The Case for Polypharmacy in the Treatment of Bipolar Disorder

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In addition to being complex and pleomorphic in its own right, bipolar disorder is often accompanied by a host of other medical and psychiatric comorbidities. Recent evidence suggests that the illness is not as benign as originally considered and in some academic and outpatient settings, patients remain symptomatic almost half of their lives despite naturalistic treatment in the community. Bipolar disorder has considerable morbidity and mortality, both from suicide and medically related premature death.

The number of previous episodes is a potent risk factor for poor outcome. Yet, average delay to first treatment often hovers around a decade and much morbidity and comorbidity occurs and evolves during this untreated interval. In addition, each episode of depression and mania is associated with decrements in brain-derived neurotrophic factor and increases in oxidative stress, each of which can endanger neurons and be one component of the mechanism of episode sensitization (in which the greater the number of previous episodes, the greater the incidence and shorter the time to the next relapse).

Thus, it would appear that new approaches to earlier and more concerted illness interventions are required for patients who have bipolar disorder. Treating with the intent of achieving remission is a goal desired by most patients. Aggressive approaches to minor breakthroughs may prevent more major episode occurrences as well. Given the complexity of the disorder and the goal of achieving and maintaining remission, it appears that polypharmacy and complex combination therapy are often required to fulfill this mission.

**Rationale for polypharmacy**

The goal of remission should not be confused with that of the achievement of monotherapy as an end in itself, because that accomplishment may run counter to the goal of remission. Given the complex nature and frequent and multiple comorbidities of the disorder, it would be unrealistic to expect monotherapy to be sufficient for most persons with bipolar illness. Moreover, the notion that monotherapy is often sufficient for the management of the illness is based on several myths and misconceptions.

First, although lithium monotherapy might appear to have a high rate of response, this medication is typically given in conjunction with other agents, such as antidepressants, antipsychotics, benzodiazepines, thyroid medications, and multivitamins. Other misconceptions derive from the FDA approval process, in which approval is based on the ability of the active drug to exceed the efficacy of placebo, not on the achievement of a preset clinically robust standard desired by most clinicians. Second, and related to this point, a success rate of 50% is used in most analyses, and only rarely is major consideration given to the desired end point of remission. Finally, FDA registration, with the sole exception of lamotrigine, has been based on approval for the acute treatment of mania rather than long-term outcome. Therefore, it is clear that approval of a drug for monotherapy is not synonymous with the establishment of sufficient efficacy against all of the therapeutic targets that one seeks for patients with bipolar disorder.

In most other chronic or recurrent medical disorders, combination treatment is not only widely practiced but also the standard of care. One need only to think about triple antiretroviral therapy for AIDS, triple antibiotic therapy for tuberculosis, or the multiple medications for cancers, heart disease, and rheumatoid arthritis to see that polypharmacy for patients with bipolar disorder is not unconventional but typical of many other disorders. Multimodal therapies are used not only to achieve the desired therapeutic goal of an excellent response or complete remission but also for the prevention of loss of efficacy because of the development of treatment resistance. There may also be multiple neurochemical systems involved in bipolar disorder and not just a single deficit, as we see with dopamine in Parkinson disease or the defect in huntington protein in Huntington chorea. Although the positive evidence for the superiority of using complex regimens in bipolar illness is
scarce, the “negative” evidence is plentiful. In a study by Calabrese and colleagues, two of the best and most widely used drugs—lithium and valproate—when used in combination, were sufficient to acutely stabilize only 25% of the patients with rapid cycling bipolar disorder so that they could enter a randomized monotherapy trial. Half of these patients proceeded to relapse with either monotherapy, suggesting that barely 12.5% of patients with rapid cycling are likely to respond to monotherapy, and this does not include achieving and/or maintaining remission. Whereas some might argue that rapid cycling patients make up only a small percentage of the total population with bipolar illness, in our outpatient network we found that approximately 40% of retrospectively reported and 38% of prospectively rated patients met the criteria of 4 or more episodes per year, despite treatment with an average of more than 3 drugs.

In a study by Denicoff and colleagues, only about one quarter of the patients who were rapid cyclers had a good response to lithium or carbamazepine monotherapy (even though each year of treatment allowed adjunctive use of antipsychotics, benzodiazepines, and antidepressants, so it was not really monotherapy). In comparison, about 50% of the patients responded to a year of combination therapy.

