European Neuropsychopharmacology (2008) **18**, 535–549

www.elsevier.com/locate/euroneuro

ECNP consensus meeting. Bipolar depression. Nice, March 2007

Guy M. Goodwin[a,*], Ian Anderson[b], Celso Arango[c], Charles L. Bowden[d], Chantal Henry[e,f], Philip B. Mitchell[g,h], Willem A. Nolen[i], Eduard Vieta[j], Hans-Ulrich Wittchen[k]

[a] *University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK*
[b] *Neuroscience and Psychiatry Unit, The University of Manchester, Room G809, Stopford Building, Oxford Road, Manchester, M13 7PT England*
[c] *Unidad de Adolescentes, Hospital General Universitario Gregorio Marañón, CIBER-SAM, Madrid, Spain*
[d] *Department of Psychiatry, University of Texas Health Science Center, San Antonio, TX 78229-3900, USA*
[e] *INSERM, U 841, IMRB, Department of Genetics, Psychiatry Genetics, Creteil, F-94000, France*
[f] *University Paris 12, Faculty of Medicine, IFR10, Creteil, Paris, France*
[g] *School of Psychiatry, University of New South Wales, Sydney, NSW, Australia*
[h] *Black Dog Institute, Sydney, NSW, Australia*
[i] *Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[j] *Bipolar Disorders Program, Institute of Clinical Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBER-SAM, Barcelona, Spain*
[k] *Institute of Clinical Psychology, Center of Clinical Epidemiology and Longitudinal Studies, Technische Universitaet, Dresden, Germany*

Received 15 January 2008; received in revised form 22 February 2008; accepted 12 March 2008

KEYWORDS
Bipolar depression;
Bipolar disorder;
Mania;
Antidepressants;
Mood stabilisers;
Anticonvulsants;
Antipsychotics;
Manic switch;
Clinical trials

Abstract

Diagnosis and epidemiology: DSM-IV, specifically its text revision DSM-IV-TR, remains the preferred diagnostic system. When employed in general population samples, prevalence estimates of bipolar disorder are relatively consistent across studies in Europe and USA. In community studies, first onset of bipolar mood disorder is usually in the mid-teenage years and twenties, and the occurrence of a major depressive episode or hypomania is usually its first manifestation. Since reliable criteria for delineating unipolar (UP) and bipolar (BP) depression cross-sectionally are currently lacking, there is a longitudinal risk – probably over 10% – that initial UP patients ultimately turn out as BP in the longer run. Its early onset implies a severe potential burden of disease in terms of impaired social and neuropsychological development, most of which is attributable to depression.

* Corresponding author.
E-mail address: guy.goodwin@psych.ox.ac.uk (G.M. Goodwin).

doi:10.1016/j.euroneuro.2008.03.003

Bipolar depression in children: Bipolar I disorder is rare in prepubertal children, when defined according to unmodified DSM-IV-TR criteria. A broad diagnosis of bipolar disorder risks confounding with other childhood psychopathology and has less predictive value for bipolar disorder in adulthood than the conservative definition. Nevertheless, empirical studies of drug and other treatments and longitudinal studies to assess validity of the broadly defined phenotype in children and adolescents are desirable, rather than extrapolation from adult bipolar practice. The need for an increased capacity to conduct reliable trials in children and adolescents is a challenge to Europe, whose healthcare system should allow greater participation and collaboration than other regions, via clinical networks. ECNP will aspire to facilitate such developments.

Bipolar depression in adults — unipolar/bipolar contrast: Despite some differences in symptom profiles and severity measures, a cross-sectional categorical distinction between BP and UP depression is currently impossible. For regulatory purposes, a major depressive episode, meeting DSM-IV-TR criteria, remains the same diagnosis, irrespective of the overall course of the disorder. However, in refining diagnosis in future studies and DSM-V, a probabilistical approach to the UP/BP distinction is more likely to be informative as recommended by the International Society for Bipolar Disorders (ISBD). Anxiety is commonly present, often at syndromal levels, in bipolar populations. Thus, RCT inclusion criteria for trials not targeting anxiety, should accept co-morbid anxiety disorders as part of the history and even current anxiety symptoms, where these are not dominating the mental state at recruitment to a study. Rapid cycling patients defined as those suffering from 4 or more episodes per year, may also be recruited into trials of bipolar depression without impairing assay sensitivity. Illness severity critically affects assay sensitivity. The minimum scores for entry into a bipolar depression trials should be >20 on HAM-D (17 item scale). However, efficacy is best detected in patients with HAM-D >24 at baseline.

