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- Know proposed mechanisms of actions of antimanic drugs.
- Predict interactions between thymoleptic treatments.

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Novel Alternatives and Supplements to Lithium and Anticonvulsants for Bipolar Affective Disorder

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Background: Most clinicians are familiar with the traditional anticonvulsants as alternatives to lithium in the treatment of bipolar mood disorders.

Method: This review of the English, French, German, and Italian language literature on novel treatments, including electroconvulsive therapy, calcium channel blocking agents, antipsychotic drugs, benzodiazepines, thyroid hormone, psychosurgery, and two new antiepileptic drugs, that have not been studied as extensively as lithium, carbamazepine, and valproate but that may have promise as alternatives or supplements to traditional thymoleptics when the standard treatments are not effective or are poorly tolerated. We searched MEDLINE and PSYCHINFO data bases using the keywords *bipolar*, *mood*, and/or *treatment*. We then searched bibliographies of articles retrieved by the first strategy.

Results: The theoretical rationale for each treatment is discussed, followed by a critical discussion of the evidence supporting its efficacy.

Conclusion: The potential risks and benefits of each treatment in actual clinical practice are placed in perspective.

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The anticonvulsants carbamazepine and valproate[1–3] have proved invaluable for the one quarter to one third of manic patients who do not respond fully to lithium[4,5] and the 25% to 50% who discontinue or reduce the dose of lithium because of side effects.[4] However, additional alternatives to lithium would be of great benefit to patients who do not have an entirely satisfactory response to the anticonvulsants or experience limiting side effects. Effective treatments for bipolar illness that have actions different from lithium and the anticonvulsants might also broaden our understanding of the pathophysiology of bipolar illness and its treatment.

Our search of the English, French, German, and Italian language literature in the MEDLINE and PSYCHINFO databases using the keywords *bipolar*, *mood*, and/or *treatment*, followed by a secondary search of the bibliographies of articles retrieved by the first strategy, revealed a wide range of treatments for bipolar affective disorder.

A number of treatments, notably electroconvulsive therapy, calcium channel blocking agents, antipsychotic drugs, benzodiazepines, thyroid hormone, psychosurgery, and two new antiepileptic drugs, may have the potential to expand the armamentarium of the clinician as well as to elucidate the pathophysiology of bipolar illness. However, insufficient funding for new research in this area has limited much of the published work to chart reviews, case reports, open trials, and relatively small prospective placebo-controlled studies. Many of these reports lack sufficient detail to assess their value critically. Since many patients who are subjects in trials of new potential antimanic drugs have not responded to standard treatments, and some have other illnesses (especially unipolar depression), failure to improve with the new treatment cannot necessarily be interpreted as proof that the new medication is not useful at all. When the experimental medication is effective, it can be difficult to factor out the effect of adjunctive and rescue medications often used by patients with complicated mood disorders. In addition, the bulk of information that is available usually applies to the acute treatment of mania and not to mood stabilization or the treatment of bipolar depression. In this review, we consider the theoretical rationale for investigating novel therapies and make suggestions about possible clinical applications given the current limited state of knowledge.

ELECTROCONVULSIVE THERAPY

Mania is the third most common indication for electroconvulsive therapy (ECT),[6] which appears to be the most

rapidly effective treatment for mania[7] and the most effective treatment for bipolar depression.[8] As is true of lithium, electroconvulsive shock in animals attenuates G protein–coupled intracellular signaling,[9,10] suggesting that ECT might normalize similar hyperactive intracellular signaling that has been reported in both mania and bipolar depression.[11] Additional theories of the mechanism of action of ECT in bipolar illness include enhancement of right brain and dampening of left brain function[12] and normalization of serotonin signaling.[13] As he has proposed for carbamazepine and valproate, Post[14] has suggested that the anticonvulsant effect of ECT could be a mechanism of its antimanic action, although Small et al.[12] dispute this.

McCabe and Norris[15] found that 24 of 28 bipolar inpatients who were treated with ECT from 1945–1949 were markedly improved or well, compared with 10 of 28 matched bipolar inpatients treated before ECT became available in their hospital (1935–1941). Some of the obvious weaknesses of a retrospective chart review in which patients were evaluated in a nonblind fashion by different clinicians in different eras were addressed in a careful review by Black et al.[16] of charts of patients treated in their hospital between 1970 and 1981. During this time, 78% of acutely manic patients treated with ECT had "marked improvement" on a scale devised by the authors, compared with 62% of patients treated for at least 2 weeks with lithium carbonate in doses producing serum lithium levels of 0.9 mEq/L and 56% of patients with lower lithium levels. Of patients who did not respond to a therapeutic trial of lithium, 68.8% had marked improvement, and 18.8% had partial improvement, after going on to receive ECT. While encouraging, this study is also limited by the nonblinded chart review method and lack of a validated instrument for evaluating outcomes.

Small et al.[6] conducted an 8-week prospective study in which acutely manic patients were randomly assigned to receive lithium at therapeutic levels or nine bilateral ECTs followed by maintenance ECT. All patients receiving ECT improved, and patients who received ECT improved more rapidly than lithium-treated patients, especially if they had mixed (i.e., depressive and manic) symptoms or severe mania. At the end of 8 weeks, the outcomes of patients who received ECT were equivalent to the outcomes of patients who received lithium. In a small open prospective trial by Schnur et al.,[17] 13 of 22 patients treated with ECT had complete remissions of mania compared with none of five patients receiving a lithium-haloperidol combination. While patients in the Small et al. study[6] had not previously been treatment refractory, manic patients in the Schnur study had not responded to an adequate trial of lithium, perhaps accounting for the lower response rate than that reported by Small's group.[6]

In a review of the published literature on the efficacy of ECT for acute mania, Mukherjee et al.[18] located a number of case series, six retrospective studies (two of them controlled and four naturalistic), and the two prospective randomized controlled studies described above.[6,17] Combining the data from the reports they reviewed, the authors found "marked clinical improvement" in 78% of 400 manic patients in early case series of at least 20 patients each, "remission or marked clinical improvement" in 85% of 150 patients in retrospective studies reported since 1976, and "clinical remission" in 30 (77%) of 39 patients in the two prospective studies; the overall rate of "remission or marked clinical improvement" was 470 (80%) of 589 patients. Interpretation of these composite figures is limited by differences in methodology and outcome measures in the studies reviewed and by the secondhand assessment of data using a nonstandard method. In a retrospective chart review of data not included in Mukherjee and colleagues' review,[18] Wehr et al.[19] found no response to treatment with ECT in 24 patients who were part of a larger group of patients with rapidly cycling bipolar illness that was largely resistant to lithium therapy; however, details of the patients' illnesses, the method of ECT administration, the number of treatments, and other relevant details were not reported, making it impossible to interpret this negative result. Even though clinicians often use ECT for refractory rapid cycling, we could find no other published reports of its application in this setting.

