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Welcome to the first edition of Psychiatric Medicine Reports*, one of the few unbiased, non-industry sponsored sources of practical clinical psychiatric information available. With each issue, we will tackle a relevant and challenging clinical issue with a comprehensive and scientific review of fair and balanced data. Readers will receive practical clinical information that will help in real-world patient care.*

This premier issue of Psychiatric Medicine Reports *addresses the long-term management of bipolar disorder. Pharmaceutical companies often aggressively promote their products in this area, yet little data are available to help clinicians make the best choice for their patients. The authors concisely review the available long-term data and the limitations in the current research, and offer specific treatment guidelines both in medication and non-pharmacological interventions.*

— The Editor

Long-Term Management of Bipolar Disorder: What Does the Research Say?

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Introduction

One of the complexities of understanding the scientific literature regarding the management of any illness is the need to understand and interpret research studies. Frequently, academics selectively cite research studies to support their own opinions, and, as is well known, a selective review of the literature can be used to support any opinion one wishes. If a specific pharmaceutical company supports a review paper, or if an academic is especially partial to a specific company, then such reviews can be even more biased.

The field of bipolar disorder has been especially susceptible to such biases. They have resulted in a tendency to ignore very effective treatments, like lithium, for no special reason, or to provide more support than a sober assessment of the data warrants for other treatments. Research on bipolar disorder also has tended to focus on the acute phases of this illness, with less data on long-term maintenance treatment. This article briefly will introduce some of the concepts related to levels of evidence and evidence-based medicine. This will be followed by a review of the literature related to efficacy of prophylaxis treatment of bipolar disorder, as well as a brief overview of side effects of specific mood-stabilizing agents, with a focus on lithium. Lastly, treatment guidelines derived from this evidence will be presented.

The Concept of Levels of Evidence

Any critical assessment of the state of treatment literature is strengthened by an initial definition of terms. The concept of levels of evidence, derived from the evidence-based medicine movement, is especially useful in this regard.[1] Levels of evidence provide clinicians and researchers with a roadmap that allows consistent and justified comparison of different studies so as to adequately compare and contrast their findings. Table 1 outlines a variation on standard definitions for levels of evidence that will help assess and summarize relevant studies.[2]

The key feature of levels of evidence to keep in mind is that each level has its own strengths and weaknesses, and as a result, no single level is completely useful or useless. All other things being equal, however, as one moves from level V to level I, increasing rigor and probable scientific accuracy occur.

One major advantage of a levels of evidence approach to an examination of data is that there is not a huge leap between double-blind, placebo-controlled studies and other, less rigorous levels. In other words, clinicians and some academics sometimes

imagine that all studies that are not level I, double-blind randomized clinical trials (RCTs) are equivalent in terms of rigor, accuracy, reliability, and information. In reality, there are many intermediate levels of evidence, each with particular strengths as well as limits. Open randomized studies and large naturalistic studies, in particular, can be extremely informative and can be as accurate as level I studies.[3] The concept of levels of evidence also can help clinicians who are loath to rely on level I controlled clinical trials, especially if those results contradict their own level V, clinical experiences. While the advantages to level V data mainly revolve around hypothesis generation, to devalue higher levels of evidence is unscientific and dangerous.

In summary, in applying evidence-based methods, it is vital to keep in mind the strengths and limits of each level, as well as the need to identify the methods of studies as pertaining to a specific level.

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Methods

Studies were identified by MEDLINE (1966-current) searches using the following keywords: bipolar disorder, treatment, pharmacology, mood stabilizers, neuroleptics, antidepressants, mania, bipolar depression, and prevention. Keywords for each agent combined with bipolar disorder also were used. Articles were screened in abstract form and reviewed in detail when they met study inclusion criteria. Further articles were obtained through bibliographic cross-referencing, consultation of major texts in the field (such as Goodwin and Jamison's *Manic-Depressive Illness*), and discussion with experts in the field. Abstracts from conference proceedings for the past five years were reviewed from meetings of the American Psychiatric Association, the American College of Neuropsychopharmacology, the International Conferences on Bipolar Disorder (Pittsburgh), and the New Clinical Drug Evaluation Unit (NCDEU).

Inclusion criteria for the study were purposefully broad, and included: a) identification of the diagnosis of bipolar disorder or manic-depressive illness; b) identification of sample size; and c) identification of treatments used. If randomization or blinding occurred, texts were screened to assess report of success of randomization or blinding. Assessment of diagnosis included whether standardized, reliable criteria were used and whether clinicians or more junior research staff applied criteria. Studies reviewed, unless stated otherwise, had primary outcomes of relapse into any mood state. No reanalysis of data was performed except when explicitly stated. *(See Table 2.)*

Results

Lithium. There have been at least 13 level I, placebo-controlled studies (total n = 509) that have demonstrated benefit with lithium in the prevention of manic and depressive episodes in bipolar disorder.[4] A Cochrane Collaboration meta-analysis has demonstrated benefit in these studies with marked reduction of risk of relapse (odds ratio 0.21). *(See Figure 1.)* These studies generally consisted of initial treatment with lithium (plus or minus an antidepressant or neuroleptic) for acute mood symptoms, and then double-blind randomization to continuation of lithium or switch to placebo. It now generally is felt that this kind of sudden discontinuation design may have overestimated the benefit of lithium due to increased risk of withdrawal mania in patients in whom lithium is stopped abruptly.[5] Three level I studies have controlled for this risk either by gradual discontinuation of lithium or by avoiding use of lithium in the initial acute treatment phase before double-blind randomization for prophylaxis. In these three studies (total n = 1010), lithium again has been shown to be beneficial, slightly more for prevention of mania than for prevention of depression.[6,7]

