The dilemma in the concept and the management of bipolar disorder

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Bipolar disorder is underdiagnosed, misdiagnosed and undertreated. The emphasis now is on the bipolar spectrum and its management is under continuous revision, for example, the controversial use of antidepressants. The recent change in the conceptualization of bipolar disorder has changed the lifetime prevalence, the difficulty in diagnosis, the syndromal and functional outcome. The bipolar spectrum encompasses many psychiatric disorders that requires a change in its diagnosis and management. There has been a shift in pharmacological and psychotherapeutic management in bipolar disorder. The dilemma in management will be discussed with a personal experience of approximately 50 years in psychiatry. Cultural and economical sensitivity will be taken into consideration. A brief account will be presented for the management and maintenance treatment of mixed, rapid cycler and psychotic bipolar disorder, whether psychopharmacological or psychotherapeutic.

Keywords:
bipolar disorder, bipolar spectrum, lithium, mood stabilizers, mixed episode, rapid cyclar

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One in four people will suffer from a mental or a neurological disorder at some point during their lifetime; 450 million people are currently affected by these disorders, 121 million people suffer from depression, 24 million from schizophrenia, 50 million from epilepsy and one million people commit suicide every year [1]. There are many Caveats in International Classifications, mainly the high rates of comorbidities among patients with these disorders that may undermine the hypothesis that the syndromes represent distinct etiologies. A high degree of short-term diagnostic instability for many disorders is a challenge; the lack of treatment specificity is the rule rather than the exception for almost all psychiatric disorders [2]. The study by Berrettini and Pekkarinen [3] indicated that three of the putative susceptibility loci associated with bipolar disorder also contribute to the risk of schizophrenia. Bipolar disorder is the second highest cause for years of life lost with a disability among neuropsychiatric conditions [4]. The reasons for the underdiagnosis of bipolar disorders are patients' impaired insight into mania, failure to involve family members in the diagnostic process, inadequate understanding by clinicians of manic symptoms and the fact that increased energy is representative of more than irritability or euphoria. Bipolar disorder is a recurrent illness in more than 90% of patients; functional recovery often lags behind symptomatic and syndromal recovery. Recurrent episodes may lead to progressive deterioration in functioning and the number of episodes may affect the subsequent treatment response and prognosis. The mortality and disability in bipolar disorder is high, and considered the sixth leading cause of disability worldwide [5]. At least 25% of the patients attempt suicide, suicide rates ranging between 11 and 19% and 25–50% suicidal ideation is found in mixed mania.

The recent change in the conceptualization of bipolar disorder shows that in the past, lifetime prevalence in the community was low (1–1.6%) whereas at present it is relatively high (3–6.5%); the diagnosis was easy and reliable but at present it is rarely so and the outcome was good and now often poor. In the past, pharmacological treatment was straightforward and effective; currently, it is complex and inconstantly effective, and it was believed that psychotherapies have no role but now several types are useful [6].

The spectrum of bipolar disorders includes the following:

(1) 'Typical' cases: Manic episodes (with euphoric or irritable mood or increased energy) and major depressive episodes;
(2) 'Atypical' and complicated cases: With mixed episodes (either dysphoric mania or agitated depression), with continuous circular course or rapid cycling, with mood-incongruent psychotic features, complicated or masked by alcohol or drug abuse or by anxiety disorders;
(3) 'Pseudounipolar' cases: Bipolar disorder II, III and IV and possibly other forms;
(4) 'Subthreshold' cases: Cyclothymic and hyperthymic forms.

'Pseudounipolar' forms indicate bipolar disorder II (major depressive and hypomanic episodes), bipolar disorder III (major depressive episodes and antidepressant-associated hypomania) and bipolar disorder IV (major depressive episodes superimposed on hyperthymic temperament); others may include recurrent depression with an abrupt

onset and offset, and seasonal depression, even without discernible hypomanic episodes [5]. Some bipolar disorder II features are more prevalent than bipolar disorder I in the community. It is frequently misdiagnosed as recurrent major depression (from 27 to 65% of patients with this diagnosis are reported to be bipolar II disorder), with a high frequency of interpersonal conflicts, marital instability and family breakdown. Other conditions that may be considered for inclusion in the bipolar spectrum are episodic obsessive–compulsive forms, periodic states of irritability, acute suicidal crises in the absence of clear-cut affective symptoms, cyclical neurasthenic or sleep complaints, severe brief recurrent depressions, impulse-ridden behaviours in the control of aggression, gambling and paraphilias. Conditions that may overlap with bipolar disorder include schizoaffective disorder, borderline personality disorder, substance use disorders and adult attention-deficit hyperactivity disorder (ADHD) [5].

