Selecting Effective Long-Term Treatment for Bipolar Patients: Monotherapy and Combinations

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This article explores the roles of monotherapy and drug combinations in finding effective long-term treatment for individual patients with bipolar disorder. While current practice relies heavily on combinations, many bipolar patients can be successfully stabilized if the initial monotherapy is carefully selected according to the patient's clinical characteristics. The data show that (1) unequivocal responders to long-term monotherapies such as lithium, lamotrigine, or atypical neuroleptics each have a very different clinical profile, including clinical presentation and course, comorbidity, and, in particular, family history and (2) bipolar patients who respond very well to a long-term monotherapy have often completely failed on other monotherapies. Combinations appear indicated particularly in bipolar patients who are treatment-resistant to monotherapy, do not tolerate it well, or have not yet exhibited the clinical characteristics needed to choose an effective monotherapy.

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A clinician treating patients with bipolar disorders often faces critical questions when sitting in front of a patient: "How do I best treat him or her to stave off further recurrences? When do I persevere with a single drug, and when do I resort to drug combinations?"

The relative role of monotherapies and drug combinations has become particularly challenging in the management of bipolar disorders. Combinations have always had their place in medicine, and they certainly continue to be needed in bipolar disorders. While a mood stabilizer has become the cornerstone of an effective treatment, there may always be the need to add further medication to improve sleep, reduce anxiety or depression, or enhance the stability of mood. To what extent, though, is the prevailing practice of combining different putative mood stabilizers helpful and appropriate in bipolar patients?

DRUG COMBINATIONS IN CURRENT PRACTICE

Currently, when a bipolar patient is started on long-term treatment, lithium or divalproex is usually prescribed first, according to recommendations in the literature (for example, see references 1 and 2). However, first treatments are very often insufficient and do not lead to stabilization. After a patient experiences additional recurrences, the situation calls for a better strategy. Rather than discontinuing the ineffective but officially recommended lithium or divalproex, common practice is to keep adding further medications until some stability is achieved. There are currently at least an additional 8 promising putative mood stabilizers, any of which a clinician can choose to add: lamotrigine, olanzapine, risperidone, quetiapine, clozapine, carbamazepine, topiramate, and gabapentin.

Furthermore, as several of the drugs employed in the treatment of bipolar disorders are used in combinations in the treatment of epilepsy,[3] it is easy to assume a similar requirement for their use in bipolar disorders. Supporting the need for combinations is also the common observation that stopping one of the combination drugs may lead to a prompt increase of symptoms such as anxiety, irritability, or restlessness. Thus, the conclusion commonly drawn from such observations, usually anecdotal, is, not surprisingly, that to achieve stability, bipolar patients should be treated with drug combinations.

LIMITATIONS IN INTERPRETING CLINICAL ANECDOTES

Anecdotal observations can be interpreted in more than one way. In bipolar patients, several issues need to be considered when attempting to draw general conclusions from individual case histories. First, the benefit that a clinician observes from a mixture of drugs can be derived either from the combination itself or from one of the drugs that was eventually included in the combination. Theoretically,

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a clinician could, of course, start testing which medications may be unnecessary by eliminating one after the other. In practice, however, when a patient finally improves on treatment with a complex combination, the last thing that appeals to both a clinician and a patient is to risk disrupting the improvement.

A second set of obstacles to interpreting anecdotal observations comes from the capriciousness of the natural course of bipolar disorder. Solid statistical predictions can be made about the course of bipolar illness of a large number of relapsing patients; an individual course is a different matter. The untreated development is difficult to predict in an individual, particularly at the early stage at which we now usually intervene with treatment. When a treated patient is free of recurrences, it is difficult to tell if such a remission is spontaneous or due to the treatment, unless the illness has previously established a clear pattern of episodes. A very long, recurrence-free first or second cycle of bipolar illness was not uncommon with no treatment.[4] Even if, after the first or second episode, a treated patient remains without recurrence for several years and later starts relapsing, it does not automatically mean that the first drug worked and should be included in a combination.