Despite these level I data, a number of large level III studies from the 1980s and 1990s reported much lower remission rates with lithium than expected from the level I studies.[8-11] These other studies led to a widespread perception, particularly in the United States, that lithium may have lost its efficacy as more diverse forms of mood illness were being diagnosed within the bipolar paradigm. A number of factors might have accounted for

these studies, such as the study of refractory patients in tertiary care academic centers, the widespread use of antidepressants in the 1990s that may have led to long-term mood destabilization, and the use of lithium in patients with other causes of poor prognosis (such as substance abuse and psychosis). Other recent level III studies, conducted in the community setting and minimizing antidepressant use, suggest that these reports of lithium's inefficacy probably were premature.[12,13]

Valproate and Carbamazepine. One level I study of valproate compared to lithium and placebo has been conducted (n = 372).[14] In that study, there was no overall benefit with valproate vs. placebo, although since only about one-third of patients relapsed in one year in each arm of this study, these low relapse rates made it difficult to demonstrate benefit. The study did report that valproate was somewhat more effective than lithium in depressive episode relapse, but this was a post-hoc analysis. Two level II comparisons with lithium (total n = 114) suggest equal or better efficacy with valproate, as do level III comparative studies.[15-18]

Two level Ia studies have been conducted on the prophylactic effects of carbamazepine, with carbamazepine being superior to placebo.[19,20] In addition, two level I, non-placebo controlled studies have reported similar efficacies between carbamazepine and lithium.[21,22]

Lamotrigine. Two recent, large prophylaxis studies (n = 1315) now have demonstrated that lamotrigine is more effective than placebo in prevention of depressive episodes in bipolar disorder. In the two studies, lamotrigine seemed more effective than lithium for depressive prophylaxis.[6,7]

Other Novel Anticonvulsants. Level IV data suggest potential long-term benefit with gabapentin and with topiramate, mainly as adjunctive agents, in bipolar disorder.[23,24] However, these studies are limited in number and difficult to interpret in the absence of more rigorous data supporting acute benefit with these agents. A small, level II, open, randomized study (n = 15) of oxcarbazepine, which is a keto-congener of carbamazepine, reported some benefit compared to lithium in prophylaxis of bipolar disorder.[25]

Typical Neuroleptic Agents. There are two level I studies (one crossover) of typical neuroleptic agents in prevention of mania in bipolar disorder (total n = 53).[26,27] In both small studies, neuroleptics added to lithium were not more effective than lithium plus placebo in preventing manic episodes, and, in contrast, neuroleptic use was associated with increased occurrence of depressive morbidity. These studies suggest that typical neuroleptics do not possess mood-stabilizing properties, but rather seem to be purely antimanic agents, bringing mood down when it is elevated, but continuing to bring mood down below euthymia.

Olanzapine. There are four level I studies of olanzapine in the prevention of mood episodes in bipolar disorder—one study in which olanzapine is used as an adjunct to mood stabilizer, two in monotherapy comparison with mood stabilizers (divalproex and lithium), and one in monotherapy comparison with placebo.

In the first study (n = 99) of patients who had responded to olanzapine plus lithium or valproate for acute mania after a six-week treatment period, the patients then were re-randomized to either olanzapine plus mood stabilizer or placebo plus mood stabilizer for up to 18 months.[28] Survival analysis demonstrated much longer time to recurrence of either mania or depression in the group maintained on olanzapine plus valproate or lithium compared to the mood stabilizer plus placebo group. Unfortunately, 19.6% of patients in the olanzapine plus mood stabilizer group gained a clinically important amount of body weight (> 7% increase in baseline body mass index [BMI]) compared to only 6.3% in the valproate/lithium monotherapy group. This is the first level I study to demonstrate long-term adjunctive mood-stabilizing benefit from continuation of a neuroleptic after recovery from acute mania.

In another level I report (n = 248), acutely manic patients were randomized to olanzapine or valproate, with somewhat better responses acutely at two months with olanzapine.[29] All patients then were continued on their original double-blind randomization for up to one year, with some apparent marginal clinical benefit with olanzapine vs. valproate, though there were no statistically significant differences regarding efficacy. Both groups had very high dropout rates, though (near 85%), with more sedation and weight gain with olanzapine compared to more gastrointestinal upset with valproate.

In a third level I report (n = 431), acutely manic patients were randomized to olanzapine or lithium for two months, and then continued on their original double-blind randomization for each drug for up to one year.[30] This study was designed and powered to be an equivalence study, which it appeared to demonstrate, with overall similar benefit clinically and statistically in both groups. Dropout rates were low (about 40%) compared to the valproate comparison study. Again, olanzapine was associated with more weight gain than lithium.

Table 1. Levels of Evidence

LEVEL I: DOUBLE-BLIND RANDOMIZED TRIALS

- Ia: Placebo-controlled monotherapy
- Ib: Non placebo-controlled comparison trials, or placebo-controlled add-on therapy trials

LEVEL II: OPEN RANDOMIZED TRIALS

LEVEL III: NATURALISTIC STUDIES

- IIIa: Nonrandomized, controlled studies
- IIIb: Large nonrandomized, uncontrolled studies (n > 100)
- IIIc: Medium-sized nonrandomized, uncontrolled studies (100 > n > 50)

LEVEL IV: SMALL, NATURALISTIC STUDIES (NONRANDOMIZED, UNCONTROLLED, 50 > N > 10)

LEVEL V: CASE SERIES (N < 10), CASE REPORT (N = 1), EXPERT OPINION

Adapted from Ghaemi S, Soldani F. Meta-analysis of observational studies in psychiatry: The case of rapid-cyling bipolar disorder. *Acta Psychiatrica Scandinavica* 2003: In press.