Some findings of the Stanley Foundation Bipolar Network can be stated: the average age of onset of the first symptoms of bipolar disorder is 19.4 years. The average age of the first treatment of bipolar disorder is 29.2 years. The onset of illness is earlier in patients with a family history of affective illness and in those who experienced early extreme stressors (i.e. physical or sexual abuse) [7]. The United States Department of Health, Education and Welfare stated that without adequate treatment, a person with bipolar disorder from age 25 years can expect to lose 14 years of effective major activity (e.g. work, school, family role function) and 9 years of life (mainly because of suicide). With appropriate treatment, 6.5 years of life expectancy can be regained. Less than one of five patients with bipolar disorder have intact marital relationships [8]. There are predictors of a less favourable outcome in bipolar disorder: consistently reported high number of previous episodes, the presence of mood-incongruent psychotic features, comorbid substance abuse, inconsistently reported and rapid cycling. Are schizophrenia and bipolar disorder phenomenologically and nosologically clearly separable? New findings from neurobiological research have made this question as one of the major issues today. First illness episodes of schizophrenia and affective disorder show similar morphological brain abnormalities, increased ventricle–brain ratios and decrease in grey matter in the frontal and temporal lobe and volume reduction in the hippocampus–amygdala area. Schizophrenic psychosis and severe unipolar disorder or bipolar disorder share various aetiological risk factors. Their onset is marked by a very similar prodromal core syndrome, which includes functional impairment, and emerges long before the climax of the first episode. Therapies target current symptom patterns such as depression, mania, psychosis and the associated neurotransmitter dysfunctions rather than specific underlying disease processes [9].

The current disease concepts of schizophrenia, bipolar disorder and unipolar depression, understood as comprising different aspects of symptom dimensions, will usher in a farewell to the dichotomous classification of the early Kraepelin [9], as they overlap in their symptomatology.

Functional disability in bipolar disorder is prevalent. After 6 months of treatment, syndromal recovery is 84% whereas functional recovery is only 30%, and after 2 years, it is 98 and 38%, respectively [10,11].

Follow-up of bipolar disorders showed that bipolar disorder subtypes tend to have a chronic course, and after 20 years of follow-up, 47.5% of BP-I patients and 54% of BP-II patients were symptomatic. Syndromal and subsyndromal symptoms fluctuated. Minor subsyndromal manic and depressive symptoms were three times more common than syndromal ones. Depressive symptoms dominated the course, wherein the ratio was depression:-mania = 3 : 1 in BP-I, 30 times more common in BP-II [12].

The goals of therapy in bipolar disorder mania are to 1- Control dangerous symptoms, such as suicide, agitation and psychosis. 2- Stabilize mood, control mania without inducing depression. 3- Treating all phases of mania including depressive, anxious and psychotic elements and restore premorbid functioning [5].

Mood-stabilizing agents include lithium, anticonvulsants [carbamazepine (tegretol), oxcarbazepine (trileptal), valproate (depakine), lamotrigine (lamictal), gabapentin (neurontin), topiramate (topamax)] benzodiazepines (clonazepam), conventional antipsychotics (e.g. haloperidol), Second generation antipsychotics (e.g. clozapine, olanzapine, risperidone, quetiapine, aripiprazole, etc.) [5].

The features of an ideal mood stabilizer over time and across episodes include the following: rapid efficacy for mania, treatment of psychotic symptoms of mania, broad efficacy (e.g. mixed, rapid cycling), reduction of depressive symptoms, favourable cognitive effects, long-term usefulness, well tolerated by patients and easy to use [5].

The efficacy of lithium ranges between 49 and 70% and the onset of action is approximately 5–21 days, whereas prophylaxis takes approximately 9 months. Predictors of response are classic mania, few episodes and bipolar disorder episode sequence. Lithium may cause neurocognitive, renal, gastrointestinal and endocrinologic side effects and weight gain. The risk of recurrence is increased in the months after discontinuation of lithium. Lithium may help exert an antisuicidal effect on patients with bipolar disorder [5].

