Bipolar Disorder Therapeutics: Maintenance Treatment

Gary S. Sachs and Michael E. Thase

Although most of the care received by bipolar patients occurs during the maintenance phase, relatively little empirical data is available to guide long-term treatment decisions. We review literature pertaining to key questions related to use of pharmacotherapy in the maintenance phase of bipolar disorder. The few double-blind trials with a reasonable sample size are restricted to bipolar I patients and address a modest range of questions mostly related to use of lithium. One rigorous multicenter trial found valproate to have prophylactic benefit. Other studies with valproate alone and in combination suggest efficacy equivalent to lithium and perhaps greater than carbamazepine. Data available for combination treatment are sparse but moderately encouraging.

Maintenance treatment with standard antidepressant medications appears destabilizing for some bipolar patients, particularly following a mixed episode. Although some bipolar patients may benefit from combined treatment with a mood stabilizer and a standard antidepressant medication, current knowledge does not allow confident selection of the bipolar patients who might benefit. Clozapine and perhaps other atypical antipsychotics are promising options for maintenance treatment but have not been evaluated in double-blind trials. The numerous other agents used in maintenance treatment are primarily adjuncts to lithium, valproate, or carbamazepine, and information about them is largely anecdotal and uncontrolled.

Study design for maintenance trials remains an imperfect art. Conclusions must be drawn cautiously, given the limited generalizability of study designs that accession samples enriched with presumed treatment responders, randomize patients after brief periods of partial remission, abruptly taper prior treatment, make no attempt to distinguish relapse from recurrence, use no formal outcome assessments, or report hospitalization as the only outcome criterion.

Key Words: Bipolar disorder, maintenance, relapse prevention, prophylaxis, continuation, combination treatment

Introduction

Maintenance phase treatment comprises the majority of care received by nearly all bipolar patients. Unfortunately, practitioners seeking evidence on which to base treatment decisions will find research on maintenance phase treatment is both sparse and difficult to interpret. Expert opinion remains the only basis for answering many fundamental questions. We review the available literature pertaining to key questions related to use of medications for maintenance phase treatment of patients with bipolar illness.

What Is Maintenance Phase Treatment?

Given the variable course of bipolar illness, the discussion of maintenance treatment starts by necessity with definition. Maintenance phase treatment is often defined as spanning the time from when the patient has recovered from an acute episode to the time of onset of a new acute episode. Once a patient has recovered, the primary focus of treatment shifts from resolution of acute phase symptoms to prophylaxis. Conceptually this shift in therapeutic focus corresponds to reaching the physiologic end point in the course of the acute episode, when the pathophysiology underlying the acute symptomatology has been corrected. Whether a true recovery is reached because the episode has run its natural course or because of treatment, the high rates of relapse observed following early discontinuation of treatment strongly support viewing the recovered state as distinct from the physiologic state at the point of initial clinical remission. In the absence of objective markers informing us that the pathology has been corrected, the maintenance phase is defined operationally. Following a tradition borrowed from unipolar depression research (Frank et al 1991), the maintenance phase follows a period of sustained remission during which acute phase treatment is continued for a period of time. Such continuation phase treatment increases the likelihood that treatment will be sustained throughout the course of the acute episode and lessens the likelihood that subsequent discontinuation will be closely followed by relapse.
This crucial phase of treatment remains under studied. What little empirical data exists comes mostly from studies of unipolar depression. That literature suggests that the continuation phase, the period of time between the onset of substantial clinical remission of acute depression or mania and the beginning of the maintenance phase, should not be less than 8 weeks (Prien and Kupfer 1986) and those with residual symptoms are at high risk for relapse (Mindham et al 1973). Prien and Kupfer (1986) found that patients who were symptom free (defined as Global Assessment Scale [GAS] score ≥ 71) for at least 16 weeks had a significantly lower relapse rate (18%) than those who were free of symptoms for less than 16 weeks (59%). In fact, patients who were well for 16 weeks or more did no better with active treatment (imipramine and lithium) than with placebo. Hlastala et al (1997) reported data indicating the conditional probability of remaining well (defined as average Hamilton Depression Scale score ≤ 7 and Bech–Rafaelsen scores ≤ 7) over 8 consecutive weeks for bipolar patients in their first week of remission following an acute episode was zero. The median times to reach recovery criteria (8 consecutive weeks in remission) following manic, depressive, and mixed episodes were 20 weeks, 40 weeks, and 50 weeks, respectively.

