DIAGNOSIS AND MANAGEMENT OF BIPOLAR DISORDER: RECENT DEVELOPMENTS AND CURRENT CONTROVERSIES

Mario Maj

Department of Psychiatry, University of Naples SUN, Italy

Bipolar disorder is one of the mental disorders whose conceptualization has changed most dramatically during the last few decades.

It was regarded as a rare condition (lifetime prevalence in the community of 1-1.6%). Its diagnosis was considered as one of the easiest and the most reliable in clinical psychiatry (due to the occurrence of such an unmistakable syndrome as mania). Its outcome was regarded as relatively good (this being the key differential feature with respect to schizophrenia). Its pharmacotherapy was considered the most straightforward in clinical psychiatry. No significant role was attributed to psychotherapies. The currently predominant conceptualization is totally different: bipolar disorder is regarded as a relatively common condition (the lifetime prevalence of the spectrum of bipolar disorders in the community is reported to be between 3 and 6.5%), with a variety of clinical presentations (in which the presence of the manic syndrome is no longer a prerequisite) and a differential diagnosis which may be difficult (especially with respect to unipolar depression and some personality disorders), whose outcome is often poor (with very significant social and economic costs and burden for the family), whose pharmacological treatment is complex (with the frequent need for polypharmacy), and in which several types of psychotherapies are useful (1).

The spectrum of bipolar disorders is now regarded as consisting of four main components: 1) the "typical" cases, with manic episodes characterised by euphoric or irritable mood and major depressive episodes; 2) the "atypical" or complicated cases, including those with mixed episodes (either dysphoric mania or agitated depression), those with continuous circular course or with rapid cycling; those with mood-incongruent psychotic features; those complicated or masked by the concomitance of alcohol or drug abuse or by anxiety disorders; 3) the "pseudo-unipolar" cases; 4) the "subthreshold" cases (cyclothymic and hyperthymic forms).

"Pseudo-unipolar" forms include bipolar II disorder (with major depressive and hypomanic episodes), bipolar III disorder (with major depressive episodes and antidepressant-associated hypomania) and bipolar IV disorder (with major depressive episodes superimposed on hyperthymic temperament). Other possible pseudo-unipolar forms mentioned in the literature are recurrent depressions with abrupt onset and offset, and seasonal depressions, even without discernible hypomanic episodes. Of all these forms, only bipolar II disorder is presently recognized in official classifications (as a specific diagnostic entity in the DSM-IV; as an example of the category "other bipolar disorders" in the ICD-10).

Bipolar II disorder is reported to be from five to ten times more prevalent than bipolar I disorder in the community. It is reported to be frequently misdiagnosed as recurrent major depression, due to the difficulty to identify hypomanic episodes retrospectively (from 27% to 65% of patients who receive the diagnosis of recurrent major depression are reported to be bipolar II). Bipolar II disorder has been found to be associated with a high risk for suicide and a high frequency of interpersonal conflicts, marital instability and family breakdown. The issue of response of bipolar II disorder to pharmacotherapy remains controversial: there are reports of a higher efficacy of lithium prophylaxis in bipolar II than in bipolar I patients, but also studies in which a bipolar II pattern was included among the "atypical features" associated with a worse response to lithium and a better response to carbamazepine.

Other conditions which, according to some authors, may be considered for inclusion in the bipolar spectrum are some episodic obsessive-compulsive forms, some periodic states of irritability, some acute suicidal crises in the absence of clear-cut affective symptoms, cyclical neurasthenic or sleep complaints, severe brief recurrent depressions, impulse-ridden behaviors in the realms of control of aggression, gambling and paraphilias. Moreover, conditions whose boundaries with bipolar disorders are regarded as uncertain include schizoaffective disorder, borderline personality disorder and substance related disorders.

