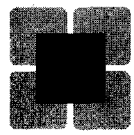

DONALD G. VIDT, MD AND ALAN W. BAKST, PHARMD, RPH, EDITORS

Anticonvulsants for treatment of manic depression

GUSTAVO A. DELUCCHI, MD AND JOSEPH R. CALABRESE, MD

■ Although lithium remains the treatment of choice for manic depression, it is now well recognized that 20%–40% of patients either do not tolerate the drug or their disease does not respond to it. This subgroup of patients accounts for a substantial majority of the morbidity that accompanies this illness. For this reason, alternatives to lithium therapy will have a significant clinical impact. In a great majority of cases, the rapid-cycling variant of this disorder accounts for the resistance to lithium treatment. Recently, a growing body of literature has suggested that several medications routinely used in the management of seizure disorders, particularly carbamazepine and valproate, have therapeutic mood-altering properties. These drugs have been evaluated in numerous drug trials using open, double-blinded, longitudinal, and (in the case of carbamazepine) randomized designs. The authors comment on the phenomenology of manic depression and review the literature on use of anticonvulsants in the management of lithium-resistant manic depression.

□ INDEX TERMS: ANTICONVULSANTS; BIPOLAR DISORDER □ CLEVE CLIN J MED 1989; 56:756–761

MOOD DISTURBANCE is a major category of psychiatric illness in which the primary abnormality is disturbance of affect, ranging from depression to mania.[1] There are two major categories of mood disturbance; of all cases reported, approximately two-thirds of the diagnoses are recurrent unipolar disease and one-third are bipolar disease (manic depression). Patients with unipolar disease experience only recurring depressions, whereas patients with bipolar disease experience both recurring depressions and recurring manias or hypomanias.

From the Department of Psychiatry, The Cleveland Clinic Foundation. Submitted April 1989; accepted July 1989.

Address reprint requests to J.R.C., Department of Psychiatry, University Hospitals of Cleveland, Case Western Reserve University, 2040 Abington Road, Cleveland, Ohio 44106.

Mood disturbance is by definition syndromal, inherited, and recurrent. Although nondegenerative, it is accompanied by significant morbidity and mortality. Fifteen percent of patients with mood disturbance successfully commit suicide. Furthermore, 10% of all the patients who attempt suicide subsequently succeed within 10 years and 45%–70% of these victims have at least a history of mood disorder.[2] The lifetime incidence of manic depression within the general population is 0.65% to 0.88%.[3–5]

Mood disturbance is accompanied by both biological and nonbiological symptoms. The physical symptoms of mood disturbance typically consist of changes in appetite, sleep, and energy. These symptoms can either be increased or decreased based on the specific mood state. Patients typically report anorexia, middle and terminal insomnia, and lethargy during depressions. In mania, they often report hyperphagia, decreased need for sleep, and increased energy. The feelings that are reported by

the depressed patient are sadness, preoccupation with guilt and wrongdoing, poor self-esteem, and feelings of hopelessness, helplessness, and worthlessness. On the other hand, the manias are typically accompanied by feelings of either elation or irritability; grandiosity frequently accompanies both. The increase in energy during manias is frequently exhibited in activities that reflect impaired judgment, i.e., spending sprees or disinhibited speech.[1]

Kraepelin first described the phenomenology of manic depression in the late 1890s,[6] but it was not until 1949 that Cade,[7] an Australian psychiatrist, discovered the mood-altering properties of lithium. Lithium continues to be viewed by most as the treatment of choice for manic depression[8] and has been demonstrated to have both antidepressant and antimanic properties.

Unfortunately, 20%–40% of manic-depressive patients either do not tolerate lithium or do not respond to it. Until recently, manic depression in these patients could not be effectively managed.[9,10] Fortunately, we now know that numerous other agents are available that have both antidepressant and antimanic properties.

