Treatment of the Interictal Psychoses

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Background: The interictal "schizophrenia-like" psychoses of epilepsy conventionally are treated with antipsychotic medication with uncertain results. In patients with these psychoses, a preceding and concomitant dysphoric disorder usually can be documented. Effectiveness of the pharmacologic treatment by the combination of drugs that is effective for severe interictal dysphoric disorders is demonstrated in a series of patients with interictal psychosis.

Method: Patients were treated with the combination of a tricyclic antidepressant and a selective serotonin reuptake inhibitor, enhanced if necessary by a small amount of the atypical neuroleptic risperidone. The series consisted of 8 consecutive patients with interictal psychosis seen over a 20-month period. Two additional patients seen over the past 10 years who required a different therapeutic intervention were also included.

Results: Five of the 8 consecutive patients achieved full remission of their psychosis; 3 patients could not be reached for the full treatment effort. One patient with a malignant psychosis had been treated successfully (prior to the series reported) by surgical removal of a left frontal epileptogenic zone; a second patient (treated after the series) recovered only upon elimination of the antiepileptic drug that had suppressed clinical seizures but had resulted in an alternating psychosis.

Conclusion: Interictal psychoses can be viewed as severe interictal dysphoric disorders with psychotic features. The same combination of psychotropic medication that is effective for severe interictal dysphoric disorders serves as the primary therapy for interictal psychoses. The interictal psychiatric disorders presumably result from seizure-suppressing mechanisms that are the targets of the proconvulsant drugs. Upon suppression of seizures, some patients with interictal psychosis may require modification of the antiepileptic medication responsible for excessive inhibition. Complete surgical removal of the epileptogenic zone can eliminate a chronic interictal psychosis upon postoperative fading of inhibitory mechanisms.

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The so-called "schizophrenia-like" psychoses of epilepsy occur during the interictal phase in clear consciousness, usually in the presence of a low seizure frequency and at times coinciding with a period of freedom from seizures. These psychoses tend to develop in patients with temporal lobe epilepsy after an average of 14 years of illness, but sometimes have a much earlier onset; they may be episodic or become chronic.[1,2] Their psychopathology is characterized by hallucinatory, paranoid, or delusional symptoms, i.e., Bleuler's accessory symptoms of schizophrenia, in the presence of intact emotionality and rapport with others. A family history of schizophrenia is usually absent, and the course of the disorder lacks the symptoms of schizophrenic deterioration. For these reasons, together with the absence of the fundamental symptoms of schizophrenia, the term *schizophrenia-like* is misleading and should be avoided. The frequency of any psychotic disorder in patients with epilepsy has been reported between 4% in a neurologic outpatient seizure clinic[3] and 60% among epileptic inpatients of a psychiatric hospital.[4] For a recent comprehensive survey on psychoses in epilepsy, refer to Schmitz and Wolf.[2]

In contrast to the wide-ranging debate over the *interictal* psychoses in the literature that followed Slater and Beard's description of the schizophrenia-like psychoses of epilepsy in 1963,[1] there has been little controversy about the *ictal* and *postictal* psychoses of epilepsy. Postictal psychoses occur in some patients after a relatively silent interval of 1 or 2 days following a flurry of seizures, with or without confusion, and are limited to a period of days to a couple of weeks. The relatively rare ictal psychoses are manifestations of a nonconvulsive status epilepticus that occurs as generalized absence status ("spike-wave stupor"), complex partial status, or simple partial status (aura continua) and usually can be diagnosed by electroencephalogram (EEG). Consciousness usually is clouded during ictal psychoses. Improved antiepileptic therapy is required to treat ictal and to prevent postictal

psychoses. Paraictal psychoses are least known and are rare: they occur if increased seizure frequency becomes associated with the development of psychosis.[2] They may be observed occasionally on epilepsy monitoring units as seizures become frequent after discontinuing antiepileptic medications. Appropriate antiepileptic medication is required for their treatment as well.[5]

To treat interictal psychoses, neuroleptic medication is usually recommended, although documentation of its effectiveness is lacking. For interictal psychoses that coincide with periods of full seizure control (alternating psychoses), Schmitz and Wolf[2] advise sleep regulation with benzodiazepines for the prodromal phase of insomnia and reduction of the antiepileptic medication if neuroleptic treatment fails. Given the wide coverage in the literature of the interictal psychoses[6] and considering their crippling effect for a large number of patients, the complete absence of any systematic treatment reports is surprising. In our experience, neuroleptic treatment of the interictal psychoses of epilepsy has a limited effect or may be totally ineffective. Therefore, over the past decade, we have developed a different type of pharmacologic treatment for the interictal psychoses that is based on successfully treating the interictal dysphoric disorder.

The interictal psychoses cannot be viewed in isolation from the most common psychiatric disorder of epilepsy, identified as the interictal dysphoric disorder. Fleeting psychotic symptoms occur frequently among patients with dysphoric disorder, while prominent psychotic symptoms occur almost exclusively among patients with severe dysphoric disorders.[7] The interictal dysphoric disorder is the characteristic pleomorphic and intermittent disorder that develops in a majority of patients with chronic mesial (limbic) temporal epilepsy, usually 2 or more years after onset of the seizure disorder.[8] The dysphoric disorder presents with up to 8 affective-somatoform symptoms appearing intermittently for the mere duration of hours to a couple of days and is readily distinguished from any of the presently recognized psychiatric disorders by its characteristic pleomorphic and intermittent nature. The disorder was well recognized by premodern psychiatrists who had the benefit of longitudinal observations of their institutionalized patients with epilepsy but has been missed completely by our modern cross-sectional studies. In the classic textbooks of Kraepelin[9] and Bleuler,[10] the dysphoric disorder (termed *Verstimmungszustand*) was noted to be ubiquitous among the institutionalized patients with epilepsy. Notably, Kraepelin viewed the interictal psychotic episodes as mere expansions of the dysphoric state.

The interictal dysphoric disorder has recently been redefined by the intermittent presence of at least 3 of the following 8 affective-somatoform symptoms: depressive moods, anergia, irritability, euphoric moods, atypical pains, insomnia, fear, and anxiety. Patients with a history of psychotic symptoms and suicide attempts tend to present with a significantly larger number of the 8 key symptoms of the dysphoric disorder than those without that history.[7] The identity of the interictal dysphoric disorder is further confirmed by the finding that the entire symptom-complex responds well to treatment with antidepressant medication.[11] If the disorder is severe and does not respond to a tricyclic medication, the tricyclic antidepressant is augmented by adding a selective serotonin reuptake inhibitor (SSRI), an approach termed *double antidepressant treatment*.

In our earlier series reported 12 years ago,[12] 19 patients with epilepsy and psychiatric disorders were treated by adding a tricyclic antidepressant to the antiepileptic medication. Twelve patients had presented not only with dysphoric but also with psychotic features. Remission or improvement of the psychotic features was concomitant with the response of the dysphoric symptoms; a small amount of neuroleptic medication was combined with the antidepressant in a few patients. We are now viewing the interictal psychoses as severe dysphoric disorders with predominant psychotic symptoms (Table 1) and accordingly have treated them for the last 7 years with double antidepressant medication.[11,13] A number of patients with psychoses, as well as a number with severe dysphoric disorders without psychotic symptoms, require the addition of a small amount of risperidone. Thus, our treatment efforts have developed in concert with a redefinition of both the affective and the psychotic disorders of the interictal phase of epilepsy.

