Antidepressant and Double Antidepressant Treatment for the Affective Disorder of Epilepsy

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Background: About half of all patients with chronic epilepsy experience an intermittent and polysymptomatic affective disorder; fewer than 10% suffer from interictal psychotic episodes. The affective disorder responds well to treatment with tricyclic antidepressant medication. The interictal psychosis tends to develop among those with severe affective disorder, responds poorly to antipsychotic medication, and has been more difficult to treat.

Method: At the Epi-Care Center, Memphis, Tennessee, we have recently begun to treat refractory cases, both nonresponders with affective disorder and those with interictal psychosis, with the combination of a tricyclic antidepressant (TCA) and a serotonin selective reuptake inhibitor (SSRI). The double antidepressant treatment of all previously intractable patients with interictal affective disorder seen over a 20-month period at the Epi-Care Center is reported here.

Results: The outcome of the novel treatment for the most severe psychiatric disorders of epilepsy has been highly satisfactory: 15 (68%) of 22 previously unresponsive patients with affective disorder were excellent or good responders.

Conclusion: Antidepressants are the psychotropic drugs of choice for the affective disorder of epilepsy and can be effective in combined form (TCA and SSRI) for otherwise intractable patients. The paradoxical therapeutic effects of proconvulsant drugs in epilepsy conform with the hypothesis that the psychiatric complications of chronic epilepsy result from the development of seizure-suppressing mechanisms that can be mitigated by antidepressants.

(J Clin Psychiatry 1997;58:3–11)

Received Aug. 3, 1995; accepted Sept. 5, 1996. From the Department of Psychiatry, College of Medicine, The University of Tennessee, Memphis, and Epi-Care Center, Baptist Memorial Hospital, Memphis, Tenn.

The support of Georgia Montouris, M.D., Medical Director of Epi-Care, has made this study possible. Jonathan Himmelhoch, M.D., has provided critical review of the manuscript.

Presented at the 1995 annual meeting of the American Psychiatric Association, Miami, Fla.

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Epilepsy is the most common chronic neurologic disease, affecting about 1% of the population. Psychiatric morbidity among patients with epilepsy is estimated to range from 20% to over 50%[1,2]; its incidence is related to the chronicity of the disorder, showing increasing prevalence as one moves from community-based samples to populations attending primary care physicians to patients seeking assistance at tertiary care centers.[1] The percentage of patients with an Axis III diagnosis of epilepsy admitted to an acute psychiatric treatment unit has been recently measured at 9.5%,[3] about the percentage of patients admitted with bipolar disorder. Psychiatric morbidity in epilepsy tends to be selectively associated with the partial epilepsy of mesial temporal lobe (limbic) origin, the type of epilepsy that is particularly chronic. A controversy about this point was engendered by a number of studies that suffered from inadequate selection of patients listed as having generalized seizure disorders and that reported equally high psychiatric complications among patients with both generalized and temporal lobe epilepsy.[4] The study of painstakingly selected comparison groups with epilepsy carried out by Gastaut et al.[5] has demonstrated that primary generalized epilepsy, in contrast to mesial temporal epilepsy, is not associated with a risk for psychiatric complications.

Epilepsy, deemed a strictly neurologic disorder for four decades, has been sorely neglected by psychiatrists over that period. In stark contrast, during the late 19th and the first half of the 20th centuries, epilepsy was considered one of the major areas of psychiatric interest and ranked in importance with schizophrenia and manic-depressive illness.[6] In view of the fact that a large number of patients with epilepsy still need help from psychiatrists, the clarification of their psychopathology and the documentation of an effective psychopharmacologic treatment represent an issue of considerable importance.

At present, there is still little agreement about the description and nature of the interictal psychopathology, which includes personality changes, affective disorders, and schizophrenia-like psychoses where interpersonal warmth is preserved.[7] It is generally assumed that depression represents the most prevalent psychiatric disorder

among patients with epilepsy,[8] and suicide risk among patients with epilepsy is increased about fivefold compared with the general population.[9,10] Recent studies of the interictal affective disorder have shown that depressive symptoms tend to occur in a characteristic intermittent pattern, mixed with brief euphoric moods, explosive irritability, anxiety, and somatoform symptoms sometimes said to be depressive equivalents.[1,11] A distinct intermittent pleomorphic syndrome termed the interictal dysphoric disorder is the result (Table 1). The interictal dysphoric disorder is atypical of the primary mental disorders defined by DSM-IV criteria and is viewed as an affective-somatoform disorder due to a general medical condition, i.e., epilepsy.[12,13] The premodern psychiatrists, who cared for patients with epilepsy on a daily basis, were very familiar with the polysymptomatic and intermittent dysphoric moods of patients with epilepsy and recognized them as the most common mental changes associated with epilepsy.[6,14]

Effective treatment for the affective disorder of epilepsy consists of prescribing antidepressant drugs, and, for the majority of patients, a tricyclic antidepressant at a modest dose is sufficient.[11,15–18] A novel double antidepressant treatment has proved effective for the smaller group of those patients in our center who did not respond to simple treatment with tricyclics. This treatment is the main topic of this paper.