Table 2. Psychopharmacology Maintenance Studies in Bipolar Disorder

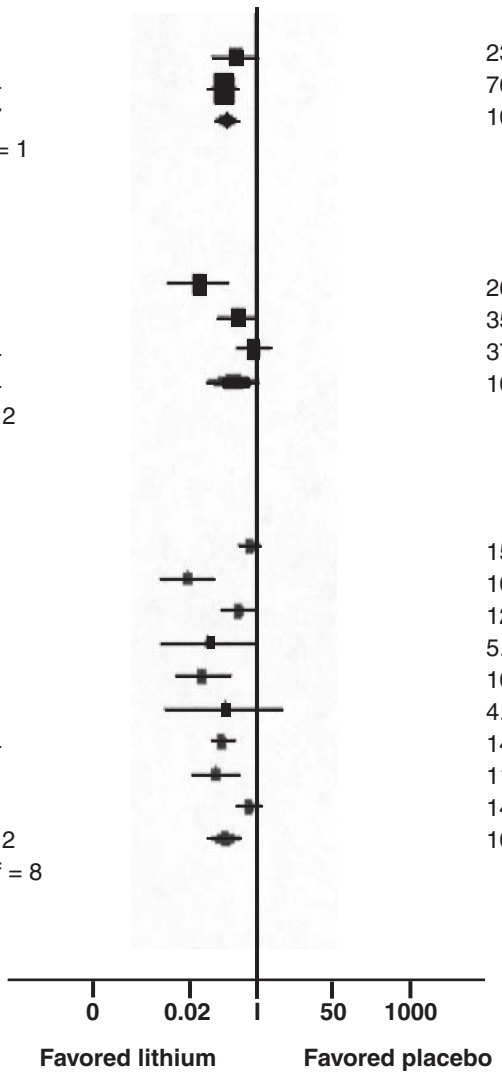
Agent	Highest level of evidence	Number of studies	Total patients	Findings
Lithium	Ia*	14	541	More effective than placebo, sudden discontinuation studies
	Ia†	3	1010	More effective than placebo, gradual discontinuation studies
	Ib	5	261	More effective than imipramine
Valproate	Ia	1	372	Equivalent to placebo and lithium in a probable failed study
	Ib	1	251	Equivalent to olanzapine
Carbamazepine	Ia	2	32	Mild benefit over placebo
	Ib	2	64	Mildly less effective than lithium in one study, mildly more effective than lithium in another
Lamotrigine	Ia	2	645	More effective than placebo; equivalent to lithium with somewhat greater benefit in depressive prophylaxis
	Ia‡	1	18	Equivalent to placebo in rapid-cycling, though possible benefit in bipolar type II subgroup
Gabapentin	IV	1	18	Possible monotherapy uncontrolled benefit
Topiramate	III	1	76	Possible adjunctive uncontrolled benefit
Oxcarbazepine	II	1	15	Equivalent to lithium
Flupenthixol	Ib	2	53	No added benefit vs. placebo when added to lithium
Olanzapine	Ib	3	778	Equivalent to lithium or valproate; more effective than placebo when added to lithium or valproate
Risperidone	III	1	358	Suggested uncontrolled benefit
Clozapine	II	1	38	Mildly more effective, when added to mood stabilizers, than mood stabilizer combinations without clozapine
Imipramine	Ia	2	66	Equivalent to or worse than placebo
	Ib	2	192	No added benefit vs. placebo when combined with lithium; more manic episodes over time in one study
Fluoxetine	Ia	1	10	Possible benefit in retrospective post-hoc analysis of bipolar II subsample from a unipolar depression cohort
ECT	IV	1	58	More benefit if continued long-term in those with acute benefit, added to pharmacotherapy, than in those in whom ECT was discontinued after acute benefit
Omega-3 fatty acids	Ib	1	30	Mildly more effective than placebo when added to standard mood stabilizers in a rapid-cycling sample
Clonazepam	Ib	1	28	Equivalent to placebo when added to lithium

* Sudden discomfort; † Gradual discontinuation; ‡ Rapid cycling
Key: ECT = electroconvulsive therapy

The above two studies are not definitive in the absence of a placebo group. The studies could be demonstrating that olanzapine is equally effective, or equally ineffective, as valproate or lithium in these samples. The high dropout rate in the valproate study raises concerns regarding mutual inefficacy, while the low dropout rate in the lithium study is reassuring. However, a placebo arm markedly would have strengthened both studies. An additional, recently completed study directly compared olanzapine to placebo (n = 136).[31] Although in this sample it, too, would have been ideal to have an active control arm (lithium or valproate), the results demonstrate that olanzapine was more effective than placebo in the prevention of relapse into any mood episode.