For example, if a patient recovers from a first manic episode after treatment with lithium and then is kept recurrence-free on lithium treatment for 3 years, the clinician often concludes that the patient has remained stable because of lithium. If the patient then suffers a recurrence on lithium treatment, the clinician may assume that lithium is losing its efficacy and will add another medication. Yet, the 3-year remission may have been spontaneous, and lithium may be of no benefit to the patient. Generally speaking, the second episode of bipolar illness emerges after a very variable period of time, sometimes several months, sometimes many years. The illness may have simply run its natural course unaffected by lithium treatment, and a careful, comprehensive clinical assessment would show that the patient is not likely to benefit from lithium and may require a different long-term approach, for example, treatment with an atypical neuroleptic or lamotrigine. Very few clinicians now have an opportunity to see the unfolding of an untreated bipolar illness, and, therefore, they overestimate their ability to assess the risk of further recurrences. The capriciousness of bipolar illness often leads to incorrect assumptions about untreated course and about the benefits of treatment.

A third complication in interpreting anecdotal observations relates to the lack of satisfactory long-term clinical trials for bipolar disorders. The information we have at this point about the efficacy of treatments comes mostly from short-term drug studies and cannot be directly extrapolated to long-term treatment. Usually, the findings from short-term antimanic drug trials have been quickly extrapolated into long-term use without sufficient justification. Sodium divalproex is a good example: this medication has been proven as an effective antimanic agent in acute trials and has not succeeded in long-term evaluation,[5] yet it is the most commonly used long-term treatment of bipolar disorders in the United States.

The next problem stems from the fact that drug trials tell us much about drugs but little about patients. Virtually all recent recommendations about the treatment of bipolar patients have come from short-term drug trials designed for regulatory purposes. Such trials are developed to answer the questions of drug efficacy and safety and do not contribute to clarifying differential treatment responsiveness. Undoubtedly, drug trials are important for clinical decisions; they can tell us which medications are effective and safe. Furthermore, post hoc analyses from drug trials may provide hints as to who might benefit, but they cannot satisfactorily answer questions for which they have not been constructed. In addition, trials comparing a new drug and placebo and involving several hundred patients may produce differences that are statistically significant but have little practical relevance because they reflect benefit experienced by only a small proportion of patients.

Evidence-based medicine should not be limited to drug trials; it must utilize all valid information, including patient-oriented studies and extensive clinical series. To clarify which patients benefit, we need studies focusing on the characteristics of bipolar patients ("patient trials")—patient-oriented evidence to find out which patients respond. Unfortunately, properly designed, randomized studies of this kind are lacking. Through compilation of this knowledge, tentative treatment recommendations can be made and the majority of bipolar patients can be selected for an effective long-term treatment according to their clinical characteristics.

THE IDEAL STUDY OF LONG-TERM BIPOLAR TREATMENT THAT WILL NOT TAKE PLACE

To answer correctly the question of effective long-term treatment for bipolar disorders, we need studies in which a large number of bipolar patients would be randomly assigned to several of the most promising putative mood stabilizers and placebo, and the long-term outcome would be carefully evaluated. If such a study included a sufficiently large number of patients and all were comprehensively assessed at the beginning of the study, the characteristics of responders to effective stabilizers would be identified. Experience has shown that such a demanding study would have to draw candidates from tens of thousands of bipolar patients[6] to end up with the number of patients necessary for a multi-pronged evaluation.

Such a definitive but ambitious and expensive study has not been performed, and there is no indication that it will take place at any time in the near future. While the

necessary resources for this kind of study are available within the pharmaceutical industry, it is impossible to imagine that a number of pharmaceutical companies would come together and pool their resources just to face the possibility that their particular drug will be rejected for long-term use. Realistically, it is more likely that other approaches such as molecular genetics will lead to new diagnostic and therapeutic thinking before any such definitive long-term study is attempted.