Table 1. Symptoms of the Interictal Dysphoric Disorder*

Symptoms	Type
Depressive mood Anergia Pain Insomnia	Intermittent depressive-somatoform symptoms
Irritability Euphoric mood Fear Anxiety	Intermittent affective symptoms

*In a study carried out with methods sensitive to the characteristics of patients with epilepsy,[1] the symptoms of irritability, depressive mood, and anergia were each noted in about 75% of patients with the disorder; each of the other five symptoms of the interictal dysphoric disorder occurred in about 55% of the patients. A mean of five symptoms per patient were present (range, three to eight), accounting for the pleomorphic pattern of the disorder. The symptoms tend to be intermittent (duration in hours or days), though in some patients a depressive and/or anergic baseline may be present; explosive irritability and blissful euphoria, the symptoms especially setting apart the interictal dysphoric disorder from traditional mood disorders, tend to be of particularly brief duration. The criteria for the premenstrual dysphoric disorder provided by DSM-IV[12] are nearly identical to those of the interictal dysphoric disorder; the significance of this finding will be reviewed in the discussion.

ANTIDEPRESSANT USE FOR PATIENTS WITH EPILEPSY

Psychiatrists are wary about the risk of lowering the seizure threshold when prescribing antidepressants and therefore may avoid this group of drugs altogether or use them with hesitation for depressed patients with epilepsy. Goodwin and Jamison expressed this bias in a categorical statement: "Patients with an underlying seizure diathesis expressed as mood disturbance will, of course, do poorly on many of the standard mood-altering drugs, since many of these drugs can lower seizure thresholds."[19pp119–120] It is generally assumed that the least proconvulsant antidepressants must be used in treating depression in patients with epilepsy.[20] A result of the bias is the paucity of reports on the use of antidepressants in epilepsy. Finally, there has been a puzzling disregard of available reports documenting the effectiveness of proconvulsant antidepressants in treating affective disorders in patients with epilepsy.

Two early reports by Ojemann et al.[21,22] reported not only improvement of depression but better seizure control among patients with epilepsy who were treated with psychotropic drugs (doxepin was used for most patients). A 6-week double-blind treatment trial of depression in epilepsy[23] failed to reveal a significant effect for subtherapeutic doses of 75 mg/day of amitriptyline and nomifensine compared with placebo. The subsequent treatment, over another 6 weeks, of the previous nonresponders with double the antidepressant dose resulted in a 65% response rate.

The clinical experience at the Epi-Care Center, Memphis, Tennessee, over the past 10 years has shown that not only depressive symptoms but the full range of interictal affective and somatoform symptoms can be effectively treated with modest doses of antidepressants at about half the amount required for traditional depressive disorders (100 mg to a daily maximum dose of 150 mg of imipramine, or a sedative tricyclic if insomnia persists) without risking an exacerbation of the seizure disorder.[11,16–18] This treatment had been advanced in psychiatric settings for patients with subtle (often not previously recognized) forms of epilepsy and for patients with symptoms or signs of an epilepsy-related disorder. Himmelhoch[15] had noted the effectiveness of antiepileptic medication, particularly in combination with an antidepressant, for the 10% of the patients from his Affective Disorders Clinic who had the diagnosis of subictal or interictal affective illness. Himmelhoch's findings were confirmed in a series of 28 psychiatric patients who had presented with the atypical, intermittent, and pleomorphic mental changes characteristic of the interictal phase of temporal lobe epilepsy and with history or signs of a CNS impairment and/or family history of epilepsy.[16] The series consisted of excellent responders to carbamazepine, usually prescribed in combination with a tricyclic antidepressant at a dose of 75 to 125 mg/day. Subsequently, this treatment has been refined for application to patients with manifest epilepsy and psychiatric disorders.[11,17,18] For the last 9 years, modest doses of tricyclic antidepressants have been routinely prescribed for several hundred patients at the Epi-Care Center in Memphis, Tennessee.