The use of ECT for mania in adolescents has not been well studied. In a recent retrospective review of charts of 12 manic and bipolar psychotically depressed patients aged 16 to 22 who received ECT because of nonresponse to an adequate medication dose for 4 to 6 weeks and of 6 patients (3 manic and 3 depressed) who refused ECT during the same time period,[20] the mean number of treatments received by the ECT group was 10.4, and 87% of the ECTs were bilateral. Patients who received ECT had significantly greater decrements in Brief Psychiatric Rating Scale (BPRS) scores than those who refused ECT. The length of hospitalization was twice as long for patients who refused ECT. In a retrospective review of records of 20 patients aged 13 to 18, Schneekloth and associates[21] found that all four patients with bipolar disorder (one manic, one depressed, two bipolar "NOS") recovered. Obviously, such retrospective analyses of small groups of patients cannot be generalized, but the findings are at least

consistent with older case reports of the usefulness of ECT in a total of 27 adolescent patients with mania or bipolar depression.[21–24]

Controversy continues about whether nondominant (right) unilateral ECT (RUL) is as effective as bilateral ECT (BL) in the treatment of acute mania. In the retrospective chart review mentioned earlier, Black et al.[16] found both methods of ECT administration to be equally effective. Milstein et al.[25] obtained different results in a prospective randomized comparison of lithium and ECT in manic patients. Of the 17 patients who received ECT, 11 began with BL and 6 with RUL. None of the RUL patients responded, but when the approach was changed to BL, the response rate was as high as it was in patients who began with BL. Bilateral ECT was superior to lithium whether it was the first or the second treatment. An open study by Small's group of a diverse group of patients with unipolar or bipolar mood disorders who received ECT found that RUL was effective in patients with major depressive disorder, while patients who responded only after a switch to BL were more likely to have had manic symptoms with or without depression.[26] Small et al.[27] noted that BL was more rapidly effective than RUL treatment in 34 acutely manic patients.

Mukherjee et al.[18] have suggested that findings of superiority of BL to RUL in the treatment of mania may be a function of the precise location of the electrodes. They point out that the Small et al. study[26] utilized the Lancaster RUL electrode placement, which has a short interelectrode distance that could shunt current through the scalp, reducing current density through the brain. In contrast, the prospective study mentioned earlier,[17] which was performed by Mukherjee's group, found that five of eight manic patients had a complete remission with the d'Elia RUL placement, which has a greater interelectrode distance. The small number of patients in this group obviously precludes any definite conclusion about whether Mukherjee and colleagues'[18] assumption is correct. Other differences in technique such as type of stimulation could also contribute to apparent discrepancies between bilateral and unilateral ECT.[28]

A review of early work with ECT found that the mean number of ECTs administered to manic patients was 17, and that some manic patients needed more than one course of ECT.[29] However, this could reflect less sophisticated use of ECT than is currently the case, and a more recent chart review suggested that seven to 10 ECTs have been sufficient for most patients.[16] In their literature review, Mukherjee et al.[18] found that the average number of treatments necessary to produce a therapeutic effect in mania was 5.4 to 11, while Small et al.[27] found that a mean of nine bilateral ECTs was superior to lithium during an 8-week trial in acute mania. The median number of treatments for adolescent patients receiving ECT in Schneekloth and colleagues' sample was 11.5.[21] It has been suggested that lower stimulus intensities might be necessary for mania than for depression,[20] but this has not been demonstrated in controlled studies. As seizure thresholds are often lower in children and adolescents than in adults, lower stimulus intensities may be necessary when ECT is administered to this group for any indication.[21,30]

Clinical Implications

ECT is a consideration for manic patients who do not respond to or tolerate antimanic drugs, who require a rapid onset of antimanic effect, or who are pregnant.[7] Economic considerations may also favor ECT, which has a more rapid onset of action as well as greater acute efficacy than medications.[27] Bipolar depression and mixed states may also respond more predictably to ECT than to medications.[7,31] Consistent with experience with depression, 45% to 80% of manic patients were found in two older surveys to have relapsed after ECT was discontinued[15,32]; more recent data are not available. Maintenance ECT was as effective as lithium in preventing manic relapse and recurrence in a prospective study and some case series.[9,33–35] In one early study that examined this question, the recurrence rate of mania in patients receiving one ECT per month for up to 6 years was only 12%, slightly more than one seventh the recurrence rate in unmedicated bipolar patients not receiving maintenance ECT.[32] On the other hand, Small et al.[27] found that lithium maintenance prevented recurrence after ECT for acute mania in 34 patients followed for an unspecified period of time.

CALCIUM CHANNEL BLOCKING AGENTS

Research has accumulated since the late 1970s supporting the use in mania of medications that reduce intracellular calcium ion (Ca^{2+}) signaling. Free intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$), which is normally regulated very tightly at around 100 nM, or 1/10,000th the Ca^{2+} concentration in the extracellular fluid, has been found to be elevated in blood platelets[36–40] and lymphocytes[38] of affectively ill manic and bipolar depressed patients but not in platelets of unipolar depressed patients, controls, or bipolar patients who are euthymic after treatment with various medications or ECT. In vitro incubation with lithium[40] and carbamazepine[41,42] lowers platelet $[Ca^{2+}]_i$ sig-

nificantly in ill bipolar patients but not in controls or euthymic bipolar patients.[39]

In the brain, potential dependent calcium channels, which allow calcium ions into neurons to replenish intracellular stores and trigger a variety of intracellular processes, are localized in regions rich in synapses (perhaps because high $[Ca^{2+}]_i$ must be produced rapidly to regulate neurotransmitter release).[43] Calcium channel blocking agents reduce Ca^{2+} influx through L (long-acting)-type potential dependent calcium channels,[44] which do not participate directly in neurotransmitter release but play an important role in determining neuronal excitability. At least four and possibly seven or more distinct binding sites for different classes of calcium channel blocking agents exist on the L channel α_1 subunit,[45,46] allosterically linked to each other and to the Ca^{2+} gating site. Different calcium channel blocking agents therefore may have different spectra of action. Nimodipine also has anticonvulsant properties[47] that could contribute to activity in syndromes different from those affected by calcium channel blocking agents without anticonvulsant properties.[48]

In a double-blind placebo-controlled protocol, verapamil was the first calcium channel blocker to be found effective as a treatment for an acutely manic patient.[49] Since that time, 18 case reports have been published involving 37 bipolar, unipolar depressed, or schizoaffective-bipolar subtype patients given calcium channel blocking agents (verapamil in all but three reports) for 1 week to 3 years.[19,49–67] Of these patients, 29 had an antimanic, antidepressant, and/or mood-stabilizing response to the calcium channel blocking agents, and 8 patients did not benefit. One case report has been published in which verapamil added to valproate produced remission of chronic mania in a brain damaged adolescent who had been refractory to standard antimanic therapies,[65] and adolescents and children generally tolerate verapamil well when it is used to treat supraventricular arrhythmias and hypertrophic cardiomyopathy[68]; however, no other reports of the use of calcium channel blocking agents in bipolar children and adolescents have been published.

These reports have been supplemented by the studies summarized in Table 1.[48,69–87,90] There have been 7 double-blind trials of verapamil in 137 manic or hypomanic individuals[71,73,76–78,82,85,86] and 1 blinded trial of nimodipine in 11 rapidly cycling patients.[48,86] In a minority of these trials, adjunctive neuroleptics or benzodiazepines were used,[72,76,82,85] but this is common in studies of manic patients, and patients taking calcium channel blocking agents did not receive adjunctive medications more frequently than those taking placebo or comparison drugs. A more important criticism of two trials is that they lasted only a week.[76,83]

Two 4- to 5-week double-blind trials[82,85] reported equivalent antimanic efficacy of verapamil and lithium, and 6-month trials each of verapamil and lithium in 20 bipolar patients in a crossover protocol appeared to suggest that verapamil had equivalent or superior mood-stabilizing effects.[33] However, sufficient details were not presented to evaluate this trial critically. Lack of detail also makes it impossible to evaluate a double-blind comparison by Giannini's group[73] of verapamil and clonidine in 20 manic patients in which verapamil produced a greater reduction of mania scores than clonidine.

