Bipolar disorders: treatment options and patient satisfaction

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Abstract: Functional recovery, the goal of treatment, has long been overlooked in the assessment of effectiveness of pharmacological treatments. However, with the recent shift in paradigm, from syndromal–symptomatic recovery to functional recovery, there appears to be a new interest in the definition and evaluation of functional recovery. Since functional recovery lags symptomatic recovery, sometimes by months or years, the attainment of functional recovery will be determined by both efficacy and long-term compliance. Quetiapine, due to its efficacy in both mania and depression, and effect on cognition may lead to improved functioning in patients with bipolar disorder.

Keywords: bipolar disorders, syndromal recovery, functional recovery, efficacy, effectiveness

Introduction

We stand in time at an important juncture in approaches to assess treatment effectiveness or outcomes in bipolar disorder. Almost all studies evaluating treatments for mania, mixed episodes, mood instability, and depression have been tested in a paradigm that focuses on the percentage of patients achieving reduction of total symptomatology (symptomatic–syndromal recovery) at time of study entry by half (response rate) or the time it takes to reach syndromal–symptomatic recovery, or, for long-term studies, the duration of time that they were maintained without developing a new affective episode or the percentage of patients who experienced a relapse or recurrence after an index episode.

This focus is despite the DSM-IV TR necessitating functional impairment as a condition *sine qua non* for the diagnosis of depressive, manic, or mixed episodes in bipolar illness (DSM-IV). Functional recovery, in bipolar illness, may be described as the return to a level of functioning that existed prior to the development of the most recent episode (Tohen et al 2000) and may involve several domains such as capacity to work, live independently, study, and engage in recreational activities (Zarate et al 2000). Several studies over the past decade have made clear that there is a disconnect between remission and response, between syndromal and symptomatic, and between syndromal and functional recovery. This article focuses on the last, but addresses the others, as each contrast is interrelated with the other.

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Comparative function in bipolar disorder and major depression

The recent report from the 2005 national comorbidity epidemiological study found that bipolar disorder had the highest percentage of patients classified in the severely ill group (83%) compared with 30% of patients with major depression and the next highest group, obsessive compulsive disorder, at 50% (Kessler et al 2005). In a separate

study, patients with bipolar disorder had twice the rate of psychosocial impairment as major depressed subjects (Hirschfeld 2005). Additionally, bipolar patients were approximately twice as impaired in their sense of vitality, and social and emotional role function as unipolar depressed patients (Yatham et al 2004). Socio-occupational dysfunction, in bipolar disorder, is positively correlated with continued depressive symptomatology (Bauer et al 2001). Bipolar patients spend nearly 50% of their time being symptomatic, with a predominance of depressive symtomatology both in bipolar I and II patients (Judd et al 2002), which may explain the associated functional impairment.

Moreover they tend to experience prominent anergic symptoms during their depressive episodes which may further account for greater burden of illness (Bowden 2001). Kessler et al also found that although the prevalence of major depression in the workplace is twice that of bipolar disorder, because of the greater persistence of symptoms bipolar patients account for significantly more workdays lost (Kessler et al 2005).

The symptomatic and functional impairment associated with bipolar disorder negatively affects family care providers. More than 90% of caregivers of bipolar family members reported moderate or greater distress, with the degree of burden predicting poor outcome at 7 and 15 months (Perlick et al 2001).

Relationship of syndromal to functional improvement

It has been consistently demonstrated, in studies lasting up to two and a half years (Dion et al 1989; Harrow et al 1990; Tohen et al 1990; Zarate et al 2000; Nemeroff et al 2003), that functional improvement lags syndromal improvement. Additionally, a much smaller proportion of bipolar patients reach functional recovery compared with those who attain syndromal recovery. In one study, 30%–60% of patients, continued to experience psychosocial dysfunction during inter-episode intervals (MacQueen et al 2001). The persistence of psychosocial impairment despite syndromal–symptomatic recovery argues against the periodic nature of bipolar illness characterized by affective episodes and emphasizes the chronic nature of this illness.