A Hypothetical Rationale for Using Antidepressants in Epilepsy

Personality changes and dysphoric disorder develop after a delay of at least 2 years after onset of the epilepsy,[5] while psychotic changes tend to develop after a more prolonged interval of an average 14 years.[7] Occasional seizures, as occur in about 10% of the population, are not followed by persistent mental changes and in fact may produce highly beneficial effects via the procedure of electroconvulsive therapy. It is apparent that the mental disorders of epilepsy are the result of a process set in motion by chronic epilepsy. Engel[24] has postulated, as had Stevens,[25] that the mental changes of epilepsy may result from the inhibitory activity that begins to develop gradually in reaction to the seizure activity. During the prodrome of a seizure and particularly in the postictal phase, the inhibitory activity is forcefully engaged in terminating the seizure, and consequently one observes at that time significant affective and somatoform changes in the form of irritability, anergia, somnolence, headaches, depressive moods, anxiety, and occasionally even hypomanic or psychotic symptoms. These transient changes are much the same ones that form the key symptoms for the more protracted interictal affective disorder termed the interictal dysphoric disorder.[26]

Landolt[27] had observed first that mental changes in epilepsy tend to occur at the very time when seizure activity abates and referred to the process as "forced normalization." Landolt's observations, as well as those described by others as the "alternating psychoses" (i.e., psychoses presenting at the time when overt seizures have remitted),[28] may be best understood as the effects of a shift from excitatory to predominantly inhibitory neural activity in chronic epilepsy. The precise nature of the inhibitory activity is not clearly understood but GABAergic and opioid peptide–mediated processes may be particularly involved.[24] An effective treatment of the psychiatric disorders of epilepsy would then, in fact, need to be directed at the inhibitory activity, and the proconvulsant effect of the antidepressants appears to make them suitable to mitigate seizure-suppressing inhibitory activity.

Until recently, we prescribed for refractory cases tricyclic drugs enhanced with a small amount of neuroleptic (1 mg of trifluoperazine per 25 mg of the tricyclic) with some success.[17,18] Since May 1992, we have combined tricyclics with a serotonin selective reuptake inhibitor (SSRI) instead of the neuroleptic with far better results. We present here the initial series of 22 consecutive patients with epilepsy and affective disorder from the Epi-Care Center who had not responded to treatment with a tricyclic and were prescribed the novel double antidepressant treatment.

METHOD

The Epi-Care Center, a tertiary care center for evaluating and treating patients with epilepsy, attracts about 250 new patients with seizure disorders per year and evaluates about 200 per year on its intensive neurodiagnostic unit. About two thirds of the patients from the latter group (including about one fourth of the total with nonepileptic seizures) require psychiatric intervention.[1] The majority of patients with chronic epilepsy require treatment for an interictal dysphoric disorder; a few patients are treated for psychotic disorders. The percentage of outpatients requiring psychiatric intervention is somewhat smaller and is estimated at less than 50%.

Since 1987, all patients admitted for intensive neurodiagnostic monitoring and all outpatients with psychiatric disturbance presenting a problem are evaluated and treated by the same psychiatrist (D.B.); an increasing number of patients with simple interictal dysphoric disorder are routinely treated with a tricyclic antidepressant by the neurologist. In May 1992, the first patient with marked interictal dysphoric disorder, having failed to respond to the customary psychopharmacologic approach, was treated by the addition of the SSRI fluoxetine to the tricyclic antidepressant (TCA) drug, with prompt success (Patient 1). Since that time, the enhancement of the TCA with a small dose of neuroleptic was abandoned in favor of the double antidepressant treatment, i.e., combining an SSRI with the TCA. Paroxetine became our first and fluoxetine the second choice among the SSRIs in the double antidepressant treatment of the patients with interictal dysphoric disorder who did not respond to a TCA alone. The shorter half-life of paroxetine made a possible transition to fluoxetine simpler than the reverse procedure.

The initial 22 patients who had severe interictal dysphoric disorder and were treated with double antidepressant treatment over a 20-month period (May 1992 through December 1993) at the Epi-Care Center are the subjects of this paper. Eleven patients were women and 11 were men. Their mean age was 36 years (range, 19–60 years), and the mean duration of epilepsy at the time of treatment was 21 years (range, 2–55 years). Two patients who responded to the treatment nevertheless dropped out (Patients 1 and 11). Of the 4 nonresponders to double antidepressant treatment, 2 discontinued this treatment, and 2 dropped out of all further treatment. All others, including the 3 partial responders, have been maintained on double antidepressant treatment. The mean follow-up period was 20 months (range, 12–31 months). The follow-up period of all patients (including the 4 dropouts) extended to the end of 1994.

All patients underwent a standardized psychiatric evaluation developed specifically to reflect the characteristics of patients with epilepsy[1,29]: Epilepsy Questionnaire,

Neurobehavioral Inventory, and semistructured interview (available from author on request); the data were obtained from both patient and next of kin. This method of evaluation has been described elsewhere.

RESULTS

The treatment results can be grouped in three categories:

A. Responders who reached a fully satisfactory adjustment (15 patients).
B. Partial responders, who had clinically significant improvement (3 patients).
C. Poor responders, without clinically significant improvement (4 patients).