The concept of a bipolar spectrum, although very popular at the moment, is not unanimously accepted by experts of the field. The most significant objections to the concept include the following: 1) the common denominator shared by the conditions included in the spectrum is not clear (actually, different organizing principles are used here and there without consistency, including the occurrence of elated mood, a cyclical pattern in mood or in various aspects of behavior, or the presence of impulsivity); 2) the scientific validation of the spectrum concept is at present insufficient (the most commonly mentioned validators are a high prevalence of bipolar I disorder in first-degree relatives, a high frequency of switch to bipolar I disorder on follow-up, and a favorable response to mood stabilizers, but for the large majority of the conditions included in the spectrum evidence concerning these validators is weak); 3) the spectrum concept is likely to reduce the reliability of the diagnosis of bipolar disorder, reproducing the situation of the diagnosis of schizophrenia several decades ago; 4) the spectrum approach could dilute the concept of bipolar disorder, hampering the collection of homogeneous patient samples for research, and delaying or impeding the discovery of the biological bases of the disorder; 5) the spectrum concept could lead to an overdiagnosis of bipolar disorder and an overuse of mood stabilizers. Particularly significant, in this last respect, is the testimony of Robert Boland and Martin Keller (2), two eminent scholars of bipolar disorder, who report that: "Here in our corner of the Northeastern United States, it seems

difficult to find a patient with any sort of chronic psychiatric illness (be it a personality or even a chronic psychotic disorder) who is not already receiving some sort of mood stabilizer" and "Though we have also had the experience of seeing chronic disorders 'melt away' when the underlying mood disorder was successfully treated, we have also observed patients undergo fruitless trials in the vain search for the 'right pill', while missing out on more definitive psychotherapeutic treatments".

It is useful to emphasize that at least two of the above arguments can be reversed in favour of the spectrum concept. The first is that concerning progress of research: in fact, the spectrum approach may lead to the identification of more meaningful phenotypes for genetic research. For instance, in a monozygotic twin study carried out in 1977, among the co-twins of 69 patients with manic-depressive illness, there were 46 cases of manic-depressive illness, but a further 14 who presented other psychoses, or personality disorders, or who had committed suicide. This brought the concordance rate from 0.58 to 0.84. The other argument that can be reversed concerns pharmacotherapy: it has been pointed out that to err in favour of the bipolar diagnosis is less harmful than to err against it (in fact, it is more harmful to treat with antidepressants a bipolar case than to treat with mood stabilizers a unipolar case, and it is more harmful not to treat with mood stabilizers a bipolar case than to treat with mood stabilizers a personality disorder).

Strictly related to the issue of the recent broadening of the concept of bipolar disorder are the issues of the delay in the diagnosis and treatment of the disorder and of the occurrence of the disorder in children and adolescents.

In 1992, the U.S. National Depressive and Manic-Depressive Association (DMDA) carried out a survey in its members who had received a diagnosis of bipolar disorder. 31% of the participants reported they had experienced the first symptoms of the illness before 14 years of age, and a further 28% between 15 and 19 years of age. A child or adolescent onset of the illness was more frequently associated than an adult onset with reported school dropout, financial difficulties, divorce or marital difficulties, alcohol or drug abuse, injury to self or others, and minor crime. 50% of the respondents reported they did not seek professional help for 5 years or longer after symptom onset. 48% reported they had consulted three or more physicians before receiving the diagnosis of bipolar disorder. For 34%, the interval between the first professional contact and the diagnosis was longer than 10 years. The survey has been replicated in the year 2000, and the results have been even more worrying in some respects: in particular, the average number of physicians consulted before the diagnosis of bipolar disorder was made increased from 3.3 to 4. These findings confirm that the onset of bipolar disorder in childhood or adolescence is not rare, that this early onset is associated with a higher frequency of psychosocial complications, and that the latency to the diagnosis of

bipolar disorder is often long, due to both the delay in seeking professional help and the frequent misdiagnosis. It is important to notice, however, that the DMDA surveys were conducted in people who reported to have received the diagnosis of bipolar disorder, but whose diagnosis was not directly verified. Moreover, the reliability of these people's recollection of their first symptoms and the relationship between those symptoms and the current illness remain doubtful. Indeed, several experts in this area have recently emphasized that only prospective longitudinal studies can clarify the relationship between early affective symptoms and adult bipolar disorder.

A significant support to the some of the DMDA findings has recently come from a survey carried out in the Netherlands, in a representative sample from the general population in which the diagnosis of bipolar disorder was made using the CIDI. In this survey, 43% of the persons receiving the bipolar disorder diagnosis had never sought help from the mental health care system. Of those who had sought help, 20% had not spoken to a professional of their manic or hypomanic episodes. Of those who had spoken of those episodes, 40% had made no use of mental health services recently. The conclusion of the authors was that 3 out of 4 people with bipolar disorder were failing to receive adequate treatment at the time of the study.