The medications studied most systematically are those that are effective anticonvulsants. Ballenger and Post[11] in 1978 reported evidence from a double-blind trial that the anticonvulsant carbamazepine had clear-cut antimanic efficacy.[11] This finding has been replicated numerous times. It is now well-recognized that this agent, as well as other anticonvulsants such as valproic acid, play a major role in the management of lithium-resistant bipolar disease.[12]

ROLE OF CARBAMAZEPINE

Although Blom[13] suggested in 1963 that carbamazepine was useful in the management of paroxysmal pain disorders, it was not until 1974 that this drug gained recognition as an anticonvulsant for managing complex partial and tonic clonic seizures.[14,15] In 1971, Dalby[16] noted that carbamazepine could favorably affect the "epileptic personality." He and others subsequently documented the ability of this drug to diminish some of the behavioral symptoms of epilepsy, such as sluggishness of thought, affective overreaction, dependence, apathy, lack of initiative, loss of interest in work and friends, and depression.[16,17] It was not until 1971, however, that Takezaki and Hanaoka[18] specifically noted the potential efficacy of this drug in the management of mood disturbance. From an open trial using low-dose carbamazepine in the acute treatment of mania, Okuma et al[19] subsequently reported substantial improvement in 19 of 33 manic depressive persons.

This finding was replicated in 1978 in a double-blind placebo-controlled study by Ballenger and Post,[11] who studied 10 patients with major mood disturbance.[11] Six had manic depression, two had recurrent depression (no manias), and two had schizoaffective disorders, bipolar subtype. Following a drug washout period, carbamazepine was systematically studied in an on-off-on design with doses ranging from 600 mg/d to 1,600 mg/d. Of the 10 patients, five experienced antimanic effects and two had antidepressant effects. Among the five patients who had been manic, four had relapsed following discontinuation of the active compound. Of the seven whose disease responded to carbamazepine, five had disease that had failed to respond to lithium. Despite the small sample size, these investigators suggested the double-blind, on-off design permitted the tentative conclusion that carbamazepine was an effective treatment of manic depression, either alone or in combination with other agents. These findings supported the original speculation of Okuma et al[19] that carbamazepine was particularly useful in the management of lithium-resistant disease. In 1980, Ballenger and Post[20] extended their previous findings and obtained similar results from a larger sample of patients with mood disturbance, this time including patients with unipolar depression.

Post et al[21] in 1987 replicated their previous findings in a similarly designed trial of carbamazepine use in manic depression and found that 12 of 19 patients who improved were significantly more manic during the baseline placebo period than the nonresponders. Surprisingly, all of the responders were without family history of mood disturbance, while half of the nonresponders had positive family histories and half did not. Of the 12 patients whose disease responded to carbamazepine, eight had a history of lithium resistance. Of particular note, the 12 patients whose disease responded to carbamazepine were found to have a history of more frequent cycles. The authors concluded that carbamazepine was a clinically effective alternative antimanic agent that was likely to have particular application in manic depression in which manias were accompanied by increased severity, dysphoria, rapid cycling, and negative family histories. Since these variables are recognized as sometimes correlating with lack of response to lithium, these authors concluded that carbamazepine would have particular application in this subgroup.

Post et al[22] in 1986 conducted a double-blind placebo-controlled study of the acute antidepressant ef-

fects of carbamazepine. Although carbamazepine was accompanied by mild antidepressant properties in 20 patients (57%) and moderate response rates in 12 (34%), the improvement in depression ratings did not become significant until the end of the second week. Similar to their findings in mania, the authors noted that the more severely ill patients were most likely to benefit from treatment. Improvement was observed in patients with both bipolar and unipolar disease, but the antidepressant effects were not significant in the unipolar subgroup. However, a few patients with unipolar depression exhibited clear-cut and dramatic clinical response. These data prompted the authors to conclude that this anticonvulsant drug had acute antidepressant efficacy.