A hypothetical rationale for the effectiveness of the proconvulsant antidepressants in treating the psychiatric disorders of epilepsy can be proposed. Engel[14] has postulated, with Stevens,[15] that the psychiatric disorders of epilepsy may result from the inhibitory activity that develops in reaction to the excessive excitatory activity of the

Table 1. Classification of the Interictal Psychiatric Disorder[a]

Dysphoric Disorder	Psychosis
8 Affective-somatoform symptoms	Dysphoric disorder with
Depressive moods	Hallucinations
Anergia	Paranoia
Irritability	Delusions
Pain	Bizarre behavior
Insomnia	
Fears	
Anxiety	
Euphoric moods	

[a]The interictal dysphoric disorder is defined by the presence of at least 3 of the 8 affective-somatoform symptoms, each to a troublesome degree, in a patient with epilepsy. The symptoms tend to be intermittent (lasting hours to a few days). The interictal psychoses are characterized by a preexisting and concomitant severe dysphoric disorder. The psychotic symptoms need to be present in a more than fleeting pattern. Psychotic episodes can be differentiated from chronic psychoses by their briefer duration (few days to a few weeks vs. months) and may be better termed *dysphoric disorders with psychotic features*.

There appears to be a continuum from the frequent interictal dysphoric disorders with fleeting psychotic symptoms to the more severe dysphoric disorders with prominent but transient psychotic features to those with more prolonged psychotic states.

chronic seizure disorder. While the nature of the seizure-suppressing inhibitory mechanisms is still poorly understood, the psychiatric observations support this hypothesis. The following findings suggest that the presence of predominant or enhanced inhibitory mechanisms, operating in homeostasis with the excitatory activity, may in fact produce the psychiatric disturbances of the interictal and perictal phases of temporal lobe epilepsy: (1) the delayed development of the interictal dysphoric and psychotic disorders following onset of the epilepsy[1,8] as inhibitory mechanisms gradually become established; this accords with the particular linkage of the psychiatric disorders of epilepsy with its most prominent chronic form, i.e., with mesial temporal lobe (limbic) epilepsy[7,8]; (2) the delayed phasing out of the psychiatric changes after surgical elimination of the epileptogenic zone, presumably with only gradual fading of inhibitory mechanisms (as documented by case 1 in the present series, as well as in an earlier series[16]); (3) the manifestation of dysphoric or at times of psychotic symptoms in the prodromal and particularly in the postictal phases when inhibitory responses become forcefully engaged[17]; and (4) similarly, the potential for psychiatric changes to emerge not only at times when inhibition is clearly predominant as seizure activity is suppressed (often referred to as "forced normalization"[18]) but also at times when exacerbation or persistence of the seizure activity prompts an enhanced inhibitory response (i.e., in the premenstrual phase,[19] in paraictal psychoses, and in ictal psychoses). In the case of the rare paraictal and ictal psychoses, the enhanced seizure activity is the primary problem and requires intervention with antiepileptic medication. In the case of the common interictal psychoses, on the other hand, the seizure activity has usually diminished or is completely suppressed, and the emerging psychiatric disorder requires intervention with proconvulsant medication to mitigate the psychotoxic inhibitory mechanisms. The published observations on the interaction of seizure activity and psychiatric changes have largely focused on the frequent emergence of dysphoria and psychosis upon lessening or suppression of seizure activity.[18,20–25]

In 1951, Gibbs[20] reported the presence of interictal psychiatric symptoms in 49% of 163 patients with anterior temporal lobe epileptic foci; in 17% of the patients a psychotic disorder was present. Gibbs noted that the antiepileptic medication (phenylacetylurea in particular), while blocking the seizures and normalizing the EEG, would exacerbate the psychiatric disorder, even to the point of precipitating a psychosis. Eliminating the antiepileptic drugs would result in prompt reappearance of seizures and disappearance of the exacerbation of the psychiatric disorder. Gibbs thus first noted the antithetical relationship of the psychiatric and the epileptic components in temporal lobe epilepsy. In 1953, Hill[21] noted 2 types of psychoses among patients with epilepsy: those occurring in association with seizures and those occurring in patients with temporal lobe epilepsy whose seizures have, after many years, ceased spontaneously, become greatly reduced in frequency, or been controlled by drugs. In the same year, Landolt[22] reported initial observations of the inverse relationship of psychiatric and epileptic manifestations: in the presence of psychosis, the EEG normalized and seizures remitted. In his first report, he expressed the view that this finding was related to an excess of inhibition ("supernormal braking action") but later, in his first comprehensive report, preferred the merely descriptive term *forced normalization* for the phenomenon.[23] He noted that the metrazol threshold was usually increased during the episodes. Landolt was very familiar with the dysphoric episodes of the interictal phase; in view of our contention that the interictal psychoses are in essence interictal dysphoric disorders with psychotic traits, it is noteworthy that Landolt described a striking correlation not only of psychoses but of dysphoric episodes with normalized EEG findings.[23,24]

More recently, Pakalnis et al.[25] reported a series of 7 patients with forced normalization, seen over a period of 28 months; they had frequent seizures, were given a new antiepileptic medication that suppressed seizures and EEG abnormalities, and after 2 days developed de novo psychotic episodes. Demers-Desrosiers et al.,[26] on the other hand, reported 2 unique cases of epileptic patients who, during admission for investigation of the epilepsy, became psychotic on the day after discontinuation of the gradually withdrawn antiepileptic medication and recovered upon reinstitution of the medication. During the patients' psychotic state, their EEGs showed increased epileptiform potentials, but no seizures occurred and consciousness remained intact. The authors pointed out that their cases represented the opposite of Landolt's forced normalization. One may hypothesize that the brief psychoses of the 2 patients were due, as in paraictal and ictal psychoses, to the forceful engagement of inhibitory mechanisms resulting from the enhanced seizure activity. Prolonged interictal psychoses, however, tend to occur in the setting of diminished or absent seizures, as the evident result of "forced normalization," i.e., of predominant inhibitory mechanisms.

The treatment of the psychiatric disorders of epilepsy with antidepressants was initially an empiric procedure.[12,27] According to the hypothesis of their pathogenesis, the pharmacologic treatment has to be directed against the inhibitory mechanisms. The proconvulsant antidepressant drugs at modest doses (100–150 mg of a tricyclic, 20–40 mg of an SSRI) may serve as effective antagonists to the excessive inhibition and in fact are indispensable for successful treatment of the interictal dysphoric and psychotic disorders.[11–13,16] They are more effective than the less proconvulsant neuroleptics. In about 15 years, we have never observed increased seizure activity in our patients with temporal lobe epilepsy treated with

antidepressants up to the combination of 150 mg of imipramine and 60 mg of fluoxetine or paroxetine. On the basis of his extensive experience with seizure provocation, Gastaut and colleagues[8] have pointed out that the interictal seizure threshold of patients with temporal lobe epilepsy, in contrast to that of patients with primary generalized epilepsy, is higher than that of nonepileptic individuals. The bias against the use of antidepressants for the psychiatric disorders of epilepsy, because they may lower the seizure threshold, is erroneous on both empiric and theoretical grounds. Patients with primary generalized epilepsy occasionally may experience dysphoric disorders and psychotic symptoms, presumably as a result of secondary involvement of mesial temporal structures. These patients with generally lowered seizure threshold respond particularly well to antidepressant medication prescribed at a more modest dose.[12]