Verapamil has been noted to be ineffective in some lithium-resistant bipolar patients,[79] but addition of verapamil to lithium has been helpful to some patients who did not respond to lithium alone.[50] A few rapidly cycling patients have benefited from verapamil[19,78,79,84,88] and nimodipine.[86,88,89] Verapamil was noted to have mood-stabilizing properties in 42 manic and rapidly cycling patients,[78,79,84] and nimodipine reduced cycle frequency in 11 rapidly cycling bipolar patients.[86]

Only one trial has been reported in which verapamil appeared to be less effective than lithium in the treatment of acute mania.[90] In this study, patients were randomly assigned to 28 days of open treatment with lithium (N = 21) or verapamil (N = 19). Decreases in Brief Psychiatric Rating Scale (BPRS), Mania Rating Scale (MRS), Clinical Global Impressions scale (CGI), and Global Assessment of Functioning scale (GAF) scores were significant for lithium but not verapamil, and mean BPRS and GAF scores were significantly lower in the lithium than in the verapamil groups. This study had a number of major flaws that make it unreliable in guiding future research. For example, p values reported for differences between the lithium and verapamil groups would not be considered significant with the statistical measures (ANOVA and ANCOVA) used in the study, the absolute numerical differences between groups in rating scale scores were small, and there was no difference between MRS scores in the lithium and verapamil groups. By rating scale scores (no actual clinical descriptions were provided), patients in the lithium group were more symptomatic than would have been expected after a month of treatment, suggesting something unusual about the milieu or the patient samples. The same number of patients in each group received adjunctive lorazepam during the study and neuroleptics at the end of the study. Finally, total verapamil doses were probably too low, and the spacing of doses too

Table 1. Formal Studies of Calcium Antagonists in Mood Disorders*

Study	Method	N	Diagnosis	Li[a]	Drugs	Dose (mg)	Time	Results
Carman and Wyatt[69]	Open trial	3	Mania	0	Salmon calcitonin	NA	min	Decreased severity and frequency of agitation lasting several hours. No further data
Mussini et al[70]	Open trial	9	Depression (unipolar or bipolar), anxiety	0	Salmon calcitonin	NA	20 d	Tranquilization; decreased BPRS scores
Giannini et al[71]	Single-blind, crossover	10	Hypomania	±	Verapamil vs placebo vs lithium	320	30 d	Verapamil = lithium
Caillard[72]	Open trial	7	Mania	+	Diltiazem (neuroleptic and chloral hydrate prn)	240–360	2 wk	Remission in 5 of 7 patients
Giannini et al[73]	Double-blind, crossover	20	Mania	–	Verapamil and clonidine	320	20 d	Verapamil > clonidine
Hoschl et al[74]	Open trial	5	Mania	0	Verapamil	120–480	1 mo	Remission in all patients
		23	Depression (unipolar or bipolar)	0	Verapamil	240–480	2 wk	9 patients improved "markedly," 6 "slightly"
Eckmann[75]	Double-blind, placebo-control	32	Unipolar depression	0	Flunarizine	NA	NA	82% of patients improved on flunarizine vs 26% on placebo
Dose et al[76]	Double-blind, placebo-control, A-B-A	8	Mania, schizo-affective	–	Verapamil or placebo + neuroleptic and/or paraldehyde	320–480	1 wk	Average 30% decreased mania on verapamil in 7; relapse on placebo in 5
Dubovsky et al[77]	Double-blind, placebo-control, A-B-A	7	Mania	+ or 0	Verapamil	480	4 wk	Full or partial remission in 6; relapse on placebo
Giannini et al[78]	Double-blind, crossover	20	Bipolar with mania in last 21 mo	+	Verapamil or lithium for 6 mo, then crossover to other drug	240	1 y	Verapamil > placebo as mood stabilizer
Barton and Gitlin[79]	Open trial	14	Mania (8), rapid cycling (4), AIH (2)	–	Verapamil	240	3 wk (mania) 8 mo (AIH)	4 manic patients became dysphoric; none responded. Decreased cycle frequency in rapid cycling. Euthymia in AIH
Dinan et al[80]	Open trial	6	Mania	0	Verapamil; temazepam at bedtime for 2 patients	400	3 wk	2 patients recovered fully. 1 patient improved initially, then relapsed. 1 patient deteriorated over 2 wk. No apparent effect on D_2 receptors
Kramer et al[81]	Double-blind, placebo-control, crossover	6	Unipolar depression	0	Nifedipine	60	4 wk	Depression worsened on nifedipine and placebo
Hoschl and Kozemy[82]	Double-blind, placebo-control, verapamil vs amitriptyline	12	Depression (unipolar or bipolar)	0	Amitriptyline vs verapamil vs placebo vs "eclectic" treatment	240–480	5 wk	"Eclectic" treatment = amitriptyline > verapamil = placebo
	Double-blind, placebo-control, verapamil vs lithium	52	Bipolar depression	+ or 0	Verapamil (12), neuroleptic (24), lithium + neuroleptic (11)	240–480	5 wk	Verapamil = neuroleptic = lithium + neuroleptic
Brunet et al[83]	Open trial	6	Mania	0	Nimodipine	360	1 wk	Rapid, significant improvement in mood, mania scale, and BPRS scores without sedation. No other details
Manna[84]	Open trial	12	Bipolar depression rapid cycling	±	Lithium vs nimodipine vs lithium + nimodipine (all patients)	90	18 mo	Lithium + nimodipine > either one alone in decreasing number of affective recurrences

(Continued)

Table 1. Formal Studies of Calcium Antagonists in Mood Disorders* (Cont'd.)

Study	Method	N	Diagnosis	Li[a]	Drugs	Dose (mg)	Time	Results
Garza-Trevino et al[85]	Double-blind randomized comparison of verapamil to lithium	20	Mania	+	Verapamil (12), lithium (8) (neuroleptic + benzodiazepine prn)	320	4 wk	Verapamil = lithium
Pazzaglia et al[86] Post et al[48]	Double-blind placebo-control, A-B-A-B	12	Rapid cycling (11), brief recurrent depression (1)	–	Nimodipine (all), verapamil (1), carbamazepine (1)	120–720	Mean = 11 wk	4 patients did not complete trial; data from 1 excluded. Overall decrease in mood swings in the rest. All 3 patients with ultradian cycling and one with typical rapid cycling improved. 1 patient with rapid-cycling bipolar disorder responded to verapamil and nimodipine. 2 rapid-cycling patients had partial response; 1 had euthymia when carbamazepine added to nimodipine
Walden et al[87]	Open trial	10	Depression (unipolar or bipolar)	0 or –	Nimodipine	90–270	36 d	9/10 patients have significant improvement after failure on antidepressants. Mean HAM-D decreased from 27 to 10; 5 had final HAM-D of 7 or less
Walton et al[90]	Open random assignment to lithium or verapamil	36	Mania	0	Verapamil, adjunctive lorazepam	230–360	28 d	Patients on lithium had significantly greater decreases in BPRS and increases in GAF scores than patients on verapamil. No difference in amount of adjunctive lorazepam. No statement of actual clinical status

[a]History of lithium response.
*Abbreviations/Symbols: 0 = not tried or not stated; + = good response to lithium; – = poor response to lithium; ± = equivocal; AIH = antidepressant-induced hypomania; BPRS = Brief Psychiatric Rating Scale; GAF = Global Assessment of Functioning scale; HAM-D = Hamilton Rating Scale for Depression; NA = not stated.

infrequent, for the medication to be reliably effective for mood disorders. The fact that the authors considered verapamil, a synthetic organic compound, to be a cation limits their interpretation of the findings.