Mixed-state (dysphoric mania) prevalence is approximately 30%, and it is a distinct entity. It is intermediate on the spectrum between mania and depression, and is considered to be a more severe form of bipolar, with significant morbidity and mortality [5].

The best treatment strategy for bipolar disorder is that which results in the fewest, mildest or briefest episodes [13].

Clinical suggestions include combination therapy with the addition of new medication and anticipation of transitional side effects. The new medication should be titrated to a therapeutic dose and the response to this should be awaited before any other alterations can be made; if the response is positive, ineffective medications can be weaned off but if the response is partial, medication should be continued.

There are aspects of overlap in bipolar disorder with other disorders. Anxiety in bipolar may be present in unipolar depression and social phobia, and hyperactivity symptoms may be linked to ADHD and substance abuse. Depressive symptoms may occur in personality disorder, unipolar depression, schizophrenia and schizoaffective disorders, whereas psychotic symptoms can occur in delusional disorders, schizophrenia and schizoaffective disorders.

Comorbidities are the rule not the exception. Medical disorders include (pain disorder, diabetes mellitus, cardiovascular, obesity, migraine) whereas psychiatric diagnoses include substance abuse, eating disorders, anxiety disorders, impulse control, ADHD and personality disorder [14]. Bipolar disorder is associated with numerous comorbidities; comorbid psychiatric disorders are reported in 31–75% of patients. Comorbid anxiety is reported in 24–28% of patients. A range of anxiety disorders, substance and alcohol abuse are highly prevalent [15,16].

We should be aware of the antipsychotic switching syndrome 'Withdrawal triad' namely: cholinergic rebound (nausea, vomiting, restlessness, sweating, tremors, etc), supersensitivity psychosis and withdrawal dyskinesias (and other motor syndromes). Antipsychotic switching strategies include either an abrupt switch, which is not advisable, or taper switch, involving gradual discontinuation of current antipsychotic and immediate start of the new antipsychotic (AP) or cross taper switch, that is, taper current AP and gradually start new AP; however, better switch is we treat with both current and new AP is gradual start of new AP and taper current AP.

Systematic Treatment Enhancement Program for Bipolar Disorder, National Institute of Mental Health is a clinical research programme designed to study treatment effectiveness with both naturalistic and randomly assigned treatment protocols. All patients received mood stabilizers or atypical antipsychotics, and patients who also received antidepressants were compared with those who did not receive antidepressants [13]. The study found that recovery from depression was independent of whether or not patients received adjunctive antidepressant treatment. These results mirror another recent publication from Systematic Treatment Enhancement Program for Bipolar Disorder, which found no advantage in adding antidepressants to mood stabilizers in the treatment of bipolar depression without concurrent manic symptoms and may lead to a risk of causing mania. These findings are also consistent with a double-blind, placebo-controlled study of bipolar depression that found that if lithium was dosed to a serum level of at least 0.8 meq/l, then the addition of an antidepressant (paroxetine, imipramine) provided no additional benefit in symptom improvement [17,18].

There is a high rate of misdiagnosis; the most frequent being unipolar depression of approximately 60%. An average of 3.5 misdiagnoses and four consultations occur before an accurate diagnosis is made and 35% of patients are symptomatic for 10 years or more before a correct diagnosis is made (Table 1) [19].

Psychotic symptoms in bipolar disorder

At least 58% psychotic symptoms are present, with auditory hallucinations being 47%, delusions being 53%, catatonia being 23% and Schneiderian first rank symptoms being 8% [20–23].

High rates of death and suicide in patients with bipolar disorder

In the United Kingdom, death rates of 18% were reported for patients with bipolar disorder over a 35-year study period, and attempted suicide rates varied between 21 and 54%. An Italian study reported that 22% of men and 54% of women with bipolar disorder I had a history of suicide attempts. In a French study, 40% of patients with bipolar disorder had attempted suicide at least once. Vieta *et al.* [24] found that 38% of patients with bipolar disorder with a comorbidity had attempted suicide, compared with only 21% of patients without a comorbidity [24–27].

