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The Use of Carbamazepine (Tegretol) in Psychiatry and Its Association to Kindling, Temporal Lobe Epilepsy and Psychopathology

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Abstract

The recent theory of kindling may help to link neurophysiologic, neurotransmitter and neuroanatomic mechanisms important in understanding the neurology of behavior. Limbic kindling is of interest in developing models of epilepsy, psychosis, learning and memory (1-5). Kindling might explain the late development of psychopathology.

This paper will first define kindling and demonstrate how kindling offers a model within which to view more prolonged behavioral deviations as neurophysiological processes. The use of carbamazepine and its association to kindling, temporal lobe dysfunction and psychopathology will be discussed.

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THE USE OF CARBAMAZEPINE (TEGRETOL) IN PSYCHIATRY AND ITS ASSOCIATION TO KINDLING, TEMPORAL LOBE EPILEPSY AND PSYCHOPATHOLOGY

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The recent theory of kindling may help to link neurophysiologic, neurotransmitter and neuroanatomic mechanisms important in understanding the neurology of behavior. Limbic kindling is of interest in developing models of epilepsy, psychosis, learning and memory (1–5). Kindling might explain the late development of psychopathology.

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As originally defined by Goddard and Morrel (2), the term kindling referred to the observation that brief electrical stimulation of limbic and cortical areas in rats by currents that were originally inadequate to evoke after-discharges or behavioral effects, eventually produces an after-discharge. When carried on long enough, kindling stimulation leads to spontaneous seizures. As suggested by the name, the term kindling is an analogy to the starting of a fire whereby application of low heat (or subthreshold stimulation) causes wood (or brain tissue) to burst into flames (or convulse). Kindling represents neuronal processes that may mediate the formation of lasting behavioral change. The process of kindling is not all or none (3). It involves a progressive, lasting lowering of neuronal threshold to evoke an afterdischarge. Both electrical and chemical stimuli can produce kindling (7). Chronic administration of CNS stimulants such as cocaine and amphetamines may cause increases in limbic system discharges and vulnerability to pathologic behavior and seizures (8, 9).

The concept of kindling has been applied to chronic psychological stress that results in progressive vulnerability to pathologic behavior. It is known that environmental events can induce synchronized electrical activity within the limbic system. There is evidence of lasting change in behavior following repeated limbic stimulation with and without changes in epileptogenicity. Animal studies have shown full-blown behavioral convulsions after epileptic activation of the limbic system without electroencephalographic evidence of seizures. It is not completely clear what role interictal phenomena have on behavioral responses (10). Kindling may explain why certain temporal lobe epilepsy (TLE) patients develop behavioral changes and psychosis.

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I would like to focus on temporal lobe epilepsy (TLE), a condition associated with personality disturbances (11, 12). Eighty-five percent of all persons with epilepsy have temporal lobe-limbic system epilepsy, in which the temporal lobe recruits the rest of the brain into a major motor seizure (13). Some of the psychic experiences which may occur during temporal lobe dysfunction that can mimic psychiatric disorders are the following (13, 14):

- Hallucinations (auditory, visual, olfactory, tactile, gustatory or vertiginous)
- Excessive water drinking
- Dreamy state
- Depersonalization
- Forced thinking
- Deja vu
- Compulsive thinking
- Jamais vu
- Confusion
- Derealization
- Amusia
- Fear
- Aphasia
- Paranoia
- Agnosia
- Elation
- Memory defects
- Depression
- Hypergraphia
- Anxious
- Hyperreligiosity
- Sexual disturbances
- Headache
- Cephalic auras (micropsia, macropsia)
- Alimentary symptoms
- Crying and laughing episodes
- Running episodes

Thus it is not enough to ask a patient suspected of having TLE whether he has seizures, convulsions or attacks of unconsciousness, and to leave it at that. History-taking in these cases demands a meticulous search for the more subtle types of temporal lobe attacks.

There are technical problems in identifying patients with temporal lobe-limbic system dysfunction manifesting clinically as psychiatric disorders, i.e., explosive, aggressive, borderline and antisocial personality structures (13, 14, 15). These individuals exhibit a wide variety of episodic behavioral disturbances including free-floating anxiety, affective disorders, impulsive destructive rages, atypical psychosis and mini-psychotic episodes (14, 15, 16, 17). Some of these patients demonstrate abnormal EEG activity, with clinical improvement after anticonvulsant medication (18). The problem is that temporal lobe-limbic system abnormalities, whether associated with an ictal or interictal state, are seldom detected by cortical, much less scalp, recordings; thus the clinical EEG is not a sensitive measure of possible neurophysiological correlates with behavior (19). In the future, computerized analysis of EEG and evoked potential data and Positron Emission Tomography (PET) could be helpful (20, 21). In the meantime, physiological and drug-activated EEG’s (sleep, hyperventilation, sedatives and stimulants) with low temporal lobe leads or nasopharyngeal leads are presumed to be the most useful clinical measures of central nervous system instability (22, 23).
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The concept of psychosis and epilepsy has been written about for the last 200 years. In 1860 Morel reported the alternation of psychotic episodes with convulsions. Lateralization was introduced into the work by Flor-Henry who reported left-sided TLE being more frequently associated with schizophrenic-like symptoms and right-sided lesions being associated with affective disorders (10).