The calcium channel blocking agents are generally well tolerated, and tachyphylaxis and withdrawal do not occur.[45] The most common side effects are related to vasodilatation and include dizziness, skin flushing, tachycardia, and nausea.[44,45,91] Verapamil and diltiazem can cause sinus bradycardia and atrioventricular block.[92] Rare adverse effects include coughing, somnolence, constipation, and parkinsonism.[44,92,93] Important interactions with other medications used by bipolar patients are noted in Table 2.[44,91,92]

Table 2. Some Interactions of Calcium Channel Blocking Agents With Medications Used for Bipolar Patients

Medication	Interaction
Lithium	Neurotoxicity Choreoathetosis Parkinsonism Cardiac slowing ?Decreased lithium levels
Carbamazepine	Increased carbamazepine Neurotoxicity
Neuroleptics	Increased parkinsonism

A concern about the safety of chronic use of calcium channel blocking agents was raised by a 1995 retrospective comparison of automated charts of a group of hypertensive patients treated with either the β-adrenergic blockers propranolol, metoprolol, nadolol, or atenolol, or one of the calcium channel blocking agents nifedipine, diltiazem, or verapamil.[94] Compared with patients taking a β-blocker, patients taking a calcium channel blocker were 1.60 (95% confidence interval [CI], 1.12 to 2.27) times as likely as those taking other antihypertensives to have a myocardial infarction during 4 years of treatment.

Limitations of this study included a retrospective, open chart review and nonrandomized treatment making it impossible to determine whether patients with more severe hypertension or with hypertension complicated by other factors that increase coronary risk were more likely to be selected for calcium channel blocker therapy; the total number of myocardial infarction patients was also too small to provide confidence that the statistically significant increased risk was clinically meaningful.[95]

Other studies have demonstrated either no increased risk of myocardial infarction in hypertensive patients taking calcium channel blocking agents[96] or a statistically significant reduction (by 25%–36%) in rates of angina, reinfarction and/or mortality over 6 months in patients taking verapamil versus placebo, beginning within 2 to 3 weeks of a myocardial infarction,[97–101] with a 60% reduction in mortality over 18 months in post–myocardial infarction patients with ventricular or atrial tachycardia or fibrillation.[97] These mixed data do not support the contention that calcium channel blocking agents pose a substantial cardiac risk, especially to patients without hypertension or cardiac disease.

A recent naturalistic study of elderly individuals[102,103] raised the concern that calcium channel blocking agents might promote cancer in this population. Medication use and medical histories were assessed between 1982 and 1983 in 10,000 people aged 65 years or older. From 1988 to 1992, Medicare review files of hospital discharges, death certificates, interviews with relatives, and examination of newspaper obituaries and the National Death Index were used to determine whether cancer developed in 5052 of these individuals. Within this subgroup, a new onset of cancer (most frequently of the colon, prostate, lung, lymphatics, blood, urinary tract, and breast) was recorded in 420 people, 169 of whom died of their cancers.[103] After controlling for cancer risk factors such as cigarette smoking and alcohol use, patients who reported taking calcium channel blocking agents (diltiazem, nifedipine, or verapamil) for any reason at the onset of the original study were more likely to develop cancer compared with all other study participants (relative risk [RR] = 1.72; $p = .0005$). Use of other antihypertensive agents, nitrates, digoxin, corticosteroids, and anticoagulants was not associated with an increased cancer risk. Within the group of 750 patients (mean age = 78 years) in the sample who were taking β-adrenergic blockers, angiotensin-converting enzyme inhibitors, or calcium channel blocking agents for hypertension at the start of the study, patients taking calcium channel blocking agents were significantly more likely to develop cancer than were patients taking β-blockers.[102]

The main problem with this study was that the use of calcium channel blocking agents was assessed only at entry into the study, 5 to 6 years before the period of follow-up for cancer began, and it was impossible to know whether these medications were still being taken in proximity to the development of cancer. In addition, the authors tallied only cancers that led to hospitalization or death. Given the small number of cancer cases relative to the total sample size, a few unrecorded or outpatient cancers in subjects who were not taking calcium channel blocking agents would change the results significantly. Although the investigators[102] and two editorialists[104,105] argue that calcium channel blocking agents could promote cancer by interfering with programmed cell death (apoptosis), a calcium-dependent process that destroys cancer and other defective cells, blocking calcium influx is equally likely to slow the growth of cancer, since an increase in $[Ca^{2+}]_i$ is also necessary for proliferation of a number of human cancer cells.[106–108] In vitro, verapamil inhibits tumor proliferation,[106] and the calcium channel antagonists verapamil, diltiazem, and amlodipine block the mitogenic action of calcium on human cancer cells[107] and reduce tumor growth and tumor size in animal studies.[107] These data call into question any cancer-promoting effect of the calcium channel blocking agents, an effect that has not been proposed in any event for nongeriatric patients.

Clinical Implications

The limited data available suggest that verapamil is more effective in lithium-responsive than in lithium-resistant patients.[79] In the few reported cases in which verapamil[49,77] or diltiazem[72] was administered to brain damaged manic patients, these calcium channel blocking agents were well tolerated. Calcium channel blocking agents might be considered in the presence of medical disorders in which a calcium channel blocker might be helpful, such as hypertension, supraventricular tachycardias, achalasia, migraine headaches, premature labor, tardive dyskinesia, Raynaud's disease, and possibly stroke and other forms of neurologic injury.[109–115] Nimodipine has been found to reduce morphine requirements in patients with cancer pain, possibly by interfering with down-regulation of opioid receptors,[116] and calcium channel blocking agents potentiate antimalarial drugs and reduce toxic reactions to gentamicin, amphotericin B, and cyclosporine.[117] Calcium channel blocking agents may be useful as adjuncts to cancer chemotherapy by inhibiting an energy-dependent chemotherapeutic drug extrusion pump that prevents intracellular accumulation of the medication.[118–120] Verapamil was

found to increase the action of tamoxifen against breast cancer in vitro, possibly through an action on an estrogen receptor.[118]

Calcium channel blocking agents have been studied in randomized trials during pregnancy for the treatment of maternal hypertension, premature labor, and fetal arrhythmias without evidence of teratogenicity and without significant effects on uterine or placental blood flow.[109,121–123] However, an insufficient number of patients have been studied during the first trimester to be certain that calcium channel blocking agents have no adverse effects on the fetus, and there are no data about later development of children who were exposed to calcium channel blocking agents during pregnancy. Verapamil therefore might be a viable alternative to other antimanic drugs for pregnant bipolar patients, but so far there is only one published report of the use of sustained-release verapamil in three pregnant patients with good control of mania and uneventful delivery of normal babies.[66]

ANTIPSYCHOTIC DRUGS

Antipsychotic medications are frequently administered to manic patients, usually to control agitation before lithium or another antimanic drug takes effect[1,124] and to treat the psychotic symptoms that are common in manic patients.[125] It is not known whether antipsychotic drugs might also have specific antimanic or mood-stabilizing actions,[125] perhaps related to their effects on serotonin 5-HT_2 receptors.[126] Opinions have been expressed that neuroleptics decrease the intensity and frequency of manic episodes,[127] that they protect against recurrences of mania and psychosis but not depression,[33] and that they increase compliance with antimanic drugs.[128] Conversely, it has been asserted that even if they are superior to lithium in the acute treatment of agitation in manic patients, neuroleptics are less effective than lithium in treating core manic symptoms, especially chronically,[125] and that neuroleptics make manic patients prone to more severe and prolonged depressive episodes and rapid cycling.[125,129] None of these assertions is supported by statistically significant or valid findings or by randomized trials.[125]