A final rationale for polypharmacy is perhaps a surprising one, and that is the achievement of the desired therapeutic goals in the absence of adverse effects. While the use of more drugs for fewer adverse effects might seem paradoxical, it can be easily realized when each agent is administered below the patient’s adverse-effects threshold, rather than attempting to push a single drug to sufficient levels to achieve efficacy. When the latter was done with lithium therapy, better effects of lithium were achieved with higher rather than lower doses or blood level targets but at the cost of a 3-fold greater incidence of adverse effects.

The lack of a controlled clinical database for complex combination therapy in bipolar disorder should not be used as the reason for not proceeding with the best clinical treatment options for a patient. Since mental health research and, in particular, research on bipolar disorder is vastly underfunded. The needed clinical trial database is not likely to be forthcoming in the foreseeable future, but its absence cannot be used as a rationale for not proceeding on the basis of one’s best clinical judgment and the patient’s best clinical interests.

Principles of polypharmacy

How one proceeds to develop the best complex combination therapy for a patient is crucial to a good outcome. Each drug and the entire regimen need to be managed with great care in attempting to balance the achievement of optimal therapeutic gains with a new medication and the absence of adverse effects. A careful patient diary that includes information on mood, medication, sleep, and side effects is of great importance in this therapeutic balancing act. Arriving most rapidly at the optimal treatment regimen for a given individual often involves a compromise of academic rigor in favor of clinical expediency.

If, for example, the addition of lithium to valproate did not make a substantial clinical difference in symptomatic improvement yet did not engender problematic side effects, one might recommend not discontinuing lithium, but adding a new adjunctive agent to the existing lithium/valproate combination. Although lithium may not have provided the desired therapeutic effect, its withdrawal could nonetheless produce a clinical exacerbation. There may be a markedly increased rate of suicide and suicide attempts during lithium discontinuation compared with its continuation. The evaluation of the efficacy of the third agent would also be potentially obscured because one would be requiring the third agent to treat both the previous residual symptomatology and the potential exacerbation related to lithium withdrawal. Thus, a clearer clinical trial evaluation of the third agent may be based on a stable continuation of the lithium/valproate combination to see to what extent the new agent provided increased therapeutic effectiveness with minimal adverse effects.

With a complex illness course such as that associated with rapid cycling, or anxiety or substance abuse comorbidities, one might consider giving the patient 2 mood stabilizers, targeting different aspects of the symptomatology from the beginning rather than engaging in sequential extended monotherapy trials, each with a low likelihood of adequate effectiveness. In this way, if the patient were to have an inadequate response to combination treatment from the outset, one would have saved the patient from 1 of the 2 protracted monotherapy trials in addition to the third combination trial.

In rational polypharmacy, conventional doses and blood level targets are not the primary goal. Rather, maximizing therapeutic efficacy and minimizing adverse effects of the entire regimen is the aim. It is largely because of the effects of pushing conventional dosage regimens to their maximum in clinical trials that the preliminary view of polypharmacy is that it causes more adverse effects. With a careful, individualized approach, the opposite is likely to be the result.
The choice of an initial agent should be based on the currently soft clinical and biological predictors of individual patient responses outlined in the Table. In the large percentage of patients with bipolar disorder who are overweight (50% of women and about 67% of men) or at high risk for obesity, one should consider the use of relatively weight-neutral compounds in an effort to avoid exacerbating weight-related problems.

The next agent should perhaps be targeted at the most prominent residual symptomatology or comorbidity. Of course, choosing an initial agent from the outset that may be effective for both the major presenting symptoms and the comorbidities is optimal (eg, valproate for a patient in a manic phase with a history of migraines, since valproate is FDA-approved for the prevention of migraine). When possible, agents with different mechanisms of action should be considered, particularly when one is choosing among several agents within the same class of mood stabilizers. Rather than using lamotrigine and carbamazepine together (both of which are potent blockers of sodium channels), a more ideal combination may be that of a sodium channel blocker (with its antiglutamatergic effects) with an agent such as valproate that also increases brain g-aminobutyric acid (GABA), or with lithium carbonate, which has a multiplicity of mechanisms of action but no potent blockade of sodium channel influx.