When Ojemann et al.[27] reported in 1983 the effect of the tricyclic doxepin on depressed patients with epilepsy, they emphasized less the expected improvement of depression than the surprising marked reduction of seizure frequency in many patients. A later report from the same epilepsy treatment center again noted that most of their patients who were prescribed psychotropic drugs (tricyclic antidepressants and, in a smaller number, neuroleptics) experienced better seizure control.[28] A recent article documents the same finding in a series of patients with epilepsy treated with fluoxetine.[29] From our experience, we cite the case of a 34-year-old patient with intractable epilepsy since age 9 who has required a high dose of double antidepressant medication for her severe interictal dysphoric disorder (with repeated impulsive suicide attempts) and now has been not only mentally stable but also seizure-free for the last 4 years, while taking trimipramine, 100 mg, combined with fluoxetine, 60 mg, and gabapentin, 1800 mg, daily. One may wonder whether the presumed mitigation of inhibitory mechanisms by the antidepressant medication may at times result in a lessening rather than worsening of the antagonistic excitatory activity. In any case, while the antidepressants are indeed proconvulsant, there is no evidence in the literature that they may in fact result in an increase of seizure frequency if prescribed for patients with epilepsy who are on antiepileptic medication.

We are by now satisfied that most interictal psychoses are fully treatable. This article documents our experience in treating the interictal psychoses of epilepsy at the Epi-Care Center, Memphis, Tenn., over the past 12 years.

METHOD

Since 1987, all patients with epilepsy seen at the Epi-Care Center who showed a troublesome psychiatric disorder were evaluated and treated by Dr. Blumer. The Epi-Care Center is a tertiary care center that annually attracts from the wider Mid-South region about 250 new patients with seizure disorders. We report here a series of 8 consecutive patients with epilepsy and interictal psychoses whose treatment began at the Epi-Care Center over a 20-month period (May 1992 through December 1993) with their follow-up through the present. All 8 patients (cases 2–9) were treated with psychotropic medication. To reflect the full range of treatment modalities for interictal psychoses used at the Epi-Care Center over the last 12 years, we include in this report 2 additional patients who had not responded to treatment with psychotropic medication: an earlier patient with exceptionally severe chronic psychosis who had to be treated by surgical removal of the epileptogenic zone (case 1, 1989) and a recent patient who required treatment by modifying the antiepileptic medication (case 10, 1997).

Our earlier report about the treatment of the affective disorder of epilepsy gave an account of all the patients with interictal dysphoric disorder seen at the Epi-Care Center during the 20-month period of May 1992 to December 1993 who had not responded to treatment with a tricyclic antidepressant and required the addition of an SSRI.[11] In May 1992, the first patient with interictal dysphoric disorder was treated with double antidepressant medication, and this treatment soon proved the most effective pharmacotherapy not only for patients with severe dysphoric disorders but also for patients with interictal psychoses. One patient had to be excluded since further treatment clarified that his paranoid fear of being killed by women antedated the onset of his epilepsy, appeared to be posttraumatic in nature, and furthermore did not disable him from an academic career, thus failing to qualify his disorder as a psychosis. The 8 remaining patients represent the series reported in this article.

The psychotic patients were initially treated with a tricyclic drug (imipramine, 100 to 150 mg at bedtime, or amitriptyline at the same dose if insomnia remained a problem) and an early addition of the SSRI (usually paroxetine, 20 mg a.m. or b.i.d.). Prior to the discovery of the effectiveness of the double antidepressant treatment, we had at times enhanced the tricyclic antidepressant with a small dose of neuroleptic drug (1 mg of trifluoperazine per 25 mg of the tricyclic) with some satisfactory results.[11] We learned only in 1995 that full remission of the dysphoric disorder, with or without psychotic features, sometimes could only be achieved once risperidone was added (usually at 2 mg twice daily) to the double antidepressant medication. For geographic reasons, the complete sequence of therapeutic steps could not be carried out in 3 patients; they are reported as patients with incomplete treatment (cases 7, 8, and 9).

Since 1992, we have had available a standardized psychiatric evaluation developed specifically to reflect the characteristics of patients with epilepsy: Epilepsy Questionnaire, Neurobehavioral Inventory, and semistructured

interview. The data are obtained from both patient and next of kin. This method of evaluation has been described elsewhere.[7,30]

CASE REPORTS

We report the history of illness and treatment of 7 male and 3 female patients who became psychotic after a mean duration of epilepsy of 15.1 years (range, 3 months to 26 years). The mean age at onset of the psychosis was 27.8 years (range, 20–38 years), and the mean duration of our psychiatric follow-up from the time of initial evaluation was 6.7 years (range, 1.5–10 years).

In 3 patients, a de novo psychosis developed between 7 and 18 months after unilateral temporal lobectomy (cases 2, 6, 9); 2 patients had shown mild or transient psychotic features during the year prior to operation and became severely psychotic within a few weeks after the operation (cases 7 and 8). The only other patient surgically treated was relieved of her psychosis by left frontal lobectomy (case 1).

With the exception of the alternating psychotic episodes that resulted from the seizure-suppressing effect of the antiepileptic medication in case 10, all psychoses were preceded by an interictal dysphoric disorder that remained concomitant with the psychotic phase. None of the patients had a schizophrenic or manic-depressive ancestry.

Case 1

At age 26, this single woman, daughter of an educator, was admitted to our psychiatric inpatient service for the first time. Her family history was negative for mental illness. She had grown up in a supportive family and was outgoing and well adjusted. During her high school years, she had joined a fundamentalist church, excelled in marathon running and swimming, and tended to be anorexic and amenorrheic. She became chronically ill at age 18, during her first year in college. The illness began with bodily malaise, dizziness, and ringing in her ears, then heart palpitations and abdominal cramps. Repeated physical examinations failed to explain her symptoms. After 1 year, she related 2 episodes of rape over the preceding 2 years that seemed to be imaginary. At age 20, she became very depressed and made a first suicide attempt. At that time, during her first psychiatric hospitalization, she had a first seizure and soon began to suffer from a persistent hallucinatory state distinguished by voices commanding her to harm herself. Thereafter, she repeatedly cut her forearms, frequently burned herself by setting fire to gauze on her forearms that had been soaked in flammable agents, and made multiple suicide attempts by overdoses. During the 6 years prior to her initial admission to our care, with the exception of intermittent episodes totaling 9 months, she had to remain confined to psychiatric hospitals, where she frequently required restraints or constant observation. She had insomnia, poor appetite, and mood swings, but only once had exhibited violent behavior toward staff.

She arrived in a parkinsonian state as the result of a massive amount of neuroleptics (fluphenazine, 80 mg, and loxapine, 400 mg, daily, with a body weight of about 100 lb [45 kg]) that had been prescribed together with phenobarbital, 240 mg, and trihexyphenidyl, 10 mg, daily. She experienced hallucinations of usually 2 male voices commanding her to cut or burn herself and threatening that she would be killed if she did not comply. The voices were constant and waxed and waned in intensity, frequently to the point she could not resist. She sometimes heard her thoughts loud inside her head and experienced thought insertion and also visual hallucinations of blood exuding from the walls or whatever she touched, as well as of bugs on her hands; she imagined there were bugs under the skin that had to be released. Both her forearms were mutilated from many cuts and burns that had required 8 skin grafts. She was otherwise rational, conversant though not vociferous, depressed commensurate with her situation in life, and seeking help from her nightmarish plight. Her seizures were infrequent, and at admission she had been free from seizures for 6 months.