In the meantime, in the spirit of evidence-based medicine,[7] we must draw useful recommendations for the long-term treatment of bipolar disorders from all relevant, valid information and compile it as best as we can. Research money is now channeled primarily into drug studies and will continue to be directed there, and randomized long-term studies to identify the true responders to different types of treatment are absent. Therefore, it is important to integrate into our thinking observations on excellent, unequivocal responders to the main long-term treatments, regardless of whether the design included randomization or blind assessment. While blinding is essential in acute trials, in prophylactic trials evaluating whether a major recurrence took place, blind and open trials resulted in similar findings.[8,9]

DATA FROM UNEQUIVOCAL RESPONDERS COMPLEMENT OUR DECISIONS

To explore the clinical characteristics of patients who will achieve long-term stabilization from a particular drug, I have utilized additional information beyond the available drug trials. In this article, I briefly review complementary data from a series of unequivocal responders to 3 main types of long-term treatments for bipolar disorders, lithium, lamotrigine, and, as a representative of atypical neuroleptics, olanzapine. All 3 treatments have been shown in controlled, double-blind randomized trials to be effective in the extended treatment of groups of patients with bipolar disorders.[10–17] On the basis of these trials, these 3 treatments could at this time be described as prototypical long-term treatments for bipolar disorders. Observations from unequivocal responders offer indications as to how we can select an effective long-term treatment for an individual patient with the help of the patient's particular clinical profile. In addition, the findings suggest that with this approach many patients can be stabilized on a single drug, without necessarily resorting to combinations and the current time-consuming trial-and-error process of establishing long-term treatment. Furthermore, the data indicate that in individual cases, not all stabilizers are equally effective; rather, that particular agents are effective for specific patient subgroups.

The body of emerging data indicates that a group of unequivocal responders to long-term monotherapies such as lithium, lamotrigine, and atypical neuroleptics has different and distinct clinical profiles. The differences include clinical presentation and course of illness, comorbidity, and, in particular, family history, thus implying that the responders to each of the 3 treatments may reflect a clinically relevant subtype of bipolar disorders.

What are these different characteristics? While the characteristics of unequivocal lithium responders have been known for some time,[18,19] the probable features of beneficiaries from lamotrigine and olanzapine have emerged in particular from 2 studies, one performed in Halifax, Nova Scotia, Canada,[20] the other, in Ottawa, Ontario, Canada.[21] The conclusions of Passmore et al. in Halifax are outlined in the lamotrigine section.

RESPONDER STUDIES

In a consecutive series of Ottawa patients diagnosed as suffering from bipolar disorder according to DSM-IV criteria, requiring long-term prophylaxis with medication, and treated in our program for 3 years or more, 112 patients have been rated as having a score of 7 points or more on Alda's scale for the outcome of long-term treatment.[22] This scale has been satisfactorily validated, and its usefulness has been demonstrated internationally. A score of 7 or more indicates a very good result of long-term treatment, associated with a high likelihood that the outcome is a result of the administered medication.

All patients were interviewed according to the Schedule for Affective Disorders and Schizophrenia (SADS)-Lifetime Version format, and the course of illness preceding long-term treatment was described on the basis of all information available about the patients, including interviews of them and their relatives, as well as their records. Family history was obtained from 2 or more first-degree relatives in each family, with the aid of the SADS-Family History Version. A total of 756 first-degree relatives have been included in this study.[21] Fifty-two percent of all first-degree relatives were interviewed directly, and when a direct interview of a relative was not possible, the information was compiled from the interviews of 2 or more relatives. This group of patients can be described as follows: mean ± SD age at onset, 24.7 ± 9.7 years; number of episodes preceding the initiation of long-term treatment, 6.1 ± 7.2; gender distribution, 58% women.

Compared with lamotrigine and olanzapine, the proportion of responders to long-term lithium followed in our program is disproportionately large. Genetic research conducted by my colleagues and me has focused on this particular group and the systematic follow-up of such patients.