The use of rating scales in bipolar depression: There is some dissatisfaction with the HAM-D or MADRS as the preferred primary outcome for trials, although they probably capture global severity adequately. Secondary measures to capture so-called atypical symptoms (such as hypersomnia or hyperphagia), or specific psychopathology more common in bipolar participants (such as lability of mood), could be informative as secondary measures.

Treatment studies in bipolar depression: Monotherapy trials against placebo remain the gold-standard design for determining efficacy in bipolar depression. The confounding effects of co-medication are emerging from the literature on antidepressant studies in bipolar depression, often conducted in combination with antimanic agents to avoid possible switch to mood elevation. Three arm trials, including the compound to be tested, placebo, and a standard comparator, are generally preferred in order to ensure assay sensitivity and a better picture of benefit–risk ratio. However, in the absence of any gold-standard, two-arm trials may be enough. If efficacy happens to be proven as monotherapy, new compounds may be tested in adjunctive-medication placebo-controlled designs. Younger adults, without an established need for long-term medication, may be particularly suitable for clinical trials requiring placebo controls.The conversion rate of initial UP depression, converting to become BP in the long run is estimated to be 10%. Switch to mania or hypomania may be the consequence of active treatment for bipolar depression. Some medicines such as the tricyclic antidepressants and venlafaxine may be more likely to provoke switch than others, but this increased rate of switch may not be seen until about 10 weeks of treatment. Twelve week trials against placebo are necessary to determine the risk of switch and to establish continuing effects. Careful assessment at 6–8 weeks is required to ensure that patients who are failing to respond do not continue in a study for unacceptable periods of time.To capture a switch event, studies should include scales to define the phenomenology of the event (e.g. hypomania or mania) and its severity. These may be best applied shortly after the clinical decision that switch is occurring. Long-term treatment is commonly required in bipolar disorder. Trials to detect maintenance of effect or continued response in bipolar depression should follow a 'relapse prevention' design: i.e. patients are treated in an index episode with the medicine of interest and then randomized to either continue the active treatment or placebo. However, acute withdrawal of active medication after treatment response might artificially enhance effect size due to active drug withdrawal effects. A short taper is usually desirable. Longer periods of stabilisation are also desirable for up to 3 months: protocol compliance may then be difficult to achieve in practice and so will certainly make studies more difficult and expensive to conduct.The addition of a medicine to other agents during or after the resolution of a depressive or manic episode, and its subsequent investigation as monotherapy against placebo to prevent further relapse (as in the lamotrigine maintenance trials) is clinically informative. Assay sensitivity and patient acceptability are enhanced if the outcome in long-term studies is 'time to intervention for a new episode' for discontinuation designs.

1. Introduction

This consensus statement builds on an earlier and more comprehensive document (Montgomery, 2001). It was noted at the time that the recommendations might need modification to take account of accumulating evidence and experience of conducting trials specifically in the bipolar area. There had been little such activity prior to the development of the original document. The present statement concerns bipolar depression, although it inevitably touches on broader issues of diagnosis and epidemiology.

2. Review and selected supporting literature

2.1. Diagnosis and epidemiology

Diagnostic convention in the Mood Disorders under DSM-IV-TR poses a paradox. On the one hand, major depressive disorder (MDD) is classified separately from bipolar disorder (BD). On the other hand, the core of both diagnoses, namely the occurrence of a major depressive episode (MDE), is defined with identical criteria for depression in unipolar and bipolar disorders. Thus, DSM-IV-TR implies that mania and depression are separate symptom dimensions which may exist separately in individual patients, whereas, within the bipolar diagnosis, depression and mania are viewed clinically as part of a unitary process where one state implies reversal to the other.

In other words there is a tension between the nosological idea of bipolarity which links mania and depression and awaits a distinctive unifying hypothesis, and a purely descriptive notion of bipolar disorder (as in DSM-IV-TR) where one simply has a co-expression of depressive symptoms on the one hand and hypomania or mania on the other. Under the latter formulation (hypo)mania is effectively a co-morbidity of depression. Clearly the nub of this argument, which we cannot yet fully resolve, reflects the particular interest of this consensus statement which is the extent to which there is a difference between unipolar and bipolar depression.