Despite concerns about their safety, antipsychotic drugs are used frequently in the treatment of bipolar illness. A naturalistic follow-up of 73 manic patients found that 34% were taking neuroleptics alone or in combination with lithium a year after the index episode.[130] In a study of 45 bipolar patients discharged from the hospital taking lithium, 89% were also taking neuroleptics.[131] After 6 months, 52% of patients discharged on a neuroleptic were taking a lower dose, 21% the same dose, and 21% a higher dose; only 5% (2 patients) had discontinued the neuroleptic.[131] Further evaluation of 40 of these patients revealed that the mean discharge neuroleptic dose of 793 ± 695 mg/day of chlorpromazine equivalent had been decreased to only 634 ± 684 mg/day 6 months later.[132] These data were interpreted as evidence of inappropriate use of neuroleptics after resolution of acute mania,[131] but it is also possible that some manic patients continue to require neuroleptics for prevention of affective recurrence even if psychosis has remitted.[133,134] Such a possibility is supported by a finding that lithium alone ameliorated bipolar psychotic depression in 10 patients, but 8 required addition of a neuroleptic to prevent relapses.[133]

The role of antipsychotic drugs in the treatment of acute mania was recently reviewed by Chou[1] and by McElroy et al.,[125] who noted that chlorpromazine, haloperidol, pimozide, thiothixene, and thioridazine have all been found to be more effective than lithium in rapidly reducing hyperactivity, but less effective in stabilizing mood. Case reports and formal studies not included in those reviews suggest that flupenthixol by itself or added to lithium is of no benefit in the treatment of mania, but chlorpromazine, haloperidol, thiothixene, and depot neuroleptics may have applications alone or as adjuncts to lithium in maintenance as well as acute treatment.[15,34,128,135–139] A double-blind comparison of 10, 30, and 80 mg/day of haloperidol for up to 6 weeks in 29 acutely manic patients found that higher doses were no more effective than 10 mg.[140]

In addition to the possibility of an increased risk of tardive dyskinesia and neuroleptic malignant syndrome in bipolar patients,[3,131,141,142] as well as neurotoxic interactions with lithium,[27] concern has been raised that neuroleptic use could be associated with withdrawal or supersensitivity (tardive) psychoses appearing with reduction in neuroleptic dosages.[143,144] Most putative cases of tardive psychoses have been reported in schizophrenic patients in whom chronic neuroleptic use was felt to induce rather than prevent relapses.[141,143,144] A bipolar patient treated chronically with lithium plus 20 mg/day of fluphenazine became acutely psychotic when the last 5 mg of fluphenazine was withdrawn. The psychosis did not return when the fluphenazine dose was decreased more slowly over "several months."[145] Steiner et al.[146] described five bipolar patients taking neuroleptics chronically who developed schizophreniform psychoses that involved psychotic symptoms they had not experienced in the past and that in some patients occurred in the absence of affective symptoms. Escalating neuroleptic doses were necessary to control the new psychotic symptoms. Supersensitivity psy-

choses seem very rare in bipolar patients in view of the small number of published reports.[144] In contrast, rapid withdrawal from antipsychotic drugs with multiple receptor actions such as clozapine can induce new affective dysregulation and psychotic symptoms that were not features of the original illness.[147,148] Slow discontinuation of antipsychotic drugs may minimize withdrawal-emergent psychotic symptoms that do not seem to reflect return of the original illness.[143,147]

Do "atypical" antipsychotic drugs that have more prominent serotonin 5-HT_2 than dopamine D_2 antagonist properties[149] have applications in bipolar disorder? No randomized controlled trials have been conducted comparing the putative mood-stabilizing properties of clozapine with those of standard antimanic drugs or of placebo. However, Table 3 lists case studies and small open trials of clozapine and risperidone in patients with refractory bipolar and schizoaffective disorder.[27,150–168] All of the published reports suggest that clozapine has an antimanic effect that occurs in nonpsychotic as well as psychotic patients. There has been insufficient experience to determine whether observations of better prophylaxis against recurrent mania than depression[157] are isolated or whether they represent a common phenomenon.

Experience in bipolar disorder with risperidone, which may have more distinct antidepressant properties than clozapine,[159,169] has been more mixed (Table 3). Reports of a positive effect of risperidone in bipolar mood disorders[150,158,162,163] have involved low doses and trials that were probably too brief for any antidepressant properties of risperidone to predominate over the sedating and antipsychotic effects. In addition, in contrast to clozapine, there have been a number of reports of increased manic symptoms with risperidone.[151,159,164–166] Since positive effects of exciting new medications are reported more frequently than treatment failures, these negative reports would seem to be reason for caution with risperidone in the treatment of bipolar illness until controlled data become available.

Other new "atypical" antipsychotic drugs, such as olanzapine, sertindole, and setoperone, also have 5-HT_2 as well as D_2 antagonist properties.[170] Since 5-HT_2 antagonism can convey antidepressant properties,[149,170] more experience with these medications is necessary to know whether they will have the potential to destabilize mood in bipolar mood disorders. As yet there are no reports of the use of new atypical antipsychotic drugs in patients with mania or bipolar depression. However, some clinicians have noted excessive activation that predominates over sedation in bipolar patients treated with olanzapine.

Clinical Implications

As desirable as it is to avoid neuroleptic use, especially chronically, in bipolar disorder, an ongoing need for antipsychotic drugs to prevent affective as well as psychotic relapses[134] may be the most likely explanation for reports of ongoing neuroleptic therapy in remitted bipolar patients.[131–133] There are no prospective discontinuation trials that might help in suggesting how long neuroleptics should be continued in such patients. However, it is possible that for some bipolar patients, neuroleptics contribute to persistence of depression, which then lowers the threshold for the expression of the psychosis.[134] For such patients, gradual withdrawal of the neuroleptic could lead to a decrease in psychotic as well as depressive symptoms. If "tardive psychosis" is in fact a rare complication of chronic neuroleptic use, one clue to this problem might be worsening psychosis on a stable dose of neuroleptic, with only temporary reduction of symptoms with each dosage increase. Gradual withdrawal of the neuroleptic would be expected to result in transient aggravation of psychotic symptoms followed by their eventual resolution. The possibility that, for patients who can tolerate it, clozapine may prove to be a useful adjunct in preventing manic recurrences in refractory bipolar illness awaits confirmation in controlled studies. The published data on risperidone are not as consistently encouraging, and while no information is available about potential uses of olanzapine, sertindole, and other alternatives to clozapine and risperidone in bipolar mood disorders, preliminary experience with olanzapine may also warrant caution.

BENZODIAZEPINES

Benzodiazepines, especially lorazepam and clonazepam, are being used with increasing frequency to control agitation in acutely manic patients. The anticonvulsant effect of benzodiazepines may play a role in any apparent antimanic action, as could the capacity of clonazepam to enhance central serotonin synthesis.[171,172] However, sedating and hypnotic actions could be equally relevant[173] since enhancing sleep can improve mania.[174]

Lorazepam has been used as an adjunct to lithium in the treatment of acute mania in case reports and series but not in any controlled studies. Individual doses have usually been 1–4 mg, with initial total daily doses of 4–30 mg/day, sometimes as high as 60–80 mg/day[175–177] and a total duration of treatment of 2 weeks to 6 months. Improvement of psychosis, pressured speech, elevated mood, grandiosity, logorrhea, agitation, and/or lack of cooperation has been reported. In a retrospective compari-

Table 3. Some Reports of Antimanic or Mood-Stabilizing Actions of Atypical Antipsychotics*