Increasing evidence suggests the value of adding an atypical antipsychotic to a mood stabilizer for treating both depressive and manic episodes. Olanzapine and quetiapine have shown efficacy in the treatment of acute bipolar depression, which is the predominant phase of bipolar illness breaking through naturalistic treatment and often the target of adjunctive treatment. The traditional unimodal antidepressants are potentially mood destabilizing in patients with bipolar disorder. Thus, in a patient who has more complex bipolar disorder and rapid cycling, adding a second mood stabilizer or an atypical antipsychotic to the first mood stabilizer might be a better option than the immediate use of an adjunctive antidepressant. Moreover, the recent data from the study by Sachs and colleagues suggest that 2 of the most widely used antidepressants, bupropion and paroxetine, were no more effective than placebo when added to a mood stabilizer.

The goal is to find synergistic pharmacodynamic effects in the therapeutic realm, while avoiding adverse effects. Although the combination of lithium and valproate is often therapeutically highly effective, in some patients the weight gain or tremor become more problematic with adjunctive treatment. The treating physician can aim for the best therapeutic index by foreseeing and trying to avoid adverse drug interactions.

Potential pharmacokinetic interactions have to be dealt with prospectively. For example, while valproate approximately doubles lamotrigine levels, this does not preclude the use of the combination, which appears to be particularly well tolerated and highly effective in patients with refractory seizure disorders. If valproate is to be added, the dose of lamotrigine needs to be reduced by half. If lamotrigine is to be added to valproate, the rate of titration needs to be markedly slowed with a final target of half the usual maximum daily dose.

Carbamazepine is thought to be a more difficult drug with which to work because of its multiple pharmacokinetic interactions based on induction of cytochrome P-450 3A4 (CYP3A4) hepatic enzymes. This will not only lower the levels of some substances (most problematically estrogen in birth control pills) but potential carbamazepine toxicity from use of common 3A4 inhibitors can occur as well. Patients who are taking doses of carbamazepine just below their adverse-effects threshold should be warned that erythromycin and its analogs and some calcium channel blockers may markedly increase carbamazepine levels and result in considerable CNS toxicity. Such well-known pharmacokinetic interactions can be anticipated and the dose of carbamazepine reduced accordingly, rather than avoiding the use of carbamazepine with an added enzyme inhibitor. Oxcarbazepine is a much less potent enzyme inducer than carbamazepine and has no black box warning for hematological toxicity, so it may be useful for someone reluctant to take carbamazepine. Whether it has efficacy equal to carbamazepine is not known. The only adverse effect more prominent with oxcarbazepine is hyponatremia.

The crucial steps are careful longitudinal monitoring, individualized choice of agents to target predominant symptomatology and comorbidities, and individualized dosage and rate of titration to maximize the effects of the adjunctive agent without incurring adverse effects. To achieve maximum clinical improvement and avoid engaging in sequential potentially ineffective mono-therapy trials, drugs with intolerable adverse effects need to be rapidly discontinued and the treatment base with a partially effective drug combination needs to be maintained.

The old rubric “what gets you well, keeps you well” makes sense with the exception of attempting to remove agents that may be causing problematic side effects. This might particularly be the case when a patient has had a good response to, for example, olanzapine, but is gaining significant...
weight, so that after the acute treatment phase, one might want to explore the potential effectiveness of replacing olanzapine with a different atypical that is more weight-neutral. In instances in which the patient is doing well and remaining well, the overriding message is to be conservative and "stay the course." Conversely, in instances in which treatment response is inadequate or adverse effects prove difficult, one should continue active exploration of other options. The point at which the basic foundation of a treatment regimen is discarded in favor of an entirely different approach is not clear. Perhaps when one reaches the point that basic drug components of a treatment regimen (2 mood stabilizers plus an atypical antipsychotic) are not proving effective even when multiple other adjunctive agents are added to the regimen, it may be appropriate to substitute multiple agents of the core treatment and then begin to engage in sequential augmentation and substitution with different treatments. Obviously, it would be preferable to have specific data about not only optimal response to complex combination treatments but also thresholds for recommending major revisions and alternative treatments. However, in the absence of such data, the clinician and patient are forced to make this risk/benefit ratio judgment based on the best individual response data available for that patient.