Figure 1. Meta-analysis of Lithium vs. Placebo Prophylaxis Treatment

STUDY	LITHIUM	PLACEBO	WEIGHT %	ODDS RATIO (RANDOM) 95% CI
Admission to hospital				
Fieve 1976	6/38	15/43	23.1	0.35 (0.12, 1.02)
Prien 1973a	31/101	70/104	76.9	0.22 (0.12, 0.39)
Subtotal (95% CI)	37/139	85/147	100.0	0.24 (0.14, 0.40)
Test for heterogeneity chi-square = 0.61 df = 1 p = 0.4358				
Test for overall effect Z = 5.41 p = 0.00				
Non-study medications				
Coppen 1971	14/28	35/37	26.6	0.06 (0.01, 0.28)
Fieve 1976	22/38	33/43	35.8	0.42 (0.06, 1.08)
Prien 1973a	12/101	14/104	37.6	0.87 (0.38, 1.98)
Subtotal (95% CI)	48/167	82/184	100.0	0.32 (0.09, 1.20)
Test for heterogenity chi-square = 8.90 df = 2 p = 0.0117				
Test for overall effect Z = 1.68 p = 0.09				
Relapse stated				
Bowden 2000	28/91	36/94	15.0	0.72 (0.39, 1.32)
Coppen 1971	5/28	32/37	10.5	0.03 (0.01, 0.13)
Fieve 1976	22/38	33/43	12.9	0.42 (0.16, 1.08)
Glen 1984	5/12	8/9	5.8	0.09 (0.01, 0.96)
Kane 1982	5/25	19/24	10.2	0.07 (0.02, 0.26)
Laurell 1968	2/4	5/6	4.4	0.20 (0.01, 3.66)
Prien 1973a	43/101	84/104	14.9	0.18 (0.09, 0.33)
Prien 1973b	12/39	17/22	11.3	0.13 (0.04, 0.44)
Prien 1984	33/75	40/73	14.8	0.65 (0.34, 1.24)
Subtotal (95% CI)	155/413	274/412	100.0	0.21 (0.10, 0.43)
Test for heterogeneity chi-square = 33.92 df = 8 p = 0.0000				
Test for overall effect Z = 4.32 p = 0.00				



Overall, lithium reduces risk of relapse by more than 200%, with statistically significant and tight confidence intervals. Although there is heterogeneity in the analysis based on the Z score, the results are still robust in magnitude and statistically significant using a random effects model.
Reprinted with permission from Burgess S, Geddes J, Hawton K, et al. Lithium maintenance treatment of mood disorders (Cochrane Review). In: *The Cochrane Library,* Issue 4. Oxford: Update Software, 2002.

However, it should be noted that these data with olanzapine are not as rigorous as the evidence with lamotrigine. In other words, with olanzapine one has suboptimal research designs in which olanzapine was compared to known treatments (lithium or valproate) separately from comparison to placebo. Since these are different samples and different studies, one therefore cannot conclude that olanzapine is as effective as lithium and more effective than placebo. Such a comparison would have to be made in the same study with the same sample of patients. Indeed, with lamotrigine, such comparisons were made twice over, with lamotrigine being at least as effective as lithium and more effective than placebo for prevention of depressive, but not manic, episodes.

It is noteworthy that tardive dyskinesia (TD) was not observed in any of these long-term prophylaxis studies of olanzapine, supporting the long-term schizophrenia clinical trial literature that indicates that TD risk with atypical neuroleptics is significantly lower than the rates observed with typical neuroleptics.

Other level III studies support the generalizability of the level I findings, particularly regarding adjunctive long-term benefit with olanzapine added to standard mood stabilizers like lithium or valproate.[32,33]

(Editors note: There are long-term data comparing olanzapine and valproate in 47-week extension trials showing similar efficacy in managing residual mania, depression, and rapid cycling. In the one-year lithium comparator study, olanzapine therapy had fewer relapses into mania and similar depression prophylaxis to lithium.)

Other Atypical Neuroleptic Agents. A large (n = 358) level III study with risperidone found long-term adjunctive mood-stabilizing benefit when combined with standard mood stabilizers for bipolar disorder, with only 25% recurrence at up to one year follow-up (mean six months).[34]

A small level II study (n = 38) with clozapine added to standard mood stabilizers vs. usual treatment (standard mood stabilizers in the absence of clozapine) found evidence of a mild amount of marginal mood-stabilizing benefit in the clozapine group.[35]

Other Agents. In one small level I study, clonazepam added to lithium compared to placebo in 28 stable euthymic bipolar patients was not found to have a prophylactic effect.[36] Time to relapse did not differ between the clonazepam and placebo groups, though somewhat less rescue medication was needed in the clonazepam group. Since this study was small, the possibility of type II false negative error cannot be discounted.

Standard Antidepressants. Five level Ia studies of tricyclic antidepressants (TCAs) (total n = 263) failed to find any benefit with use of TCAs in conjunction with lithium for the prevention of depressive episodes in bipolar I or II disorder.[37] Two level I studies of the newer antidepressants buproprion and fluoxetine have been conducted.[38,39] The limited total number of subjects available for assessment at one year follow-up, six in the bupropion study and 10 in the fluoxetine study, precludes a meaningful statistical analysis. One of these studies found evidence of long-term worsening with antidepressants, with more manic episodes over time compared to lithium alone (and no benefit in terms of reduction of depressive episodes).[40] These data would seem to support the recommendation, recently gaining in popularity among researchers, that antidepressants be discontinued after use for the acute major depressive episode in bipolar disorder, given lack of evidence of long-term preventive benefit.[41]

However, a level III, nonrandomized, controlled comparison study has reported increased one-year depressive relapse rates in patients in whom antidepressants are discontinued after recovery from the acute major depressive episode, compared to those in whom mood stabilizer plus antidepressant combination treatment is continued long-term.[42] In contrast, it is important to note that larger, more rigorous level I data are available from another study, clearly demonstrating that, after recovery from an acute major depressive episode with lithium plus imipramine, discontinuation of imipramine did not lead to increased one-year relapse rates compared to continuation of imipramine plus lithium.[43]

Overall, these studies fail to provide any rigorous evidence of long-term benefit with antidepressants in the prevention of depression in patients with bipolar disorder.

Novel Agents: Omega-3 Fatty Acids, Vitamin/Mineral Supplements. When omega-3 fatty acids vs. placebo were added to standard mood stabilizers in a small level I study, investigators found shorter time to need for intervention with other medication in the placebo-treated group.[44] However, patients were only moderately symptomatic, with a mixture of manic and depressive symptoms, and no statistical differences in mood ratings scales or episode frequency were demonstrated. No follow-up level I data have been made public, and thus, at this point, the putative mood-stabilizing benefit of omega-3 fatty acids remains a matter of controversy. Significant level II or level III data also are unavailable.