Study	Method	N	Drugs	Diagnosis	Results
Privitera et al[160]	Case report	1	Clozapine 125 mg + 5 mg dextroamphetamine	Mixed psychotic bipolar	Mixed psychotic bipolar state in a 44-year-old woman refractory to other treatments resolved with this combination
Klapheke[168]	Case report	1	Clozapine 700–800 mg	Schizoaffective, bipolar subtype	Higher clozapine dose produced remission when ECT and lower clozapine doses were only partially effective in a 26-year-old schizoaffective bipolar woman
Calabrese et al[155]	Case report	2	Clozapine	Rapid cycling	Marked improvement after failure of other treatments
Suppes et al[156]	Case report	3	Clozapine 150–400 mg with or without lithium	Rapid cycling, not psychotic	Remission in 2 patients, moderate improvement in 1. Patients had been resistant to standard treatments and remained well for 12–20 months of follow-up
Frye et al[167]	Case report	4	Clozapine 350–400 mg	Rapid cycling, 3 psychotic	3 patients had substantial reduction in cycle frequency; 1 had decreased severity but not frequency of affective recurrences. All patients had been refractory to mood stabilizers and neuroleptics
Suppes et al[154]	Case report	7	Clozapine	Dysphoric mania	Significant improvement of all symptoms in all patients; 6 required no further hospitalization
McElroy et al[153]	Chart review	14	Clozapine + lithium or valproate	Psychotic bipolar	12 of 14 had moderate to marked reduction of psychotic and affective symptoms. Improvement persisted over 3–5 years of follow-up
Calabrese et al[161]	Open trial	22	Clozapine up to 494 mg	Bipolar depression; schizoaffective bipolar	Nonblinded assessments with BPRS and YMRS showed 43%–59% improvement with clozapine monotherapy in patients who were unresponsive to or intolerant of lithium, valproate, or carbamazepine. Improvement in bipolar > schizoaffective bipolar; nonrapid cyclers > rapid cyclers
Banov et al[157]	Retrospective assessment by interview	183	Clozapine	Mania (N = 26); schizoaffective, bipolar subtype; schizophrenia; bipolar depression; unipolar depression	Clozapine better at preventing recurrences of mania in bipolar and schizoaffective bipolar patients than preventing recurrences of depression for a mean of 18.7 months
Zarate et al[152]	Retrospective assessment by interview	17	Clozapine 182–304 mg	Bipolar depression; schizoaffective, bipolar subtype	For a mean of 16.1 ± 5.6 months of treatment, 88% much or very much improved on CGI. 12 patients did not require any other medication; 11 patients had no further hospitalization
Zarate et al[152]	Literature review	94	Clozapine	Bipolar depression	70% had significant improvement during 49 days–4 years of follow-up
Singh and Catalan[158]	Case report	4	Risperidone 1–2 mg	Secondary mania in AIDS patients	Patients improved but followed for only 7–10 days
Tohen et al[150, 162]	Open trial	15	Risperidone 6 mg	Psychotic mania	7 patients dropped out. 7 of the remaining 8 improved 50%–75% during 6 weeks

(Continued)

Table 3. Some Reports of Antimanic or Mood-Stabilizing Actions of Atypical Antipsychotics* (Cont'd.)

Study	Method	N	Drugs	Diagnosis	Results
Madhusoodanan et al[163]	Case report	5	Risperidone	Bipolar depression; schizoaffective	1 bipolar and 2 schizoaffective elderly patients had "marked" improvement. No rating scales. Doses and duration of follow-up not reported
Schaffer and Schaffer[165]	Case report	10	Risperidone 0.5–1 mg	Mania, hypomania	3 patients had immediate increase in mania. 5 patients had initial "therapeutic effect" (details not stated), but 3 had aggravation of mania with increased risperidone dose
Dwight et al[159]	Case report	8	Risperidone 6–8 mg	Schizoaffective, bipolar subtype	Reduced depression in 2 patients; induction or aggravation of mania in 6. Possibility of natural progression of illness could not be excluded
Koek and Kessler[166]	Case report	1	Risperidone 2 mg	Posttraumatic stress disorder; psychotic depression	Mania developed on risperidone and did not recur spontaneously or on doxepin
Sajatovic et al[151,164]	Open trial	6	Risperidone 2–8 mg	Psychotic mania	Rapid exacerbation of mania and psychosis in 1 patient and oversedation in 2 patients on 2 mg/d. Increased mania and psychosis in 1 patient and no benefit in 1 patient on 6–8 mg/d. Only 1 patient improved
Small et al[27]	Random assignment	11	Lithium + risperidone 6 mg	Mania	Single-blind assessment found lithium + typical neuroleptic other than haloperidol superior to lithium + risperidone, which was slightly superior to lithium + haloperidol over 8 weeks of assessment. Detail not provided

*Abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions scale; YMRS = Young Mania Rating Scale.

son of charts of 30 acutely manic patients treated with lithium and neuroleptics with charts of another 30 manic patients treated with lithium, neuroleptics, and 1.6 ± 3.64 mg/day of lorazepam equivalent,[178] patients receiving benzodiazepine supplementation required mean daily neuroleptic doses of 310 ± 250 mg/day of chlorpromazine equivalent, compared with 590 ± 550 mg of chlorpromazine equivalent for patients not taking benzodiazepines. There was a lower frequency of seclusion and restraint in the group receiving benzodiazepine supplementation, but no difference between the two groups in frequency of extrapyramidal side effects.[178]

A total of 72 published cases have reported a reduction of psychosis, pressured speech, hyperactivity, anxiety, agitation, violence, intrusiveness, and hypersexuality has been found with clonazepam in doses ranging from 0.5–2.5 mg/day to as high as 4–16 mg/day alone or with neuroleptics and/or lithium.[172,179–182] Some lithium-treated patients who were refractory to or intolerant of neuroleptics were improved but not well when clonazepam was used instead of the neuroleptic.[183]

In a double-blind crossover comparison of lithium with clonazepam (mean dose = 10.4 mg/day) in 11 acutely manic patients receiving each drug in random order for 10 days along with haloperidol supplementation as needed, clonazepam was found to be superior to lithium in reducing motor hyperactivity; significantly less haloperidol was needed with clonazepam than with lithium.[171] This does not necessarily indicate an antimanic so much as a sedative effect, and continuation of lithium for a longer period of time might well have produced superior overall results than continuation of clonazepam. Bradwejn et al.[177] found that a mean dose of 11.3 mg/day of clonazepam for 14 days had no effect on any measure of mania or illness severity in manic patients, whereas lorazepam was effective in the same subjects. Another situation in which clonazepam did not substitute for neuroleptics occurred when five bipolar patients taking lithium

who in the past had required addition of a neuroleptic to prevent relapses and who were euthymic at baseline had a recurrence of an affective episode (mania or depression) within 2–15 weeks of starting clonazepam alone (1 patient) or a lithium-clonazepam combination (four patients) at mean clonazepam doses of 3.2 mg/day; increasing the dose of clonazepam was without benefit.[179]

Clinical Implications

In the treatment of acute mania, addition of benzodiazepines appears to provide more rapid control of agitation than neuroleptics alone[171,184,185] as well as reduction of neuroleptic requirement, but not always with fewer extrapyramidal side effects.[178] The effectiveness of benzodiazepines as adjuncts in maintenance therapy with any goal other than to normalize sleep or reduce anxiety or agitation has not been demonstrated. Benzodiazepines can have neurotoxic interactions with lithium.[179–182] Tolerance may develop to the psychotropic effects of clonazepam,[186] as can occur to its antiepileptic effect.[180]

THYROID HORMONE

Thyroid hormones play an important role in the regulation of biological cycles,[187] as well as neurotransmitter[187,188] and receptor function.[187,189,190] Thyroid dysfunction can induce abnormal fluctuations of monoaminergic systems involved in mood regulation,[187,188] which may occur at normal circulating thyroid hormone levels if central nervous system delivery or processing of thyroid hormones is reduced, levels of thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone (TRH) are altered,[191] or cycling of the thyroid axis is disrupted.[192]