Their findings suggest that carbamazepine is effective in a poorly defined subgroup of patients, possibly those with more severe illness. The authors noted that since carbamazepine does not cause drug-induced manias, as do most antidepressants, it may be better suited for the depressed phase of manic depression. This would suggest that conventional use of tricyclic antidepressants and monoamine oxidase inhibitors should be restricted to patients with unipolar depression, or possibly patients with manic depression who are in the depressed phase of the illness and in whom neither lithium nor carbamazepine is effective. Due to this confusion, additional data will be needed before the role of this anticonvulsant in managing the depressed phase of manic depression or unipolar depressive disorders can be determined.

Placidi et al[23] documented similar efficacy and safety of carbamazepine *v* lithium in a randomized double-blind three-year trial of 66 patients with manic depression. They reported a response rate of at least 66% with each agent, using nonspecific measures found in the Brief Psychiatric Rating Scale,[24] such as thought disturbances, activation, and anergy.

Both agents were noted to exert their maximal therapeutic effects within the first three months, although the authors do not specify whether these effects were acute or prophylactic. The incidence of side effects was similar between the two groups. Patients taking lithium reported more diarrhea, weight gain, and tremors. The patients given carbamazepine reported more lethargy and exhibited more abnormal hematologic and hepatic laboratory findings. Although the authors concluded the two agents were accompanied by similar efficacy and safety, their data are difficult to interpret.

In these studies, the acute antidepressant and antimanic properties of each agent were not specifically evaluated for each patient. Neither was the prophylactic efficacy of each agent individually assessed. Additionally, it is now recognized that trials evaluating the efficacy of a drug used in the treatment of manic depression must specifically include evaluation of such measures as frequency, duration, and severity of individual mood swings. Although the convention is to view lithium as the treatment of choice for manic depression, this literature suggests that carbamazepine is a reasonable alternative to lithium.

ROLE OF VALPROATE

Whereas the data suggesting carbamazepine is efficacious in acute and prophylactic management of manic depression are substantial, available information on the potential role of valproate in this patient population is somewhat controversial. The mood-altering properties of this agent were first recognized by Lambert et al[25] in 1966, ushering in substantial interest in this area. Their early work culminated in a 1971 review[26] in which they reported data from an open longitudinal trial involving 53 patients with manic depression. Doses of 900–1,800 mg of valproate were combined periodically with neuroleptics and tricyclic antidepressants as needed; 20% of the patients showed a marked response, 50% a partial response, and 20% no response.

In 1976, Semadeni[27] studied 32 patients with manic depression; although 16 had lithium-resistant disease, results were similarly encouraging. During this longitudinal trial, patients received 900–2,400 mg of valproate periodically supplemented with neuroleptics and antidepressants. Of particular interest was the observation that 50% had complete remissions with no minor mood swings. Twenty-two percent had marked responses and 28% had little or no response.

Emrich et al[28] published data on double-blind monotherapy in 1980 and demonstrated acute antimanic efficacy in five patients with manic depression. Using an ABA placebo-controlled design and 1,800–3,850 mg of valproate, they were able to obtain an 80% marked response rate; one patient exhibited no effect. They also reported on valproate augmentation in seven patients with lithium-resistant disease who had either manic depression or schizoaffective disorder. In an open trial of 18–36 months duration, they noted complete remissions in 86%.

In a similarly designed study, Brennan et al[29] studied the acute antimanic properties of valproate monotherapy in a double-blind ABA placebo-controlled trial and noted a 75% response rate; no effect was seen in two

patients. They also reported a complete response rate in four of four patients with lithium-resistant manic depression who were followed up for 9–33 months.

In a more sophisticated trial, Puzinski and Kosiewics[30] studied valproate efficacy in patients with lithium-resistant disease by specifically evaluating such chronobiologic measures as duration, frequency, and severity of affective episodes. Ten patients with manic depression and five with schizoaffective disorder were given valproate concomitantly with neuroleptics and tricyclic antidepressants. Although these investigators noted a 50% decrease in the number of affective episodes and a dramatic decrease in the total duration of disease, of particular interest was the finding that response rates were better for acute mania than depression. This trial lasted 26–51 months and substantially contributed to knowledge of the agent's prophylactic efficacy.