Responders Differ in Family History

The investigated bipolar patients had 756 first-degree relatives; 82 with the diagnosis of bipolar I and II disorders, 52 with major depressive disorders, 19 with anxiety/panic disorders, 38 with substance and alcohol addiction,

Table 1. Family Study of 112 Bipolar Patients Who Responded to Lithium, Lamotrigine, or Olanzapine: Diagnoses of 756 Relatives[a]

Disorder	N
Bipolar I and II disorders	82
Major depressive disorders	52
Anxiety, panic disorders	19
Substance, alcohol addiction	38
Schizophrenia, other psychoses	19

[a]Data from Grof.[21]

Table 2. Family Study of Bipolar Patients Who Responded to Lithium, Lamotrigine, or Olanzapine: Diagnoses of 756 Relatives (%)[a]

Disorder	Lithium	Lamotrigine	Olanzapine
Bipolar I and II disorder	13*	4	6
Major depressive disorder	3	20	15
Anxiety, panic disorder	0.4	15*	3
Substance, alcohol addiction	3	16*	5
Schizophrenia, other psychoses	0.7	4	11*

[a]Data from Grof.[21]
Symbol: * = statistically significant difference.

and 19 with schizophrenia and other psychoses (Table 1). It is apparent that, overall, the rate of alcoholism in relatives of bipolar probands is less than that reported in some U.S. studies.

The family history loading was, however, strikingly different for each group of responders. When the responders to long-term treatment with 3 different medications were compared, only the lithium responders had a significant excess of bipolar disorders. The first-degree relatives of bipolar patients responding to lamotrigine had an overabundance of anxiety disorders, panic attacks, substance abuse, and alcohol addictions, while those benefiting from olanzapine had no excessive bipolar or anxiety disorders but did have a higher rate of psychotic illnesses among relatives. For an easier, more direct comparison, Table 2 presents the findings in percentages rather than as the raw data that were used for statistical analysis.

Responders Differ in Comorbidity

The types of psychiatric disorders found among the relatives of bipolar responders also trouble the responders themselves, as comorbid conditions. Not only their relatives, but also the lamotrigine responders, tend to have more problems with substance and alcohol addiction, anxiety, and panic, while a history of mood-incongruent psychotic symptoms is present among the olanzapine beneficiaries (Table 3).

Responders Differ in Clinical Course

Our study[22] also found differences in pretreatment clinical course between responder groups. Lithium responders present with an episodic, fully remitting course and often have a predominance of depressive over manic episodes. On the other hand, lamotrigine and olanzapine responders tend to have mostly nonepisodic courses with residual symptoms and exacerbations, and olanzapine responders additionally have a predominance of manic episodes. The differences in long-term clinical course are striking. For lithium responders in particular, the episodic fully remitting course is very characteristic. However, the findings are described only briefly here, because in current practice, clinicians often treat before a pattern of recurrences is established and frequently do not have enough time to evaluate the clinical course thoroughly enough to be able to use the findings in treatment decisions.

Table 3. Comorbidity and Symptoms in Responders to Lithium, Lamotrigine, or Olanzapine (%)[a]

Disorder	Lithium	Lamotrigine	Olanzapine
Substance, alcohol addiction	12	56	44
Anxiety, panic disorders	3	28	6
History of mood-incongruent psychotic symptoms	11	13	59

[a]Data from Grof.[21]

Table 4. Comorbidity in Responders to Lamotrigine and Lithium (%)[a]

Diagnosis	Lamotrigine (N = 7)	Lithium (N = 14)	χ^2	p
Panic disorder and/or panic attacks	57.1	0	9.88	.002
Substance abuse	71.4	21.4	4.95	.03

[a]Data from Passmore et al.[20]

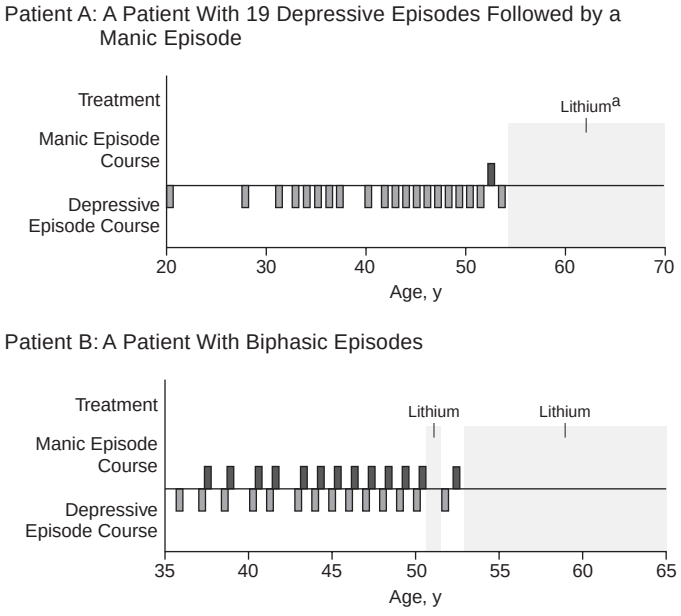
Halifax Study of Differential Responsiveness