Monroe has data that directly support the concept of limbic ictus as an etiological mechanism in a group of patients with the diagnosis of atypical psychosis. Psychoses were correlated with electrographic data recorded from chronically implanted subcortical electrodes (14, 16, 17, 22, 23, 24, 25, 26). Monroe describes a young female patient diagnosed as having chronic paranoid schizophrenia who would become psychotic with intense rage reactions. At this time dramatic electrographic abnormalities from subcortical electrodes were noted although these abnormalities were not present in the corresponding scalp leads. During the intervals between attacks when her chronic paranoid symptoms were the only deviant behavior noted, interictal types of recordings were noted from subcortical electrodes (17). Ictal fear has been found by neurosurgeons, who have implanted electrodes in the brain, to arise from a medial temporal focus in the region of the amygdala and hippocampus, i.e., limbic system lesions as opposed to lateral cortical lesions (3, 12). A recent study by Hermann showed that a subgroup of TLE patients did have abnormal MMPI test data. This subgroup was composed of TLE patients whose seizures began with fear (25). These patients showed elevated scores of MMPI Psychasthenia and Paranoia scales.

The following question arises; is the psychosis seen in epilepsy related to the psychosis seen in non-epileptic patients? Perez and Trimble performed a recent study on 24 patients with psychosis and epilepsy and 11 controls that just had psychosis diagnosed clinically by two different psychiatrists (27, 28). The technique used the examination of Wing (27). This examination collects symptoms by a standard interview. This information is put into a computer using a special program which then yields a computerized diagnosis of the psychosis to objectify the diagnosis. Twelve of the epileptic psychotics were diagnosed as having a form of schizophrenia. The other half had various other diagnoses. Eleven of the twelve had the nuclear schizophrenia which was based on Schneiderian first rank symptoms. The group was divided up into those that had generalized epilepsy and those that had TLE. This diagnosis was done clinically and by an EEG. The results showed that only those patients with the nuclear schizophrenia described by Schneider had TLE. Nuclear schizophrenia did not occur in generalized epilepsy.

This is the most objective evidence obtained so far linking nuclear schizophrenia and TLE. The study also looked at the profile between left and right TLE. The nuclear syndrome appeared significantly more in left TLE. The laterality was established by an independent electroencephalographer, the diagnosis of nuclear schizophrenia by a computer. This is a direct confirmation of the observations made in the sixties by Flor-Henry of a direct link between left-sided TLE and nuclear schizophrenia (10, 26).

Studies supporting Flor-Henry’s observation of right sided temporal lobe epilepsy
in the nondominant hemisphere yielding affective psychosis can be found in the literature (10, 26). It is also important to note that in the majority of TLE patients the epilepsy precedes the psychosis by several years.

**Carbamazepine**

Carbamazepine (CBZ) (Tegretol) was developed by J.R. Geigy in Basel, Switzerland, in the 1950’s (29). Its anticonvulsant properties were described by Theobold and Krinz in 1963, based on animal studies. The compound was introduced in Europe as an antiepileptic in the early 1960’s. Not until 1974 was CBZ approved for use in epilepsy in the U.S. CBZ is chemically related to the tricyclic antidepressants, such as imipramine.

The drug of choice for temporal lobe epilepsy is CBZ (13). Most patients with uncontrolled temporal lobe epilepsy have severe personality problems. There is a dramatic change in behavior with control of the epilepsy, not seen with the use of phenytoin and phenobarbital. Evidence has been accumulated which indicates that CBZ has beneficial psychotropic effects. Initially these effects were noted in psychiatric syndromes associated with seizure disorders (30, 31). CBZ has shown clinical usefulness in the following disorders:

1. Temporal lobe epilepsy (TLE, Partial complex seizures) (1, 32)
2. Grand mal seizures (32)
3. Alcohol withdrawal seizures (33)
4. Mixed seizure patterns (32)
5. Kindling phenomenon in amygdala (34, 35, 36, 37)
6. Trigeminal neuralgia (38, 39, 40)
7. Tabes dorsalis (40, 41)
8. Paraesthesias associated with multiple sclerosis
9. Paraesthesias associated with phantom limb (42)
10. Postherpetic neuralgia (43)
11. Glossopharyngeal neuralgia (44)
12. Digitalis-induced ventricular arrhythmias (45)
13. Motor and verbal tics in Gilles de la Tourette’s syndrome (46, 47)
14. Myokymia (48, 49)
15. Myoclonic tinnitus (50, 51, 52, 53)
16. Manic depressive illness (1, 3, 14, 54–66)
17. Affective dysregulation of TLE (31)
18. Borderline personality disorder (1, 14, 15)
19. Atypical psychosis (14)
20. Episodic dyscontrol syndrome (3, 14, 17)
21. Limbic ictus with atypical psychosis (12, 14, 66)
22. Schizophrenia (12, 60, 64)
23. Diabetes insipidus (67, 68, 69)

A mechanism which would explain the spectrum of usefulness of CBZ from
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paroxysmal or shooting pain to affective dysregulation is still unclear. Theories as to the antidepressant and antimanic effects of CBZ have been related to the noradrenergic system and its ability to stabilize limbic system dysfunction. The possibility of a previously undescribed antipsychotic effect or anticonvulsant (antikindling) effect has to be considered. CBZ effects on GABA, opiates, vasopressin, somatostatin are but a few areas of interest (1, 3, 62, 67, 68, 69, 70).

Although a number of theories suggest various mechanism of action of CBZ, none fully elucidates the molecular mechanism of action and the observed clinical efficacy of this extremely important and interesting drug.

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