Recently, a prospective level IV study suggested some benefit with a multivitamin, multimineral supplement for acute mania, and an accompanying commentary describes cases of long-term benefit.[45,46] A level I study of this agent currently is under way.

Rapid-cycling Bipolar Disorder as a Proxy for Prophylaxis

Unfortunately, no agent has been shown to be effective in a primary outcome analysis of a level I study in rapid-cycling bipolar disorder. The only level I study conducted to date has been with lamotrigine.[47] In that study, efficacy with lamotrigine vs. placebo was not demonstrable in the total sample primary outcome measure of time to relapse into an episode. However, in a post-hoc secondary analysis, there was a suggestion that the observed lack of efficacy was due to the subgroup with bipolar I disorder, with statistically significant benefit noted in the bipolar II subgroup. This observation is the only positive level I treatment shown to provide benefit in this difficult-to-treat population.

Indeed, the only intervention that has been demonstrated in a level I trial to improve rapid cycling in bipolar I disorder is the discontinuation of antidepressants. Two different small studies (total n = 15), using an on-off-on paradigm, found that TCAs tended to be associated with rapid cycling, and discontinuation of TCAs led to reduction in cycling rate and/or resolution of rapid cycling.[48,49] Some, but not all, level III reports also suggest that discontinuation of antidepressants is a potentially important intervention in recovery from a rapid-cycling course.[50,51]

Despite a widespread conception that anticonvulsants have been shown to be more effective than lithium in treating rapid cycling, this view is based on level III data only.[52] In fact, other level III data indicate that lithium, in the context of minimization of antidepressant use, may not be ineffective in the treatment of rapid-cycling.[53]

In summary, no definitive randomized data support any agent for treatment of rapid-cycling bipolar disorder, with the exception of discontinuation of antidepressants.

Summary of Prophylaxis Studies. As shown in Table 2, as with acute mania and acute depression, the largest number of studies demonstrating efficacy have been conducted with lithium. In this case, there is clear and widely accepted superiority of the lithium data regarding efficacy as a first-line agent. Anticonvulsants and possibly atypical neuroleptics also are useful. Standard antidepressants and typical neuroleptics appear to be ineffective at best and potentially harmful at worst.

Polypharmacy

Polypharmacy in psychiatry is a large topic that has been examined in detail elsewhere.[54] It is fairly common in bipolar disorder, with long-term mood stabilizer monotherapy usually in no greater than one-third of patients.[55] The larger question is whether

polypharmacy, and with what agents, is supported by evidence in long-term prophylaxis of bipolar disorder.

There is only one level I study of polypharmacy with lithium plus valproate in the maintenance treatment of bipolar I disorder, in which 12 patients followed for one year randomly were assigned either placebo or valproate added to lithium. The combination treatment was associated with less relapse but more side effects.[56] In a level II open randomized, one-year outcome study, 52 patients were followed on either lithium alone, carbamazepine alone, or the combination for up to three years. While treatment response (based on moderate to marked improvement on the clinical global impression [CGI] scale) was higher on the combination treatment (55%) than lithium (33%) or carbamazepine (31%) monotherapy, this difference was not statistically significant, possibly due to the small sample sizes. However, statistically significant benefit to combination therapy clearly was present in patients with rapid-cycling bipolar disorder (56% combination therapy response vs 28% lithium response and 19% carbamazepine response).[55]

In summary, while usually necessary for bipolar disorder, polypharmacy can be both harmful and helpful. The most rigorous evidence basis for combination treatments for bipolar disorder tends to support primary use of standard mood stabilizers (i.e., lithium, valproate, or carbamazepine), with adjunctive use of atypical neuroleptic and novel anticonvulsant classes. Use of typical neuroleptic agents and standard antidepressants would be limited mainly to acute phase purposes. Ineffective polypharmacy can result from a reversal of these emphases, with less aggressive long-term use of mood-stabilizing agents, and chronic neuroleptic or antidepressant pharmacotherapy.

Psychotherapy

Historically, treatment of bipolar disorder has focused on psychopharmacology, with psychotherapy remaining underused as a treatment strategy. All studies are at best level II, since it is not possible to blind psychotherapeutic interventions. *(See Table 3.)* As seen in Table 3, psychoeducational interventions appear to be the best established. In the largest and best designed study, 120 patients were randomized equally to adjunctive group psychoeducation (six months in duration) vs. treatment as usual, added to pharmacotherapy.[57] At six months, recurrent to manic or depressive episodes occurred in 38% of the psychoeducation group vs. 60% of the control group. At two years, recurrence had occurred in 67% of the psychoeducation group vs. 92% of the control group, all differences being statistically significant. Survival analysis also showed large periods of remission in the psychoeducation group (median time to new episode was approximately seven months in the psychoeducation group vs approximately 4.5 months in the control group).

Table 3. Psychotherapy Maintenance Studies in Bipolar Disorder

Type	Highest level of incidence	Number of studies	Total patients	Findings
Psychoeducation	II	4	299	All of these types of psychotherapy have been found to increase remission rates and decrease relapse when combined with pharmacotherapy.
Interpersonal	II	1	82	
Family-based	II	5	273	
CBT	II	4	242	
Total:		13	896	

Key: CBT = cognitive behavior therapy

Side Effects

In the maintenance treatment of bipolar disorder, a careful consideration of side effects is even more important than in acute settings. It is well known that acutely manic patients appear to tolerate much higher doses of medications with fewer side effects than the same patients when euthymic. Further, since acutely manic or depressed patients often are hospitalized, it is notable that the hospital setting also often is associated with fewer complaints about side effects than one tends to hear in the outpatient setting. For all these reasons, clinicians treating bipolar disorder in the outpatient setting often will observe much higher rates of side effects than they might have been led to believe based on acute treatment studies. Further, subjects enrolled in level I acute mania or bipolar depression studies are not the same patients often seen in real-world clinical treatment. Level I research patients are homogeneous, highly selected, generally motivated persons with few medical or psychiatric comorbidities. Consequently, they will experience fewer side effects than real-world patients will. In epidemiological terms, it is an accepted fact that level I data, though valid, may not be generalizable to a larger population of patients.