The findings from Ottawa presented here are in good agreement with findings that Alda and colleagues reported in 2001 from Halifax.[20] In a smaller but methodologically sound study, they compared lamotrigine and lithium responders and their families. The authors hypothesized that lithium- and lamotrigine-responsive patients differ with respect to phenotypic variables other than treatment response. Among the variables included in the study were clinical characteristics, such as the course of illness, comorbidity, and rates of psychiatric illness among first-degree relatives. Their findings supported the idea of distinct subtypes of bipolar disorder. In particular, the group found an excess of bipolar disorders among first-degree relatives of lithium responders (16.6% for the first-degree relatives of lithium responders as compared with 2.5% for relatives of lamotrigine responders) and greater comorbidity among lamotrigine probands with panic and anxiety disorders, as well as alcohol and substance abuse (Table 4). Given the current interest in the use of lamotrigine and atypical neuroleptics in bipolar disorders, more comparable studies will hopefully be completed in the near future.

Table 5. Characteristics of Lithium, Lamotrigine, and Olanzapine Responders

Characteristic	Lithium Responders	Lamotrigine Responders	Olanzapine Responders
Presentation	Typical, classical	Atypical features	Atypical features, presence or history of psychotic and mood-incongruent symptoms
Family history	Bipolar disorders, with episodic course	Anxiety and panic disorders, substance and alcohol addiction	Increase of psychotic disorders
Course	Episodic, fully remitting, predominance of depressions	Nonepisodic, with residual symptoms	Nonepisodic, with residual symptoms; overactive episodes often more frequent than depressions
Comorbidity	Rare	High, with anxiety and panic disorders and alcoholism and addiction	Substance and alcohol addiction

Figure 1. Lithium Response in 2 Patients With Bipolar Disorder



[a]Patient remained stable on lithium monotherapy for over 25 years.

CHARACTERISTICS OF RESPONDERS

Lithium Responders

To summarize for clinical practice, lithium responders present with depressions and manic episodes of the classical type without mood-incongruent symptoms, depressive syndromes dominated by mood abnormalities (for example, emphasis on sadness and hopelessness rather than inability to think clearly and low motivation), and often euphoric rather than dysphoric manias (Table 5). In their family history, they tend to have bipolar disorders with episodic course. The patients themselves also have an episodic, fully remitting course. If the course has already evolved into several recurrences, the clinician can usually see a predominance of depressions over overactive episodes. Finally, these patients relatively rarely have any comorbid conditions.

Two characteristic examples of excellent lithium responders are presented graphically in Figure 1. The female patient represented in Figure 1A, who has a bipolar family history, suffered 19 classical depressions with a fully remitting course. Eventually, she experienced a manic episode, was placed on lithium treatment, and remained fully stable over 25 years on monotherapy.

The patient represented in Figure 1B, who had similar clinical characteristics, but biphasic episodes, was placed on lithium treatment, remained stable for a while, then discontinued treatment and manifested a recurrence; after the reintroduction of adequate lithium dosage, this patient has remained stable on lithium monotherapy for many years. Overall, the characterization of this group of unequivocal lithium responders is similar to the description we published earlier.[18,19]

Lamotrigine Responders

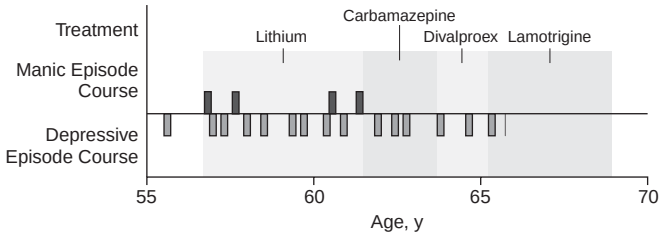
The characteristics of responders to lamotrigine prophylaxis are different from those of lithium responders. In the clinical presentation, they often have atypical features: their low mood is often characterized as emotional emptiness, apathy, or indifference, with great difficulty to motivate themselves, while hypomanias appear more frequently as activations than euphoria (Table 5).