Approximately 70% of patients with bipolar disorder are not gainfully employed; only 30% of patients with bipolar disorder in Germany were employed full time at a level that was appropriate for their qualifications. In Europe,

Table 1 Food and Drug Administration approved labelling for antipsychotic medications

Antipsychotic	Schizophrenia	Acute bipolar manic/ mixed episodes	Acute bipolar depression	Maintenance treatment of bipolar disorder I	Prevention
Chlorpromazine (largactil)	+	+	–	–	–
Haloperidol (haldol)	+	–	–	–	–
Perphenazine (trilafon)	+	–	–	–	–
Clozapine (leponex)	+	–	–	–	–
Aripiprazole (abilify)	+	+	–	+	–
Olanzapine (zyprexa)	+	+	+ (only in Combination with Fluxetine)	+	–
Paliperidone (invega)	+	–	–	–	–
Quetiapine (seroquel)	+	+	+	+	+
Risperidone (risperidone)	+	+	–	–	–
Ziprasidone (zoldox)	+	+	–	–	–

+, approved by Food and Drug administration;
–, not approved by Food and Drug administration.

34% of patients with bipolar disorder have difficulty finding a job and 34% have difficulty retaining a job. An Italian study found that 63–67% of patients with bipolar disorder were unemployed. A Europe-wide survey revealed that patients with bipolar disorder disease feel stigmatized and also have difficulties in maintaining relationships with friends and family and enjoying leisure activities [28–30].

The impact of bipolar disorder on lifestyle of patients with bipolar disorder shows interference in: relationships with family – 54%, relationships with friends – 44%, relationships with partners – 43%, retaining job – 34%, finding job – 34%, career prospect – 29%, relationships with colleagues – 26%, education – 24%. while present lifestyle difficulties exhibit feeling stigmatized – 55% carrying out job – 45% relationships with family – 44% enjoying leisure activities – 41% feeling ridiculed – 39% relationships with friends–37% expressing own opinion [29].

A survey of European psychiatrists indicated that over 60% of patients with bipolar disorder had to undergo at least two changes of therapy before stabilization. The average number of therapy changes before patients were stabilized was 2.4 [31].

A few developments have led to renewed interest in psychotherapies for bipolar disorder, especially the lack of effectiveness of long-term pharmacotherapy under ordinary clinical conditions and the significant role of patients' poor adherence in reducing the effectiveness of pharmacotherapy; however, there is evidence that life stressors and social support can have an influence on the course of the disorder and that social, family and occupational dysfunction is very frequent in patients with bipolar disorder. Psychotherapeutic techniques that can be used systematically in patients with bipolar disorder include cognitive-behavioural techniques, interpersonal and social rhythm therapies, psychoeducational techniques and family and couple interventions. The common psychotherapeutic techniques of proven efficacy in bipolar disorder include providing information on the disorder, focusing on triggers of episodes, seeing the individual as part of a group and formulating a patient-specific action plan [6].

Table 2 Food and Drug Administration approved treatments for bipolar disorder

Phases of bipolar disorders	Mania	Depression
Acute treatment	Lithium	(Lithium)[a]
	Valproate	(Lamotrigine)[a]
	(carbamazepine)[a]	Olanzapine/fluoxetine
	Olanzapine	(SSRIs)[a,c]
	Risperidone	
	Quetiapine	Quetiapine
Maintenance treatment	Lithium[c]	
	Lamotrigine[d]	
	Quetiapine	

[a]Off label for this indication.
[b]Not recommended as monotherapy (can induce mania and rapid cycling).
[c]Predominantly effective against mania.
[d]Predominantly effective against depression.

Need for new and effective treatments in bipolar disorder

There is a recognized need for new and effective treatments in bipolar disorder maintenance. The episodic and chronic nature of bipolar disorder requires long-term treatment in all patients, and yet, there is an unmet need for well tolerated and clinically effective maintenance therapy with enhanced patient adherence. A substantial number of patients with bipolar disorder do not respond, have relapses or cannot tolerate the side effects of common treatments for bipolar disorder. Treatment guidelines for bipolar disorder recommend a wide range of treatments, with no obvious trend in recommendations across guidelines. This suggests that there is an unmet need for treatment that is effective across all phases of bipolar disorder (Tables 2 and 3) [33–37].