Recent preliminary data from the Stanley Foundation Bipolar Network also document a prolonged lag (ten years) between first affective symptoms and first treatment.

The social consequences of the underdiagnosis and undertreatment of bipolar disorder are very significant. Without adequate treatment, a person with bipolar disorder from age 25 can expect to lose 14 years of effective major activity (e.g., work, school, family role function) and 9 years of life (mainly for suicide). With appropriate treatment, 6.5 years of life expectancy can be regained. The risk for suicide is reported to be particularly high in the first years after the onset of the disorder, so that delay in accurate diagnosis and treatment can increase significantly that risk. The forensic complications of untreated bipolar disorder are presently understudied: however, it has been reported that bipolar illness may exist in at least 10% of prison populations in the United States, although the formal diagnosis is frequently missed or ignored. The impact of concomitant substance abuse may be particularly important in this respect. Marital conflict, separation and divorce are frequent in patients with bipolar disorder, especially if untreated or inadequately treated: it has been estimated that less than 1/5 of bipolar patients have intact marital relationships. The burden on relatives and caregivers of bipolar patients, especially if untreated or inadequately treated, has been found to be more profound than that associated with major depression alone or schizophrenia: over 90% of caregivers report moderate or greater distress.

The outcome of bipolar disorder, however, may be poor even if state-of-the-art treatment is provided. The literature on predictors of a less favorable outcome is not consistent. The most

frequently reported predictors include a high number of previous episodes, the presence of mood-incongruent psychotic features, and the concomitance of substance abuse. The prognostic significance of mixed states is controversial, while rapid cycling per se does not seem to be a meaningful predictor of outcome, because it tends to represent a transient pattern.

One possible prognostic indicator which has been overlooked in the recent literature is the regular switch from one polarity of mood to the other. It is useful to recall that a switching pattern was the key component of the concept of "la folie circulaire" according to Falret and "la folie à double forme" according to Baillarger. Both these authors emphasized that the condition they were describing was different from those cases in which mania and melancholia occur separately, and Falret made the very crucial statements that "mania and melancholia, when they occur in isolation are more treatable than when they occur together in circular insanity" and that "the prognosis of this form of illness [la folie circulaire] is very grave". This observation has been then confirmed by several authors, who have reported that the tendency to switch is associated with a poor prognosis. In a study we have published in the American Journal of Psychiatry (3), we found that a polyphasic index episode (i.e., an index episode including at least two switches from one polarity of mood to the other) was associated with a poor long-term outcome, especially if the episode was initiated by depression. This last observation may reflect at least in part the more significant impact of currently available mood stabilizers on the cycle initiated by mania than on that initiated by depression.

This brings us to the second part of our overview, concerning the management of bipolar disorder. In this area, perceptions have changed in recent years not less dramatically than in the area of diagnosis. The optimism about the efficacy of lithium prophylaxis generated by the controlled trials of the 1970s has vanished, due to four main circumstances: 1) the publication of several naturalistic studies documenting that the impact of lithium on the course of bipolar disorder in clinical routine is much less significant than originally believed; 2) the appearance of some reports underscoring the methodological limitations of the controlled trials of the 1970s, in particular the fact that, in part of those trials, patients assigned to placebo had just interrupted lithium treatment abruptly, and were therefore at increased risk for recurrence (which may have inflated the difference between lithium and placebo); 3) the increased occurrence of (or attention to) atypical or complicated cases of bipolar disorder, which are less responsive to lithium than typical manic-depressive ones; 4) the introduction and vigorous marketing of other mood stabilisers. Of the above four circumstances, the first two have certainly been misinterpreted or overemphasized. That lithium is less effective in ordinary clinical practice than it is efficacious in controlled trials is not at all a surprise: this gap between efficacy and effectiveness is a well-known phenomenon, documented for several other medications. In the case of lithium prophylaxis, at least two factors

which are known to increase the efficacy-effectiveness gap for all medications are certainly very powerful (they are patients' poor adherence to treatment and physicians' poor adherence to good clinical practice in the selection of patients for treatment and in treatment surveillance) (4). On the other hand, part of the trials of the 1970s did not adopt a discontinuation design, and, after all, the fact that lithium discontinuation is followed by a high recurrence rate is itself a proof of the effectiveness of the drug. Overall, the quality of the lithium trials of the 1970s is reasonably good, and the bulk of the evidence they provide is impressive. Moreover, the more recent evidence of the impact of lithium prophylaxis on suicide risk in bipolar disorder is very significant.