These patients often have in their family history anxiety disorders or substance abuse and alcoholism, with an illness course that is nonepisodic and between episodes often entails residual symptoms of, for example, anxiety or panic attacks. Similarly, these patients usually have substantial comorbidity similar to that in their family history (S. Chiu, M.D.; G. Sidhu, M.D., manuscript submitted). An example of a lamotrigine responder is presented graphically in Figure 2, which shows a man with a preexisting anxiety disorder who later in life developed bipolar episodes unresponsive to lithium, carbamazepine, and divalproex but has since been completely free of mood problems on lamotrigine treatment.

Responsiveness to Other Antiepileptics

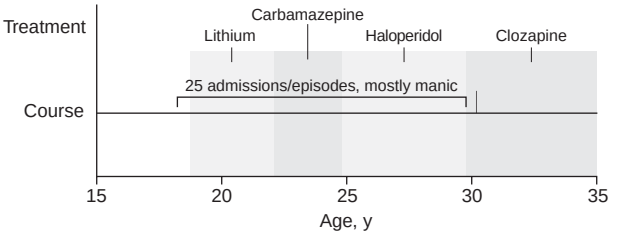
It is interesting that so far lamotrigine occupies a special position among antiepileptics in terms of the responsiveness of bipolar illness to long-term treatment. Our observations of lamotrigine responders indicate that they had not achieved complete stabilization on carba-

Figure 2. Lamotrigine Response in a Patient With Bipolar Disorder[a]



[a]Patient had a preexisting anxiety disorder prior to the onset of the mood disorder. The thin vertical line on the timeline indicates a recurrence of milder intensity.

Figure 3. Clozapine Response in a Patient With Bipolar Disorder[a]



[a]Patient had slight residual symptoms in cognition and motivation. The thin vertical line on the timeline indicates a recurrence of milder intensity.

mazepine or divalproex when such treatment was attempted earlier.

Despite divalproex being the most frequently used medication in the long-term treatment of bipolar disorders in the United States, the data on it are missing from our investigations for 2 reasons. First, unlike lithium, lamotrigine, and olanzapine, the evidence from controlled clinical trials for the long-term efficacy of divalproex is not available. The long-term trial by Bowden et al.[5] failed to prove a superiority of divalproex over placebo on the primary efficacy indicator. Furthermore, in our studies, the number of patients treated with divalproex who had a benefit score of 7 or more was too small for statistical analysis. It may be of interest that the few patients benefiting from long-term divalproex differed from the lamotrigine responders in their clinical characteristics; for example, they experienced mainly overactive episodes during the pre-divalproex course of illness.

Observations relevant to carbamazepine response have emerged particularly from investigations performed by Greil et al.[23] This large German study illustrated well the existence of response subtypes. Patients suffering from typical, classical bipolar disorders responded significantly better to long-term lithium compared with carbamazepine treatment, while those with atypical bipolar disorders benefited somewhat more from carbamazepine.