Mean duration of the epilepsy was 21.7 years for group A and 19.7 years for the combined groups B and C. Thus, duration of the epilepsy was not a factor in the outcome. The sex distribution, on the other hand, was uneven: 10 of the 11 female patients but only 5 of the 11 male patients reached fully satisfactory adjustment.

All 22 patients met the proposed criteria[1] for the interictal dysphoric disorder (presence of at least three of the eight key symptoms in a patient with epilepsy [Table 1]). With the apparent exception of Patient 3, their psychiatric disorder invariably developed some time after the onset of the epilepsy. According to DSM-IV classification, their presentation conforms best to a diagnosis of mood disorder due to epilepsy, with mixed features.

The treatment of 4 responders (Patients 1, 2, 3, and 4) is described in full detail below.

CASE REPORTS

Case 1

At age 18 years, Mr. A, a single college freshman, developed partial seizures with a right temporal EEG focus and was started on carbamazepine treatment. Four months after the diagnosis was made, he began to suffer from episodes of depressive moods with crying spells and suicidal thoughts, irritability, and headaches. The addition of fluoxetine resulted in prompt remission of the dysphoric disorder, but after 6 months he stopped taking the fluoxetine. When the dysphoric disorder resumed, the carbamazepine was blamed and he was switched to phenytoin. On this drug he felt much better, but the seizures reappeared. Eighteen months after the diagnosis of epilepsy was made, he sought help from the Epi-Care Center. With primidone and again with phenobarbital, he had fewer seizures but was more dysphoric. When carbamazepine was resumed, he again became seizure free, but the dysphoric disorder returned; anergia, insomnia, and weight loss were added to his previous symptoms. The addition to carbamazepine of imipramine up to 150 mg/day and the further addition of trifluoperazine 6 mg/day were ineffective. He dropped out of college as his dysphoric disorder became unbearable. In view of his earlier response, fluoxetine at 20 mg every morning was added to 150 mg/day of amitriptyline, and the novel combination resulted in complete remission of the dysphoric disorder. Mr. A could now be maintained on carbamazepine and completed his education with success, even though he was not fully compliant with his subsequent treatment at the Epi-Care Center.

Case 2

Ms. B, a 31-year-old single woman, had had complex partial seizures since 9 years of age. She led a life without a job and was confined to the narrow circle of her family. Her chronic dysphoric disorder marked by depressive mood, anergia, insomnia, pains, and irritability had started at age 13 years when a left temporal lobectomy had decreased her seizure frequency significantly. At age 16 years, she made the first of several serious impulsive suicide attempts by overdose and thereafter was treated unsuccessfully by a number of psychiatrists. At age 31 years, after her fifth suicide attempt, Ms. B became our patient. She appeared to be improved on tricyclic antidepressant medication, but 2 years later made another sudden suicide attempt. One year later, after the clinic was successful in treating the first patient, 20 mg/day of fluoxetine was combined with 100 mg/day of clomipramine. Ms. B's dysphoria improved remarkably and her range of activities increased. She obtained a job for the first time and during the course of 2 years on the new treatment regimen, her family lost all their concern about a repeat suicide attempt.

Case 3

Ms. C, a 40-year-old divorced woman, was referred to the Epi-Care Center with an intractable psychiatric illness. Perhaps as a result of a fall from a bike at 5 years of age, she had became hyperactive and belligerent. Dysphoric moods became prominent during adolescence, and a suicide attempt at age 18 years led to the first of innumerable psychiatric hospitalizations. A first observed nocturnal seizure at age 23 years led to the diagnosis of epilepsy. She lost jobs because of her irritability and was declared disabled at age 30 years. Between ages 35 and 40 years, she was hospitalized on 15 occasions for a severe dysphoric disorder with marked mood swings and outbursts of anger, fear of harming others or herself, anxiety, agitation, obsessive counting, fatigue, and severe insomnia. At times, Ms. C heard vague voices in her head or was fleetingly paranoid. During this time, it was recognized that she suffered complex partial seizures and consequently her diagnosis was changed from major depression, or bipolar disorder, or schizoaffective disorder with borderline personality to that of organic mood disorder and temporal lobe epilepsy. She was treated variously

with lithium, diazepam, clonazepam, neuroleptics, or amitriptyline without ever achieving stabilization of her mental state.