However, due to the influence of the above four circumstances, lithium is currently underused in several clinical contexts. The testimony of Ronald Fieve, one of the pioneers of the use of lithium in the United States, is, in this respect, remarkable: "For years, in an average week I have seen four to six bipolar patients who have been given smatterings of all the above drugs [anticonvulsants and new antipsychotics] for a few weeks to 2 years, by one to five psychiatrists. The patient and family report that lithium has not been used, or was used for a short time and has not worked". Most residents are not adequately trained to the "subtleties of lithium treatment". "Therefore, on graduation they are poorly equipped and tend to underuse lithium as the first line of treatment. Instead, they begin the new bipolar patient on an anti-epileptic, since it is easier to use and requires less knowledge". "In my estimation, the above scenario today results in 40-50% of bipolar patients being inadequately treated".

It is a fact, however, that lithium tends to be less effective in atypical and complicated cases of bipolar disorder than it is in classical manic-depressive forms. It is less effective, but indeed it exerts some activity. For instance, in a study published in the Journal of Affective Disorders (5), we found that the time to 50% risk of recurrence during lithium treatment was significantly increased in bipolar patients with as well as without mood-incongruent psychotic features, although the increase was more significant in those without such features. Anologously, both we and the group of Baldessarini have found a significant reduction of affective morbidity during lithium treatment in patients with rapid cycling.

That anticonvulsants are superior to lithium in these subtypes of bipolar disorder is at present not convincingly proven. Greil et al., in their multicentre randomized open trial of lithium vs. carbamazepine, found that lithium was superior in the prophylaxis of classical bipolar disorder (bipolar I disorder without mood-incongruent delusions and without comorbidity), whereas there was a non-significant trend in favour of carbamazepine in the other bipolar patients. In a randomized, double-blind trial, Denicoff et al. found that lithium was actually slightly superior to carbamazepine in rapidly cycling bipolar patients, and that the combination of the two drugs was

significantly better than either drug used alone. Lamotrigine is the first drug whose superiority over placebo in the prophylaxis of rapidly cycling bipolar disorder has been documented. However, this superiority was observed for only some of the outcome measures, and for bipolar II but not bipolar I patients. There was no lithium comparison group.

Lithium remains at the moment the only drug whose prophylactic efficacy in bipolar disorder has been convincingly demonstrated. Only one placebo-controlled trial is available for valproate, and it failed to show a superiority of that drug over placebo on the primary outcome measure (time to any mood episode during treatment), although also lithium was not superior to placebo. In that trial, the less severe forms of bipolar disorder were overrepresented (e.g., 39% of the patients had never been hospitalized and 82% were not hospitalized for the index episode). Only one double-blind placebo-controlled trial is available for carbamazepine, which found a non-significant difference between the drug and placebo in the 1-year recurrence rate during treatment. One recent placebo-controlled trial is available for lamotrigine, which found this drug to be superior to placebo in extending the time to a depressive episode, but not to a manic episode (whereas lithium was superior to placebo in extending the time to a manic episode, but not to a depressive episode). Lamotrigine has been also found superior to placebo in the treatment of bipolar depression. This peculiar effect of lamotrigine is probably the most significant recent finding in this research area, which warrants independent replication. The usefulness of olanzapine and risperidone in the treatment of mania has been recently documented, but no controlled trial of prophylactic treatment is at present available.

Some experts have recently argued that long-term treatment of bipolar disorder may require routine polypharmacy. The evidence that lithium is effective (or more effective) in preventing manic episodes while lamotrigine is effective in preventing depressive episodes seems to point in this direction. However, placebo-controlled combination therapy trials are presently lacking.

