Carbamazepine in Treatment of the Violent Psychotic Patient

Lauren A. Pate, M.D.

Violence in the psychiatric setting may be perpetrated by patients with a variety of diagnoses including character disorders, episodic dyscontrol syndromes, and drug or alcohol intoxication. The violent behavior of aggressive psychotic patients is typically the most bizarre, unpredictable, and the least responsive to intervention with neuroleptics or lithium carbonate. Carbamazepine, an established anticonvulsant, has achieved growing prominence as an adjunctive measure in treatment of the violent psychotic. This paper will review the literature and summarize the posited pharmacological mechanisms, reported side effects, and clinical experience with carbamazepine in controlling the symptoms of violence and aggression in psychosis.

Anticonvulsants were first used in the treatment of aggressive psychotic patients in 1943 (1). Carbamazepine, introduced in 1963 as an anticonvulsant particularly effective in temporal lobe epilepsy, has been reported to be useful in treating aggression associated with psychosis in patients with bipolar affective disorder, schizoaffective disorder, and schizophrenia with and without EEG abnormalities. The first successful open clinical trials in patients with bipolar disorder were conducted in Japan in the early 1970's. Two groups of investigators demonstrated anti-manic and slight anti-depressive effects in 75% (2) and 55%, respectively, of their patients with bipolar affective disorder, and prophylactic effects in both manic (71%) and depressive (64%) episodes (3,4), although some patients received combinations of carbamazepine and lithium and/or other drugs.

A series of double-blind controlled trials followed these studies. Okuma et al. compared chlorpromazine and carbamazepine and reported equivalent anti-manic effects (5). Ballenger and Post conducted double-blind, placebo-controlled trials of carbamazepine in nine manic patients, seven of whom had partial to marked therapeutic responses (6); an additional patient who had been unresponsive to lithium and other anticonvulsants also improved on carbamazepine (7). Subsequent published cases and open studies reported the efficacy of carbamazepine combined with lithium carbonate (8–15), particularly in patients in whom lithium was less effective or who experienced a continuous circular or a rapidly cycling course. Post et al. also provided case reports which suggest that carbamazepine may have prophylactic effects (16). Okuma et al. conducted a

Dr. Pate is a third-year resident at Baylor College of Medicine, Houston, Texas.

double-blind controlled trial showing prophylactic effects of carbamazepine in 60% and placebo in 22.2% of their patients (U-test, $p < 0.10$) (17). Kishimoto et al. found some prophylactic effects of carbamazepine in manic and depressive episodes in 75% of their thirty-two cases, all followed for at least seven years; the effects being significantly greater in the group with onset of illness before age 20 ($p < 0.01$, Fisher's exact test) (18). A double-blind controlled study comparing carbamazepine plus haloperidol and placebo plus haloperidol in lithium carbonate- and neuroleptic-resistant patients with "excited psychoses" found a significant improvement of symptoms including "hostility" and "excitement" in the treatment group over the placebo group ($p < .03$), although both groups improved (19).

There are also reports of patients with schizoaffective disorder who responded to carbamazepine. Folks, King et al. observed improvement in two of three such patients given carbamazepine (14). Brooks and Lessin reported the successful carbamazepine treatment of a man with schizoaffective disorder and resistant lithium-induced nephrogenic diabetes insipidus (20). Kraft, Hassenfeld, and Zarr published the case of a previously treatment-refractory patient whose auditory hallucinations responded to carbamazepine (21). Despite encouraging case reports, to date there has been no controlled trial of carbamazepine in schizoaffective disorder.

Carbamazepine has been prescribed for schizophrenics with and without abnormal EEG's in whom violent behavior was particularly problematic. In an open trial, Hakola and Laulumaa treated eight schizophrenics with combinations of carbamazepine and neuroleptics. The eight patients all showed EEG abnormalities but had not been diagnosed as epileptic. Following the combination treatment, all eight patients showed decreased aggressive behavior, and four of the eight showed diminished symptoms of schizophrenia as well (22). Luchins had similar results in six schizophrenics with normal EEG's (23), and Yassa and Dupont reported a similarly-responsive case (24). Neppe conducted a double-blind, randomized study of carbamazepine in eleven chronic schizophrenics with EEG abnormalities, eight of whom improved while on carbamazepine ($p = .03$, Wilcoxon; $p < .005$, ANOVA) (25). In contrast, Stevens and Bigelow et al. reported two cases of psychosis aggravated by therapeutic doses of carbamazepine (26). In summary, the available literature suggests that carbamazepine may be a useful adjunctive measure in the treatment of aggressive or violent psychotic patients, some of whom may have EEG abnormalities. Carbamazepine's apparent effect on both aggressive behavior and psychotic symptoms raises questions about the compound's mechanism of action. The only anticonvulsant with a tricyclic structure, carbamazepine is a polycyclic drug whose steric structure resembles that of chlorpromazine, imipramine, and maprotiline. Because its three rings lie in a plane different from that of the amide group, it resembles other anticonvulsants as well (27). Carbamazepine is classified as a neutral lipophilic substance, which enables the molecule to pass easily through lipid membranes and facilitates its transport into the central nervous system.