At the Epi-Care Center, we initially had little success in stabilizing her severe dysphoric disorder, and over the next 3½ years, she had to be hospitalized again 14 times. Tricyclic antidepressants, at times combined with lithium or low doses of a neuroleptic, had only temporary effects. Clomipramine raised to 200 mg/day seemed to worsen the seizure disorder and did not improve her obsessive counting. During her 14th hospitalization in our care, she received two electroconvulsive treatments and was finally stabilized with the addition of felbamate to a lesser dose of carbamazepine for the seizure disorder, fluoxetine 20 mg/day, and doxepin 150 mg at bedtime. Over the period of nearly 2 years after this last hospitalization, she has had only an occasional seizure, is free from any mood swings, irritability, and anxiety, feels energetic, and sleeps well. She keeps herself busy all week with volunteer work and part-time jobs. She likens her newly found state of well-being with how she used to feel prior to her first hospitalization some 26 years ago. Her obsessive counting has persisted.

Case 4

Mr. D, a 31-year-old single bioscientist, had suffered for 10 years from a mood disorder characterized by episodes of depressive mood lasting days and sometimes weeks, by fears and bouts of anxiety occurring at times daily, and by irritability and insomnia. At around 5 years of age, he started to experience simple partial seizures that lasted less than 15 seconds and consisted of a peculiar and stereotyped sensation in his limbs and a funny taste in his mouth. At age 17 years, he suffered the first of a few generalized tonic-clonic seizures. Upon treatment with phenytoin at age 21 years, his seizures diminished and have been fully controlled for the last 5 years. He dated most of his dysphoric symptoms back to a young age, but they became troublesome only once he was treated with phenytoin and upon full control of the attacks. He required psychiatric treatment and responded to desipramine at a dose of 450 mg/day.

Upon referral to Epi-Care, Mr. D was prescribed 200 mg of imipramine (in view of a persisting insomnia with early awakening) together with 400 mg of phenytoin daily. He felt better, but still reported early morning awakening, had marked difficulties concentrating on his work, and even thought of quitting his job. Paroxetine 10 mg/day was therefore added to the 200 mg/day of imipramine with excellent results: his energy, sleep, and concentration were fine, and he was free from irritability; his anxieties were under control, and he had fewer fears. He reported feeling better than he had any time in the last 5 years. He has remained in full remission for the follow-up period of 2 years.

Table 2 summarizes the features and treatment outcomes of the remaining 18 patients in the series (Patients 5–22).

DISCUSSION

Of the 22 patients with severe and previously intractable interictal dysphoric disorder, 15 (68%) showed a good or excellent outcome upon adding an SSRI (paroxetine or fluoxetine) to a TCA. This entire group represents an estimated 15% of all patients with interictal dysphoric disorder requiring psychiatric treatment at the Epi-Care Center over the same 20-month period. The large majority, if compliant, responded to treatment with a TCA at a dose of 100 to 150 mg daily. The findings indicate that the interictal dysphoric disorder is a highly treatable disorder.

In view of the disabling nature of the interictal dysphoric disorder, including risk of suicide and development of psychosis, withholding treatment with proconvulsant antidepressants for fear of lowering the seizure threshold represents a serious and potentially fatal error. In fact, patients with mesial temporal epilepsy, in contrast to patients with primary generalized epilepsy, show a higher than normal seizure threshold during their interictal phase,[5] and the use of TCAs or SSRIs may, in fact, reduce seizure frequency significantly.[21,22,30] In my entire experience, I observed a possible relationship between tricyclic dose and increased frequency of seizures in only 1 patient from the present series (Patient 3) and in one other patient, both times when the tricyclic dose was raised to 200 mg/day. I therefore prefer to hold the prescription of TCAs to a maximum of 150 mg daily. The success of the antidepressant treatment for the interictal dysphoric disorder tends to confirm the hypothesis that the disorder is related to the predominance of seizure-suppressing mechanisms in mesial temporal epilepsy, and the findings suggest that the use of a single antidepressant or of the TCA and SSRI combination may offer a safe technique for creating therapeutic disinhibition.

The interictal psychiatric disorders frequently become a more serious problem upon better seizure control, i.e., with predominance of seizure-suppressing mechanisms. In 9 of the 22 patients, the affective disorder clearly worsened once the seizures were controlled or significantly improved (Patients 1, 2, 4, 6, 7, 10, 11, 20, 21). Improved seizure control upon introducing felbamate, on the other hand, coincided with the excellent recovery of one patient from severe interictal dysphoric disorder (Patient 3). One other patient (Patient 14) clearly benefited from the addition of felbamate. In all other patients, the choice of antiepileptic drugs appeared to exert no obvious direct influence on the mental state of the patients in our series. It is well known, however, that barbiturates tend to precipitate or worsen an interictal affective disorder. They are not considered antiepileptic drugs of first choice; if they

Table 2. Double Antidepressant Treatment of Patients 5–22 With Interictal Dysphoric Disorder (IDD)*