Accordingly, clinicians should be cautioned against using numbers for frequency of side effects derived from clinical trials to guide their real-world practice. A common example of this kind of error occurs with the frequency of antidepressant-induced mania. Often clinicians will assert that the frequency of mania induced by serotonin reuptake inhibitors (SRIs) is low, meaning about 5% or less. Indeed, some level I studies report these kinds of numbers, as well as quite low numbers with TCAs (10% or less). Many studies in non-clinical trial settings demonstrate TCA-related acute mania to occur in about 50% of patients, and SRI-related acute mania in about 40% of patients. This discrepancy may be due to a problem of generalizability. In this case, level I data are less accurate than real-world level III or lower data. In other words, the highly controlled environment of level I studies only allows a categorical answer to a yes-or-no question such as, "Do antidepressants cause mania more frequently than placebo?" But for the quantitative question of "How frequently

Table 4. Side Effect Profiles for the Most Commonly Used Mood-Stabilizing Agents

AGENT	NUISANCE SIDE EFFECTS	MEDICALLY SERIOUS SIDE EFFECTS
Valproate	Sedation, nausea, diarrhea, cognitive, hair loss	Hepatitis, pancreatitis
Carbamazepine	Sedation, nausea, ataxia diplopia	Hepatitis, aplastic anemia, Stevens-Johnson syndrome
Lamotrigine	Nausea	Stevens-Johnson syndrome
Olanzapine	Extrapyramidal symptoms, sedation	Diabetes, hypercholesterolemia, potential tardive dyskinesia
Gabapentin	Sedation, nausea	None
Topiramate	Sedation, cognitive	Renal stones

do antidepressants cause mania?" one needs to turn to observational data in unselected clinical populations. While level I clinical trials tell us if something happens, observational experience studies tell us how frequently something happens.

Another example that no longer is disputed is the issue of sexual dysfunction with SRIs. In this instance, sexual dysfunction was not observed frequently in the highly selected samples of the early clinical trials, but it immediately was found to be a common occurrence through clinical experience.

Hence, clinicians are urged to rely on their own experience and observational studies, and not only clinical trials, in assessing frequency of side effects. Table 4 summarizes some common side effects with the most commonly used mood-stabilizing agents, excluding lithium, which will be reviewed in more detail below.

Long-term Effects with Lithium

Medically serious side effects (excluding toxicity) fall into three categories: thyroid abnormalities, chronic renal insufficiency, and cardiac effects (these issues are reviewed extensively by Goodwin and Jamison).[4]

Lithium's thyroid effects can occur early in treatment, but often appear after years of use, as well. Lithium has a direct reversible antithyroid effect, and thus it can lead to hypothyroidism (usually in about 5% of patients). It inhibits the thyroid gland's sensitivity to thyroid-stimulating hormone (TSH). High TSH levels on laboratory tests indicate a need to either discontinue lithium or supplement it with thyroid hormone replacement. Either T_4 or T_3 formulations can be used, alone or in combination; the most common practice is to use T_4 (l-thyroxine), since it is metabolized in the body to T_3 naturally.

Lithium's kidney effect is more long-term, usually seen after 10-20 years of chronic therapy. Unlike the acute direct inhibition of renal concentrating ability (including diabetes insipidus), this long-term effect of lithium often is irreversible and may involve renal glomerular function, resulting in a mild azotemia in most cases (mildly elevated creatinine levels). Lithium appears to reduce glomerular filtration rate, usually slightly. In rare instances, it can lead to severe chronic renal insufficiency and nephrotic syndrome, with glomerular pathologies of varying types. In the setting of new azotemia, the clinician needs to consider switching from lithium to another agent, although sometimes lithium can be continued safely, as long as future kidney function tests do not worsen beyond mild abnormalities.

Lithium's cardiac effects mainly consist of some decrease in cardiac conduction efficiency, which can result in sick sinus syndrome. Lithium can produce blockade of the sinoatrial node, premature ventricular beats, and atrioventricular blockade. If lithium use is essential in a patient with these effects, a cardiac pacemaker may be necessary. Otherwise, the use of a different mood stabilizer may be indicated.

It is noteworthy that lithium mildly increases free calcium levels, possibly by stimulating direct release of parathyroid hormone from the pituitary gland, but this effect has little clinical significance, and hypercalcemia is not a serious problem.

Lithium also can produce a mild leukocytosis, although this also is without clinical sequelae.

Lithium toxicity occurs in non-elderly adults usually beginning at a level of 1.2, with minimal side effects of tremor, nausea, diarrhea, and ataxia. Levels from 1.5-2.0 are associated with a higher risk of seizures. Above 2.0, acute renal failure can occur and dialysis may be warranted. Above 2.5, coma and death can occur and dialysis is indicated. In the elderly, these signs of toxicity can occur at half the levels. A special warning is appropriate for the elderly depressed patient who experiences diminished appetite: Decreased fluid intake will raise lithium levels to toxic ranges quickly. If renal failure is produced, lithium levels rise exponentially, greatly increasing the risk of death. Thus, dialysis is essential in such cases.