Treatment attempts over the 6 years preceding her initial admission to our care had consisted of various combinations of antiepileptics with neuroleptics (including clozapine) and also, at times, antidepressants or benzodiazepines, psychotherapy, biofeedback treatments, physical exercises, and 3 courses of electroconvulsive therapy. During her first hospitalization of 5 weeks at the Epi-Care Center, her neuroleptics were promptly discontinued and a full remission was obtained on carbamazepine, 600 mg; divalproex sodium, 2500 mg; and amitriptyline, 100 mg, daily. She at first felt lonely without her voices and listened to music constantly. Six weeks later, she had to be readmitted upon recurrence of her hallucinatory and self-destructive psychosis. She remained ill on further pharmacotherapeutic efforts during her second stay of 14 weeks, managed to burn or cut herself repeatedly, and was told by a plastic surgeon she might soon need to have her left arm amputated.

Efforts now concentrated on establishing the presence of an epileptogenic focus. Magnetic resonance imaging (MRI) results showed no abnormalities. A positron emission tomography (PET) study showed left to right differences in the metabolic rate of glucose in the temporal lobes (right higher than left) and frontal lobes (left slightly higher than right). EEG results provided contradictory findings, from normal readings to various focal and generalized epileptiform discharges. A scalp EEG/video monitoring effort had to be terminated when the patient smashed a chair against the window and attempted to run away. A subsequent subdural EEG/video monitoring, undertaken after

gradual phasing out of carbamazepine and clonazepam, was successful: 4 seizures were recorded on the first day of monitoring, and all were of left frontal origin (3 mesial, 1 lateral). Dr. Wyler removed 80% of her left frontal lobe; the tissue study showed the nonspecific changes of focal moderate leptomeningeal fibrosis and mild to moderate supial gliosis. Though her voices resumed postoperatively, she was now calmer, less irritable, less preoccupied with her illness, and more cooperative. She was discharged on daily carbamazepine, 1400 mg; amitriptyline, 100 mg; and loxapine, 15 mg. At home, her hallucinations lessened and seemed to fade out, but then worsened 3 months after surgery. She cut herself again and had to be hospitalized near her home. She began to swallow tissue paper and even jewelry pieces to keep from cutting herself, then gradually became able to resist the voices. She stopped injuring herself about 8 months after surgery. She was able to leave the hospital on passes, and, 14 months after the operation, the hallucinations stopped completely. She was discharged from the hospital, and, 7 months later, her psychiatric follow-up could be terminated. She was followed by a behavioral neurologist and maintained on daily carbamazepine, 1300 mg, and amitriptyline, 100 mg. Except for a seizure event on 1 occasion early in the follow-up period, when she had forgotten her medication, she remained seizure-free after surgery and became able to drive and to work. A recent follow-up, 8 years after removal of the epileptogenic zone, revealed that she continued to do very well. She works 2 part-time jobs taking care of the elderly and animals and is completing college. Her carbamazepine had been discontinued 1 year earlier. She is taking amitriptyline, 50 mg, daily as her only medication because she experienced occasional migraines. She wears short sleeves in the summer, and people may wonder about her scarred forearms; a teacher once asked her if she had been in a fire. She prefers not to relate her story.

Comment. The surgical removal of the left frontal epileptogenic zone was not carried out for intractable seizures but rather in an effort to eliminate an intractable malignant psychosis. The patient's initial prompt response to 100 mg of amitriptyline in place of exorbitant doses of 2 neuroleptics raises the question of whether use of double antidepressant medication with a small dose of neuroleptic, the combination that proved most effective for interictal psychoses a few years later, might have had a more permanent effect. The choice of antiepileptic medication for patients with interictal psychiatric disorders, in general, is of no psychiatric consequence except for some alternating psychoses (see cases 3 and 10). However, replacement of the notoriously sedative and depressing phenobarbital with the combination of carbamazepine and divalproex sodium may have exerted some beneficial effect in our patient. The initial persistence of the psychotic disorder after the operation was a disappointment to everybody at the time, but our later experience has taught us that we should have expected the delay in recovery.[16] Fading of a psychotoxic inhibition generally takes many months; in this patient, it was complete 14 months after successful surgery.

In our experience, we have noted essentially similar psychopathology and treatment response among the patients with temporal lobe epilepsy and the much smaller group of patients with frontal lobe epilepsy.[16] This is not a surprising finding in view of the intimate connection of the frontal and temporal limbic systems, but it does require further study. Noteworthy in case 1 is the exceptionally brief interval between onset of the seizure disorder and onset of the psychosis.

Case 2

This male patient, son of a prominent educator and a fine arts teacher, had developed normally until age 4 when he began to experience brief episodes of daydreaming, rapid breathing, and occasional posturing of the right arm, followed by sleepiness. The seizures persisted. In his adolescence he required psychiatric treatment for social immaturity and acting out. He would often tease younger children excessively and did the same with animals. He was inattentive in school and required special classes. After completing high school, he was unable to hold any jobs, lived at home, and showed much interest in church-related activities. He was generally very polite and pleasant, but episodically would be uncooperative and rude and at times exploded in sudden acts of rage. At age 19, he broke his mother's nose and 2 years later, in another fit of temper, stabbed his father with a knife.

At age 22, he underwent a right temporal lobectomy for his persistent seizures, with only temporary success. While still seizure-free, about 18 months after surgery he began to display paranoid fears and felt that he was watched by the police, and his dysphoric moods worsened. His seizures soon recurred, then became frequent; he underwent a more extensive right temporal resection at age 24, with minimal improvement. He attempted to complete rehabilitation training at a state institution but was unsuccessful. Nine months after the second surgery, he became more paranoid and heard people talking about him. Paranoia and dysphoric moods tended to be present at times when his seizures were suppressed. At age 26, he began to require steady psychiatric attention. He was prescribed a modest dose of tricyclic antidepressant, soon enhanced with a low dose of neuroleptic (trifluoperazine), with limited improvement. After an episode of destructive behavior at home, he required the first psychiatric hospitalization. A third surgical treatment effort (resection of residual right-sided hippocampus) $2\frac{1}{2}$ years after the second showed no improvement. Nine months later, he had to be readmitted to the psychiatric inpatient service because of extreme paranoid ideas (the house being peculiarly wired, having a crystal phone that told him everything), bizarre

behavior (he shaved his head), and weight loss. He improved on clomipramine, 100 mg, with loxapine, 30 mg, but did not remain stabilized. Eighteen months after the second psychiatric admission, he had to be readmitted after the pet dog of his aunt nipped him and he stabbed the dog with his pocket knife. During the subsequent 30 months, 7 more psychiatric admissions were necessary for assaultive behavior, severe paranoia, or both. The combination of paroxetine with a tricyclic (clomipramine, then doxepin) had limited effect.

When his parents feared too much for their safety, he was set up in an apartment of his own, where he became paranoid more frequently. He entered a care home, left on 2 occasions, and was not allowed back. When felbamate combined with carbamazepine controlled his seizures, his dysphoria and paranoia tended to be worse. Attempts to improve his mental state by decreasing the antiepileptic medication were temporarily effective. During 2 hospital stays, electroconvulsive treatments (3 and 1, respectively) had a temporary effect. His mental state improved markedly 3 years ago with his 10th psychiatric admission when he was prescribed risperidone, 3 mg b.i.d., in place of paroxetine, together with doxepin, 150 mg at bedtime, and a modest dose of carbamazepine. He now had more frequent seizures. At times, he still was somewhat dysphoric or restless, tended to sleep a lot, and occasionally displayed paranoid fears. Therefore, 6 months later, paroxetine, 10 mg twice daily, was again added to his medication. His behavior became exemplary; he completed with aplomb a 6-month rehabilitation training program at the same state institution where he had previously failed and is living at home in harmony with his parents. We now have a follow-up period of 3 years of excellent remission since the last adjustment of his psychotropic medication. His seizure frequency decreased upon gradual increase of the carbamazepine to 1000 mg daily and has become rare upon the recent addition of lamotrigine at 300 mg daily without any recurrence of his former dysphoric moods and psychotic symptoms.