Sex and Age at Time of DAT	Epilepsy	Psychiatric Disorder (IDD)	Treatment
A. Responders			
Patient 5 female age 26	CPS with occasional GTCS since age 10; left temporal lobectomy at age 23, with modest decrease of seizures	Mild MR; episodes of severe depressive mood and anergia, intermittent irritability, and anxiety	Excellent response with imipramine 100 mg and paroxetine 10 mg bid; follow-up, 17 mo
Patient 6 male age 29	CPS and GTCS before age 2; right frontal resection of cortical dysplasia at age 21; right temporal lobectomy for seizure focus at age 24 with marked reduction of seizures	Mild MR; placid when having seizures; verbally and physically abusive upon suppression of seizures; severe insomnia, back pain, and fears; numerous psychiatric hospitalizations since adolescence	Neither trimipramine nor fluoxetine alone helpful, but combination of both effective; complete remission with paroxetine 40 mg/d and doxepin 150 mg/d; follow-up, 21 mo
Patient 7 female age 37	Onset of CPS at age 13; right temporal lobectomy age 36, resulting in fewer CPS	Some irritability prior to operation; 3 months postop, increased irritability and depressive moods, with anxiety and insomnia; premenstrual exacerbation of IDD with rages	Imipramine and paroxetine alone ineffective. Imipramine 100 mg/d with paroxetine 20 mg/d fully effective; follow-up, 17 mo
Patient 8 female age 34	Onset of CPS at age 29 after blow to left frontotemporal region (abusive spouse); successful left temporal lobectomy, age 31	Depressive moods, anergia, irritability, insomnia, headaches, and nonepileptic seizures; unable to work by age 30; symptoms persist postop. Marked PMDD	Full remission of all symptoms of IDD and of nonepileptic seizures with amitriptyline 100 mg/d and paroxetine 20 mg/d, 3 years postop; returns to work; follow-up, 15 mo
Patient 9 female age 25	Age 13 myoclonic attacks, then GTCS; seizures infrequent	Depressive moods interspersed with euphoric episodes, rages alternating with exemplary behavior; premenstrual exacerbation of disorder with two suicide attempts; PMDD	At age 25, paroxetine 20 mg/d added to desipramine 100 mg/d with full remission
Patient 10 female age 60	Chronic epilepsy since age 5; right temporal lobectomy at age 53; only occasional seizures thereafter	Psychiatric hospitalizations at age 39, 50, 56, and 58 for depression, anergia, dysphoric moods, anxiety, and at times paranoid features	Postop seizure free when felbamate is added, but becomes more dysphoric; full remission on clomipramine 125 mg/d and fluoxetine 20 mg/d; follow-up, 12 mo
Patient 11 female age 43	Head injury at age 29; CPS with GTCS since age 32; right temporal lobectomy age 41, thereafter rare seizures upon noncompliance with medication	Psychiatric hospitalizations at age 33 and 40; dysphoric moods with anergia, insomnia, and headaches worsening after the operation; marked PMDD	Good recovery 2 years postop except for headaches, when treated with fluoxetine 20 mg/d and clomipramine 100 mg/d; drops out of treatment after 11 mo of DAT; follow-up, 13 mo
Patient 12 female age 35	First seizures at age 4; right temporal lobectomy age 30 and reoperation at age 32, but seizures persist	Mild MR; irritability, anergia, headaches, insomnia, depressive moods with suicidal threats, marked after first operation; after reoperation develops frequent nonepileptic seizures; two psychiatric hospitalizations at age 33	Satisfactory remission with paroxetine 20 mg/d added to clomipramine 100 mg/d; follow-up, 21 mo
Patient 13 male age 47	Seizures since age 2 secondary to birth injury with porencephaly and arachnoid cyst; CPS with occasional GTCS	Mild MR; depressive moods with weight loss, anergia, and irritability	Fluoxetine 10 mg/d with imipramine 125 mg/d results in very satisfactory remission; follow-up, 21 mo
Patient 14 female age 28	CPS with occasional GTCS since age 6; head injury with prolonged coma at age 20	Mild MR; severe depressive moods after head injury; at age 27 admitted with insomnia, anorexia, lethargy, and mutism	At age 28, fluoxetine 30 mg/d added to amitriptyline 100 mg/d, with satisfactory remission of depressive moods; use of felbamate further enhances activating effect of DAT; follow-up 28 mo
Patient 15 male age 41	Left temporal lobectomy for meningioma age 38, with subsequent SPS	Dysphoric moods, anergia, insomnia, headaches and back pain, anxiety, and fears; unable to resume work; dependent on alcohol	3 years after operation recovers on doxepin 150 mg/d with paroxetine 20 mg bid; follow-up, 17 mo
B. Partial Responders			
Patient 16 male age 19	GTCS onset at age 5 after head injury; CPS onset at age 8; left temporal lobectomy at age 18 followed by reduction of seizures	Onset at age 8 of increasingly severe rapid mood shifts with rages; daily anergic and hypersomnolent episodes; IDD worse after operation	Combination of maprotiline 150 mg/d and paroxetine 20 mg bid proves most effective: moods are stable and episodes of rages rare, but remains anergic; follow-up, 25 mo
Patient 17 male age 55	Onset of frequent GTCS age 48, after repair of ruptured cerebral aneurysm; reoperation for rest of aneurysm at age 50 leaves him 80% aphasic	Frequent dysphoric moods, anergia, brief euphoric moods, and anxiety	Excellent improvement with addition of fluoxetine 20 mg/d to desipramine 100 mg/d, but regresses upon difficult prostate operation and develops insomnia; progresses slowly on paroxetine 20 mg/d and amitriptyline 100 mg/d; follow-up, 19 mo

