7 Tables and 5 Figures

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

Paul Grof, M.D., Ph.D., FRCP(C)

Professor, Department of Psychiatry

University of Ottawa

Royal Ottawa Hospital

1145 Carling Avenue

Ottawa, Ontario

K1Z 7K4, Canada

Phone: 613-722-6521, X 7025

Fax: 613-798-2974

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Running Head: Selecting Effective Long-term Treatment

Abstract

Selecting Effective Long-Term Treatment for Bipolar Patients:

Monotherapy and Combinations

This paper explores the roles of monotherapy and 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;
2. bipolar patients who respond very well to one 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.

Introduction. A clinician treating patients with bipolar disorders often faces critical questions when sitting in front of them: "How do I best treat him or her in order 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 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 to enhance the stability of mood. But, **to what extent is the prevailing practice of combining different putative mood stabilizers helpful and appropriate in bipolar patients?**

Combinations in current practice. When a bipolar patient is currently started on long-term treatment, lithium or divalproex is usually prescribed first, according to recommendations in the literature (e.g.[1,2]). But first treatments are very often insufficient and do not lead to stabilization. After the 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. But there are currently at least an additional eight 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, however, 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, a clinician could, of course, start testing which medications may be unnecessary by eliminating one after the other. But in practice, when a patient finally improves on 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 without any 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 into a combination.

For example, if a patient recovers from his first manic episode after treatment with lithium and then is kept on lithium recurrence-free for three years, the clinician often concludes that the patient has remained stable because of lithium. If a patient then suffers a recurrence on lithium, the clinician may assume that lithium is losing its efficacy and will add another medication. Yet, the 3 year-long remission may have been spontaneous and lithium may be of no benefit to this 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 of the patient would show that he is not likely to benefit from lithium and may require a different long-term approach, for example, an atypical neuroleptic or lamotrigine. Very few clinicians now have an opportunity to see the unfolding of an untreated bipolar illness, and therefore they over-estimate 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 our treatment.

A third complication in interpretating 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 analysis from drug trials may provide hints as to who might benefit but they cannot satisfactorily answer the 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 may have little practical relevance because they reflect benefit experienced only by 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 who benefits, 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. By 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 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 randomized to several of the most promising putative mood stabilizers and

placebo, and the long-term outcome 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] in order 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 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 blindness is essential in acute trials, in prophylactic trials - evaluating if a major recurrence has taken place - similar findings were made in blind and open trials.[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, we

have utilized additional information beyond the available drug trials. In this paper I briefly review complementary data from a series of unequivocal responders to three main types of long-term treatments for bipolar disorders - lithium, lamotrigine, and olanzapine as a representative of atypical neuroleptics. All three 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] Based on these trials, these three 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, they 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 have 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 three 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 likely features of beneficiaries from lamotrigine and olanzapine have emerged in particular from two studies, one performed in

Halifax,[20] the other in Ottawa.[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 three years or more, 112 patients have been rated as having 7 or more points in Alda's scale for the outcome of long-term treatment.[22] This scale has been satisfactorily validated and its usefulness demonstrated in international use. A score of seven or better 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 have been interviewed according to SADS-L format and the course of illness preceding long-term treatment described from all information available about the patient, including the patients' and their relatives' interviews, as well as their records. Family history was obtained from two or more first-degree relatives in each family, with the aid of SADS-FH. A total of 756 first-degree relatives have been included into this study. 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 two or more relatives. This group of patients can be described as follows: age at onset 24.7 ± 9.7 years, the number of episodes preceding the initiation of long-term treatment 6.1 ± 7.2 episodes, gender distribution 58% women.

Compared to lamotrigine and olanzapine, the proportion of responders to long-term lithium followed in our Program is disproportionately large. Our genetic research has focused on this particular group and the systematic followup 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, and 19 with schizophrenia and other psychoses (Table1). It is apparent that overall the rate of alcoholism in relatives of BP probands is less than that reported in some U.S. studies.

[insert Table 1 approximately here]

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

[insert Table 2 approximately here]

Responders differ in comorbidity. The types of psychiatric disorders found among the relatives trouble also the bipolar 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).

[insert Table 3 approximately here]

Responders differ in clinical course. There are differences in the pre-treatment 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 in addition has a predominance of manic episodes (Table 4). 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.

[insert Table 4 approximately here]

Halifax study of differential responsiveness. The findings from Ottawa presented here are in good agreement with findings that Alda and his team reported last year 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, Alda's 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 to 2.5% for relatives of lamotrigine responders) and a greater comorbidity of lamotrigine probands with panic and anxiety disorders as well as alcohol and substance abuse. 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.

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. They, 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 have relatively rarely any comorbid conditions.