Early reports based on retrospective data found that lithium was associated with increased levels of congenital cardiac malformations in children of mothers treated during pregnancy. Specifically, Ebstein's anomaly, a malformation of the tricuspid valve, was associated with lithium use in the first trimester of pregnancy. Recent prospective studies report lower risks than in the past. However, cardiac malformations, specifically Ebstein's anomaly, still generally are thought to be a risk with lithium use during pregnancy. These risks are probably lower than the risks of neural tube defects associated with the use of anticonvulsant mood stabilizers, like divalproex and carbamazepine, in pregnancy. Thus, in the severely ill manic patient who requires treatment, lithium use, with or without high-potency conventional antipsychotics, at times may be necessary, ideally after the first trimester of pregnancy. However, if possible, lithium use generally should be avoided during pregnancy.

Long-term Cognitive Benefits of Lithium

When considering these various risks, clinicians should be careful always to consider for themselves and present to patients the relevant benefits to be expected with lithium so that

both clinician and patient can make an appropriate risk-benefit assessment.

Clearly, lithium has many benefits in terms of being the best-established agent in prevention of mood episodes in bipolar disorder, as documented above. However, in addition to the benefit for mood, lithium has benefits in two other areas that deserve special attention: mortality and cognition.

It is important to note that lithium is the only psychotropic agent for any psychiatric condition that definitively has been shown to reduce completed suicide.[58,59] It not only reduces suicide rates in bipolar disorder, but it also reduces mortality due to cardiovascular disease, which is the top cause of death in patients with bipolar disorder.[60,61] The most rigorous data on this difficult-to-study topic are from a level II study that supported the superiority of lithium in its antisuicide effect compared to carbamazepine in a 2.5-year outcome.[62] In this study, antisuicide benefit with lithium was not related specifically to efficacy in prevention of mood episodes, and thus, regardless of whether lithium reduced mood episode relapse rates, it appeared to reduce suicide rates.

Further, recent studies demonstrate that lithium has a neuroprotective effect that may be especially beneficial for the long-term cognitive functioning of patients with bipolar disorder. It recently has been shown that persons with bipolar disorder appear to experience cognitive decline with time that exceeds normal age-related deterioration.[63] In fact, there appears to be greater impairment of cognitive function associated with number of mood episodes experienced, and this cognitive impairment has been correlated with hippocampal atrophy.[64] It is thought that repeated mood episodes lead to hypercortisolemia that over time leads to hippocampal injury. The result is progressive cognitive impairment that is independent of mood state, persisting even when patients eventually become euthymic with appropriate treatment.

One study appears to show that this cognitive decline does not occur with lithium, and that hippocampal size is preserved in patients receiving long-term lithium treatment.[65] This observation is consistent with animal studies that show that lithium increases levels of the neuroprotective agent brain-derived neurotrophic factor.[66]

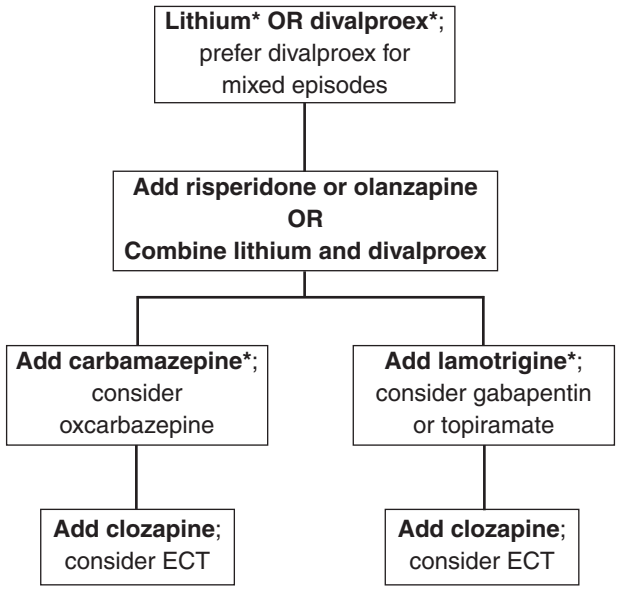
Hence, even separate from its direct mood benefits, lithium has benefits for mortality and cognition that may improve long-term functional outcome and survival in patients with bipolar disorder. Other mood stabilizers or antidepressants have not been shown to have these benefits.

Discussion. As discussed previously, and as shown in Table 2, the largest number of studies demonstrating efficacy in prophylaxis treatment of bipolar disorder have been conducted with lithium, and there is clear and widely accepted superiority to the lithium data regarding efficacy as a first-line agent.

Psychotherapy also appears to present an option for the treatment of bipolar disorder, as shown in Table 3, where all types of psychotherapy have been found to decrease relapse rates when combined with pharmacotherapy. Polypharmacy also presents a potential avenue for effective maintenance treatment of bipolar disorder. Although there is a relative dearth of controlled data on polypharmacy, the existing data suggest that rational use of polypharmacy is useful in long-term management of bipolar disorder.

Limitations to this review may include missed studies in the databases searched and unpublished negative studies. Furthermore, interpretations of the evidence can vary, leading to different conclusions.

Figure 2. An Algorithm for the Polypharmacy of Bipolar Disorder, Type I



The same approach is suggested for acute mania, acute depression, rapid-cycling, or prophylaxis. In the case of acute bipolar depression, antidepressants can be introduced at any point, and we generally recommend tapering off the antidepressants two months after recovery from the acute depressive episode, with long-term antidepressant treatment reserved for those who repeatedly relapse into depression after tapering off antidepressants. The two antidepressants with the lowest risk of acute mania are bupropion and paroxetine.

* Agents with significant evidence of benefit in acute mania or depression and the prophylaxis of mood episodes. We tend to see them as primary mood stabilizers that can be used in monotherapy. All other agents are adjuncts for bipolar I disorder. In bipolar disorder type II, there is less available evidence upon which to base treatment guidelines.