Comment. The persistent severity of the patient's psychiatric disorder was a factor prompting repeated surgical efforts to eliminate the epileptogenic zone after the first operation had failed. In fact, his dysphoric and psychotic disorder gradually worsened, a not infrequent outcome if the operation does not eliminate the epileptogenic zone (as achieved in case 1).[16] Our prolonged psychiatric efforts were satisfactory only after we combined a small amount of the atypical neuroleptic risperidone with the double antidepressant medication.

Case 3

This woman, a preacher's daughter with a 6th-grade education, was evaluated psychiatrically for the first time at age 42. At age 10, as the result of having been raped by a relative, she had given birth to a son. One year later, seizures began. Chronic complex partial seizures were well documented and occurred perhaps weekly, but, as a result of the early abuse, she also experienced more prolonged nonepileptic attacks preceded by severe headache and crying. She lives with her second child, a daughter, since her alcoholic husband left her, and she receives steady support from family members and a church she attends faithfully. We learned that she had intermittent episodes of listlessness and depression, tended to be fearful of certain people, and experienced frequent headaches, backaches, and abdominal pains; she had been operated on 3 times without relief from pains. At age 38, reportedly at a time when no seizures occurred, she had experienced an acute psychosis during which she was delusional, hallucinatory, and paranoid, shot off a gun at some of her relatives, and required brief psychiatric hospitalization. A similar, though milder, psychotic episode had occurred about 1 year later.

At age 42, she was treated at the Epi-Care Center, initially with the addition of imipramine to her antiepileptic medication. Because of recurrent hallucinatory episodes, the imipramine was first increased to 150 mg at bedtime, then perphenazine (8 mg daily) was added. She seemed more disturbed at times when she was relatively seizure-free, although this was difficult to judge since she also had nonepileptic attacks. Three years after her initial evaluation, upon combining imipramine with first 20 mg then 40 mg of paroxetine daily, her psychotic episodes remitted. Her seizures persisted. Then, after 8 years of follow-up, topiramate was added to phenytoin and lamotrigine. Her seizures became infrequent, but soon she began to hallucinate off and on. Upon increasing topiramate to 200 mg twice daily, she became more depressed and irrational. She temporarily improved upon decreasing topiramate to 100 mg twice daily and adding risperidone (2 mg twice daily) to her basic psychotropic regimen of imipramine, 100 mg daily, and paroxetine, 20 mg twice daily. In spite of further decreases of the topiramate, she soon became worse again: hallucinations became pervasive and very frightening, she accused a neighbor of trying to poison her, she imagined that toxic fumes abounded, and she was agitated and unable to sleep. In this acute psychotic state, she had to be hospitalized for a period of 5 days on the epilepsy monitoring unit. On the first day, the remaining 50 mg of her topiramate was discontinued and she was given amitriptyline, 150 mg, in place of imipramine to provide restful sleep, while paroxetine and risperidone were continued. After 2 days of diminishing hallucinations and agitation, and having slept well, she experienced—after 2 weeks without seizures—2 of her simple partial seizures (a brief and peculiar stomach sensation rising up), and the previously unremarkable EEG began to show epileptiform potentials. On the following day, her psychosis had remitted. She was discharged 2 days later, after we were satisfied that

nortriptyline, 100 mg at bedtime, provided sound sleep in place of the amitriptyline, whose common side effect of weight gain was of concern.

Comment. This patient had a supportive family who ensured compliance with her medication, and the double antidepressant regimen kept the interictal psychosis in remission. Upon prescription of the new antiepileptic drug topiramate, her seizure activity was suppressed, but the psychosis reappeared as alternating psychosis and remitted only upon complete discontinuation of topiramate, perhaps aided by the replacement of imipramine with the more sedative amitriptyline. As her EEG was monitored during the acute psychosis, it was possible to document the emergence of epileptic potentials simultaneous with the termination of the psychosis. The phenomenon of normalization of the EEG concomitant with emergence of a psychiatric disturbance is well known as forced normalization, but may be best understood as evidence for the presence of marked and psychotoxic inhibition.

Case 4

At age 43, this disabled divorced man was admitted in an acute psychotic state from the emergency room. He had a history of occasional seizures since age 8, reportedly after he had been hit in the head by a brother. He had a history of many psychiatric admissions since age 20 and of alcohol and drug abuse. He had no family members relating to him and lived in care homes or boarding rooms. He recently revealed that prior to adolescence he was both physically and sexually abused by his alcoholic father.

On admission, he was unable to sleep and in great distress over threatening auditory hallucinations that commanded he kill himself. Recently, he identified the tormenting voice as that of his father. After trials including fluoxetine and imipramine, he responded fully to the combination of amitriptyline, 100 mg, and paroxetine, 20 mg, added to carbamazepine and was discharged after 3 weeks. Over the intervening 5 years, he has rarely kept follow-up appointments and has required repeated hospitalizations for psychotic states, which promptly responded to the same double antidepressant treatment. It became evident that he was abusing drugs, cocaine in particular, and financing his habits by theft. When he was able to obtain street drugs, he would stop taking his medication. At times, he was jailed for thievery and given a neuroleptic for his recurrent psychosis with poor results. He would then try to get in touch with us to obtain the double antidepressant treatment that provided prompt relief. This pattern has persisted for 5 years to the present, although after the last hospitalization for a particularly tormenting psychotic episode and a subsequent jail term for theft, he seems more determined to abstain from his drug abuse and to adhere to his medication.

Comment. This lonely man has remained drug dependent and noncompliant with treatment to the present. The psychosis invariably and promptly responded to double antidepressant treatment.

Case 5

This patient had worked at various odd jobs and since adolescence had been involved in petty criminal activities. At age 31, he was shot in the head by a security guard and suffered a persistent left hemiparesis. Complex partial and generalized seizures began 1 year later, but occurred only about twice per year, usually when he failed to take antiepileptic medication. About 2 years after the brain injury, he experienced the first of numerous psychotic episodes requiring hospitalization.

After at least 4 psychiatric hospitalizations elsewhere, he was admitted to our service for the first time at age 38. His psychotic episodes were preceded by insomnia, depressive moods, and at times by constant reading of the Bible, followed by increasing agitation, marked irritability, delusions, hallucinations, cleansing rituals, and wandering. The police would have to bring him to the hospital. During his first admission on our service, he was treated with daily carbamazepine, 600 mg; amitriptyline, 100 mg; and paroxetine, 10 mg, and his psychosis remitted within a few days.

He was noncompliant with medication and follow-up appointments and had to be hospitalized on our service on 4 subsequent occasions over the following 4 years, with similar presentation and outcome. Amitriptyline, 100 to 150 mg at bedtime, and paroxetine, 10 to 20 mg daily, provided prompt remission within a few days.

