boston, Massachusetts, October, 1992. Address correspondence to Dr. Young, Whiting Forensic Institute, Box 70, Middletown, CT 06457.

In the course of its widespread and often satisfying utilization for unresponsive patients, an additional property of carbamazepine has gained recognition, its particular ability to ameliorate aggressive behavior.[11-13] Although ictal violence is rare,[14] reports have shown significant associations of aggressive behavior with psychomotor epilepsy[15] and with other EEG abnormalities.[16] In view of these observations, the authors believe that a review of clinical reports on the effectiveness of carbamazepine in the treatment of aggressive behavior is warranted.

## Clinical Reports on Carbamazepine in the Treatment of Aggression

The earliest report on the use of carbamazepine to alleviate aggressive behavior known to the authors is by de

Vogelaer,[17] a psychiatric resident in Tienen, Belgium, in 1981. The work reported was directed at improving the treatment of patients without evidence of seizure disorder who remained agitated and aggressive despite treatment with neuroleptics. They were further described as diagnostically diverse but sharing an "active-ambivalent personality pattern." Twenty patients completed a double-blind crossover study comparing a week each of carbamazepine and placebo. Using a clinical description of the results, the author claimed a 73 percent improvement rate with carbamazepine compared with placebo, with many of the subjects enabled to discontinue their antipsychotic medication.

Despite de Vogelaer's study, Hakola and Laulumaa[18] are generally credited with the first report on this subject, a letter in 1982. They found that mean doses of 600 mg/day of carbamazepine, added to high doses of neuroleptics, made a dramatic difference in all eight of Finland's most violent women patients. They were psychotic, and seven of them had EEGs showing "irritative activity."

Within weeks, a double-blind crossover controlled study by Neppe[19] of 11 patients appeared, also in a letter. Results were similar, particularly for the six patients considered to be aggressive. Later, the same author reported in more detail on 11 patients who had been hospitalized at least six months without responding to adequate antipsychotic medication treatment.[20] As in his previous study, they were predominantly schizophrenic, and all had temporal lobe abnormalities on EEG. They alternately received six weeks of carbamazepine, 200 mg t.i.d., and placebo in addition to their ongoing regimens. Using the Brief Psychiatric Rating Scale, "overt aggression was rated twice as severe and 1.5 times as common on placebo compared with carbamazepine." Neppe next focused on hostility as a potential predictor of response to carbamazepine, reporting on a chart review of nine refractory psychotic patients given carbamazepine. All improved dramatically, especially in regard to hostility and dangerousness to self or others.[21]

Mattes[22] reported briefly on a much larger study of aggressive patients on carbamazepine. It involved 34 inpatients who experienced "rage outbursts of diverse aetiologies" and had a high incidence of neurological findings. In an open trial, carbamazepine was administered so as to achieve levels between 8 and 12 mg/L. This led to a significant decrease in severity of physical assault as measured on the author's own scale.

Luchins[23, 24] reported the results of an interesting experiment of administration. He reviewed the charts of seven violent predominantly schizophrenic chronic patients with normal EEGs and without affective disorders, rating them before and during carbamazepine administration, and again after the drug was discontinued by the hospital authorities. He found that the frequency of aggressive episodes had been significantly less while on the medication than before or after for six of the seven patients. There were similar decreases in verbal hostility and in the use of PRN

medication. The hospital authorities then made carbamazepine again available, and similar improvements were noted for 19 additional patients, 11 with normal and 8 with abnormal EEGs.

Patterson[25] followed eight aggressive males with known organic pathology in an open study with levels of carbamazepine between 8 and 12 mg/L. They showed rapid, significant, and sustained decreases in assaultive behavior. The author commented that the effect of discontinuing the treatment could not be evaluated because this would have interfered with efforts to obtain long-term placement for his patients.

Foster and his colleagues[26] began to address the issue of whether beneficial effects might continue after cessation of carbamazepine treatment. From a group of nine assaultive male forensic patients carrying mixed diagnoses they treated four with 200 mg of carbamazepine twice daily for one week, observing them for a week before and after treatment and comparing them with a control group of five patients on placebo. The experimental group improved in the cognitive and affective spheres and became markedly less aggressive during the treatment week, returning to pretreatment levels on placebo. However, these patients maintained improved frontal lobe functioning after carbamazepine was discontinued. The authors suggest that this finding may indicate lasting structural improvement.