continued

Table 2. Double Antidepressant Treatment of Patients 5–22 With Interictal Dysphoric Disorder (IDD) (Cont'd.)*

Sex and Age at Time of DAT	Epilepsy	Psychiatric Disorder (IDD)	Treatment
Patient 18 male age 52	Onset of CPS with GTCS at age 15; left temporal lobectomy age 49; significant postoperative verbal memory deficit, and seizures persist	Age 47, evaluated for marked dysphoric moods with rages; age 49, psychotic state with rages upon flurry of seizures; age 52, postictal psychosis with outbursts of rage and insomnia	Significant improvement with amitriptyline 100 mg/d and paroxetine 20 mg/d, but remains somewhat depressed and is still at times irritable; follow-up, 17 mo
C. Poor Responders			
Patient 19 male age 27	Onset of myoclonic and generalized seizures at age 19; corpus callosotomy at age 23 not successful	Rapid dysphoric mood shifts with predominant depression, episodic rages, insomnia, brief euphoric moods; anxiety, fear of leaving home; 3 suicide attempts and becomes disabled before age 22; psychiatric hospitalizations age 22 and 27	Modest effects from alprazolam with amitriptyline and paroxetine; follow-up, 21 mo; duration of DAT, 14 mo
Patient 20 male age 53	CPS with GTCS since age 14; left temporal lobectomy age 47; postop only occasional simple partial seizures	Age 40 onset of chronic anxiety, depressive moods, and anergia; gradual worsening after temporal lobectomy and becomes disabled; psychiatric hospitalizations once at age 48 and twice at age 51	Transient recoveries after series of four ECTs and upon DAT with trimipramine 100 mg/d and paroxetine 20 mg/d; follow-up, 15 mo; duration of DAT, 4 mo
Patient 21 male age 23	Head injury at age 3 results in left spastic hemiparesis and intractable seizure disorder; MRI shows right cerebral hemiatrophy; right hemispherectomy at age 20 results in near freedom from seizures	Mild MR; frequent irritable and depressive moods, anxiety, headaches, and back pain; since operation, increasingly dysphoric and stubborn; threatens to kill others or himself and has insomnia; psychiatric hospitalizations age 22 and 23	Failure of DAT; improvement with combination of imipramine 150 mg/d and chlorpromazine 100 mg/d; follow-up, 17 mo; duration of DAT, 6 mo
Patient 22 female age 33	Left hemiatrophy since birth; onset of CPS at age 20	History of episode of major depression; increasing depressive mood, anger, anergia, hypersomnia; history of early sexual abuse	In psychotherapy; increasingly discouraged upon unsuccessful drug treatment efforts over 4 years, then cooperates with a brief trial of DAT (desipramine 100 mg/d and paroxetine 20 mg/d) without any improvement; follow-up, 14 mo; duration of DAT, 1 mo

*Psychiatric disorder (IDD) invariably followed onset of seizures, at various intervals. Medication is listed as prescribed daily (SSRI: am or bid; TCA: at bedtime, except for desipramine). Abbreviations: CPS = complex partial seizures, DAT = double antidepressant treatment, ECT = electroconvulsive therapy, GTCS = generalized tonic-clonic seizures, MR = mental retardation, MRI = magnetic resonance imaging, PMDD = premenstrual dysphoric disorder, SPS = simple partial seizures.

must be prescribed, the addition of a TCA is often required.

