chapter 22

Improving outcome by selecting effective long-term treatment

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Introduction

If we took the literature on bipolar disorders at face value, we would have to conclude that over time the outcome of long-term treatment has become much worse. While the earlier reports showed very promising results with 75% of bipolar patients benefiting from long-term lithium treatment,[1] recent findings have been very discouraging suggesting response rates between 20 and 35%. However, these numbers are not directly comparable, primarily because of major shifts in the patients under study. Bipolar disorders are now diagnosed much more broadly and more frequently, as a bipolar spectrum, with negative implications for outcomes. In this brief chapter I will review the observations indicating that the current unsatisfactory outcome can be markedly improved by recognizing the striking heterogeneity of bipolar disorders and by selecting the treatment for each individual according to a characteristic clinical profile.

Heterogeneity of bipolar disorders

The recognition that the bipolar disorder diagnosis includes a heterogeneous collection of illnesses has been emerging for some time, both from the classical studies (e.g. reference 2) and more recent investigations (e.g. references 3–5). So far this concept has been neglected by mainstream psychiatry.

Angst analysed the data from his long-term studies of bipolar illness and found three subtypes (Dm, MD and Md) that differed markedly not only in

the clinical course, but also in a number of other important clinical characteristics. Patients of the Dm type experienced major depressive episodes accompanied only by occasional hypomanias; these patients were predominantly women (over 80%) and their age of onset was in the late thirties on average, significantly later than the other two groups. The Md group experienced primarily or exclusively hospitalized manic episodes and in comparison with the other two groups had significantly less chronicity, mortality and suicidal behaviour.

In large multicentre studies Bellivier et al[4] identified and replicated three subtypes of bipolar I patients, based on the age of onset of bipolar illness. Benazzi[6] then reported three similar subgroups from a large series of bipolar II patients. In a comprehensive review Alda[5] also found support for the existence of three main types of bipolar disorder that differed with respect to clinical presentation, course of illness, family history and possibly long-term treatment response.

Together these examples of heterogeneity raise a question: can we improve the outcome of stabilizing treatments by respecting the types of bipolar disorder? This important question could best be resolved in a specifically designed, long-term, cross-over clinical trial, with proven stabilizing treatments, and focusing on the characteristics of bipolar patients. However, given the ethical and feasibility dilemmas involved, such a trial may never happen. In the meantime we need to treat bipolar patients effectively. In addition, evidence-based medicine should not be limited to drug trials; it has to utilize all valid information.[7] Much practically useful information about treatment responsiveness of bipolar patients can be gained from patient-oriented studies, from some drug studies and from extensive clinical observations.

Heterogeneity of responders

Here we briefly review data extracted from a series of unequivocal responders to three main types of long-term treatment for bipolar disorders – lithium, lamotrigine and olanzapine (as a representative of atypical neuroleptics). All three have been shown in controlled, double-blind trials to be effective in groups of patients with bipolar disorders.[8–10] The body of emerging data appears to show that unequivocal responders to long-term monotherapies, such as lithium, lamotrigine and atypical neuroleptics have distinct clinical profiles. The differences include clinical presentation and course of

illness, co-morbidity and in particular family history, thus suggesting that these are clinically relevant subtypes of bipolar disorders.

While the characteristics of unequivocal lithium responders have been known for some time,[11] the likely features of patients who benefit from lamotrigine and olanzapine have emerged mainly from two studies, one performed in Ottawa, and the other in Halifax. In Ottawa a consecutive series of patients was studied who were diagnosed as suffering from bipolar disorder according to DSM -IV criteria, required long-term prophylaxis with medication and were treated in our programme for 3 or more years. To assess the characteristics of unequivocal responders to prototypic long-term treatment, the diagnosis and co-morbidity of each patient was assessed with the SADS-L interview and family history with SADS-FH completed with the patient. In addition, available and consenting first-degree relatives were blindly interviewed using the SADS-L. To be classified as a good responder, each patient had to receive a score on the Alda scale[12] of 7 or better; 112 patients met all criteria and had 756 evaluated relatives.