A 1989 letter dealt with a specialized application of the antiaggressive potential of carbamazepine to elderly demented patients who reacted with agitated aggression to nursing care. In three cases the problem resolved with modest doses and low levels of the medication. The report also broached the issue of discontinuation: it included one patient whose behavioral improvement continued when his dose was lowered to 100 mg per day because of leukopenia (which then resolved, as often happens). The carbamazepine level was then 1.5 mg/L.[27]

In 1990, a conference presentation reported a chart review of 27 chronic aggressive patients of varied diagnoses in a state hospital who were given carbamazepine at doses averaging 900 to 1000 mg/day with serum levels averaging 6.6 mg/L.[28] In 23 of the cases, the treating psychiatrists judged that the medication had caused a decrease in aggressive behavior. The authors concluded that their "preliminary review suggests that treatment of aggressive behavior in chronic patients represents a primary reason for the use of carbamazepine by psychiatrists in a state hospital."

We have so far found six individual case reports indicating dramatic alleviation of aggressive behavior for a year or more with the use of carbamazepine.[29-34] These individuals had marked neurological abnormalities, described in some detail along with the aggressive behavior that was alleviated. In four of the cases, various other drugs, including other anticonvulsants, had been tried unsuccessfully. A recent letter reported on three young male outpatients with episodic dyscontrol who responded to carbamazepine and then relapsed when they stopped taking the medication.[35]

In addition to the studies and case reports that address the subject of carbamazepine for aggression, a few articles refer indirectly to this topic. A recent report by Blumer and his colleagues,[36] primarily addressing issues other than aggression, described 28 diagnostically diverse patients who responded strikingly to carbamazepine. The authors included several case vignettes, three of which indicated clear improvement in aggressive behavior within days. A report by Okuma *et al.*[37] is instructive because of its sample size and frequent citation, although it, too, was not focused specifically on aggressive behavior. The authors compared two large groups of patients with schizophrenia or schizoaffective disorder, 82 who received carbamazepine in addition to their current regimen and 80 who were given a placebo. Global improvement was significantly greater in the experimental group, and the aggressive patients who improved accounted for much of the difference. Among patients classified as having violent behavior, 25 of the 44 given carbamazepine showed marked or moderate improvement, compared with 15 of 50 such patients who improved on the placebo.

From a study designed to compare carbamazepine with propranolol for treatment of aggressive behavior, Mattes[38] reported on a total of 56 individuals who received carbamazepine. Their predominant diagnoses were intermittent explosive disorder or attention deficit disorder, often with substance abuse. This was the largest group of aggressive patients receiving carbamazepine in any study we found. Little was found to distinguish the two medications, both of which produced significant improvement. Many of the patients maintained their improvement after either medication was discontinued.

This review has deliberately centered on adult patients; thus, a cautionary note should be sounded regarding the use of carbamazepine in children and adolescents. A recent report described six males aged between 10 and 16 years carrying diagnoses of conduct disorder and/or attention-deficit hyperactivity disorder with aggressive behavior unresponsive to various medications.[39] In all six, aggressivity worsened when carbamazepine was given and improved when it was withdrawn. In a younger but similarly diagnosed group, however, carbamazepine proved quite helpful.[40]

## Discussion

The first issue upon completing the present literature review might well be that of its small size. This refers to both the number of studies and the number of subjects. Also noteworthy is the closely related and often mentioned issue of inadequate methodology. Not only are the sample sizes small, but desirable rigor is lacking where it would have seemed possible. In addition, significant conceptual problems need to be recognized. Some time ago, Lion[41] made the observation that aggressive behavior is particularly difficult to frame in ways amenable to clinical study. Others have recently agreed.[42] The diagnostic diversity of responsive patients is a particular

quandary that concerned the author of the earliest report on carbamazepine and aggression.[17] With good reason, more recent writers have advocated for a detailed symptom-based approach.[43, 44] A disturbing point was made in a recent letter: episodic dyscontrol left untreated leads to interpersonal and occupational dysfunction that over time gives the appearance of antisocial personality disorder.[45]

Clinical issues regarding carbamazepine should be mentioned. One study has raised the far-reaching questions of whether its therapeutic effects might prove not to be long sustained and whether there may be unrecognized long-term side effects.[4] In contrast, another author has suggested that carbamazepine may have a more benign side effect profile than other anticonvulsants,[46] and we have mentioned the evidence that its antiaggressive effects may be sustained even after drug administration is discontinued.[26, 27, 38]

Carbamazepine increases the rate of metabolism of numerous other medications.[47–55] These include many commonly used psychoactive substances, other anticonvulsants, and, notably, oral contraceptives. In addition, sexual dysfunction can become a problem.[51] Liver function can be affected, at least temporarily, as well as bone marrow function.[52] Much more rarely, thyroid function abnormalities and hyponatremia may develop. The usual cardiac precautions for tricyclics must be observed since carbamazepine belongs to this chemical class.