2.2. Epidemiological evidence

The advantage of general population samples is that they allow a representative description of any disorder without bias from severity, help-seeking and treatment effects. Diagnosis in the community, as in the clinic requires a reliable instrument to detect the full range of symptoms for DSM-IV diagnosis: the Structured Clinical Interview for DSM-IV (SCID) or comparable instruments (SCAN, CASH, MINI-Plus) and even scales to measure severity (i.e. the Inventory of Depressive Symptoms (IDS)) identify the relevant symptoms of depression including those that are atypical. European cross-sectional surveys have given broadly consistent estimates of prevalence (Pini et al., 2005): this also corresponds with similar figures from the most recent American survey (Merikangas et al., 2007), which gave lifetime figures for bipolar I disorder of 1% and bipolar II disorder of 1.2%. In addition they identified BP-NOS from DSM-IV in a further 2–3% of respondents. However these estimates from cross-sectional studies are likely to represent conservative lower bound estimates of the true lifetime risk, because longitudinal studies with several assessment points have suggested that (hypo)manic episodes might be underreported in retrospect (Angst, 2007; Wittchen and Jacobi, 2005).

A key finding relates to the time at which symptoms appear in bipolar mood disorder. The cumulative incidence of mania and hypomania more or less seems to reach an asymptote in the third decade. Conversely, the overall prevalence for unipolar major depression, continued to grow across the third decade (Wittchen et al., 2003), and into old age. This divergence suggests a difference in the underlying illness processes for unipolar and bipolar disorders. However, since the majority of studies are both retrospective and cross-sectional, and the few longitudinal studies confined to narrow time periods of the years up to age 30, the age-related incidence patterns remain incomplete. We are currently likely to under-estimate somewhat mania and hypomania. There is a substantial need for long-term prospective studies across the age spectrum to estimate incidence and risk of recurrence. We do not know how frequently clinically significant mood elevation is a late development occurring in mid- and late life (Leboyer et al., 2005). In addition, the natural course and the factors, including treatment, that may influence the risk of depressive and (hypo)manic episodes under naturalistic conditions remain poorly studied and understood. Thus, for example, there is a good deal of variation in the published estimates for the natural length of episodes of hypomania or depression in bipolar patients. This might be due to a lack of consensus about the most appropriate assessment as well as to differences in the age composition of the sample (episodes may be shorter in adolescents and longer in adults). In general, estimates from before the treatment era tend to be longer than those published more recently and may again reflect older age groups. An average figure of around 3 months is commonly accepted (Angst and Sellaro, 2000). However, clinical experience and case series suggest that long episode duration and chronicity may be much commoner than this as suggested in cases coming for treatment, especially with depression (Perlis et al., 2004).

The definition of bipolar states not meeting the full DSM-IV criteria for bipolar I or bipolar II remains of great contemporary interest. When the duration criteria for 'hypomania or mania' symptoms are relaxed from the mandatory four, to only three or two days, the rates of 'bipolar II disorder' increase substantially, without a corresponding drop in clinical correlates of impairment, suffering, or professional help-seeking. This also implies that there is a substantial increase in the number of cases – originally classified as major depression – that may be said to have a bipolar diathesis: they comprise the so-called bipolar spectrum. This must also include the bipolar NOS group in DSM-IV, although they will not be considered further here. Depending on what level of symptoms one regards as evidence of mood elevation, as many as 50% of patients with major depression may be said to have experienced mood elevation (Angst et al., 2003; Cassano et al., 2004). Indeed, on the basis of symptom endorsement over a lifetime in clinic samples, Cassano et al. have suggested that mood elevation forms a continuous bridge between unipolar and bipolar disorders (Cassano et al., 2004). The intensity of illness, either depressive or manic, increased in parallel and simply showed

a higher baseline of elated experience for the bipolar group compared to the so-called unipolar cases. Together, these findings have generated interest in how eventually to implement dimensional bipolarity scores in future revisions of the DSM criteria (Vieta and Phillips, 2007).