Olanzapine Responders

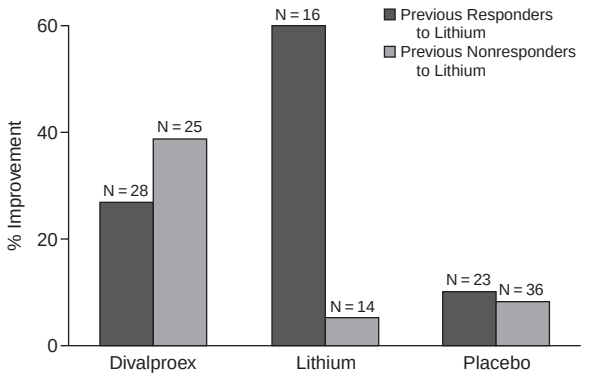
Finally, olanzapine responders again have atypical features characterizing both their depressions and manias. It is often possible to identify mood-incongruent psychotic symptoms in their past or present clinical presentation (Table 5). Family history, if positive, tends to show psychotic disorders or chronic psychiatric disorders. Similar to lamotrigine responders, the clinical course for olanzapine responders includes residual symptoms between episodes of depressions and manias, but, if fully developed over time, shows more manias than depressions. Comorbidity with other psychiatric disorders is frequent, particularly with alcoholism and substance abuse. In a cluster analysis, a history of mood-incongruent psychotic symptoms, residual symptoms between the recurrences, and a family history of nonepisodic psychiatric disorders contributed markedly to separating olanzapine response from lithium response. While in acute studies of manic patients treated with olanzapine both psychotic and nonpsychotic patients seemed to benefit,[24] such conclusions were drawn post hoc and cannot be directly extrapolated to long-term treatment.

Responsiveness to Other Atypical Neuroleptics

The efficacy of olanzapine in bipolar patients has already been demonstrated in double-blind randomized trials. For other atypical neuroleptics, such findings in bipolar patients have not been available. Therefore, the main group of patients receiving atypical neuroleptics included in this study was on olanzapine treatment. Nevertheless, responders to clozapine and risperidone successfully treated in our program present with clinical features that are, so far, indistinguishable from those of olanzapine responders. Despite similar features of responders to atypical neuroleptics, however, the most dramatic changes in the course of bipolar illness were observed in patients treated with clozapine (for example, see Suppes et al.[25]). Yet, our observations do not allow for a direct comparison between clozapine and other atypical neuroleptics, because clozapine was employed only as the treatment of last resort in these patients. Clozapine is available to us only under special restrictions. These striking findings are compatible with Meltzer's observations in schizoaffective patients (H. Y. Meltzer, M.D., oral communication, May 2000).

An example of a clozapine responder is presented in Figure 3: a divorced woman, a very talented artist, was extremely ill between the ages of 18 and 29 years, with very acute manic episodes, constantly requiring readmissions, and had failed treatment with lithium, carbamazepine, and haloperidol, both oral and injectable. She has now been completely well on clozapine treatment for nearly 6 years. One of her sisters has shown personality changes resembling chronic psychotic illness.

Figure 4. Improvement in Manic Patients With Known Lithium Responsiveness (N = 142)[a]



[a]Data from Bowden et al.[27]

SELECTIVITY OF RESPONSE TO LONG-TERM TREATMENT

Thus, the body of emerging data shows that a group of unequivocal responders to long-term monotherapies such as lithium, lamotrigine, and atypical neuroleptics have different profiles. It is important to consider that these responses appear selective: bipolar patients who benefit from a long-term monotherapy have often completely failed on other monotherapies. A few examples are mentioned here. Earlier, I published a report[26] describing a group of excellent responders to lithium prophylaxis who requested a trial of carbamazepine and failed and a group of patients who benefited from carbamazepine and later failed a trial of lithium. The later observations of Greil et al.[23] are compatible with these differences. Bowden et al.[27] observed (Figure 4) that manic patients who previously responded well to lithium later responded well to lithium again, but not to divalproex.

More recently, Tohen et al.[28] reported that olanzapine treatment succeeded in patients who had previously failed on lithium and divalproex treatment. Long-term treatment responders included in this study demonstrated a similar selectivity of response. Most of the lamotrigine and olanzapine responders in particular failed to respond previously to lithium prophylaxis. This observation of selective response does not support the clinical impression that many bipolar patients benefit partially from several different treatments and that, therefore, these treatments usually need to be combined.

STABILITY OF RESPONSE TO DRUG MONOTHERAPY

Finally, there is also a large published body of clinical data on bipolar patients systematically treated with long-term monotherapy who have remained successfully stabilized for years or decades. This is particularly true for lithium,[29–35] although the observations of stable, long-term response are also accumulating for clozapine, lamotrigine, and other long-term treatments. In addition, the patients on long-term lithium treatment also show a striking normalization of mortality and markedly decreased suicidal behavior.