Accepting that the median duration of the acute episode is 12–42 weeks, we must recognize the limitations of studies that randomize patients after periods of remission as brief as 1 week. Withdrawal of medication during the early months of recovery appears analogous to early removal of sutures following physical trauma. This point should be kept in mind when reviewing the literature. Some otherwise rigorous published studies claim to report results of maintenance treatment, but can only be observing relapse because subjects are randomized to discontinue acute phase treatment after very brief periods of relative euthymia.

Who Should Have Maintenance Treatment?

This question generates considerable debate. Many experts recommend offering maintenance treatment to all patients who have suffered even a single acute manic episode, whereas others feel it is appropriate to reserve long-term maintenance treatment for patients who have experienced two or more manic episodes. Experts with the former opinion point out the 95% lifetime risk of recurrence and studies showing loss of acute and prophylactic benefit (at least of lithium) among patients with as few as three episodes (Gelenberg et al 1989; Swann et al 1999). Experts who hold the latter opinion point out that the median duration of remission following the first acute episode is more than 4 years (Angst 1981; Kreapelin 1921; Roy-Byrne et al 1985; Zis et al 1980) and the paucity of evidence justifying chronic treatment for bipolar patients beyond 32 weeks (Coryell et al 1987).

Another aspect of selecting patients for maintenance treatment relates to the likelihood that patients will discontinue treatment regardless of the psychiatrist’s recommendations. Patients who discontinue lithium treatment, particularly when discontinuation is abrupt, appear to be at increased risk for recurrence. Guy Goodwin and colleagues have attempted to quantify the risks and benefits of lithium maintenance and recommend against offering maintenance treatment to patients judged unlikely or unwilling to adhere to treatment for at least 2 years (Goodwin 1994). It is unclear when in the course of treatment the liability to such discontinuation phenomena develops or if similar phenomena apply to other maintenance treatments. In a large prospective study, Bowden et al (2000) found no evidence of discontinuation phenomena following discontinuation of acute treatment with lithium or divalproex.

Although current literature does not resolve the issue of who should have treatment, from a practical point of view the areas of agreement extend so broadly as to largely render the question itself a matter of little clinical significance. First, by the time most patients receive a bipolar diagnosis they have already suffered multiple episodes. There is general agreement that patients with three or more episodes warrant long-term maintenance therapy. Second, since many clinical experts recommend continuation of effective acute phase treatments for a period of 1 year beyond the onset of clinical remission, a substantial portion of bipolar patients will relapse within the period of prudent continuation of treatment. Third, a surprisingly large proportion of patients simply never achieve the period of sustained euthymia considered a sufficient prerequisite to consideration of treatment discontinuation (Hlastala et al 1997; Maj et al 1998; Peselow et al 1994; Prien et al 1984). Thus two distinct subgroups exist among the population of patients receiving long-term care: those who have achieved a stable remission and those who have not. Fourth, serious consideration of when to recommend long-term treatment becomes pointless in the absence of measures to improve treatment adherence. Johnson and McFarland (1996) have demonstrated that among patients prescribed lithium half discontinued treatment in less than 3 months. Until the improved adherence techniques used in manualized psychosocial interventions (Cochran 1984) become integrated into routine practice, discussion of long-term treatment may be best postponed in favor of attention to sustaining the therapeutic effort through the first 3 months of remission.
Which Treatments Are Effective in the Maintenance Phase?