In a 10 year prospective study in the community across 4 waves of sampling using the DSM-IV CIDI, the course of different groups of depression with and without lifetime hypomania or mania has been described (Pfennig et al., 2005). The depressive episodes seen in those patients with manic or hypomanic experience showed clear evidence for a greater severity, more atypical symptoms and more psychosis at least in those patients who had also experienced hypomania. There are also a larger number of episodes and the mean time in episodes is slightly elevated in the bipolar cases. Interestingly the trend was for patients with a history of hypomania to have more severe depression than those with mania. Moreover, bipolar II depressed patients may be more likely than bipolar I to present with depressive atypical features, and less likely to experience psychosis.

There has been a widespread interest in assessment and screening tools for hypomania. This follows the fact that a substantial proportion of patients with bipolar I and bipolar II disorders in the community are not recognised or treated. This might be of critical importance, particularly in cases presenting with major depression as the onset condition, who turn out later on – after occurrence of a (hypo)manic episode – to be bipolar. More sensitive screening tools below the current criteria-based threshold for (hypo)manic episodes carry the promise of being able to provide appropriate treatment at an earlier stage. Clearly screening may increase awareness and prompt better diagnosis for earlier treatment. However, it is inevitable that screening thresholds sacrifice specificity for sensitivity. Of the scales that are available, including the MDQ and the HCL-32 (Hirschfeld et al., 2003; Meyer et al., 2007), negative predictive values are between 35 and 51% and positive predictive values similarly between 31 and 52%.

In summary, the estimates of the frequency of bipolar disorder using DSM-IV-TR criteria are relatively stable: they show little indication of substantial variation by culture and region and there is convergent evidence for relatively early onset of illness, in the mid-teens and twenties. The onset of bipolar cases tends to be earlier than those showing only MDD in population samples, which may reflect a partly different causation. The current limitations in the epidemiological literature relate to incomplete information across the life cycle, limited data on episode type, form, length and typical symptoms, limited reliable data on disability, recognition and treatment at a population level and insufficient epidemiological evidence to support independently the definition of thresholds and boundaries. The use of DSM-IV criteria remains the preferred diagnostic system and the supplementary extension of the bipolar II concept can probably be allowed without losing reliability, although there are clear questions about its clinical relevance, utility and consequences in regard to treatment.

2.3. Bipolar depression in children

There is wide acceptance that bipolar mood disorder commonly starts in the mid-teens and twenties, but the age at which bipolar disorder can first be diagnosed remains controversial. While increased prevalence of bipolar disorder among children in clinical samples has been claimed in some (Cassano et al., 2004; Geller et al., 2004; Ghaemi and Martin, 2007; Weller et al., 1995), although not in all studies (Wals et al., 2001), current epidemiological studies using conventional criteria do not document cases of bipolar disorder in children either in Europe or in USA (Costello et al., 2002). Despite this epidemiological data, there has been a huge increase in the clinical diagnosis in children, especially in the USA, where the frequency of bipolar diagnosis from 1996 to 2004 in children discharged from psychiatric care has gone from 1.3 to 7.3 per 10,000 children, without a comparable rise in the adult diagnosis (Blader and Carlson, 2007). Can a 5–6-fold rise in frequency of diagnosis of bipolar disorder in children simply reflect improved awareness, and accurate diagnosis? Or is there a rising rate of the mis-diagnosis of bipolar disorder, due to other disorders of the externalizing spectrum (ADHD, ODD) being counted? At the transition to adulthood, such bipolar diagnoses are unlikely to be confirmed. The rise in outpatient visits of young patients with a diagnosis of childhood bipolar disorder in the same interval in the USA is even more extraordinary – 40-fold (Moreno et al., 2007) - however the absolute rates in this survey remain quite low and the high relative increase may be in large part attributable to improved detection.