Comment. This patient's poor judgment and noncompliance may be at least partly due to his brain damage. His psychosis was never chronic and had remitted on a past occasion when he was prescribed haloperidol. His remissions were always prompt and complete when he took double antidepressant treatment.

Case 6

At age 18, this patient suffered a head injury in a beating during a holdup, resulting in 4 weeks of coma. Seizures began 1 year later and became more frequent and severe, with episodes of status epilepticus. He became unable to work and was divorced at age 33. At that time, he had abused alcohol for a period.

At age 35, he came to the Epi-Care Center because of his intractable seizures. He had suffered from depressive moods, anergia, and daily headaches for many years and from insomnia for the past 2 years. An MRI showed left temporal encephalomalacia with some involvement of the left parietal and frontal lobes as well as of the right hippocampus. He underwent a left temporal lobectomy and was prescribed amitriptyline, 100 mg at bedtime, for his dysphoric disorder.

Postoperatively, he initially had only 1 major seizure, but his recent memory was markedly impaired. After 1

year, he required psychiatric hospitalization on our service because of depression, insomnia, anergia, and auditory hallucinations. He had been treated unsuccessfully with chlorpromazine by a local physician. After we discontinued the neuroleptic and prescribed amitriptyline, 100 mg at bedtime, and paroxetine, 20 mg a.m., his dysphoric and psychotic features remitted and he was discharged after 10 days. With the exception of 1 brief confusional period, he remained stable by increasing the paroxetine to 20 mg twice daily.

Comment. He lived at a distance, and the last follow-up we were able to obtain dates to 18 months after surgery.

Case 7

This male factory worker, married since age 19, had begun to have generalized seizures at age 8. He was free of seizures from age 21 to age 27 when he suffered a motorcycle accident with 1½ hours of coma and began to have almost daily complex partial seizures followed by brief visual hallucinations; generalized seizures occurred about monthly. At age 32, he underwent a right temporal lobectomy. Partial complex seizures resumed a few months after surgery at a much lesser rate. His psychiatric disorder then became the main problem and soon rendered him disabled.

About a year prior to surgery, he had developed a severe dysphoric disorder with intermittent depressive moods and diminished energy, insomnia, daily headaches, severe anxieties, and heightened irritability. Paranoid feelings and brief hallucinations of people being present became associated with the interictal dysphoric disorder. The surgery was soon followed by a worsening of his psychiatric disorder, and 4 months postoperatively he required psychiatric admission in an acute depressive and hallucinatory state. Explosive anger alternated with gentle and remorseful behavior; he felt suicidal and voiced homicidal ideation against his boss at work. His fear of people had become overwhelming, and he had disappeared from home for 4 days. During 3 weeks in the hospital, he revealed that he had suffered an episode of violent sexual abuse at the age of 4 and still would visualize the face of the perpetrator regularly upon closing his eyes. This feature was abolished by hypnotherapeutic intervention. His subsequent course over 7 years after surgery was less stormy, although he required 2 more psychiatric hospitalizations 2½ and 4 years after the operation. Treatment with various combinations of tricyclic antidepressants, neuroleptics, SSRIs, venlafaxine, double antidepressant medication, and atypical neuroleptics was only partially effective. Seven years after surgery, he has remained fearful of the outside world to the point of not going out by himself and being unable to attend church services; he is intermittently depressed and anergic, spending entire days in bed, and he still has daily headaches. His wife may find him talking to himself, and he admits to occasional brief hallucinatory episodes. He sleeps with the help of trazodone, has been very good-natured, and has felt best on 40 mg of paroxetine daily combined with carbamazepine. He lives at a distance and complies with the medication prescribed, but prompting him to leave his home for follow-up visits or hospitalization has been difficult.

All along, our effort was directed at his psychotic disorder. He had an occasional generalized seizure and at times reported frequent minor seizures; at other times he claimed his seizures were rare, and his wife assumed the peculiar events were just part of his common confusion. In view of the ineffectiveness of our psychotropic treatment, we are trying to persuade him to return for remonitoring.

Comment. This patient became acutely psychotic 4 months after his right temporal lobectomy. He has continued to suffer from a marked dysphoric disorder with psychotic features, in spite of prolonged treatment efforts that still continue. We consider that his intractable psychotic state may not be interictal (i.e., with rare seizures) but paraictal (i.e., with frequent seizures) and may require more effective antiepileptic medication.

Case 8

This single unemployed woman came to the Epi-Care Center from out of state at age 37 for intractable seizures that had started at age 12, 1 week after a head injury. At a time when all seizures were controlled by carbamazepine, we noted periods of peculiar behavior consisting of sitting motionless or alternatively laughing or crying. During EEG/video monitoring with subdural strips, she had several seizures and thereafter became incoherent and hallucinatory. She had to be transferred to the psychiatric unit for 2½ weeks for postictal psychosis.

Six months after the initial evaluation, she underwent a right temporal lobectomy, which eliminated the seizures during the entire follow-up period of 9 years. Her psychiatric disorder became her single major impairment. Three weeks after surgery, psychotic episodes recurred at a greater frequency, with prolonged motionless behavior, incoherent utterances, and at times with threats to set fire to the house or to strangle her mother; she did at times attack her mother physically or often spent periods of several days in bed. Four years after surgery, her last antiepileptic medication was discontinued. Over the subsequent couple of months, she required 2 psychiatric hospitalizations for psychotic episodes with catatoniform behavior, unpredictable actions, and violent outbursts with her own family. Neuroleptic and double antidepressant medications combined with clonazepam (but without an antiepileptic) were of uncertain effect. Four electroconvulsive treatments during the second hospitalization achieved an excellent but very short-lasting recovery. Thereafter, she was cared for by a local psychiatrist with repeated hospitalizations near her home. She was remarkably stable,

with decreased irritability, for a period when divalproex sodium was combined with haloperidol, but the improvement again proved transient.

Except for a year in college and a brief period of part-time secretarial work in her parish, she had spent all of her life at home, sheltered by parents who suffered from her outbursts of abusive behavior that alternated with quiet and removed behavior. She had entered menopause 5 months before the last follow-up inquiry, 8 years after surgery, at the age of 46. It became evident that her severe psychotic episodes had always occurred at premenstrual times. Her disturbed behavior was now present for the first time in a constant pattern. She had none of her good periods during which she would cook, do needlepoint work, show some interest in reading, or leave the house with a parent. She just sat or lay in bed. The family was not willing to bring her back to the Epi-Care Center, and the local psychiatrist was unwilling to try the more innovative treatment that was suggested to him.

Comment. This patient postoperatively remained seizure-free even after discontinuation of the antiepileptic drugs, yet her dysphoric and psychotic disorder became much worse. We assume that (unlike in case 1) her epileptogenic zone had not been entirely removed. Her psychotic episodes worsened after discontinuation of carbamazepine, and we failed to reintroduce an antiepileptic when we treated her with double antidepressant medication. We assume that the combination of antiepileptic with double antidepressant medication, perhaps with the addition of an atypical neuroleptic, would still offer the chance for recovery. Together with cases 7 and 9, we consider her as incompletely treated. The patient is 1 of 4 women with epilepsy and marked catamenial exacerbation of a dysphoric disorder with psychotic features we have observed at the Epi-Care Center.[19]

Case 9

At the age of 23, this single male college student was referred to the Epi-Care Center with a history of complex partial seizures since age 14. The seizures remained intractable, and after 18 months a left temporal lobectomy was carried out. Six months after surgery, his seizures recurred at a lesser frequency and with occasional secondary generalization.