Hypothyroidism of varying degrees has been implicated in treatment-resistant and rapidly cycling bipolar illness. As many as 60% to 90% of bipolar patients with rapid cycling have been found to have hypothyroidism, which often is subclinical and too mild to produce medical morbidity but perhaps not to contribute to mood instability.[187,193] Correcting subclinical forms of hypothyroidism could help to stabilize mood in these patients.[194]

The first reported use of thyroid hormone to treat bipolar disorder was by Gjessing,[195] who used doses of desiccated thyroid high enough to cause tachycardia to treat patients with "periodic catatonia" who would meet modern criteria for rapidly cycling bipolar illness.[187] The mood of one of these patients was known to have remained stable for 16 years before the beneficial effect of thyroid "wore off."[189] It is impossible to know whether patients in such early reports might have initially been hypothyroid by modern criteria. In case reports of patients treated openly, L-thyroxine (T_4) in doses of 0.025–0.5 mg/day added to lithium or taken alone appeared to reduce or totally eliminate rapid affective recurrences in patients with bipolar mood disorders.[188–190,192] Most of these patients had laboratory evidence of hypothyroidism (usually in the form of an elevated TSH level), while in some cases thyroid testing, including a TRH stimulation test, revealed normal levels.[190] In one case,[188] the effect of adding thyroxin could not be distinguished from discontinuing an antidepressant at the same time. A series of 53 bipolar patients treated openly in a naturalistic setting demonstrated superior prophylaxis of affective recurrences when lithium was combined with 0.075 mg/day of thyroxine than with lithium alone,[196] but because thyroid function tests were not obtained, it remains unclear whether thyroxine had a primary therapeutic effect or whether it was correcting peripheral hypothyroidism.

Bauer et al.[193] prospectively studied 11 patients with rapidly cycling bipolar I and bipolar II illnesses who were taking lithium (6 patients), lithium and carbamazepine (2 patients), antidepressants alone (2 patients), a benzodiazepine alone (1 patient), as needed neuroleptics combined with other medications (4 patients), and thyroxine with other medications (3 patients). At the beginning of the study, only 3 patients had normal thyroid function, including normal TRH stimulation test results. In all patients, open addition of 0.15–0.4 mg/day of thyroxine (or increase of the existing thyroxine dose for patients already taking thyroxine) resulted in increases in serum T_4 and decreases in TSH concentrations into the hyperthyroid range. Of the 11 patients, 10 demonstrated significant decreases in depression and mania ratings and increases in ratings of quality of life for 78 to 370 days of follow up. Three of 4 patients in the sample for whom placebo was then substituted in a single-blind protocol for thyroxine experienced a return of cycling. While provocative, this study is complicated by the open method in most patients, a single-blind discontinuation protocol in only 4 patients, a diverse group of patients likely to have had highly variable courses, and different lengths of thyroxine trials in different patients. To the extent that these high doses of thyroxine did in fact enhance the therapeutic effect of the thymoleptics, it is not clear whether this involved a primary action of the hormone or correction of peripheral or central hypothyroidism.

Clinical Implications

Although correction of hypothyroidism is an important component of the treatment of bipolar mood disorders,

contemporary experience does not suggest that thyroxine by itself has antimanic or mood-stabilizing properties in euthyroid patients. However, there may be a group of rapidly cycling bipolar patients resistant to traditional therapies for whom adjunctive thyroxine increases responsiveness to other treatments.[193] Dosage should be changed gradually since it takes 4 weeks for the thyroid axis to equilibrate after each adjustment.[193] It may be necessary to produce elevated thyroid function in euthyroid patients treated with this maneuver.[189,191] High-dose thyroid supplementation is a risky intervention that should not be undertaken lightly. Exogenous thyroid hormone, especially in suprametabolic doses, can produce substantial medical morbidity, including tremor, anxiety, agitation, tachycardia, congestive heart failure, osteoporosis, and atrial fibrillation.[197]

PSYCHOSURGERY

Psychosurgery is often considered an outmoded and dangerous treatment.[198] However, stereotactic subcaudate tractotomy (SST), which involves precise localization of a lesion beneath the caudate nucleus, has been found on unstructured follow-up to benefit 50% to 60% of the small number of patients with refractory bipolar disorder who have undergone this procedure.[199] Since there are no controlled studies of SST, it is impossible to rule out a placebo response; however, patients who have not responded to multiple interventions over many years seem unlikely to have had any sustained benefit from placebo. Spontaneous improvement or remission after years of active illness also is an unlikely explanation of any observed benefit as affective recurrences tend to increase with time in bipolar illness. The actual mechanism of action of this kind of neurosurgery is obscure but could involve reestablishment of interhemispheric balance similar to that proposed for ECT.[12]

Two cohorts of 9 patients each have been followed more carefully after SST. In the first, 9 women aged 51 to 60 years with Research Diagnostic Criteria bipolar I illness (7 with continuous cycling) of 19.4 ± 8.8 years' duration that had been unresponsive to multiple treatments including ECT were interviewed at least 2 years after SST.[200] In addition, medical records were reviewed and the patients' physicians were interviewed. At the time of evaluation, 3 patients were symptom-free and required no treatment, 1 had mild residual symptoms, 4 were improved but still symptomatic, and 1 was unchanged; hypomania appeared to be under better control than depression. Positive results were tempered by the finding that 1 patient who was asymptomatic 2 years postoperatively committed suicide unexpectedly 6 months after the assessment. "Mild or moderate cognitive impairment" that was not assessed with neuropsychological testing was noted in 3 patients.

The second cohort of 9 bipolar patients (7 women and 2 men aged 38 to 70 years) also had demonstrated unresponsive rapid cycling or continually abnormal mood.[201] Follow-up of an unspecified nature 2 to 13 years after SST indicated that affective episodes continued but were less severe and more responsive to medication that had been ineffective prior to surgery. As was true of the first sample, SST was more effective in ameliorating hypomania than depression. While there were no major surgical complications, a patient with preexisting neurologic disease developed schizophreniform symptoms after surgery, and over time the beneficial effects of surgery diminished in some patients.

Clinical Implications

Obviously, controlled studies of psychosurgery will never be performed. The small number of patients followed without structured rating scales or blind assessments precludes any conclusion about this drastic treatment. A major confounding factor would be postoperative administration of anticonvulsants, which could account for any therapeutic effect. However, awareness that this operation is still being performed may be a source of interest to clinicians and comfort to patients with life-threatening bipolar illness that remains completely refractory to every other treatment.

NEW ANTICONVULSANTS

The rationale for the use of carbamazepine and valproate as antibipolar agents has been extensively discussed.[48,197] Although no formal studies have been completed, two new anticonvulsants, lamotrigine and gabapentin, have been used recently in clinical settings to treat refractory bipolar illness, and informal reports of positive results in refractory bipolar illness have emerged in electronic psychopharmacology discussion groups such as the psychopharmacology list (Psycho-Pharm@Psycom.Net) owned by Dr. Ivan Goldberg and sponsored by InterPsych, an international coalition of internet groups specializing in mental health. Unlike carbamazepine and valproate, lamotrigine and gabapentin have been approved only as adjuncts in the treatment of refractory epilepsy,[202–204] particularly partial seizures,[203] and have not yet been shown to be effective as monotherapies.[202] Con-

trolled studies of lamotrigine or gabapentin monotherapy in refractory bipolar illness are probably a long way off since most of these patients take multiple medications.