It is highly controversial whether DSM-IV 'adult' criteria for bipolar disorder can or should be modified to allow diagnosis more readily (and hence earlier) in children (Duffy, 2007). Diagnostic practice in children is polarised between those who prefer to adopt a narrow phenotype characterised in the manic phase by euphoria, grandiosity and classical episodic manic symptoms and those who favour a broad phenotype, more characterised by irritability and non-specific mood lability. Where a narrow phenotype applies and a bipolar I diagnosis can be made, clinicians may be confident that the diagnosis will still be valid as the child matures. However, they have little choice but to follow the treatment guidance suggested by the adult literature, because of the absence of data from studies in childhood itself. The numbers of cases identified will also be small. Kraepelin documented onset before the age of 10 years in 4 of almost 1000 patients that he reviewed in 1921 and, more recently, in the Spanish network for early onset psychosis there were 35 cases in 2 years for a catchment area of approximately 7 million people (Castro-Fornieles et al., 2007 and Arango personal communication): these would, of course, be severe presentations. Nevertheless, in many child psychiatric services there may be prejudice against making any form of diagnosis, because of habit or the considerable degree of developmental plasticity in this age group. This will mean that the narrow version of bipolar disorder, although rare, may still be under-diagnosed and the proper application of even conservative criteria might increase the numbers of patients detected.

In favour of a broad phenotype is the potential for detection and intervention before severity, suicidality, drug misuse and other variables related to early onset bipolar disorder have become evident. These negative consequences might, in principle, be preventable. Moreover, treatment studies of the broad phenotype in children are legitimate,

irrespective of the validity of the bipolar diagnosis. What is more dubious is the extrapolation of adult bipolar treatment options to young children with a speculative bipolar diagnosis. This has been pejoratively described as disease-mongering. It certainly risks bringing discredit on psychiatry if the adequate efficacy and safety studies are not performed, and there is the potential for significant harms (metabolic syndrome with antipsychotics, abnormal involuntary movements, etc. (Laita et al., 2007)).

There are several difficulties in accepting the broad bipolar diagnosis in children especially in ordinary practice as opposed to a research setting. The first is to adopt irritability as a defining symptom of bipolar disorder. This risks confounding with other childhood psychopathology, in which it is a common symptom. These other disorders include ADHD, oppositional defiant disorder and conduct disorder and it may even be a temperamental trait (impulsivity in childhood). Hence, predictably, for the most liberal definitions of bipolar disorder, co-morbidity with ADHD becomes extremely high and figures of between 70% and 98% exist in the literature (Geller et al., 2004; Wozniak et al., 1995). It is difficult to see where one condition can be said to end and the other to begin. Indeed, some authors have argued that some children diagnosed with bipolar disorder may have severe ADHD and stress the importance of differentiating between chronic and episodic irritability (Leibenluft et al., 2006). A further confound, seldom addressed in the current literature, is the potential for the use of stimulants and antidepressants to induce bipolar disorder or mimic its symptoms: if correct, this explanation is likely to be most relevant to the North American context where prescribing rates for children are much higher than elsewhere (Reichart and Nolen, 2004).

The most extreme advocates of the broader diagnosis also describe a chronic course with an absence of relapsing and remitting episodes characteristic of adult patients, a more common rapid cycling or mixed episode presentation and non-mood congruent psychotic symptoms. This must tend to confound the bipolar diagnosis with, rather then divide from alternative childhood psychopathology. Accordingly it is encouraging that *episodic changes in mood* are assuming increasing importance for definition of bipolar disorder NOS. Definitions with this core feature have shown similar evidence of being on the bipolar spectrum: conversely, neither the number of other manic symptoms present, nor the duration of the index mood, appeared to have a big impact on the validity of definitions. Clinical implications of these findings include that bipolar NOS is best defined by episodic changes in mood (Birmaher and Axelson, 2006; Birmaher et al., 2006). Emphasizing the core mood criterion and episodicity may mark an important homogeneous subset of cases.

A further difficulty remains the lack of predictive validity and stability of the disorder when a broad phenotype is used as compared to a diagnostic stability of around a 80–90% when a narrow phenotype is used (Fraguas et al., 2007; Hollis, 2000). Finally, and perhaps most obviously, young children normally indulge in impulsive behaviours, grandiose fantasy and may have difficulty reporting complex emotions, ideas and experiences: inferences may be drawn from particular child behaviours that may not be strictly warranted (Geller et al., 2002).