In the last two decades, there has been a revival of the interest in the use of psychotherapeutic techniques, as an adjunct to pharmacotherapy, in the management of bipolar disorder. This renewed interest has been generated by at least four circumstances: 1) the more pessimistic view of the impact of long-term pharmacotherapy on the course of bipolar disorder in ordinary clinical conditions; 2) the evidence for the significant role of patients' poor adherence in reducing the effectiveness of pharmacotherapy; 3) the evidence that life stressors and social support can have an influence on the course of the disorder; 4) the observation that social, family and occupational dysfunction is very frequent in patients suffering from the disorder.

The psychotherapeutic techniques whose efficacy has been systematically tested in bipolar disorder include cognitive-behavioral techniques (aiming to help the patient to deal with cognitive distortions which may increase the impact of life stressors); interpersonal and social rhythm

therapies (aiming to address interpersonal difficulties and to stabilize the pattern of social interactions); psychoeducational techniques (aiming to foster the patient's role as a co-manager of his/her illness); family and couple interventions (aiming to address family and marital problems which may have an impact on the course of the disorder).

For each of the above techniques, there is at least one randomized controlled trial showing that its adjunct to pharmacotherapy has a significant effect on one or more outcome measures, as compared to pharmacotherapy alone. Almost all published studies concerning psychotherapies for bipolar disorder have reported at least some positive results, and more rigorous studies are not less likely to be positive than less accurate ones. This may reflect a publication bias (positive results are obviously more likely to be submitted for publication and published than negative ones). On the other hand, no specific type of psychotherapy seems to be more effective than the others; this may be due at least in part to the fact that all the above-mentioned psychotherapies have some ingredients in common (imparting education, focusing on triggers of episodes, seeing the individual as part of a group, building a patient-specific action plan). These common ingredients may be more significant for the outcome than the specific components of the various psychotherapies.

Several questions remain open concerning psychotherapies for bipolar disorder. The first is whether the various techniques differ in their impact on the various subtypes or phases of the disorder (in other terms, whether there is any criterion which may guide the choice of one or another psychotherapy in an individual patient). There is no convincing evidence at the moment in this respect, although it has been suggested that family and interpersonal therapies may have more positive effects on the outcome measures of depression, while cognitive-behavioral and psychoeducational techniques may have a greater impact on the outcome measures of mania. Another issue is how much flexibility should be allowed in the implementation of each technique: as a matter of fact, several professionals tend to pick up components of the various techniques at brief workshops and seminars, and to combine them in a personal approach. This on the one hand may improve the quality of routine case management, but on the other may trivialize the techniques and reduce their effectiveness. Other problems are those of the cost of psychotherapies in ordinary clinical settings, of the access of professionals to training, and of patients' adherence, especially to the most demanding forms of psychotherapy, like family or couple interventions.

Finally, it is useful to report that at least two programs focusing on the context of care are currently being tested in randomized controlled trials. These programs share some key elements (patient education, provider education and improved access of patients to care) and aim to reduce the gap between efficacy and effectiveness in the management of bipolar disorder.

This is my view of the state of the art of the diagnosis and management of bipolar disorder. Of course, I have had to summarize several issues and to overlook some others due to space constraints. However, I hope to have conveyed the sense of an area in which the recent developments have been very significant, but have also generated many questions which remain to be addressed. To keep our mind completely free in identifying and addressing these questions is today an imperative for all of us.

References

1. Maj M., Akiskal H.S., Lopez-Ibor J.J., Sartorius N. (eds.) Bipolar disorder. Wiley, Chichester, 2002
2. Boland R., Keller M.B. Broadening the definition of bipolar disorder. In: Maj M., Akiskal H.S., Lopez-Ibor J.J., Sartorius N. (eds.) Bipolar disorder. Wiley, Chichester, 2002.
3. Maj M., Pirozzi R., Magliano L., Bartoli L. The prognostic significance of “switching” in bipolar disorder: a 10-year prospective follow-up study. Am J Psychiatry 2002; 159, 1711-1717.
4. Maj M, Pirozzi R, Magliano L, Bartoli L. Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 1998; 155:30-35.
5. Maj M, Pirozzi R, Bartoli L, Magliano L. Long-term outcome of lithium prophylaxis in bipolar disorder with mood-incongruent psychotic features: a prospective study. J Affect Disord 2002; 71:195-198.