The answer differs depending on which evidence is considered. Double-blind controlled trials appear to provide consistent strong evidence of prophylactic efficacy for lithium. Coryell’s analysis of this data suggests the benefit of prophylaxis might be confined to the first 32 weeks following recovery from an acute episode (Coryell et al 1997). The 58 respondents participating in an expert consensus guideline development survey (Sachs et al 2000); however, unanimously recommend continuing maintenance treatment with lithium, valproate, and/or carbamazepine when such treatment appears effective during the acute phase. Less data are available for valproate and carbamazepine. Data from naturalistic follow-up raises concerns about treatment effectiveness (Coryell et al 1997; Harrow et al 1990; Maj et al 1998; O’Connell et al 1991; Peselow et al 1994; Sachs et al 1994; Tohen et al 1990).

Randomized Controlled Trials

Early lithium prophylaxis studies generally show a strong benefit for lithium maintenance. Overall, the 10 available reports of placebo-controlled trials (for a review, see Goodwin and Jamison 1990) involved 514 patients and reveal recurrence rates of 81% for placebo-treated patients and 34% for lithium-treated patients. Unfortunately, serious shortcomings limit the generalizability of this literature. First, most of the studies were published before 1975 (Baasstrup et al 1970; Coppen et al 1991; Cundall et al 1972; Melia 1970; Stallone et al 1973), and few used formal assessment instruments (Bowden et al 2000; Prien et al 1984). Second, with one exception (Bowden et al 2000), all use an “enriched design,” which limits participation to subjects with known positive response. Third, all studies in which subjects were randomized after apparently successful long-term response to lithium and the control condition begins with abrupt lithium discontinuation are likely to overestimate the protective effect of lithium due to the effect of lithium discontinuation (Suppes et al 1993). Fourth, response rates for the prophylactic portion of the trial are reported as a percentage of patients who achieve remission criteria rather than as a percentage of patients entering the initial acute treatment phase.

Although eight maintenance study reports are available showing an overall response rate of 72% in bipolar and schizoaffective patients treated with carbamazepine (Baller and Post 1978; Coxhead et al 1992; Greil and Kleindienst 1999; Greil et al 1997, 1998; Luszmar et al 1988; Okuma et al 1981; Placidi et al 1986; Small et al 1995; Watkins et al 1987), results for carbamazepine are not impressive. Three studies (Coxhead et al 1992; Okuma et al 1981; Watkins et al 1987) found the outcome of maintenance treatment with carbamazepine no different than the outcome of lithium maintenance. Greil found better results with lithium maintenance than with carbamazepine maintenance (Greil and Kleindienst 1999; Greil et al 1997, 1998). In the only placebo-controlled study, however, Okuma et al (1981) reported that the benefit of carbamazepine over a placebo did not reach statistical significance. Several reports suggest the apparent benefit of carbamazepine may fade after years of apparent success. These suggestions are hardly unique to carbamazepine but do not suggest robust long-term benefit either.

The most valuable data come from the few studies with samples larger than 80 subjects. Interpretation of these studies requires detailed consideration of each study design (Table 1). The National Institute of Mental Health (NIMH) Collaborative Study (Prien et al 1984, 1988) compared long-term outcome of treatment with lithium, imipramine, or combined lithium and imipramine for patients with bipolar disorder (n = 117) and unipolar disorder (n = 150). Bipolar patients (n = 216) included in this trial entered an open preliminary treatment phase in which depression, manic, and mixed episodes were treated with lithium and imipramine along with any other treatments deemed appropriate. Subjects were randomized to double-blind maintenance treatment with lithium, imipramine, or continued combination treatment, if they were able to meet three conditions: 1) patients were able to discontinue other acute treatments and remain on stable maintenance doses of both lithium (with serum levels of ≥0.6 mmol/L) and imipramine (≥75 mg/day) for 2 consecutive months, 2) their GAS rating was above 60, and 3) neither the depression nor the mania score on the Raskin Severity of Depression and Mania Scale exceeded 7. Those randomized were not necessarily well. In fact, 15% of the randomized sample (n = 18 of 117) never met recovery criteria (remain well 8 consecutive weeks).