Two different metabolic pathways are discernible: epoxidation of position 10,11 by hepatic monooxygenases, and hydroxylation in one of the aromatic rings by hepatic oxygenases. Both metabolites undergo subsequent glucuronide formation. The epoxidation pathway is quantitatively the more important one, and there is speculation that 10,11-epoxycarbamazepine contributes to the drug's antiepileptic (and possible anti-aggressive) activity (28). There is also evidence which suggests that carbamazepine induces certain enzymes, e.g., cytochrome P-450 and epoxide hydrase, and may hasten its own degradation. The measured half-life after a single dose (37 hours) is significantly greater than the half-life after repeated doses (28 hours) in multiple trials (28).

Animal studies initially demonstrated carbamazepine's anticonvulsive effects and located its site of action in the limbic region of the brain. Carbamazepine's anti-epileptic properties were most evident in electrically-induced seizures in rats and mice, and somewhat less pronounced in chemically induced seizures in these animals. Hypothalamically-induced rage in cats was also controlled by carbamazepine, suggesting effectiveness in specific types of aggression. In the cat epilepsy model, electrical stimulation of various limbic structures produced after-discharges recorded in the stimulated structures themselves and interrelated areas. The hippocampal after-discharge, possibly involved in psychomotor epilepsy and a particularly useful measure of anticonvulsant efficacy, was shortened by carbamazepine at a dose of 3 mg/kg in cats. The drug had no effect on the Purkinje cells of the cerebellar cortex, suggesting that the mode of anticonvulsant action of carbamazepine differs from that of diphenylhydantoin and diazepam (29). Studies of the fighting behavior of mice suggest that carbamazepine in high doses has general anti-aggressive and anxiolytic effects. Antiparkinsonian and anticholinergic properties also appear only at very high doses. Contrary to clinical reports in humans, traditional reserpine and amphetamine antagonism trials in animals have not demonstrated antidepressant or antipsychotic effects for carbamazepine. To measure carbamazepine's possible anti-depressant activity, 1,000 mg/kg of the drug was administered to rodents with reserpine-induced ptosis but produced no antagonistic effect. Similarly, to test for neuroleptic properties, 300 mg/kg of carbamazepine was given to rats with amphetamine-induced stereotypy, again without antagonism (29). These findings have led investigators to focus on the limbic system-temporal lobe area as the primary site of carbamazepine's action and to attempt to identify possible neurochemical explanations for its psychotropic efficacy.

Postulating an association between the high density of opiate receptors in the limbic system and carbamazepine's mechanism of action, Post et al. measured opioid activity in patients with affective disorders treated with carbamazepine. They reported that the drug exerted no significant effect on cerebral spinal fluid (CSF) opioid activity (30), and found no significant association between CSF GABA levels and carbamazepine dose or blood level of the drug (31). They subsequently examined the effects of carbamazepine on receptors of various major neurotransmitters and other substances. Data sug-

gested that, unlike neuroleptics, carbamazepine does not block dopamine receptors. It did not produce parkinsonian symptoms, tardive dyskinesia, or inhibition or suppression of unit firing dopaminergic neurons of the substantia nigra by apomorphine; it did produce minimal elevations of prolactin but did not diminish cocaine- nor amphetamine-induced hyperactivity. Benzodiazepine receptor antagonists did not affect carbamazepine's anticonvulsant activity in amygdaloid seizures, suggesting little effect of carbamazepine at the benzodiazepine receptor as well. Carbamazepine failed to inhibit binding at several receptor sites, including muscarinic-cholinergic (^{3}H-QNB), dopamine (^{3}H-spiroperidol), GABA (^{3}H-muscimol), imipramine, beta-adrenergic (^{3}H-DHA), and opiate (^{3}H-naloxone) receptors. However, displacement of adenosine analogs was demonstrated, indicating effects on the adenosine receptor, and a blockade of both release and reuptake of norepinephrine, which may be related to carbamazepine's apparent efficacy in bipolar illness (32). Other documented effects of carbamazepine include decreased circulating T_3 and T_4, efficacy as a vasopressin agonist, increased urinary free cortisol, and decreased CSF somatostatin (32).