With regard to family history, loading was strikingly different for each group of responders. When the responders to long-term treatment with three different medications were compared, only the relatives of lithium responders had a significant excess of bipolar disorders. While the first-degree relatives of bipolar patients responding to lamotrigine had an excess of anxiety, panic, substance abuse and alcohol addictions, while the relatives of those benefiting from olanzapine had no excessive bipolar or anxiety disorders but a high rate of chronic psychotic illnesses.

In parallel with the differences in family history between responder groups, there were corresponding dissimilarities in co-morbid disorders. Like their relatives, the lamotrigine responders also had more problems with substance and alcohol addictions as well as anxiety disorders, while a history of mood-incongruent psychotic symptoms was more prevalent among the olanzapine responders.

There were also differences in the pre-treatment clinical course in that lithium responders presented with an episodic, fully remitting course and often had a predominance of depressive over manic episodes. On the other hand, lamotrigine and olanzapine responders tended to have mostly a non-episodic course with significant residual symptoms and exacerbations, with predominance of manic episodes.

The observations on lithium and lamotrigine responders in Ottawa were in good agreement with the findings from Halifax.[13]

The approaches in the two centres had several aspects in common: for example, both teams evaluated the outcome of long-term treatment with the

same Alda scale that takes into consideration the risk of recurrences and various aspects of treatment such as length and compliance; also both teams blindly evaluated the first-degree relatives of the responders, for the purpose of genetic studies.

Clinical characteristics of responders

From these and earlier studies it is possible to derive the main clinical characteristics for bipolar patients responding to each of the major stabilizing treatments: lithium, olanzapine and lamotrigine. These characteristics can be useful in clinical practice in order to identify the treatment of choice for an individual bipolar patient.

Lithium

Responders to lithium stabilization present with depressive and manic episodes of the classical type, without mood-incongruent symptoms, clearly sad depressions and often euphoric manias. In their family history, they tend to have bipolar disorders with an episodic course. They, themselves, have an episodic full-remitting course and, if the course has been extensive, one can usually see a predominance of depressions. Finally, these patients have relatively rare co-morbid conditions (Table 22.1).

Lamotrigine

Responders to lamotrigine stabilization. The characteristics of responders to lamotrigrine prophylaxis are different. In the presentation they often have atypical features: the depression is described as emotional emptiness and apathy, indifference, slow motivation and hypomanias as activations without euphoria. These patients often have anxiety and panic disorders or substance use disorders in their family history; the course of illness is non-

Table 22.1 Characteristics of responder to long-term lithium treatment

Clinical course: episodic, fully remitting, predominance of depressions
Family history: bipolar disorders, with episodic course
Comorbidity: relatively rare, as in the general population
Presentation: classical, as described in earlier textbooks (e.g. depressions with sadness, manias with euphoria, absence of mood-incongruent psychotic symptoms)

episodic and often entails residual symptoms. Similarly, these patients have substantial co-morbidity similar to their family history (Table 22.2).

Olanzapine

Olanzapine responders again have atypical features characterizing both their depressions and their manias, and one can often identify mood-incongruent psychotic symptoms in their history or in their acute presentation. Family history, if positive, tends to show psychotic disorders or chronic psychiatric disorders. The clinical course has residual symptoms between the episodes of depressions and manias, and the history, if fully developed, shows more manias than depressions. Co-morbidity is frequent, particularly with alcoholism and substance abuse. We have preliminary evidence to suggest that the clinical features of responders to olanzapine may generalize to indicate response to other atypical neuroleptics (Table 22.3).

Divalproex

The data on divalproex are missing from these investigations, mainly because the evidence from controlled clinical trials for long-term efficacy of divalproex is not available.[14]

Table 22.2 Characteristics of responder to long-term lamotrigine treatment

Clinical course: non-episodic, with residual symptoms, mostly depressions (often 'bipolar II' type)
Family history: anxiety and panic disorders, substance and alcohol addictions
Comorbidity: high, anxiety and panic disorders, substance and alcohol addictions
Presentation: atypical, non-textbook features (e.g. depressions characterized by anergia or emotional emptiness, hypomanias by general speeding without euphoria)

Table 22.3 Characteristics of responder to long-term olanzapine treatment

Clinical course: non-episodic, with residual symptoms, overactive episodes often more frequent than depression
Family history: non-remitting or psychotic disorders
Co-morbidity: alcohol abuse or addictions
Presentation: atypical, non-textbook features, often history or presence of mood-incongruent psychotic symptoms

Selectivity of responses

There has been a line of investigation documenting that the response to some stabilizers has been associated with specific clinical correlates, for example for lithium,[11,15] carbamazepine,[14] valproate[17] and lamotrigine.[13] In addition however, there is a growing body of literature that good responses to each of these substances are selective and often mutually exclusive.