In the aggregate, this consistent evidence of greater difficulty in achieving functional recovery, and the longer time to achieving it, has contributed to recent efforts to incorporate measures of patient function and quality of life in prospective clinical trials. Even the assessment of

remission as a primary efficacy measure, rather than a response, may serve this purpose. Although remission is a more stringent criterion to assess efficacy of a treatment modality than response, in one recent placebo-controlled study comparing quetiapine and lithium with placebo in manic patients over a 12-week period of blinded treatment, the magnitude of the advantage of both drugs over placebo was larger for proportions remitted than for those simply responsive (Bowden, Grunze, et al 2005). Whereas the remission rate remained almost as high as the response rate for the two active treatments, remission was notably lower with placebo treatment than was response. This suggests that response incorporates some partial and non-specific improvement that is unlikely to lead to major recovery in function or quality of life.

Efficacy vs effectiveness

The single focus on global symptomatic improvement in studies of acute depression and mania, usually lasting 3–12 weeks, essentially meant that not only functional recovery but also tolerability to treatment regimens was given almost no attention. This approach was in part consequent to studies of mania and depression being short term, and studies of mania being conducted in hospitalized patient samples, and acceptability of side-effects were quite secondary. With a paradigm shift toward an illness-focused rather than an episode-focused overall approach to treatment, the acceptability of a treatment regimen began to receive more attention. Acceptability of a medication regimen, particularly long term, is an integral part of ease of administration and tolerability. A treatment that must be taken, for example, three times daily will be less acceptable than one that is taken once daily (Mulleners et al 1998). A treatment that has subjectively distressing side-effects will lead to high rates of drop out (Vieta et al 2005). Such studies are both more feasible and more important in longer-term trials. For example, the sexual interest-impairing effects of selective serotonin re-uptake inhibitors (SSRIs) may be borne by most patients over a 6-week acute study while initially depressed, but prove less acceptable over an indefinite period of use, particularly with resolution of depressive symptomatology. Although the high side-effect burden of lithium was well known from its early use, the serious adverse effect on outcomes from this has become especially apparent in long-term studies published in the past 15 years. In a follow-up of patients discharged from hospital taking lithium following a manic episode, the mean duration of time that patients

continued to take the drug was only 65 days (Johnson and McFarland 1996). Simply put, a treatment may have *limited effectiveness*, despite proven *efficacy* in clinical studies

Impact of function on pharmacotherapy

Pharmacotherapy can affect functional status over time just as aspects of daily function can impact pharmacotherapy, both positively and negatively. A patient who does not obtain adequate sleep will experience reduced benefits of medications for bipolar disorder. Conversely, developing a daily routine that includes reasonably early and sustained sleep can augment benefits of drugs (Frank et al 2005). Stimulants or other drugs of abuse–dependence, worry, anxiety-provoking stressors, and medical illnesses are among the many life events that can serve as acute and long-term stressors, adversely affecting outcomes, by such pathways as worsening insomnia or destabilizing mood (Nemeroff et al 2003)

Potential for drugs to affect function

For all classes of drugs, there is more inferential information than experimental. And for each drug, side-effects will dampen function, while beneficial effects may improve it.

Lithium

Lithium may well have the least potential to improve function due to the large number of adverse effects, particularly cognitive, many of which worsen with age and duration of treatment. There is evidence that patients with bipolar disorder have significant cognitive deficits, even when asymptomatic (Atre-Vaidya et al 1998; van Gorp et al 1998), which are closely related to psychosocial and functional impairments. Moreover, lithium may lead to induction of depressive symptomatology which may further impair functionality (Bowden, Collins, et al 2005). Conversely, mostly open studies compared with normative data suggest that lithium may reduce suicidal behavior even when not effective as a mood stabilizer (Tondo et al 2001).

Valproate

Valproate has a relatively broad spectrum of efficacy, and some evidence of benefits on irritability not reported with other mood stabilizers. Valproate may also positively affect cognition, when used with both typical and atypical antipsychotics, by causing a larger increase in prefrontal cortical dopamine release via 5-HT-1A receptor activation (Ichikawa et al 2005). Valproate, unlike lithium, does not cause precipitation of depressive symptomatology in bipolar patients and hence will not negatively impair psychosocial functioning. With the exception of causing weight gain, valproate does not have adverse effects that routinely develop over time. In comparison randomized studies with lithium, carbamazepine, and olanzapine, valproate has had fewer adverse effects (Bowden et al 1994, 2000; Vasudev et al 2000; Tohen et al 2002)

Lamotrigine

Lamotrigine has efficacy principally on depressive components of bipolar disorder. Since depressive components are more strongly associated with functional impairment than are manic symptoms, it is plausible that on an efficacy basis alone lamotrigine should contribute to improving function. Lamotrigine also has a remarkably well tolerated adverse effect profile which positively affects effectiveness. The limitation of potential for hypersensitivity syndrome is serious, but largely unrelated to issues of long-term function.