Post and his group proposed that carbamazepine, through its anticonvulsant properties, may represent a new class of psychotropic agents for the treatment of affective dysregulation, including aggression as a symptom of a hyperexcited state or limbic seizure (33). This hypothesis was based on Dalby's successful use of carbamazepine in patients with temporal lobe epilepsy and mood disorders (34,35), carbamazepine's inhibition of experimentally induced kindling in the limbic system (particularly amygdaloid seizures), and Post and his coworkers' success in treating affectively disordered patients with carbamazepine. In Post's model, these subcortical seizures, which could manifest as behavioral aberrations such as aggression and psychosis, would not necessarily produce EEG abnormalities; kindling could occur with either environmental or endogenous stimuli (36). Heath's work with deep brain EEG recordings in epileptics and schizophrenics also provides some support for Post's model. Heath describes seizure-like activity in the amygdala, hippocampus, and septal region of epileptics with violent psychotic episodes which closely resembled the spike and slow-wave patterns obtained from the same brain regions in nonepileptic aggressive psychotic patients and psychotic schizophrenics (37).

Although the use of carbamazepine in psychiatric patients is increasing as more data are published, treatment guidelines and side effect profiles have not yet been fully agreed upon. Experimental protocols have suggested administration of carbamazepine in doses ranging from 200 mg/d to 2,000 mg/d, with most recommending initial doses of 200–400 mg/d with gradual upward titration to the point of maximum clinical efficacy or dose-limiting side effects (6). Post et al. report treatment with 1,600–2,000 mg/d with few side effects (38). Blood and CSF levels of the drug have been shown to bear no relationship to clinical response when the drug is used to treat aggressive psychotic psychiatric patients, although CSF levels of carbamazepine-10,11-epoxide correlated

significantly with clinical response when measured after a month of treatment (38). Side effects, however, do appear to be related to the plasma level in some patients, becoming more intolerable when the serum concentration exceeds 9 ug/ml (38). The most commonly reported side effects include diplopia, skin rash, fatigue, unsteadiness, transient paresthesias in the extremities, reversible lupus erythematosis syndrome, nystagmus, drowsiness, nausea, vomiting, and neutropenia (39). Though decreases in white blood cell counts are usually clinically insignificant, there have been cases of aplastic anemia (40) and agranulocytosis (41) reported with carbamazepine. Other hematologic effects include thrombocytopenia (42), reticulocytosis (43), and leukocytosis (44). Although the incidence of these blood dyscrasias is low, hematologic monitoring should include a complete blood and platelet count prior to therapy and weekly complete blood counts for the first month, followed by monthly white blood cell counts (40). If leukopenia develops, the dose of the drug should be decreased and the white cell count monitored biweekly. In the event of infection or severe leukopenia (WBC less than $3,000/mm^3$ or neutrophil count less than $1,500/mm^3$), carbamazepine should be discontinued (41).

There are reports of additional side effects and some drug interactions involving carbamazepine. Because its chemical structure is so closely related to tricyclic antidepressants, carbamazepine may potentiate the action of these drugs when they are used in combination (39,45). Reiss and O'Donnell report two cases of paradoxical carbamazepine-induced mania in children with family histories of affective disorder (46). Fogelson suggests that ataxia, confusion, and vomiting can occur when carbamazepine dosage is increased too abruptly in patients previously unexposed to the drug, as they have lower clearance than those who take it regularly (47). At toxic levels, carbamazepine is also known to produce encephalopathy (39) or schizophrenia-like psychosis (48) in susceptible patients. Kanter et al. described a patient with bipolar disorder who was started on carbamazepine and haloperidol and developed an acute organic brain syndrome with low serum levels of carbamazepine. The syndrome resolved with discontinuation of both medications, and the mania was subsequently controlled on carbamazepine 200 mg b.i.d. alone. The authors suggest that a central nervous system interaction between the two drugs was responsible for the organic symptoms (49). Lithium carbonate-carbamazepine combinations can produce signs of neurotoxicity (50,51), despite therapeutic serum levels of both drugs, and there is one case report of an organic brain syndrome with a lithium carbonate-carbamazepine-haloperidol combination (52). Isoniazid, when given with carbamazepine, produces delirium (53,54). There is one report of neuro-toxicity when carbamazepine was combined with metoclopramide (55). Uhde and Post observed significant decreases in serum sodium, choride , and calcium in their patients treated with carbamazepine, but these changes were not correlated with treatment response, although those patients who improved on carbamazepine tended to have greater depression of serum sodium levels. They also suggested that some "nonspecific" side effects may actually be symptoms of

hyponatremia (56), possibly due to water intoxication, which has also been reported (57,58). Finally, carbamazepine administration has sometimes led to hypothyroidism with and without elevations of thyroid stimulating hormone (59,32), as well as to hepatitis (60).

Although the Food and Drug Administration has not yet approved the use of carbamazepine in refractory violent psychiatric patients, the literature suggests that this compound, used alone or in combination with conventional agents, may be beneficial in the treatment of psychoses associated with bipolar affective disorder, schizoaffective disorder, and schizophrenia. Through its anticonvulsant action or another yet unidentified mechanism, carbamazepine appears to control limbic seizures, which may be related to both psychosis and aggression. Familiarity with potential side effects and drug interactions is necessary as the use of carbamazepine increases. Finally, additional clinical trials are necessary to further assess the safety and spectrum of carbamazepine's efficacy.

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