Prior to surgery, he had shown no significant psychiatric symptoms. Postoperatively, he was lethargic, moody, and complained of dizziness. Except for occasional mood changes, these symptoms resolved after several weeks, but he tended to be withdrawn. After returning to college, he soon experienced his first postoperative seizure, 7 months after surgery. Concomitantly, he became depressed and intermittently delusional and irritable. Imipramine up to 150 mg at bedtime was prescribed and relieved his depression, but the addition of trifluoperazine showed little effect on his delusions. He had to drop out of school and returned abroad to his parents' home, where he was followed by a local psychiatrist and was not compliant with the psychotropic drugs. He improved some 4 years after surgery when fluoxetine was prescribed up to 60 mg daily, but remained withdrawn, homebound, and dependent on his parents.

Comment. This is the fifth patient in our series whose psychosis emerged or worsened after surgery for epilepsy. The psychiatric disorder was clearly a de novo postoperative development.[16] For geographic reasons, he was not available for a complete treatment effort, i.e., double antidepressant medication plus risperidone.

Case 10

This single male accountant had experienced a prolonged convulsion when 9 months old, followed by recurrent febrile convulsions. At the age of 9 years, he began to have minor seizures that were recognized as complex partial seizures 4 years later. At age 19, while in college, he was evaluated at the Epi-Care Center as a candidate for surgical treatment of intractable seizures and at that time was free of psychiatric symptoms. Monitoring with subdural strips showed the presence of bilateral independent mesial temporal foci, and he was judged not to be a candidate for surgical treatment. His seizures remained intractable on various combinations of antiepileptic medications.

Four years after evaluation, he was started on increasing doses of topiramate in addition to phenytoin and carbamazepine. After about 3 months on topiramate treatment, as his seizure frequency decreased, his response time and performance at work gradually slowed. After about 10 months on topiramate treatment, he became paranoid, believing that people talked about him, and he was so ineffective at work that he lost his first steady job as an accountant. Another 10 months later, upon further increase of the topiramate, from 900 mg to 950 mg daily, he became more depressed and paranoid, believing the Internal Revenue Service had his phone tapped, and talked strangely. His topiramate was slightly decreased, and he suffered a flurry of seizures, followed by a brief postictal psychosis with confusion and bizarre behavior. He was admitted to the epilepsy unit where he was assessed only neurologically.

Topiramate was now replaced by gabapentin, and he was discharged after 6 days when the psychotic state appeared in remission. On gabapentin, 3000 mg daily (with phenytoin and carbamazepine), his seizures were now fully controlled, but a week later he required psychiatric admission elsewhere for marked depression with anergia, loss of appetite, marked weight loss, suicidal ideation, and auditory hallucinations. He did not respond to the combination of haloperidol, 10 mg, and sertraline, 150 mg, and after 25 days he was transferred to our psychiatric unit. He was now treated with double antidepressant medication (imipramine and first sertraline, then paroxetine), combined first with risperidone (to 4 mg b.i.d.) and then with

loxapine. He was less depressed but remained confused, hallucinatory, and incoherent. After 2 weeks, the gabapentin was phased out over 3 days. After 6 weeks of freedom from seizures, 1 day after withdrawal of the gabapentin, he had a simple partial seizure. Four days after discontinuing the gabapentin and having experienced 2 more simple partial seizures, he was in full remission mentally and ready for discharge. He remained on daily paroxetine, 20 mg, and imipramine, 100 mg, resumed work, and remained free from psychiatric symptoms for 8 months. His complex partial seizures continued at a frequency of 1 or 2 per week, then diminished upon adding divalproex sodium 10 weeks after his discharge from the hospital.

When the divalproex sodium (raised to a dose of 2500 mg daily) caused tremors and he still had about weekly seizures, this medication was gradually phased out. At this point, he again became increasingly paranoid, depressive, and indecisive. Increasing paroxetine from 10 mg to 20 mg b.i.d. and adding risperidone, 2 mg b.i.d., did not improve his mental state. When he took a slight overdose, he was rehospitalized and admitted that voices told him life was not worth living. His responses were again slowed and he appeared perplexed. Upon admission, the divalproex sodium was discontinued, and on the third day of hospitalization he had a major seizure, followed by 2 complex partial seizures the following day. This time, probably due to some prolonged confusion after the flurry of more severe seizures, his mental slowness and paranoid thinking cleared up less promptly over the following 7 days. Within a few days after discharge, he regained his perky disposition and could return to work. However, he had to cope now with about weekly seizures and was dismissed from his job after seizure events on 2 successive days. Upon increase of fluoxetine to 40 mg daily (combined with imipramine, 100 mg) and the addition of tiagabine up to 32 mg daily (together with phenytoin, 400 mg, and carbamazepine, 1200 mg), he is doing well with fewer seizures and a new job.

Comment. This patient is unusual because of the absence of a prepsychotic dysphoric disorder. His psychosis developed insidiously upon treatment with topiramate, which diminished his seizure frequency. Upon treatment with gabapentin, he became completely seizure-free and overtly psychotic. Psychotropic treatment was ineffective, but removal of the gabapentin resulted in prompt remission accompanied by reappearance of his seizures. A similar psychosis resulted from treatment with divalproex sodium. The 3 events are similar to the last psychotic episode that occurred in case 3.

DISCUSSION

Case 1, treated before the series, and case 10, treated after the series, were included to report 2 methods of treatment for interictal psychoses other than the use of psychotropic drugs we have administered at the Epi-Care Center over the last 12 years. The other patients (cases 2–9) represent a consecutive series of patients with interictal psychosis whose treatment began over a 20-month period from 1992 to 1993. This form of reporting allows for a prolonged follow-up period. On the other hand, we did not have the complete treatment method (double antidepressant plus risperidone) in place for all patients whose treatment began during the 20-month period, and 2 of the 8 consecutive patients could not be reached for the complete treatment effort (cases 8 and 9). Only 1 of the 6 patients who were available for the full treatment did not reach remission (case 7), and we believe now that this patient may need to be classified as a case of paraictal psychosis requiring improved antiepileptic medication. In our subsequent experience at the Epi-Care Center, treatment by double antidepressant medication, if necessary augmented by risperidone, has been very effective for patients with interictal psychosis,[16] except for the few patients who required discontinuation of an antiepileptic drug, as in case 10. On the basis of our entire experience, we consider the interictal psychoses of epilepsy a well-treatable disorder.

The treatment for interictal psychoses is identical to that required for severe interictal dysphoric disorder and supports our view that interictal psychoses, with their preceding and concomitant dysphoric states, in fact may be viewed as severe dysphoric disorders with psychotic features. Neuroleptic medication, except for augmentation of the double antidepressant medication, is of unproven effect and, in our experience, is useless for treating interictal psychoses.