Carbamazepine

This drug has a mixed adverse-effect profile that may appear less conducive to good function than is actually the case. It causes substantial psychomotor sedation, ataxia, blurred vision, and impaired coordination in early dosing; however, such symptoms often abate with continued use. Although, like lamotrigine, it is associated with hypersensitivity syndrome, this infrequent and early complication is unlikely to affect function. However, carbamazepine has been little studied in long-term trials, and the two principal recent trials have shown it to be generally inferior to and less well tolerated than lithium.

Antipsychotic drugs

Although there are class-effect adverse problems associated with antipsychotics, it is more realistic to view the individual atypical agents separately, and similarly the first generation typical drugs as a group.

First-generation drugs

Although efficacy in mania is equivalent for these drugs, there is substantial evidence that these antipsychotics may precipitate depressive episodes with long-term usage, which may affect functioning negatively. Moreover, these agents have a range of side-effects that are generally lacking in all

atypical antipsychotics such as anticholinergic, extrapyramidal, and histaminergic actions, which may also interfere with tolerability and hence long-term adherence.

Olanzapine and clozapine
These two drugs appear to share more similar profiles than do any other atypical antipsychotics, in part linked to their common dibenzodiazepine structures. At therapeutic doses, low-density lipoprotein levels increase, insulin resistance occurs, glucose is consequently dysregulated, and obesity is difficult to control with dosing or dietary strategies, although some promising results have been observed with concurrent use of appetite-suppressant drugs. Early discontinuation rates have been relatively high for the two drugs, in part consequent to such side-effects that are associated with all of the medical consequences of the metabolic syndrome (Lakka et al 2002)

Quetiapine
Quetiapine has a spectrum of efficacy that should contribute toward improved functioning. It has established benefits both for mania and depressive syndromes in patients with bipolar I and II disorders, therefore potentially benefiting both facets of the disorder (Bowden, Grunze, et al 2005). Additionally, it has moderate sedative effects, which in doses of around 100 mg at bedtime appear anecdotally to be useful in the sleep disruption, not simply insomnia, which is intrinsically common in bipolar disorder. The sedative effects are dose dependent, and have been associated with increased early discontinuation rates in studies. Moreover quetiapine, in a randomized, blinded study (Velligan et al 2003), has been shown to improve cognition in patients with schizophrenia. This cognitive-enhancing property of quetiapine may positively affect psychosocial functioning given the direct correlation of the two. In bipolar disorder, quetiapine has not yet been studied in large-scale, long-term, randomized, controlled studies, but studies in schizophrenia suggest mild to moderate weight gain, and substantially less affect on facets of the metabolic syndrome.

Most major studies of quetiapine have included rating scales to assess functional status and patient satisfaction. In the 12-week study of acutely manic patients, 88% of patients achieving response after 3 weeks of treatment continued to show response, at 12 weeks, and had similarly maintained rates of remission at the two time points.

Depressed bipolar I and II patients treated with quetiapine for 8 weeks reported significant improvement on a self-rated quality of life scale (Q-LES-Q) for both a 300 mg/day dose and a 600 mg/day dose of quetiapine. Degree of improvement was equivalent for the two dosages, as was degree of improvement on the MADRS (Calabrese et al 2005). Unlike SSRIs, quetiapine at both doses was not associated with sexual side-effects. These results indicate that quality of life and patient satisfaction can be meaningfully assessed in a relatively short 8-week study of treatments for depression, and that significance levels are essentially as high as seen for symptomatic change. Further, they indicate that for quetiapine the combination of symptomatic efficacy, breadth of effectiveness, adequate tolerability, particularly in several areas that are functionally impairing with other antipsychotic treatments for bipolar disorder, and association of improved quality of life with improved symptoms is indicative of the kind of profile of benefit desirable for treating a multifaceted, lifelong disorder such as bipolar disorder.

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