Vencovsky et al[31] in 1984 published data involving 38 patients with bipolar disease. They did not systematically quantify the degree of improvement, so we are unable to interpret their data.

In 1985, Emrich et al[32] followed up their previous findings by comparing the original cohort of five manic-depressive patients treated with valproate to seven given oxacarbazepine. Again using a double-blind ABA placebo-controlled design, they noted that the relatively acute antimanic efficacy of these two agents was similar. McElroy et al[33] retrospectively reviewed outcome after valproate therapy in 17 patients with severely resistant manic depression in whom lithium, carbamazepine, or neuroleptic therapy had previously failed . Of these 17, 64% had moderate or marked responses to valproate augmentation. The variables that were thought to predict good response were histories of full manic syndromes and presence of nonparoxysmal EEG abnormalities.

In an ongoing study of the efficacy of valproate in the treatment of manic depression, we have preliminary data that replicate the previous findings reviewed in this paper.[34] In order to explore valproate's spectrum of efficacy in rapid-cycling manic depression, 55 patients underwent a prospective open 7.8-month trial designed to assess the drug's acute and prophylactic properties. Twenty patients received monotherapy and 35 received combination therapy. Moderate to marked acute antidepressant responses were seen in 47%, prophylactic antidepressant responses in 76%, acute antimanic responses in 91%, prophylactic antimanic responses in 94%, acute antimixed-state responses in 86%, and prophylactic antimixed-state responses in 93%. Consistent with other literature on anticonvulsants, these data suggest that valporate has marked antimanic and mixed-state efficacy, but minimal to moderate antidepressant properties.

ROLE OF CLONAZEPAM

The mood-altering properties of this high-potency benzodiazepine are not as well documented as those of carbamazepine and valproic acid. The literature is primarily anecdotal but suggests this agent may play an important role at least in the acute management of mania.[35–44] One 12-patient study, however, more systematically evaluated the acute antimanic efficacy of clonazepam. This double-blind study used a crossover design with lithium and clonazepam and suggested that the anticonvulsant was more effective for the acute treatment of mania because of its more rapid onset of action. Lithium-related side effects were tremor, diarrhea, and polyuria/polydipsia, whereas clonazepam side effects were ataxia and drowsiness.[45]

Anecdotal literature evaluating another 72 patients suggests that clonazepam is accompanied by an acute antimanic response rate of 45% to 66%.[35–44] In addition to the drug's acute antimanic effects, it has also been documented as having a role in the management of biological anxiety.[46–48] For this reason, clonazepam is particularly well-suited for patients with manic depression who have mood swings accompanied by state-dependent panic attacks.

Although quite controversial, some preliminary data suggest that this benzodiazepine may have acute antidepressant properties as well.[49] Of particular note is this drug's ability to treat antidepressant-induced mania.[41] In conclusion, these data suggest this anticonvulsant, like the others reviewed, plays a major role in at least the acute management of mania, panic/anxiety attacks, and possibly depression.

OTHER ANTICONVULSANTS

Phenytoin

Although lithium, carbamazepine, and valproic acid have received much attention recently, several reports published during the 1940s evaluated the mood-altering properties of phenytoin.[50–52] In 1943, Kalinowsky and Putnam[50] evaluated the role of phenytoin in the treatment of psychiatric illness by assessing its effects on schizophrenia, manic depression, and involutional psychosis. They concluded the drug was accompanied by nonspecific therapeutic effects in states of excitement independent of diagnosis. Of note, however, was the ob-

servation that 89% of 13 patients with manic depression exhibited moderate or marked responses.