Treatment success (completed at least 1 year without a recurrence) was significantly more common in the lithium-alone (33%) and lithium plus imipramine (33%) groups than the imipramine-alone group (8%). The rate of depression was nearly the same across the three groups; however, in the imipramine-alone group 53% experienced a manic or mixed recurrence, compared with 26% and 28% for the patients receiving lithium and lithium plus imipramine, respectively. Patients who entered the study in a mixed or manic episode enjoyed significantly higher success rates in the lithium (53%) and the combination (47%) groups, compared with the imipramine-alone group (8%). A similar but less robust trend is observed for patients entering the study depressed, with success rates favoring lithium (22%) and the combination (18%) over imipramine (9%) but not reaching statistical significance.

Rapid cycling patients and those with mixed episodes...
had extremely poor outcomes. Among rapid cycling patients \( (n = 9) \) only three were randomized and none met criteria for treatment success. All 12 patients treated with imipramine alone following a mixed episode (Prien et al 1988) suffered recurrences, and almost all were mania (75%) or mixed episodes (17%). The recurrence rate for patients with mixed episodes who received lithium or the combination was significantly lower (38% and 41%, respectively). Combination treatment offered no advantage over lithium monotherapy.

Results for prophylaxis in the unipolar sample include a placebo control group and are relevant for the observation of mania or mixed episodes in 6% of placebo-treated patients as well as 8% in the imipramine and 5% in the combination group but none of the lithium-treated patients. Severity of the index episode was not a significant influence on outcome in the bipolar sample. Among unipolars, however, all three active treatments appear to have prophylactic benefit for patients following a moderate index episode, but among unipolar subjects with severe index episodes a clear disadvantage for lithium alone is evident.

These studies found no disadvantage due to the addition of a standard antidepressant to the lithium maintenance regimen. Quitkin et al (1978, 1981), however, found that bipolar patients maintained on lithium alone experience superior overall outcome, compared with those receiving lithium and imipramine. The discrepancy may be an artifact of the NIMH Collaborative Study design and the frequency with which patients received low doses of imipramine. The Collaborative Study simply did not randomize those patients with poor response to combination treatment during the stabilization phase.

It is worth noting that the statistical methodology used in the above studies involved comparing the proportion of patients suffering a recurrence. A reanalysis (Shapiro et al 1989) of the NIMH Collaborative Study data using the Kaplan–Meier product-limit method of survival analysis found similar overall results and results for subjects with index manic episodes (Shapiro et al 1989). For subjects with index depressive episodes, however, median remission duration was significantly longer for combination treatment (7.8 months), compared with lithium (3.4 months) and imipramine (4.8 months). Maintenance studies now routinely employ survival analysis. To date, study analyses carried out using survival analysis have not detected significant differences in any subsequent parallel-group maintenance study; however, some of these same studies (Bowden et al 2000; Greil et al 1997) have detected significant differences using the simpler comparison proportions methodology.

Gelenberg and colleagues (1989) reported results from a multicenter study that randomized bipolar patients who

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GAS, Global Assessment Scale; SADS-C, Schedule for Affective Disorders and Schizophrenia (Change Version).
were well on lithium for 6 months to maintenance treatment targeting serum lithium to either a standard range (0.8–1.0 mmol/L) or a low range (0.4–0.6 mmol/L).

The two main findings from this study were a 2.6-fold higher risk of relapse among patients randomized to the low serum lithium group and the observation that the protective benefit of lithium was only evident among subjects with two or fewer episodes before study entry. Furthermore, higher serum lithium levels were associated with higher rates of adverse effects and lower rates of compliance. Among the sample randomized to the 0.8–1.0 mmol/L range, 50% were found to have lithium levels below the 0.8 on half their visits.