Baseline studies before starting carbamazepine should include a CBC with platelet count, liver and thyroid function tests, serum electrolytes, EKG, and urinalysis. It is usual to begin with a dose of 200 mg/day and increase it slowly, checking serum levels frequently, while observing for therapeutic effect. At two to four weeks, the serum drug level may dip due to autoinduction.[48] The CBC and platelet count should be checked on a weekly basis for at least four weeks, then gradually less often. An idiosyncratic reaction requiring withdrawal of the drug is likely if the platelet count drops;[52] a decrease in the leukocyte count can be addressed more flexibly. Once the carbamazepine dose is stable, its level along with CBC, platelet count, electrolytes, and liver function tests should be monitored every three to six months. A serum level of 6 to 12 mg/L is generally considered standard for control of aggressive impulses; however, our experience is that lower levels often suffice to provide adequate control. Several good recent clinical overviews of carbamazepine treatment are available.[10, 53, 54]

As was the case for several other psychotropic agents, the discovery of the beneficial effects of carbamazepine in the treatment of aggressive behavior appears to have been serendipitous. Many theories have come along after the fact to account for its calming effect. This is to be expected in view of the complex relationship recognized to exist between epilepsy and behavior. A recent pair of reports begins with a reminder of the importance of environmental influence on aggressive behavior and goes on to

distinguish the four different possible linkages between abnormal electrical discharges and violent behaviors.[55, 56] Abnormal behavior occurring between seizures may be a function of the related structural abnormality, and behavior closer in time to a clear seizure can occur as part of a prodrome, as a manifestation of the discharge itself, or as a result of postictal confusion. Not surprisingly, then, a direct anticonvulsant effect was the first mechanism proposed, with ample support from animal studies.[57]

The mediation of the anticonvulsant effect has two major aspects. The possibility of an antikindling effect was pointed out early.[58, 59] Kindling is a natural process whereby repeated subthreshold stimulation eventually lowers the threshold for a seizure and/or an aggressive act. The other aspect is the possibility of carbamazepine's action at the neurotransmitter and neuroendocrine levels.[27,60–63] For example, the drug appears to decrease the availability of norepinephrine in the synapse by both inhibiting release and promoting reuptake. As for location, the temporal and frontal lobes are both often mentioned, as well as the limbic system, especially the amygdala.[64]

The violent behavior of a person with epilepsy may also be entirely unrelated to the seizure disorder.[65] There is yet another logical possibility, namely that an individual with an abnormal EEG may show aggressive behavior at the same time as the EEG changes to become less abnormal. Trimble[66] has called this phenomenon "forced normalization" and pointed out that it may explain the occasional paradoxical reaction to carbamazepine that is unfortunately observed. As research continues, more will undoubtedly be learned about the mechanism of carbamazepine's antiaggressive action.

In addition to mechanisms of action, many other questions can be posed for future investigation. Certainly, the principal agenda continues to be the search for a more satisfactory explanation of the phenomenon, using large well-defined subject groups and appropriate prospective double-blind methods. Continuing efforts to define aggression and relate it to diagnostic categories will be helpful here.[67] There is reason to expect that such improved nosology may also enable identification of clinically relevant subgroups. This might be done on the basis of detailed symptom analysis,[44] as well as through structured history-taking.[43]

The suggestion that for some patients benefit may be maintained after discontinuation of the drug[26, 27, 38] especially invites further study. In particular, more prolonged exposure to carbamazepine would be worthwhile to study. So far, the search for biological markers to predict who will respond has apparently been unfruitful, but it has only begun. Also the other anticonvulsants merit additional study, and this work is in progress.[68–70]

The suggestion[28] that carbamazepine might be utilized for the purpose of merely quieting aggressive chronic public sector patients is disturbing. Rather, it is to be hoped that clinical improvement would lead to the enjoyment of a

better quality of life. So far, it is clear that carbamazepine is effective in lowering aggression across varied diagnostic groups. The future is bright for the pharmacological treatment of aggressive behavior, as both diagnostic acumen[71] and chemical ingenuity[72] are advanced.

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