Although this finding suggested phenytoin had antimanic properties, Freyhan[51] unsuccessfully attempted to replicate it two years later. Instead, he reported nonspecific therapeutic effects on states of chronic psychotic excitement. In a population of 45 psychiatric patients with diagnoses including manic depression and schizophrenia, he noted little improvement. In 1946, Kubanek and Rowell[52] studied the therapeutic effects of this agent in 73 psychotic patients with diagnoses including schizophrenia, manic depression, and involutional melancholia. Of the manic depressives, 56% improved. Half of the entire sample exhibited improvement in pathologic excitement. These data suggest phenytoin may have specific antimanic properties. Until it is more systematically studied, the findings should be viewed as preliminary.

Ethosuximide

Ethosuximide was documented more recently in a double-blind placebo-controlled crossover trial as having efficacy in the treatment of episodic dyscontrol syndrome, a disorder believed to be related to manic depression.[53]

CONCLUSION

The available evidence suggests carbamazepine has clear-cut efficacy in the treatment of manic depression. These findings have been generated by double-blind trials involving substantial samples as well as studies that have randomized carbamazepine against lithium. There is reason to believe the efficacy and safety of lithium and carbamazepine are similar, calling into question the role of lithium as the treatment of choice for this illness. The majority of the evidence looking at the spectrum of efficacy for carbamazepine would suggest that, like lithium, carbamazepine has acute and prophylactic antimanic efficacy that is superior to its antidepressant efficacy.

On the other hand, the literature assessing the efficacy of valproate is compromised by open-study designs and only small double-blind samples. Therefore, these data merit caution but also appear to suggest the spectrum of efficacy of valproate will be similar to both lithium and carbamazepine. Until these data are replicated in a more systematic fashion involving large double-blind samples with randomized design, the role of valproate in the management of lithium-resistant manic depression must remain tentative.

Other anticonvulsants, including clonazepam, are also likely to be accompanied by mood-altering properties, but this conclusion awaits further systematic study.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Third Edition, Revised. Washington, DC, American Psychiatric Association, 1987.
2. Avery D, Winokur G. Suicide, attempted suicide, and relapse rates in depression. Arch Gen Psychiatry 1978; **35**:749–753.
3. Weissman MM, Myers JK. Rates and risks of depressive symptoms in a US urban community. Acta Psychiatr Scand 1978; **57**:219–231.