Reanalysis of the Gelenberg et al results (Rosenbaum et al 1992) taking into account the baseline lithium level calls the original conclusion into question. There was no difference in outcome between those patients who started with and maintained lithium treatment in the low range (n = 11) and those who started and maintained lithium in the standard range (n = 41). Patients who entered the study with lithium in the standard range and were randomized to the low range had a risk of recurrence threefold higher than that experienced by either of the other two groups. This group for whom lithium dosage was reduced by 50% at randomization accounts for nearly all relapses in the original study. This post hoc reanalysis suggests a strong influence of abrupt reduction as well as abrupt discontinuation and makes it clear that this effect needs to be taken into account in the design and interpretation of all maintenance phase research.

The only placebo-controlled parallel-group study published in the past 25 years is a large multicenter trial with rigorous methodology. Bowden et al (2000) enrolled 571 bipolar patients into the open phase of a double-blind study that required at entry an index episode of mania or hypomania within the preceding 12 weeks. Patients (both well and ill) entering the open prerandomization treatment phase received any treatment deemed appropriate by the study psychiatrist. To enter the randomized phase, subjects had to sustain remission criteria (Schedule for Affective Disorders and Schizophrenia [Change Version] subscale scores of <13 and <11 for depression and mania, respectively) for at least one visit after discontinuing all treatments except lithium or valproate within 3 months of study entry. Those subjects (n = 372) meeting remission criteria on consecutive evaluations at least 6 days apart were randomized 2:1:1 to receive valproate, lithium, or a placebo in the double-blind treatment phase. Over the course of the double-blind treatment median serum levels were 1.0 ± 0.48 mEq/L for lithium and 84.8 ± 29.9 μg/mL for valproate (mean ± SD). Overall, significantly more subjects relapsed in the placebo group (38%) than in the valproate group (24%; p = .017). Relapses on lithium (31%) were not significantly different from either group. Other results fail to meet the traditional (p < .05) levels for statistical significance; however, several trends are worth noting. Median times to 50% survival without any mood episode were 40 weeks, 24 weeks, and 28 weeks for valproate, lithium, and the placebo, respectively (p = .06). These results are striking because they contradict expert opinion (Sachs et al 2000) that lithium among patients with fewer prior episodes and fewer prior hospitalizations did not find a relationship between maintenance serum lithium level and outcome. In this study rapid cycling patients and those with psychosis had particularly poor outcomes.

Peselow et al (1994) reported results of a naturalistic study for 305 bipolar patients who received lithium prophylaxis for up to 5 years at a clinic associated with Bellevue Hospital. Perhaps the most interesting result in the article is reported in Methods. The inclusion criteria required a period of remission lasting at least 6 months while the patient received lithium monotherapy. Although about 1200 bipolar patients were treated with lithium at the clinic over a 15-year period, only about 25% met this entry criteria. Observed rates of recurrence (depression and mania) were relatively low, with 83% remaining episode free at 1 year and 37% at 5 years. Dropout rates were high and may reflect the policy of withholding adjunctive anamnestic antidepressant treatment from clearly symptomatic patients and not meeting rigorous operational criteria for recurrence. By 22 months the
sample was 50% depleted, and only 56 subjects (18%) entered the last year of the follow-up.

**Antipsychotics**

Despite widespread clinician recognition of potential risks associated with chronic neuroleptic use, bipolar patients often receive neuroleptic maintenance treatment (Sachs 1990; Sernyak et al 1994). Given the frequency of this practice, it is surprising that there are no controlled studies reporting any advantage for neuroleptic maintenance in bipolar patients. Recurrence of mania or psychotic symptoms is frequently encountered in the course of tapering neuroleptics and provides a clinical rationale for this treatment.