In the absence of adverse effects, data support maintaining full doses of each agent in the entire regimen that resulted in the acute improvement into the continuation and long-term prophylactic phases for a number of reasons. In their study of antidepressant discontinuation in unipolar depression, Kupfer and colleagues\textsuperscript{13} found that dose reductions may produce relapses at almost the same rate as complete drug discontinuation. Moreover, if one has experienced repeated bouts of tolerance development to single agents or their use in combination, applying maximum well-tolerated doses rather than the traditional minimally effective dose may be less likely to result in the development of tolerance.\textsuperscript{14}

\textbf{Choosing first and second agents}

As outlined in the Table, there are only weak clinical indicators of an increased likelihood of response to a major mood stabilizer (lithium, valproate, carbamazepine, or lamotrigine). Nonetheless, several of these may be useful, including a positive family history in first-degree relatives of response to lithium for bipolar disorder or response to lamotrigine for anxiety disorder, and a negative family history of affective disorders in those responding to carbamazepine. Comorbidities are particularly pertinent, often problematic, and require specific adjunctive pharmacological treatments. About 40\% of patients with bipolar disorder present with a comorbid anxiety disorder.\textsuperscript{15} One of the correlates of lithium nonresponse or inadequate response is the presence of an anxiety disorder, leading to the necessity of using an adjunctive agent if lithium is in the core regimen. In the realm of anxiety disorder treatments, it is noteworthy to emphasize that 2 agents that are not effective in the treatment of acute mania, and therefore not considered mood stabilizers, ie, gabapentin and topiramate, may nonetheless be useful in targeting specific anxiety disorder comorbidities.\textsuperscript{7} For example, gabapentin is effective in the treatment of panic disorder and social phobia and, in the absence of data to suggest otherwise, one may infer that this drug would also be effective when these anxiety disorders are comorbid with bipolar illness. Whether this is actually the case ultimately deserves specific clinical trials in patients with bipolar disorder, but in their absence, the physician needs to decide whether to use such agents as adjunctive therapy on an individual basis.

A number of studies indicate that patients with bipolar disorder and comorbid anxiety disorders have a poorer outcome and more difficult course of illness than those without anxiety comorbidity.\textsuperscript{16} However, in those patients with a complicated course of illness such as that manifested by ultrarapid or ultradian cycling, the traditional use of antidepressant agents for a variety of anxiety disorders may be problematic. In these instances, there is much data to support the addition of another mood stabilizer with evidence of anxiolytic properties such as valproate, lamotrigine, or carbamazepine or an atypical antipsychotic such as quetiapine (which has been shown to have marked anxiolytic effects as monotherapy in bipolar depression, in addition to its antidepressant and sedative effects).\textsuperscript{17} The addition of a mood stabilizer or an atypical antipsychotic may further target mood stability and may provide anxiolytic effects better than the addition of an antidepressant, which may be mood-destabilizing. Again, the principle of attempting to yield a "2-for-1" benefit of an adjunctive agent is highly desirable compared with a "1-for-1" agent or a "0-for-1" agent, such as in the hypothetical antidepressant example noted above (where the positive anxiolytic effects are canceled out by the mood-destabilizing effects, yielding no additive benefit).

Many of the same caveats are appropriate for considering agents that may be used for substance-abuse comorbidities in patients with bipolar illness when they have only been tested in the primary syndrome. The study by Johnson and colleagues\textsuperscript{18} suggests that topiramate has marked
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Efficacy in reducing intake of and craving for alcohol in those with primary alcoholism. However, since topiramate has been widely used as an adjunct in multiple clinical trials in patients with bipolar illness with some success, the potential utility of this agent instead of one such as acamprosate or disulfiram, which have not been widely studied or used in patients with bipolar illness, would appear greater.