[insert Table 5 approximately here]

Two characteristic examples of excellent lithium responders are presented graphically (Figures 1 and 2). This female patient (Figure 1) with a bipolar family history suffered 19 classical depressions with a fully remitting course. Eventually she experienced a manic episode, was placed on lithium and remained fully stable over 25 years on monotherapy.

[insert Figure 1 approximately here]

A patient (Figure 2) with similar clinical characteristics but biphasic episodes was placed on lithium, remained stable for a while, discontinued treatment and manifested a recurrence; after the re-introduction 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]

[insert Figure 2 approximately here]

Lamotrigine responders. The characteristics of responders to lamotrigine prophylaxis are different. In the clinical presentation they often have atypical features: their low mood is often

characterized as emotional emptiness, or apathy, or indifference, with great difficulty to motivate oneself, while hypomanias appear more as activations than euphoria (Table 6).

[insert Table 6 approximately here]

In their family history these patients often have anxiety disorders, or substance abuse and alcoholism, the illness course is nonepisodic and in between episodes often entails residual symptoms of, for example, anxiety or panic attacks. Similarly, these patients usually have substantial comorbidity similar to their family history.[23] An example of a lamotrigine responder is presented graphically (Figure 3): a man with a pre-existing anxiety disorder later in life developed bipolar episodes unresponsive to lithium, carbamazepine and divalproex but has since been completely free of mood problems on lamotrigine.

[insert Figure 3 approximately here]

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 on lamotrigine responders indicate that earlier they had not succeeded to achieve complete stabilization on carbamazepine or divalproex when such treatment was attempted.

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 two reasons. First of all, 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 and having the 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 as, 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.[24] This large German study illustrated well the existence of response subtypes. In comparison with carbamazepine, the patients suffering from typical, classical bipolar disorders responded significantly better to long-term lithium treatment while 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 7). Family history, if positive, tends to show psychotic disorders or chronic psychiatric disorders. Similar to lamotrigine responders, the clinical course again has residual symptoms between the 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 in 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 non-psychotic patients seemed to benefit,[25] such conclusions were drawn post-hoc and cannot be directly extrapolated to long-term treatment.

[insert Table 7 approximately here]

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 on atypical neuroleptics included into this study were on olanzapine. Nevertheless, responders to clozapine and risperidone successfully treated in our program present with clinical features so far indistinguishable from 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 (e.g. [26]). 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.[27]

An example of a clozapine responder is presented graphically (Figure 4): A divorced woman, very talented artist, was extremely ill between the ages of 18 and 29, with very acute manic episodes, constantly requiring re-admissions, failing on lithium, carbamazepine and haloperidal, both oral and injectable. She has now been completely well on clozapine for nearly six years. One of her sisters has shown personality changes resembling chronic psychotic illness.

[insert Figure 4 approximately here]

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 one long-term monotherapy have often completely failed on the other monotherapies. A few examples are mentioned here. Earlier we

published a report[28] describing a group of excellent responders to lithium prophylaxis who requested a trial on carbamazepine and failed, and vice versa a group of patients who benefited from carbamazepine. The later observations of Greil et al.[24] are compatible with these differences. Bowden et al.[29] observed (Figure 5) that manic patients who previously responded well to lithium, did well on lithium again but not on divalproex.

[insert Figure 5 approximately here]

More recently, Tohen et al.[30] reported that olanzapine treatment succeeded in patients who had previously failed on lithium and divalproex. Long-term treatment responders included into this study demonstrate a similar selectivity of response. Most of 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,[31-37] although the observations of stable, long-term response are building up also for clozapine, lamotrigine and other long-term treatments. In addition, the patients on long-term lithium 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.[38-41] 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, 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 four or five, 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 on a sufficient dosage of a single one. In addition, an incorrectly chosen combination can be detrimental to the long-term course of bipolar illness.

Initial failure on 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.[42] As Alda et al. 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 - there is no single strategy that 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 their 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, later in treatment mostly because that is when we encounter patients who failed on previous strategies, including monotherapies.

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

As the 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.

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Questions

1. Excellent responders to long-term lithium treatment are characterized by

   a) complete remissions

   b) family history of bipolar disorder

   c) rapid cycling

   d) classical symptom presentation

2. Long-term treatment of bipolar patients with combinations of medications is preferable if

   a) clinical data provide no leads as to which monotherapy to choose

   b) adequate monotherapies have failed

   c) patient refuses long-term treatment

   d) the patient does not tolerate monotherapy

3. Responders to long-term treatment with lithium, lamotrigine and atypical neuroleptics differ in

   a) comorbidity

   b) cortisol response to hypoglycemia

   c) family history

   d) clinical presentation