The only prospective studies of neuroleptic maintenance in bipolar patients suggest that this approach is seldom beneficial. A 2-year double-blind crossover study compared the neuroleptic flupentixol with a placebo as adjuncts to lithium maintenance. Patients receiving flupentixol experienced more episodes of depression than did placebo-treated patients (Sernyak et al 1994). Sachs (1990) observed no significant difference in outcome for bipolar patients continuing lithium and a neuroleptic versus those openly switched to lithium and clonazepam, but a higher incidence of depressive relapse was observed in the neuroleptic-treated patients. Among patients suffering breakthrough mania during lithium maintenance, Peselow et al (1994) found a higher frequency of depression associated with open adjunctive neuroleptic treatment (37.5%), as compared with open adjunctive treatment with benzodiazepine (14.3%) or carbamazepine (7.7%).

In a review of lifecharts, Littlejohn et al (1994) found dramatic reduction in rates of affective episodes and readmission during periods when bipolar patients \( (n = 18) \) were treated with depot neuroleptic, as compared with periods of oral neuroleptic use.

The atypical antipsychotic agents, particularly clozapine, appear to offer better results. In case reports and open series, bipolar patients refractory to neuroleptics, anticonvulsants, and lithium are reported to derive substantial improvement that persists in the maintenance phase when atypical agents are added to their treatment regimen. In an open randomized follow-up study Suppes et al (1999) found long-term benefit when clozapine was added to the regimen of refractory bipolar patients. Although in need of replication in rigorous double-blind studies, these very encouraging results justify the use of clozapine for treatment-refractory bipolar patients.

Other atypical antipsychotics are not well studied for maintenance treatment. Tohen et al (1999) reported encouraging results of open treatment with olanzapine for patients leaving an acute mania trial. Through a 1-year follow-up, average mania ratings continued to improve over several months and remained low. None of the patients developed tardive dyskinesia, one third required the addition of lithium, and another third received treatment with fluoxetine. Experience with risperidone in bipolar disorder is limited at this point, but like olanzapine, risperidone has promising open reports (Ghaemi and Sachs 1997). Guille et al (in press) found impressive sustained improvement in prospective ratings on the Clinical Global Impressions scale \((\text{mean } \Delta \text{ CGI} \geq 1.0)\) after open addition of clozapine, risperidone, or olanzapine to the treatment regimen of refractory bipolar patients. These findings require replication in controlled trials. Expert consensus opinion supports using atypical antipsychotic agents, particularly risperidone and olanzapine, as alternatives to typical neuroleptics and to clozapine in this population.

**Antidepressants**

Use of antidepressants alone as maintenance treatment for bipolar disorder appears to be hazardous (Altshuler et al 1995, 1999; Kukopulos et al 1980; Prien et al 1984; Wehr and Goodwin 1979). Open reports indicate 31–70% of bipolar patients treated openly with antidepressants will experience affective switch (Goodwin and Jamison 1990). The use of antidepressants as adjuncts to lithium, valproate, and carbamazepine is common but controversial. There are no prospective randomized comparisons other than the results noted above from the NIMH Collaborative Study. This data set demonstrates no harm from maintenance treatment with imipramine in combination with lithium but used doses of imipramine so modest that antidepressant activity was not evident either.

Altshuler et al (1999) used blind raters to review lifecharts of treatment refractory bipolar patients and found negative outcomes were common (61%) following the addition of a standard antidepressant medication to the treatment regimen. In addition to mania (35%), another 26% experienced cycle acceleration. In a separate study, Altshuler et al (1995) report more frequent recurrence and shorter time to recurrence in bipolar patients who tapered antidepressant medications, as compared with those who continued use of standard antidepressant agents. Peselow et al (1994) also reported that adding standard antidepressants increased the mean period of remission \((\Delta = 17.3 \text{ months}, p = .01)\) in lithium-treated bipolar patients who had suffered a breakthrough depressive episode. During the 35 months of follow-up, 41.9% did not meet criteria for recurrence; manic episodes were reported in 14.0% and depression in 30.2%. The absence of prospective double-blind data makes it impossible to know which patients might benefit from long-term treatment with standard...
antidepressant and which will experience a destabilization due to antidepressant medication.