INDICATIONS FOR COMBINATIONS

Combinations of medications have always had their place in medicine and are still needed for the treatment of bipolar patients.[36–39] While for bipolar patients a mood stabilizer has become the cornerstone of long-term treatment, there may always be the need to add further medication to improve sleep and reduce anxiety or depression. Furthermore, clinicians use combinations because they experience treatment failures during the initial stage of treatment of a bipolar patient and because they are not familiar with the characteristics that identify responders to mood stabilizer monotherapies. Because monotherapies often can be helpful in carefully selected bipolar patients, it is preferable to focus the use of combinations on more specific situations, for example, when a patient fails on adequate monotherapy, when clinical data provide no leads as to which monotherapy to choose (such as in an early episode), or when a patient does not tolerate adequate monotherapy.

There is a question, however, as to what extent the current practice of combining different putative mood stabilizers is justifiable in virtually all bipolar patients. Patients with bipolar disorder referred for consultation to our program usually arrive taking a combination of 4 or 5 or more putative mood stabilizers. This is not difficult to understand, because we are dealing with a very capricious illness and a number of promising mood stabilizers are easily available. What is most disconcerting, though, is that often patients treated with a combination of mood stabilizers have not had an adequate trial with a sufficient dosage of a single mood stabilizer. In addition, an incorrectly chosen combination can be detrimental to the long-term course of bipolar illness.

Initial failure of a mood stabilizer should be expected very frequently because the probability of arriving at an effective long-term treatment by the usual approach of trial-and-error is quite low, less than one third.[40] As Garnham et al.[40] have shown in a series of long-term treated DSM-IV–diagnosed bipolar patients, the percentage of patients benefiting from individual monotherapies ranges between 15% and 30%. Many patients responded well, but none of the monotherapies benefited more than one third of the patients, suggesting that the important task is to find when to use which drug as early in treatment as possible.

CONCLUSIONS

Psychiatric illnesses that meet DSM-IV criteria for bipolar disorders affect a large segment of the population and

vary tremendously in their presentation, clinical course, and psychobiological underpinning. Effective long-term strategies need to be correspondingly varied; no single strategy will work for everyone. Data presented here indicate that many patients can be successfully treated with monotherapies. To achieve a skillful matching of a patient and an effective drug, bipolar patients should initially be carefully evaluated. If possible, the most effective monotherapy should be selected on the basis of the patient's clinical profile. While the criteria for selecting lithium responders have grown out of extensive experience and research, the promising observations about patients benefiting from lamotrigine and atypical neuroleptics are still at an early juncture.

For many other bipolar sufferers, however, combination treatment remains the advisable approach, particularly early and late in treatment; in the early stage, because the detailed clinical information needed for the correct selection is often not available, and later in treatment mostly because that is when we encounter patients for whom previous strategies, including monotherapies, failed.

So far, evidence is lacking that polypharmacy with stabilizers is necessary in the majority of bipolar patients, despite current practice. It is, moreover, difficult to justify exposing patients to the side effects of several drugs if mood stabilization could be achieved by 1 primary mode such as lithium, lamotrigine, or atypical neuroleptics.

As definitive, simultaneous comparative trials of putative mood stabilizers will almost certainly not take place, our clinical decisions should be based on a compilation from the available evidence. Such evidence should include not only the findings from acute and long-term drug trials, but also studies designed to clarify characteristics of excellent responders to specific mood stabilizers.

Drug names: carbamazepine (Tegretol, Epitol, and others), clozapine (Clozaril and others), divalproex sodium (Depakote), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), topiramate (Topamax).

Disclosure of off-label usage: The author has determined that, according to the United States Pharmacopeia DI 2002, the off-label use of carbamazepine is the treatment of bipolar disorder, pain, and psychotic disorders; off-label use of divalproex sodium is the treatment of bipolar disorder, epilepsy simple and myoclonic; off-label use of haloperidol is the treatment of nausea, autism, and chorea; and off-label use of lithium is the treatment of depression, headache, and neutrophilia.

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