Table 3 Food and Drug Administration approved treatments/bipolar disorder

			Maintenance		Depression	
	Mania	Mixed	Mania	Depression	Bipolar disorder I	Bipolar disorder II
Mood stabilizer						
Lithium	+	−	+	−	−	−
Divalproex DR	+	−	−	−	−	−
Divalproex ER	+	+	−	−	−	−
Carbamazepine ER	+	+	−	−	−	−
Atypical antipsychotics						
Risperidone	+	+	−	−	−	−
Olanzapine	+	+	+	−	−	−
Quetiapine	+	+	+	+	+	+
Ziprasidone	+	+	−	−	−	−
Aripiprazole	+	+	+	−	−	−
Other						
Lamotrigine	−	−	+	+	−	−
Olanzapine/fluoxetine	−	−	−	−	+	−

Physicians' Desk Reference 2009 [32].
+, approved by Food and Drug administration;
−, not approved by Food and Drug administration;
DR, Delayed release;
ER, Extended release.

Summary

Bipolar disorder is a lifelong illness and is associated with a substantial health, social and economic burden. An accurate diagnosis of bipolar disorder is essential to initiate effective treatment and prevent relapse. Evidence supports a range of treatments for the improvement of manic and depressive symptoms in bipolar disorder. The ideal treatment would achieve mood stabilization by effectively treating mania and depression and preventing relapse among patients with bipolar disorders I and II and rapid cyclers. The most successful treatment strategy would involve a holistic approach that is tailored to the individual patient inclusive of the following aspects: physical (symptom control), emotional (become calmer, feel good about themselves), mental (able to think clearly, make sense of life and regain control) and social (return to work, reengage in social activities and family).

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Conflicts of interest

There is no conflict of interest to declare.

References

1 Mental Health Resources in the World. Initial results of Project ATLAS. J Adv Nurs 2001; 36:7–8.

2 Asaad T, Okasha T, Okasha A. Sleep EEG findings in ICD-10 borderline personality disorder in Egypt. J Affect Disord 2002; 71 (1–3):11–18.

3 Berrettini WH, Pekkarinen PH. Molecular genetics of bipolar disorder. Ann Med 1996; 28:191–194.

4 Murray CJL, Lopez AD. *The global burden of disease: a comprehensive assessment of mortality and disability form diseases, injuries and risk factors in 1990 and projected to 2020*. Cambridge: Harvard School of Public Health; 1996.

5 Tandon R, Belmaker RH, Gattaz WF, Lopez Ibor JJJ, Okasha A, Singh B, *et al*. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res 2008; 100:20–38.

6 Hafner H, Maurer K. Prodromal symptoms and early detection of schizophrenia. In: Maj M, López Ibor JJ, Sartorius N, Sato M, Okasha A, editors. *Early detection and management of mental disorders*. 1st edition Wiley; 2005.

7 Post RM, Speer AM, Hough CJ, Xing G. Neurobiology of bipolar illness: implications for future study and therapeutics. Ann Clin Psychiatry 2003; 15:85–94.

8 Gitlin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. Am J Psychiatry 1995; 152:1635–1640.

9 Hafner H, Maurer K, Trendler G, An der Heiden W, Schmidt M, Konnecke R. Schizophrenia and depression: challenging the paradigm of two separate diseases – a controlled study of schizophrenia, depression and healthy controls. Schizophr Res 2005; 77:11–24.

10 Tohen M, Jacobs TG, Grundy SL, McElroy SL, Banov MC, Janicak PG, *et al*. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo - controlled study. The Olanzipine HGGW Study Group. Arch Gen Psychiatry 2000; 57:841–849.

11 Robb JC, Cooke RG, Devins GM, Young LT, Joffe RT. Quality of life and lifestyle disruption in euthymic bipolar disorder. J Psychiatr Res 1997; 31:509–517.

12 Judd LL, Schettler PJ, Akiskal HS, Maser J, Coryell W, Solomon D, *et al*. Long-term symptomatic status of bipolar I versus bipolar II disorders. Int J Neuropsychopharmacol 2003; 6:127–137.

13 Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, *et al*. Rationale, design and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2003; 53:1028–1042.

14 McIntyre RS, Konarski JZ, Yatham LN. Comorbidity in bipolar disorder: a framework for rational treatment selection. Hum Psychopharmacol 2007; 19:369–386.

15 Faravelli C, Rosi S, Alessandra Scarpato M, Lampronti L, Amedei SG, Rana N. Threshold and subthreshold bipolar disorders in the Sesto Fiorentino Study. J Affect Disord 2006; 94:111–119.