A positive effect of lamotrigine on mood is suggested by reports that it improves global impressions of well-being in epileptic patients more than it improves seizure control, and that patients in continuation studies elect to keep taking this medication more frequently than would be expected on the basis of improved seizure control alone.[203–205] In animal studies, lamotrigine does not prevent kindling, but it does increase the stimulus intensity necessary to produce kindling.[203] Gabapentin binds to a calcium channel[206] and could have calcium antagonist properties.

The only published case report of the use of new anticonvulsants in bipolar mood disorder has been a letter to the editor by Calabrese and colleagues[207] describing a 49-year-old man with an unstated disability and a bipolar I mood disorder with continuous cycling who did not respond to lithium and could not tolerate carbamazepine. The patient became euthymic and GAS scores increased from 32 to 69 over 11 months of follow-up with open monotherapy with 200 mg/day of lamotrigine. The patient had been taking fluoxetine for 4 years, and whether the antidepressant was discontinued prior to starting lamotrigine, which could have accounted for the improvement, was not stated.

The elimination half-life of lamotrigine averages 30 hours.[208] Doses of lamotrigine as high as 500–700 mg/day have been well tolerated by epileptic patients also taking enzyme-inducing drugs like carbamazepine.[209] Gabapentin, on the other hand, has an elimination half-life of about 5 to 9 hours, necessitating divided dosing[204,210]; doses up to 1800–3600 mg/day in conjunction with other anticonvulsants have been well tolerated in formal studies[204] with doses of 1200–1800 mg/day appearing to be most frequently effective in the long-term treatment of refractory epilepsy.[204] Optimal doses for bipolar mood disorders remain to be investigated.

Neither lamotrigine nor gabapentin induces P450 enzymes,[208,210] and therefore neither medication has significant pharmacokinetic effects on concentrations of commonly used psychiatric medications[202,204,210] or with oral contraceptives.[202,210] However, medications like carbamazepine, which induce glucuronide conjugation, reduce lamotrigine and gabapentin levels,[208] while valproate impairs elimination of lamotrigine and gabapentin and increases serum levels.[203,208] Lamotrigine may have a pharmacodynamic interaction with carbamazepine leading to neurotoxicity.[203]

The most frequent adverse effects of lamotrigine and gabapentin have been dizziness, headache, diplopia, ataxia, nausea, amblyopia, somnolence, fatigue, ataxia, rash, weight gain, and vomiting.[203,204,209–211] Both lamotrigine and gabapentin were associated with similar rates of sudden unexplained deaths in some epileptic patients during premarketing trials.[203] However, these rates were similar to the expected rate of sudden unexplained death in epilepsy and were not felt to be attributable to the medications.[203] Fatal toxic epidermal necrolysis associated with lamotrigine was reported in one patient.[212] Oculogyric crises occurred in two patients taking gabapentin.[213] Gabapentin was thought to induce mania in one bipolar patient[214] and was associated with aggressive behavior, hyperactivity, and tantrums in a number of children, most of whom had attention-deficit/hyperactivity disorder.[215,216]

Clinical Implications

Lamotrigine and gabapentin seem to be well tolerated and have a lower risk than carbamazepine and valproate of interactions with other medications likely to be taken by bipolar patients. However, even though preliminary anecdotal experience has been positive, controlled trials will be necessary to clarify the efficacy and safety of these medications in the treatment of bipolar mood disorder. The enthusiasm with which these medications have been utilized by clinicians on the basis of word of mouth to treat refractory bipolar illness should be tempered by awareness of the limitations of available data supporting their use for psychiatric disorders.

If lamotrigine and gabapentin do prove to be effective thymoleptics in formal studies, certain features could turn out to be useful in special circumstances. For example, dose-limited absorption of gabapentin reduces the risk of overdose,[204] possibly making this medication relatively safe for suicidal patients. Because lamotrigine inhibits ischemia-induced release of the excitotoxin glutamate,[203,217] it reduces neuronal damage and was associated with improved recovery after cerebral ischemia in animals.[218] If the same applies to people, this medication might be considered for mania associated in patients with recent strokes. Gabapentin may augment the analgesic action of opiates or possess analgesic effects of its own,[210,219] warranting consideration for patients with chronic pain.

CONCLUSIONS

Clinicians increasingly are confronted with patients who have treatment-resistant and complicated bipolar mood disorders.[7] Of the diverse group of novel somatic

therapies that have been tried for these patients, electroconvulsive therapy is the best established. Calcium channel blocking agents appear promising, especially for patients who respond to lithium but cannot tolerate it; however, larger carefully controlled studies are necessary to define the uses and limitations of these medications. Clozapine may turn out to be the most effective of the antipsychotic drugs for patients with intractable manic recurrences, even if the recurrences are not associated with psychotic symptoms, while more caution may be warranted with administering risperidone and olanzapine chronically to bipolar patients. Benzodiazepines have become standard supplemental therapy for mania, but there is no real evidence that their action extends beyond improving sleep.[220,221] Thyroid supplementation is important for hypothyroid patients, but adding suprametabolic doses to antimanic drugs in euthyroid patients carries the risk of significant medical morbidity. The new anticonvulsants seem promising, but much must be learned about potential uses and limitations of these medications in bipolar patients. Psychosurgery, an extreme intervention without substantial experimental evidence to support it, would be considered only for patients whose lives were in danger and for whom all other approaches had proved completely ineffective.

The fact that these and other novel therapies are being used in everyday practice to an extent beyond that supported by controlled studies attests to the clear need for more satisfactory alternative treatments for bipolar illness. Most of the novel therapies that have been reviewed, like the standard treatments, appear to be more effective at preventing manic than depressive recurrences. A priority should be to study novel therapies more thoroughly and to develop new treatments that are equally effective for both poles of bipolar illness.

Drug names: amitriptyline (Elavil and others), amphotericin B (Fungizone), atenolol (Tenormin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonazepam (Klonopin), clonidine (Catapres), clozapine (Clozaril), cyclosporine (Sandimmune), dextroamphetamine (Dexedrine and others), digoxin (Lanoxin), diltiazem (Cardizem), doxepin (Sinequan and others), fluphenazine (Prolixin and others), gabapentin (Neurontin), gentamicin (Garamycin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), levothyroxin (Levothroid, Synthroid), lorazepam (Ativan and others), metoprolol (Lopressor), nadolol (Corgrad), nifedipine (Adalat, Procardia), nimodipine (Nimotop), pimozide (Orap), propranolol (Inderal and others), risperidone (Risperdal), sertindole (Serlect), tamoxifen (Nolvadex), temazepam (Restoril and others), thioridazine (Mellaril and others), thiothixene (Navane), verapamil (Calan and others).

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1. Studies of calcium channel blockers in patients with mood disorders have demonstrated
   a. Antimanic efficacy
   b. Mood stabilization
   c. Aggravation of depression
   d. All of the above
   e. None of the above

2. Premarketing trials suggested that lamotrigine improved
   a. Quality of life
   b. Mood cycling
   c. Mania
   d. Psychosis
   e. Anxiety

3. "Tardive psychosis" refers to
   a. Late onset psychosis
   b. Psychosis plus tardive dyskinesia
   c. Psychosis in manic patients
   d. Psychosis appearing with neuroleptic withdrawal
   e. Intermittent psychosis

4. Compared with lithium, the response of mania to ECT is
   a. Less frequent
   b. Faster
   c. Equivalent
   d. More variable
   e. More poorly tolerated

5. Calcium channel blockers are useful for all of the following conditions *except*
   a. Achalasia
   b. Hypertension
   c. Tardive dyskinesia
   d. Schizophrenia
   e. Mania

CME

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