4. Helgason T. Epidemiological investigation concerning affective disorders. [In] Schor M, Stromgren M, eds. Origin, Prevention and Treatment of Affective Disorders. London: Academic Press 1979 pp 241–257.
5. Wing JK, Mann SA, Leff JP, Nixon JM. The concept of a 'case' in psychiatric population surveys. Psychol Med 1978; **8**:203–217.
6. Kraepelin E. Manic Depressive Insanity. Salem, NH, Ayer Company, Reprint edition, 1987.
7. Cade JFJ. Lithium salts in the treatment of psychotic excitement. M J Australia 1949; **2**:349–352.
8. Goodwin FK, Murphy DL, Dunner DL, et al. Lithium response in unipolar versus bipolar depression. Am J Psychiatry 1972; **129**:44–47.
9. Davis JM. Overview: maintenance therapy in psychiatry. II: Affective disorders. Am J Psychiatry 1976; **133**:1–13.
10. Post RM. Carbamazepine's acute and prophylactic effects in manic depressive illness: an update. International Drug Therapy Newsletter 1982; **17**:5–10.
11. Ballenger JC, Post RM. Therapeutic effects of carbamazepine in affective illness: a preliminary report. Comm Psychopharmacol 1978; **2**:159–175.
12. McElroy SL, Pope HG, eds. Use of Anticonvulsants in Psychiatry: Recent Advances. Clifton, NJ, Oxford Health Care, Inc., 1988.
13. Blom S. Tic douloureux treated with new anticonvulsant. Arch Neurol 1963; **9**:285–290.
14. Rall TH, Schleifer LS. Effective drugs in the treatment of epilepsy. [In] Goodman Gilman A, Goodman LS, Gilman A, eds. The Pharmacological Basis of Therapeutics. New York, Macmillan 1980, p 469.
15. Kosteljanetz M, Christiansen J, Dan AM. Carbamazepine vs. phenytoin. Arch Neurol 1979; **36**:22–24.
16. Dalby MA. Anti-epileptic and psychotropic effect of carbamazepine (Tegretol) in the treatment of psychomotor epilepsy. Epilepsia 1971; **12**:325–334.
17. Dalby MA. Behavioral effects of carbamazepine. Adv Neurol 1975; **11**:331–344.
18. Takezaki H, Hanaoka M. The use of carbamazepine (Tegretol) in the control of manic-depressive psychosis and other depressive states. Seishin-igaku (Clin Psychiat) 1971; **13**:173–183.
19. Okuma T, Kishimoto A, Inoue K, et al. Antimanic and prophylactic effects of carbamazepine (Tegretol) on manic-depressive psychosis. A preliminary report. Folia Psychiat Neurol Jpn 1973; **27**:283–297.
20. Ballenger JC, Post RM. Carbamazepine in manic-depressive illness: a new treatment. Am J Psychiatry 1980; **137**:782–790.
21. Post RM, Uhde TW, Roy-Byrne PP, et al. Correlates of antimanic response to carbamazepine. Psychiatry Research 1987; **21**:71–83.
22. Post RM, Uhde TW, Roy-Byrne PP, et al. Antidepressant effects of carbamazepine. Am J Psychiatry 1986; **143**:29–34.
23. Placidi GF, Lenzi A, Lazzerini F, et al. The comparative efficacy and safety of carbamazepine versus lithium: a randomized, double-blind 3-year trial in 83 patients. J Clin Psychiatry 1986; **47**:490–494.
24. Overall JE, Gorham DR. The brief psychiatry rating scale. Psychiatry Res 1962; **10**:799–812.