16 Henry C, Den Bulke DV, Bellivier F, Etain B, Rouillon F, Leboyer M. Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. J Clin Psychiatry 2003; 64:331–335.

17 Binder EB, Kinkead B, Nemeroff CB. Neuropeptides. In: Brier A, Bymaster F, Tran P, Lewis M, editors. *Current issues in the psychopharmacology of schizophrenia*. Lippincott Williams & Wilkins; 2001.

18 Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, *et al*. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007; 356:1711–1722.

19 Hirschfeld RM, Baker JD, Wozniak P, Tracy K, Sommerville KW. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine and placebo in the treatment of acute mania associated with bipolar disorder. J Clin Psychiatry 2003; 64:841–846.

20 Goodwin FK, Jamison KR. *Manic-depressive illness: bipolar disorders and recurrent depression*. 2nd edition. USA: Oxford University Press; 2007.

21 Keck PE, McElroy SL, Strakowski SM. Anticonvulsants and antipsychotics in the treatment of bipolar disorder. J Clin Psychiatry 1998; 59 (Suppl 6): 74–81. discussion 82.

22 Pope HGJ, Lipinski JFJ. Diagnosis in schizophrenia and manic-depressive illness: a reassessment of the specificity of 'schizophrenic' symptoms in the light of current research. Arch Gen Psychiatry 1978; 35:811–828.

23 Taylor MA, Abrams R. Manic-depressive illness and good prognosis schizophrenia. Am J Psychiatry 1975; 132:741–742.

24 Vieta E, Colom F, Corbella B, Martínez Arán A, Reinares M, Benabarre A, *et al*. Clinical correlates of psychiatric comorbidity in bipolar I patients. Bipolar Disord 2001; 3:253–258.

25 Dutta R, Boydell J, Kennedy N, Van Os J, Fearon P, Murray RM. Suicide and other causes of mortality in bipolar disorder: a longitudinal study. Psychol Med 2007; 37:839–847.

26 Benedetti A, Fagiolini A, Casamassima F, Mian MS, Adamovit A, Musetti L, *et al*. Gender differences in bipolar disorder type 1: a 48-week prospective follow-up of 72 patients treated in an Italian tertiary care center. J Nerv Ment Dis 2007; 195:93–96.

27 Henry JD, Rendell PG, Kliegel M, Altgassen M. Prospective memory in schizophrenia: primary or secondary impairment? Schizophr Res 2007; 95:179–185.

28 Hummel B, Dittmann S, Forsthoff A, Matzner N, Amann B, Grunze H. Clozapine as add-on medication in the maintenance treatment of bipolar and schizoaffective disorders: a case series. Neuropsychobiology 2002; 45 (Suppl 1):37–42.

29 Morselli PL, Elgie R. GAMIAN-Europe/BEAM Survey I: global analysis of a patient questionnaire circulated to 3450 members of 12 European advocacy groups operating in the field of mood disorders. Bipolar Disord 2003; 5:265–278.

30 Pini S, Cassano GB, Dell'Osso L, Amador XF. Insight into illness in schizophrenia, schizoaffective disorder and mood disorders with psychotic features. Am J Psychiatry 2001; 158:122–125.

31 Altamura AC, Armadoros D, Jaeger M, Kernish R, Locklear J, Volz HP. Importance of open access to atypical antipsychotics for the treatment of schizophrenia and bipolar disorder: a European perspective. Curr Med Res Opin 2008; 24:2271–2282.

32 Physicians' Desk Reference. Physicians' desk reference 2009; 63rd edition. Thomson Reuters, 2008.

33 Vieta E, Rosa AR. Evolving trends in the long-term treatment of bipolar disorder. World J Biol Psychiatry 2007; 8:4–11.

34 Suppes T, Dennehy EB, Hirschfeld RM, Altshuler LL, Bowden CL, Calabrese JR, *et al*. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry 2005; 66:870–886.

35 Scottish Intercollegiate Guidelines Network (SIGN). Bipolar affective disorder: a national clinical guideline. 200582. Scottish Intercollegiate Guidelines Network (SIGN).

36 Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht R, *et al*. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders, Part I: treatment of bipolar depression. World J Biol Psychiatry 2002; 3:115–124.

37 Yatham LN, Kennedy SH, O'donovan C, Parikh SV, Macqueen G, McIntyre RS, *et al*. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disord 2006; 8:721–739.