In this series, the patients were all initially treated with a TCA. In view of the severity of the illness of the patients and the generally outstanding response upon the addition of the SSRI, the effectiveness of the SSRI alone was not systematically assessed. Although no remission was obtained in several cases by prescribing either paroxetine or fluoxetine alone, one cannot exclude the possibility that a number of patients from the series reported here may have responded to an SSRI alone. The double antidepressant treatment appears related to a synergistic action and not to an increased level of the TCA upon the addition of the SSRI, an effect that has been a major concern when the two types of antidepressants are combined in psychiatric practice. Many case reports and a few controlled studies have demonstrated that all SSRIs may raise the serum levels of concurrent TCAs, at times with marked adverse effects such as seizures and delirium (reported only in single case reports).[31] For this reason, the TCA/SSRI combinations have been recommended for treating refractory depression only after other methods have failed and when plasma TCA levels are monitored. None of our patients experienced signs of tricyclic toxicity, and their tricyclic levels, when measured, remained in the range considered subtherapeutic for major depressive disorders. Subsequent to the completion of this series, however, my colleagues and I have observed two patients on double antidepressant treatment who presented with tricyclic toxicity; both had fluoxetine added to a low dose of the tricyclic drug.

Sertraline was not systematically assessed as an add-on to the TCA for the interictal dysphoric disorder. Experience at the Stanford Comprehensive Epilepsy Center in California has shown that sertraline at low-to-moderate doses can be very effective for the affective disorder of epilepsy (Barry JJ. 1996. Personal communication). Other antidepressants, including the proconvulsant bupropion, were likewise not assessed for their usefulness in treating the interictal dysphoric disorder. The TCAs, however, appear to be highly effective first-line drugs for treating the psychiatric disorders of epilepsy. At the low dose required, their side effects are usually negligible, and they are an economic choice; furthermore, they promptly achieve the regulation of sleep necessary for patients with the interictal dysphoric disorder.

In view of the severity and chronicity of the interictal dysphoric disorder in the reported series of patients, their history of innumerable drug trials, and their sustained and characteristic response over a follow-up period of a mean of almost 2 years, a placebo effect of the drug combination can be ruled out. The tricyclic treatment and the double antidepressant treatment of the interictal dysphoric disorder share the characteristics of a broad-spectrum effect on the entire affective syndrome (depressive and somatoform symptoms, irritability, fears, and anxiety) that occurs within a couple of days, while plasma TCA levels are "subtherapeutic." A specific and prompt mitigating effect on inhibitory (seizure-suppressing) mechanisms may be postulated. The therapeutic effect is independent of the duration of the affective disorder, and patients whose severe interictal dysphoric disorder had extended over decades (Patients 2, 3, and 10) reached excellent remissions.

Patients with marked interictal dysphoric disorder may develop psychotic symptoms (i.e., interictal psychoses)[1] and will require the double antidepressant treatment. In addition to the 22 patients with previously refractory interictal dysphoric disorder, 9 with interictal psychosis were also treated during the same 20-month period; 5 of the 9 patients experienced remission with double antidepressants (these 9 patients will be discussed in a separate report).

The psychiatric changes characteristic of the interictal dysphoric disorder may be observed in patients whose seizure disorder has been under control for years and may, in fact, date back to the time when overt seizures subsided (Patient 4). The frequent diagnosis of active or inactive epilepsy encountered by psychiatrists should alert them not to merely make a notation on Axis III but to consider a diagnosis of interictal or subictal dysphoric disorder and to carry out a combined treatment with antiepileptic and antidepressant medications. The same treatment is indicated for the patients with a subictal dysphoric disorder who never had overt seizures.[15,16]

Female patients with chronic epilepsy frequently experience an exacerbation of their affective symptoms premenstrually,[15] as was noted to a striking degree in four of our patients (Patients 7, 8, 9, and 11) and to a moderate degree in three others (Patients 3, 10, 12). Herzog[32] relates catamenial (as well as postpartum and menopausal) psychiatric disorders to a deficiency of progesterone with its antiseizure effects (in relation to estrogen, which favors seizure activity) in women with an epileptiform brain substrate. It is of interest that the criteria provided for the premenstrual dysphoric disorder in DSM-IV[12] are nearly identical to those proposed for the interictal dysphoric disorder. Thus, both endocrinologic and psychiatric features suggest that therapeutic trials with the combination of antiepileptic and antidepressant medication will be successful for the premenstrual dysphoric disorder.

A consideration that specific affective and psychotic disorders may be associated with epilepsy and with epilepsy-related afflictions is not new to psychiatry.[6] Evidence that these disorders appear to respond well to a specific treatment should lend urgency to further study of this area.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clomipramine (Anafranil), clonazepam (Klonopin), desipramine (Norpramin and others), diazepam (Valium and others), doxepin (Sinequan and others), felbamate (Febatol), fluoxetine (Prozac), imipramine (Tofranil and others), maprotiline (Ludiomil), nomifensine (Merital), paroxetine (Paxil), phenytoin (Dilantin and others), primidone (Mysoline), sertraline (Zoloft), trifluoperazine (Stelazine), trimipramine (Surmontil).

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