Key: ECT—electroconvulsive therapy

Adapted from Ghaemi SN, Sachs GS, Chiou AM, et al. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affective Disorders* 1999; 52:35-144.

Treatment Guidelines

Recent treatment guidelines on bipolar disorder have tried to provide an overall interpretation of this literature.

Earlier treatment guidelines were limited to literature derived largely from lithium, traditional neuroleptic, and TCA studies. Since, besides lithium, those studies were quite limited, most of

the earlier guidelines were rather broad in their recommendations, generally including the use of lithium in all phases of the illnesses, along with neuroleptics for manic symptoms and antidepressants for depressive symptoms.

In the past decade, greater attention in the United States was placed on the lack of evidence of efficacy for traditional neuroleptics and antidepressants.[41,67] Along with level III evidence of potential risks with those agents, recent U.S.-based guidelines have tended to be more conservative.[68,69] Typical neuroleptics are largely not recommended given the availability of atypical neuroleptics. And standard antidepressants have been recommended as second- or third-line agents, used for more severe cases of bipolar depression, rather than as routine treatments for depressive symptoms in bipolar disorder.

In contrast, atypical neuroleptics (especially olanzapine) and novel anticonvulsants (especially lamotrigine) have been emphasized in the newest guidelines in the United States. This shift has engendered criticism in some quarters in Europe, particularly among researchers in Munich, Germany.[70] This review of evidence-based treatment of bipolar disorder tends to provide support for the recent trends in treatment guidelines from the United States with overall emphasis on use of lithium and anticonvulsants as primary mood stabilizers, with frequent use of atypical neuroleptic and novel anticonvulsant agents, mainly as adjuncts. Typical neuroleptics are best avoided in general, while standard antidepressants should be used mostly for severe acute depression that is unresponsive to other mood-stabilizing treatments. Figure 2 provides a visual representation of one interpretation of how this literature can be conceptualized for clinical use.

Conclusion

Editor's note: The authors have presented an informative and thorough review of the long-term data on management of bipolar disorder. The article supports the use of lithium and outlines the growing evidence for the utilization of some of the anticonvulsants and atypical antipsychotics as maintenance therapy. We need more evidence to support our clinical feeling that long-term polypharmacy is useful. However, the pervasive use of antidepressants as well as typical neuroleptics may be contraindicated in many of these patients.

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Physician CME Questions

1. Only double-blind, randomized clinical trials provide reliable evidence for clinical practice.
   A. True
   B. False

2. Which of the following is true regarding research of lithium in bipolar maintenance?
   A. Lithium has not been shown to be effective for prevention of mania.
   B. Lithium is equally effective for prevention of mania and depression.
   C. Sudden discontinuation of lithium in studies has overestimated its benefit in long-term studies.

D. Naturalistic studies show higher remission rates with lithium than double-blind, randomized studies.

3. Low remission rates in some level III lithium studies may be a result of:
   A. inclusion of refractory patients in the database.
   B. comorbid diagnosis such as substance abuse or psychosis.
   C. concomitant use of antidepressants.
   D. All of the above

4. In Bowden's maintenance study comparing lithium, valproate, and placebo, which of the following is true?
   A. Valproate was clearly superior to placebo in prevention of relapse.
   B. There were such low overall relapse rates in each group that it was difficult to demonstrate benefit of drug vs. placebo.
   C. Valproate was less effective than lithium in depression relapse.
   D. There was such a small sample size that no reliable analysis of the data could be done.

5. Regarding anticonvulsants in long-term bipolar management, which of the following is/are true?
   A. Carbamazepine has shown efficacy in maintenance therapy.
   B. There are good level 1 long-term data on gabapentin in bipolar management.
   C. Lamotrigine has been shown to be superior to lithium in depression prophylaxis.
   D. *Only* A and C are true.
   E. A, B, and C are *all* true.

6. Long-term data in bipolar studies of olanzapine, like typical neuroleptics, showed prevention of mania relapse but failed to show depression prophylaxis.
   A. True
   B. False

7. Which of the following is *false* regarding antidepressant use in bipolar maintenance?
   A. Tricyclics have been shown to be effective in the prevention of depressive episodes.
   B. There is evidence of long-term worsening of manic episodes with antidepressants compared with lithium alone.
   C. Antidepressants may be continued comfortably after treatment of an acute depressive episode.
   D. Several large level 1 studies of the newer antidepressants in bipolar maintenance have been conducted with sufficient evidence to show consistent worsening of mania.

8. In rapid cycling patients, which of the following is true?
   A. Lamotigine demonstrated delay of relapse into an episode vs. placebo in Bipolar I.
   B. Lithium has demonstrated efficacy.
   C. Some of the newer antidepressants have demonstrated efficacy.
   D. Discontinuation of antidepressants has shown to be an effective treatment.

9. The best evidence of polypharmacy in bipolar maintenance is with a mood stabilizer and atypical neuroleptic and novel anticonvulsant.
   A. True
   B. False

10. Psychodynamic psychotherapy has been shown to be more effective in bipolar maintenance than psychoeducational interventions.
   A. True
   B. False

Answer Key:

1. B	5. D	8. D
2. C	6. B	9. A
3. D	7. A	10. B
4. B		

CME Objectives

The CME objectives for *Psychiatric Medicine Reports* are to help psychiatrists:

(a) recognize psychiatric conditions encountered in the clinical setting;
(b) be educated about methods of treating psychiatric conditions, including use of traditional drugs, experimental methods, and off-label uses;
(c) understand the progression of treatment for conditions described; and
(d) understand both likely and rare complications or side effects of the condition and treatments described.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

In Future Issues:

Postpartum Depression