25. Lambert PA, Carraz G, Borselli S, Carbel S. Action neuro-psychotrope d'un nouvel anti-épileptique: le dépamide. Ann Med Psychol 1966; **124:**707–710.
26. Lambert PA, Borselli S, Marcou G, Bouchardy M, Cabrol G. Action thymo-régulatrice à long terme du Dépamide dans la psychose maniaco-dépressive. Am Med Psychol 1971; **2:**442–448.
27. Semadeni GW. Étude clinique de l'effet normothymique du dipropylacetamide. Acta Psychiatr Belg 1976; **76:**458–466.
28. Emrich HM, von Zerssen D, Kissling W, Moller HJ, Windorfer A. Effect of sodium valproate on mania. The GABA-hypothesis of affective disorders. Arch Psychiatr Nervenkr 1980; **229:**1–16.
29. Brennan M, Sandyk R, Borsook D. Use of sodium valproate in the management of affective disorders. Basic and clinical aspects. [In] Emrich HM, Okuma T, Müller AA, eds. Anticonvulsants in Affective Disorders. Amsterdam, Elsevier, 1984, pp 56–65.
30. Puzinski S, Kosiewics L. Valproic acid amide as a prophylactic agent in affective and schizoaffective disorders. [In] Emrich HM, Okuma T, Müller AA, eds. Anticonvulsants in Affective Disorders. Amsterdam, Elsevier, 1984, pp 68–75.
31. Vencovsky E, Soucek K, Habes J. Prophylactic effect of dipropylacetamide in patients with bipolar affective disorder. [In] Emrich HM, Okuma T, Müller AA, eds. Anticonvulsants in Affective Disorders. Amsterdam, Elsevier, 1984 pp 66–67.
32. Emrich HM, Dose M, Zerssen D. The use of sodium valproate, carbamazepine and oxacarbazepine in patients with affective disorders. J Affect Dis 1985; **8:**243–250.
33. McElroy SL, Heck PE, Pope HG. Sodium valproate: its use in primary psychiatric disorders. J Clin Psychopharmacol 1987; **7:**16–24.
34. Calabrese JR, Delucchi GA. Spectrum of efficacy of valproate in rapid cycling manic depression. Am J Psychiatry, In press.
35. Chouinard G. Use of clonazepam in the maintenance treatment of manic-depressive illness. [In] Shagass C, Josiassen RC, Bridger WH, et al., eds. Biological Psychiatry 1985. New York, Elsevier Science Publishing Co., 1986, pp 723–725.
36. Harms L. Clonazepam and mania (letter). Pharmabulletin (Health Department of Victoria, Australia) 1985; **104:**117–119.
37. Freinhar JP, Alvarez WA. Clonazepam: a nobel therapeutic adjunct. Int J Psychiatry Med 1985-86; **15:**321–328.
38. Zetin M, Freedman MJ. Conazepam in bipolar affective disorder (letter). Am J Psychiatry 1986; **143:**1055.
39. Victor BS, Link NA, Binder RI, et al. Use of clonazepam in mania and schizoaffective disorders. Am J Psychiatry 1984; **141:**1111–1112.
40. Jones BD, Chouinar G. Clonazepam in the treatment of recurrent symptoms of depression and anxiety in a patient with systemic lupus erythematosus. Am J Psychiatry 1985; **142:**354–355.
41. Laporta M, Chouinard G, Goldbloom D, et al. Hypomania induced by sertraline, a new serotonin reuptake inhibitor (letter). Am J Psychiatry 1987; **144:**1513–1514.
42. Frykholm B. Clonazepam-antipsychotic effect in a case of schizophrenia-like psychosis with epilepsy and in three cases of atypical psychosis. Acta Psychiatr Scand 1985; **71:**539–542.
43. Freinhar JP, Alvarez WH. Use of clonazepam in two cases of acute mania. J Clin Psychiatry 1985; **46:**29–30.
44. Greenspan D, Levin D. Use of clonazepam in a patient with schizoaffective disorder (letter). Am J Psychiatry 1985; **142:**774–775.
45. Chouinard G, Young SN, Annable L. Antimanic effect of clonazepam. Biol Psychiatry 1983; **18:**451–466.
46. Chouinard G, Labonte A, Fontaine R, et al. New concepts in benzodiazepine therapy: rebound anxiety and new indications for the more potent benzodiazepines. Prog Neuropsychopharmacol Biol Psychiatry 1983; **7:**669–673.
47. Spier SA, Tesar GE, Rosenbaum JF, et al. Treatment of panic disorder and agoraphobia with clonazepam. J Clin Psychiatry 1986; **47:**238–242.
48. Tesar GE, Rosenbaum JF, Pollack MH, et al. Clonazepam versus alprazolam in the treatment of panic disorder: interim analysis of data from a prospective, double-blind, placebo-controlled clinical trial. J Clin Psychiatry 1987; **48(suppl):**16–19.
49. Kishimoto A, Kamata K, Sugihara T, et al. Treatment of depression with clonazepam. Acta Psychiatr Scand 1988; **77:**81–86.
50. Kalinowsky LB, Putnam TJ. Attempts at treatment of schizophrenia and other non-epileptic psychoses with Dilantin. Arch Neurol Psychiatry 1943; **49:**414–420.
51. Freyhan FA. Effectiveness of diphenylhydantoin in management of nonepileptic psychomotor excitement states. Arch Neurol Psychiatry 1945; **53:**370–374.
52. Kubanek JL, Rowell RC. The use of Dilantin in the treatment of psychotic patients unresponsive to other treatments. Dis Nerv Syst 1946; **7:**47–50.
53. Andrulonis PA, Donnelly J, Glueck BC, et al. Preliminary data on ethosuximide and the episodic dyscontrol syndromes. Am J Psychiatry 1980; **137:**1455–1456.