In some instances, there may be direct discrepancies between the estimate of the efficacy of a given agent in the primary syndrome, based on controlled clinical trials, and the potential or theoretical value of that agent in patients with bipolar disorder. A good example of this may be baclofen: preliminary data indicate that it is more effective than placebo in reducing cocaine abuse\(^{19}\), however, this agent might be considered relatively contraindicated in those with bipolar disorder because it has been reported to exacerbate depression in a small series of affectively ill patients studied in a double-blind, on-off-on design.\(^{20}\)

In addition to the possible consideration of topiramate because of its positive effects compared with placebo in a controlled study of cocaine abuse, one might also consider a clinical trial of modafinil in light of the report of its efficacy in a controlled trial in primary cocaine users.\(^{21}\) Emerging evidence also shows that modafinil may have positive effects on residual depression, fatigue, attention, and energy symptoms in inadequately treated patients with bipolar disorder who are depressed.\(^{22}\)

**Minor augmenting agents**

Some data support the use of triiodothyronine (T\(_3\)) augmentation in those patients with more difficult-to-stabilize bipolar disorder. There is considerable evidence for the efficacy of T\(_3\) augmentation, particularly in unipolar depression, and potentially positive effects in patients with bipolar disorder have been seen as well (Frye et al, unpublished data, 2000). Moreover, Kocsis and colleagues\(^{23}\) reported that T\(_3\) augmentation of lithium improved subtle aspects of cognition. It is pertinent to remember that T\(_3\) augmentation has been found to be useful independent of abnormalities in the thyroid axis. The use of low doses (25 to 37.5 µg in the morning) with the short half-life of T\(_3\) and usually a benign adverse-effects profile should be distinguished from the supraphysiological doses of T\(_4\) recommended by Bauer and Whybrow\(^ {24}\) and Bauer and colleagues\(^ {25}\) for treatment-refractory depression and rapid cycling.

In these instances, one might expect minor increases in tachycardia, nighttime sweating, etc, where one is attempting to push the patient toward a free thyroxin index of 150% of normal, often that achieved with 200 to 400 µg daily. However, because of the long half-life of T\(_4\), titration should proceed extremely slowly. Because of questions about acute and long-term tolerability, this strategy should be reserved for later in the sequence of clinical trials as opposed to T\(_3\) augmentation, which is often benign and useful early in augmentation strategies.

On the basis of multiple rationales, augmentation with folate (1 mg in women and 2 mg in men) can be considered a useful early strategy in those with difficult-to-treat depressive components of bipolar illness. Controlled clinical trials, albeit small, indicate that folate was more effective than placebo in potentiating the antidepressant effects of serotonin-selective antidepressants in patients with unipolar depression\(^ {26}\) and augmenting the effects of lithium prophylaxis in patients with bipolar disorder.\(^ {27}\) Moreover, it reduces levels of homocysteine, which have been associated with a greater degree of cognitive impairment and are a risk factor for cardiovascular disease. Valproate increases homocysteine levels so that regular use of folate with this agent would appear indicated. Folate supplementation in women of childbearing age is also worthy of consideration in relation to the possibility of unwanted pregnancy during treatment with valproate, carbamazepine, or lithium, which have been associated with the potential for severe congenital malformations.

Topiramate and zonisamide have both been shown to decrease the number and amount of binges in eating disorders.\(^ {28, 29}\) In addition, in those with nonbinge eating disorders, both have been associated with the potentially positive side effect of weight loss in numerous studies in both patients with seizure disorders and those with affective illness. Thus, use of these agents in conjunction with a drug that is prone to cause weight gain or as an adjunctive weight-loss drug in those who have already gained weight may be considered. Because some patients taking topiramate may have cognitive impairment and word-finding difficulties, even with low doses, zonisamide may be a useful alternative. Although no controlled trials are available, open clinical observations suggest the potential usefulness of zonisamide against affective symptomatology, particularly mania.\(^ {30}\)

Although the results of a recent study of 6 g of eicosapentaenoic acid (EPA) versus placebo were negative,\(^ {31}\) a number of studies of 1 to 2 g of omega-3 fatty acids or higher doses of the combination have shown positive results in controlled clinical trials in unipolar and bipolar depression.\(^ {32}\) There is some ambiguity about efficacy, but the high tolerability and safety of this compound make it worthy of consideration, particularly in youths, where the risk-benefit ratio is paramount.
In this article I have not dealt with the crucial variable of augmenting with cognitive-behavioral and psychoeducational approaches, but it should be understood that these are an absolute necessity for the long-term optimal treatment of almost all patients with bipolar illness. Adequate psychoeducation is likely to facilitate the goal of achieving and maintaining remission with the fewest adverse effects, independent of the number of agents required.

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