**Thyroid**

There are no double-blind studies reporting the use of thyroid hormone in bipolar patients. In an open trial, high-dose levothyroxine was added to the mood-stabilizing treatment regimen of 11 rapid cycling bipolar patients (Bauer and Whybrow 1990). Ten of the 11 experienced clear-cut improvement in the depressive phase, and among the seven with mania at baseline, five responded. Interestingly, response in these patients was independent of initial thyroid status. At the time of clinical response, however, thyroxine and free thyroxine were found to be above the upper limit of normal in nearly all subjects, and loss of benefit followed when patients tapered thyroid below supranormal levels (with some patients having tapered thyroid under blind conditions). Like thyroid augmentation of antidepressant therapy, hypermetabolic thyroid treatment is carried out as an adjunct to a standard mood-stabilizing regimen.

**Other Combination Treatments**

When bipolar patients experience recurrence during monotherapy with lithium, carbamazepine, or valproate, expert consensus supports combining these agents. Many agents have been used in combination with these primary mood-stabilizing treatments, but little high quality experimental data are available as yet to support use of combination maintenance treatment (for reviews, see Freeman and Stoll 1998; Solomon et al 1998).

Solomon (1998) reported pilot data from a randomized trial suggesting benefit of combined treatment with lithium and valproate over lithium and a placebo. Denicoff and colleagues (1997) report outcomes for 24 patients who had failed to respond to 1-year trials of lithium, carbamazepine, and the combination of lithium and carbamazepine. The sample was reduced 25% by dropout due to side effects ($n = 3$) or noncompliance ($n = 3$). Of the 18 evaluable subjects, one had a marked response (5%) and five (28%) were considered moderate responders. A triple therapy trial consisting of lithium, valproate, and carbamazepine was carried out in seven subjects, and of these, three (43%) were considered responders.

These trials suggest that combination treatment offers some refractory patients incremental improvement. A few have marked response and about 40% seem to derive little or no benefit. The data do not address the merits of combination treatment for less refractory bipolar illness. For instance, when a patient experiences a breakthrough episode after 1–2 years of treatment with a therapeutic but submaximal dose of lithium, valproate, or carbamazepine, it is not known whether raising the dose or initiating combination therapy is the wisest plan for the next maintenance phase.

**Other Putative Mood Stabilizing Agents**

Numerous agents have been described as beneficial based on case reports, small controlled trials, and/or studies reporting only acute outcome. As yet the data do not warrant routine recommendation of unconventional treatments such as calcium channel blocking agents, Omega 3 fatty acids, or donepezil for maintenance treatment. The Expert Consensus Guidelines (Sachs et al 2000) suggest limiting use of such agents to cases in which well established agents fail to produce acceptable benefit.

**Summary**

In summary, the available empirical data, while admittedly scant, provide the most reliable basis for clinical practice. Withdrawal of treatment during the early stage of remission is clearly inappropriate. The ideal dose and duration of maintenance treatment are not known. Higher dosages of prophylactic medication have not been proven to be more effective for patients who relapse while maintained within the standard therapeutic range. Higher doses are associated with increased adverse effects and decreased compliance. It is conceivable but unproven that some patients will do as well managed with episodic acute and continuation therapy as they would with sustained prophylactic treatment. Since continued wellness may reflect treatment benefit or quiescent illness, it is not possible to know which patients might be managed effectively without prophylactic medication. It is relatively easy, however, to know which patients are not candidates for episodic treatment. These include patients with clinically significant residual symptoms, a history of clinical remissions lasting less than 2 years, or a history of breakthrough episodes during prophylaxis. There appears to be no doubt that patients with frequent or severe relapses should be offered prophylactic treatment.

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