Next to the problem of suicidality, the prolonged interictal psychoses that tend to occur upon lessened seizure activity represent clearly the most serious problem among the psychiatric complications of epilepsy. The paraictal psychoses (that occur not upon decrease but upon increase of clinical seizures), the ictal psychoses, and the 2 cases of psychosis with marked epileptiform deterioration of the EEG upon discontinuation of the antiepileptic medication reported by Demers-Desrosiers et al.[26] are much less frequent events. During 12 years at the Epi-Care Center, we have observed only 1 event of clear paraictal psychosis, in a severely dysphoric patient who had been hospitalized for EEG/video monitoring of his seizure disorder and had been taken off all antiepileptic medication (the same patient later also suffered a postictal psychosis). De Leon and Furmaga[5] have recently reported 2 patients with very active seizure disorders whose (paraictal) psychoses remitted upon the addition of lamotrigine without the need for any psychotropic medication. Paraictal psychoses appear to be akin to the definite ictal psychoses that present with clouded sensorium and clearly need to be treated with antiepileptic medication. We hypothesize that in the paraictal and ictal psychoses, as well as in the unique psychotic episodes reported by

Demers-Desrosiers and colleagues,[26] the psychotoxic inhibition is merely secondary to the primary problem of increased seizure activity. These psychotic episodes all require optimal antiepileptic medication.

Treatment with the standard combination of psychotropic drugs (tricyclic plus SSRI antidepressant, enhanced if necessary by risperidone) represents our primary treatment modality for the interictal psychoses with predominant inhibition and decreased seizure activity. The 2 patients reported here beyond the series of 8 consecutive patients document the 2 additional modalities of treatment known to us that can be effective for interictal psychoses: complete surgical elimination of the epileptogenic zone (case 1) and elimination of the antiepileptic drugs responsible for alternating psychotic episodes (case 10).

The high prevalence of patients surgically treated in our series reflects the association of interictal psychoses with intractable epilepsy. The patient whose chronic psychosis remitted after excision of the left frontal epileptogenic zone was treated before the most effective psychopharmacologic treatment approach was developed, and surgical treatment was prompted not by her infrequent seizures but by the severity of her psychosis. Her case demonstrates that complete elimination of the epileptogenic zone by surgery can abolish not only the seizures but also a malignant chronic psychosis. Conversely, in 4 patients from the series of 8 consecutive patients, the seizures persisted after surgical treatment, and the psychoses emerged de novo or became more severe (cases 2, 6, 7, 9). Analysis of the psychiatric outcome of 44 patients treated surgically for temporal lobe epilepsy showed that 17 patients (39%) experienced postoperative psychiatric complications, including 6 de novo psychotic episodes.[16] The significant risk for postoperative psychiatric complications presumably is due to the postoperative reduction of excitatory activity and relative predominance of inhibitory mechanisms; the latter may persist for over a year even when the epileptogenic zone has been fully abolished, as in case 1. The psychiatric complications in this series of surgically treated patients, including the psychoses, were well treatable by our psychotropic medication in all compliant patients. Complete absence of seizures after surgery was a significant predictor of ultimate excellent psychiatric outcome. The postoperative exacerbation and persistence of an interictal psychosis, in spite of postoperative freedom from seizures, in case 8 of our present series suggests that, in spite of eliminating all clinical seizures, sufficient subictal excitatory activity persists to prevent remission of the psychosis; the main flaw in our treatment was the failure to reintroduce an antiepileptic together with the psychotropic medication. Surgical treatment for epilepsy is not contraindicated if a patient suffers from psychosis[31] but is indicated for the treatment of an interictal psychosis only in an exceptional case. Most patients with interictal psychosis have remained psychotic after temporal lobectomy even though they may be free from clinical seizures.[31,32] This result may indicate that seizure activity in patients with psychosis tends not to be confined to a well-definable epileptogenic zone.

Case 10 was added to demonstrate that after failure of the psychopharmacologic treatment, antiepileptic medication may have to be eliminated in order to obtain remission of alternating psychotic episodes. Severe psychiatric disturbances secondary to antiepileptic treatment had been reported particularly with phenylacetylurea[20] and vigabatrin.[33] Earlier, the occurrence of dysphoric and psychotic disorders upon treatment with phenobarbital had delayed the use of this drug for epilepsy for many years.[23] Our recent experience with psychosis secondary to topiramate includes 2 patients reported here (cases 3 and 10) and 2 additional patients. Reduction of the topiramate, attempted in 2 of the 4 patients, was insufficient, and the drug had to be completely removed before remission of the psychosis was achieved. If an antiepileptic drug must be decreased or discontinued to eliminate the interictal psychosis, patients will be exposed to the risk of injury or even death that may be associated with intractable seizures. Both patients and their families need to be reminded of the risk that is taken for the sake of mental stability. Alternating psychoses may be caused by most antiepileptics (see case 10) and are becoming more frequent with the advent of more effective antiepileptic drugs. The so-called alternating psychoses vary from the other interictal psychoses only in the degree of seizure control that has been achieved. Treatment is initially the same: double antidepressant medication, enhanced if necessary by risperidone. If, however, patients remain psychotic, the antiepileptic medication needs to be diminished or modified.

Until about 1950, the care of patients with chronic epilepsy was part of the domain of psychiatrists. The premodern textbooks of psychiatry[9,10] described as the most common syndrome of the interictal phase an intermittent and pleomorphic dysphoric disorder identical to our interictal dysphoric disorder. Suicidality was at times noted but was not considered a significant risk among patients with epilepsy. Psychotic episodes were observed mostly after seizures, but at times in the prodromal phase or "in place of seizures," lasting hours or days and rarely for longer periods. The modern predominance of more prolonged interictal psychoses appears to be an effect of our more potent antiepileptic treatment. The same statement may be made with respect to the significant risk for suicide among patients with epilepsy reported in the modern era.[34–36] Both the interictal psychoses and suicide attempts occur almost invariably among patients who develop a marked interictal dysphoric disorder. In contrast to the psychoses, the characteristic intermittent and pleomorphic dysphoric disorder of the interictal phase has been overlooked in the modern era, even though it is the most common complication of chronic epilepsy. The early

recognition and treatment of the interictal dysphoric disorder are necessary for the quality of life of our patients[11] and may be of crucial importance for those at risk for psychosis or suicide.

With the advent of a rapidly advancing specialty of epileptology that focused exclusively on the neurologic aspects of seizure disorders, at a time when psychiatrists were focusing on the psychosocial conflicts of their patients and had little interest in cerebral disorders, epilepsy became accepted as a neurologic disorder. It is correct that a majority of patients with epilepsy will not need psychiatric attention, yet more than 50% of patients with chronic epilepsy admitted to seizure-monitoring units need psychiatric intervention.[7] Furthermore, about 13% of patients in mental institutions suffer from epilepsy,[37] confined because of psychosis, suicidality, or recurrent harmful outbursts of rage; close to 10% of admissions to psychiatric acute treatment units may have an Axis III diagnosis of epilepsy,[38] a percentage comparable with that of patients admitted with the diagnosis of bipolar disorder. Psychiatrists still fail to recognize epilepsy as a disorder with distinct psychiatric changes that require specific treatment. A major gap in health care for a significant number of patients needs to be bridged by widening the understanding of both the neurologic and the psychiatric specialist who must collaborate in the care of the patients with epilepsy and psychiatric complications that are in fact well treatable.

Drug names: amitriptyline (Elavil and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clozapine (Clozaril), divalproex sodium (Depakote), doxepin (Sinequan and others), felbamate (Felbatol), fluoxetine (Prozac), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), loxapine (Loxitane), nortriptyline (Pamelor and others), paroxetine (Paxil), perphenazine (Trilafon and others), phenytoin (Dilantin and others), risperidone (Risperdal), sertraline (Zoloft), tiagabine (Gabitril), topiramate (Topamax), trazodone (Desyrel and others), trifluoperazine (Stelazine), trihexyphenidyl (Artane and others), trimipramine (Surmontil), venlafaxine (Effexor), vigabatrin (Sabril).

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