For example, excellent lithium responders failed on long-term carbamazepine and vice versa.[18] Post et al[19] made a similar observation: most patients with a good acute response to carbamazepine had a clear history of non-response to lithium. Bowden et al.[20] found that previous lithium responders did well on lithium but not on divalproex. Similarly, Swann et al.[21] noted that responders to valproate had evidence of prior non-response to lithium. Tohen et al[22] observed that olanzapine succeeded in patients who had failed previously on lithium and divalproex. Despite some methodological limitations of these observations, together they provide a credible picture of a degree of selectivity among these medications. These data do not support the often reported clinical impression that many bipolar patients require combination treatment in order to get well.

The issue of selectivity is also indirectly supported by the clustering of prophylactic responses in families. For lithium there is evidence that response to long-term treatment markedly clusters in families.[12] Evidence is also slowly mounting that affected children of bipolar parents tend to benefit markedly from the long-term treatment to which the parent responded (A. Duffy et al, unpublished data).

Discussion

The critical task in the long-term management of bipolar disorders is matching the patient and the effective treatment. Much of the current literature stresses that bipolar patients should be treated by a combination of medications and that the right combination can be established by following an algorithmic sequence, adding one drug at a time. This recommendation is based on practical experience that many bipolar patients fail on the initial medication, and respond only after several more drugs are added. However, such anecdotal observations have more than one possible explanation.

At present, there is much misunderstanding about long-term treatment of bipolar disorders. In particular, the natural course of atypical forms has

not been well described and there are major misinterpretations about indications for effective lithium treatment. As a result, the interpretation of the outcome of treatment is often incorrect.

Clinicians use combinations because they experience treatment failures during the initial stage of treatment of a bipolar patient. Very frequent initial failures should be expected. In DSM-IV-diagnosed bipolar disorders, long-term monotherapy chosen by the current practice of trial-and-error is effective in one-third of patients at best,[23] but can be markedly improved by treating according to clinical profile of the patient and family as described above. Observations supporting this are particularly convincing for lithium and clozapine.

The majority of bipolar patients who have been correctly selected for lithium treatment and adequately monitored can be completely stabilized with lithium monotherapy. On the other hand, some patients benefiting substantially from an atypical neuroleptic or lamotrigine will intermittently or sometimes chronically require an addition of an antidepressant or another psychotropic drug.

A combination of medications appears to be indicated, particularly in bipolar patients who are treatment-resistant to monotherapy, do not tolerate it well, or do not have clinical characteristics helpful for a clear treatment choice. Evidence is lacking that combinations of several medications are necessary in the majority of bipolar patients, despite the current practice. It is difficult to justify exposing patients to the side-effects of several drugs if mood stabilization can be achieved without a multiple combination.

Heterogeneity of bipolar disorders poses a major problem for the interpretation of the results of clinical trials. The results of any long-term drug trial may depend as much on the composition of the patient sample and the proportion of the subtypes as on the efficacy of the tested drug.

Currently we are developing a computer program that forecasts the treatment outcome based on the individual bipolar patient's clinical characteristics. This program should be ready for predictive testing soon.

Conclusions

There are at least three distinct types of bipolar disorder that markedly differ both in clinical characteristics and in treatment outcome. Comprehensive clinical assessment is needed in order to identify the type; the patient can then be matched with a more effective long-term treatment.

Despite prevailing practice, evidence is lacking so far that polypharmacy with multiple stabilizers is necessary for the majority of bipolar patients. However, for patients who can achieve stabilization by one primary medication, whether it is lithium, lamotrigine or atypical neuroleptics, it is difficult to justify exposing them to the side-effects of complex polypharmacy.

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