The validity of the broad childhood bipolar phenotype requires testing by well designed prospective studies to determine the adult outcome of such cases. In the COBY study of patients with BP-NOS, 20% were said to have converted to bipolar I after two years and 10% to bipolar II. However, this is a highly selected clinical cohort. In the Oregon Adolescent Depression Project, a representative community sample of adolescents aged 14–18 showed a prevalence of bipolar disorder of about 1%, about half of whom were diagnosed as having bipolar II disorder (Lewinsohn et al., 1995): 97 cases of subsyndromal mood disorder (about 6% of the original sample) were followed up and showed elevated rates of MDD and anxiety disorders but not an increased incidence of bipolar disorder in their mid-twenties. Almost similar findings were reported from the Early Developmental Stages of Psychopathology Study in Germany (Wittchen et al., 2003) and a reanalysis of several other European studies (Pini et al., 2005).

The Great Smokey Mountain study also suggested that the broad bipolar phenotype is more predictive of depression than bipolar disorder. Other studies looking at males with co-morbid mania and ADHD suggest that manic symptoms may not persist in subsequent follow up (Hazell et al., 2003). There have been no studies explicitly comparing unipolar and bipolar presentations in children or indeed their longitudinal outcomes. Prospective, longer follow up of larger samples is needed to clarify these issues: this will require regional and supra-regional networks to acquire a sufficiently large sample. Bipolar I and related bipolar II/spectrum diagnoses should be included in such research studies and there is need for a greater understanding of the effects of developmental family and co-morbid factors in the course of the disease. Notwithstanding the uncertainty around the broad phenotype, bipolar disorder has been largely neglected in child psychiatry and may still be under-diagnosed in Europe, as prepubertal depression used to be not so long ago (Geller and Tillman, 2005; Reddy and Srinath, 2000).

The different perspectives on a broad and earlier diagnosis of bipolar disorder in children remain polarised with the most extreme advocates of the advantages being North American, and the most conservative being European. The correct conclusion is probably that the evidence remains sufficiently limited to allow very different perspectives to be defended.

The diagnosis of bipolar II disorder in children has little evidence based supporting studies, hence even greater uncertainty, and for this reason, the recommendations of NICE (http://www.nice.org.uk/guidance/index.jsp?action=byID&o=10990#documents) were that in clinical practice a bipolar II disorder in children was unlikely to be reliable or useful. In a research setting, however, structured interview may be useful to establish boundaries between bipolar I and II sub-types in children.

In conclusion bipolar disorder exists in children and adolescents. Although bipolar-like symptoms may be quite frequent, reliably defined bipolar I disorder is rare in prepubertal children. It assumes increasing importance in adolescence with early onset increasingly recognised for bipolar patients in their late teens. Such cases appear to merit treatment by extrapolation from experience in adults. Since early intervention may improve prognosis, trials of such treatment are an important objective for future

research. Treatment studies can obviously legitimately recruit populations with adequately and operationally defined disorders which may include bipolar NOS in children.

2.4. Bipolar depression in adults — unipolar/bipolar contrast

Kraepelin's writings on the issue of potential differentiating features between "bipolar" and "unipolar" depression are inconsistent. In his best known monograph, "Manic–Depressive Insanity and Paranoia" (English translation 1921, Kraepelin and Robertson, 1921), he made no distinction between the clinical features of depressed episodes in those with or without prior manic episodes. However, in his "Lectures on Clinical Psychiatry" (3rd Edition, 1913, Kraepelin, 1913), he contrasted the characteristics of depression in 'melancholia' (unipolar depression) and 'depressed stages' of 'manical-depressive insanity' (bipolar depression). He stated that "… this condition differs from that of our melancholic patients, in a very definite way, through the strong impediment of volition (psychomotor slowing and impaired motivation), and the absence of the apprehensive restlessness so clearly marked in them (page 12)". He then describes how such impediments in volition and cognition allowed him to predict which patients would go on to experience future "attacks of excitement".

In developing the separation between bipolar and unipolar disorders, Leonhard, Perris and Angst placed the emphasis primarily upon the euphoric features of the condition, not upon differences in the depressive episodes. This indifference to phenomenological or other distinctions is reflected in both DSM-IV and ICD-10 nosological systems. However there are obvious potential advantages, where it is possible to distinguish bipolar/unipolar depression. The most obvious is in relation to detecting and making the diagnosis in young people before the onset of mood elevation, where a past history of hypomania is ambiguous or cannot be elicited and in those depressed patients with a positive family history of bipolar disorder. In addition it would be interesting and important if there were differential treatment response between unipolar and bipolar disorders, which is often mooted, and it would help in developing the understanding of the distinct biology of the two conditions implied in some studies.

Since the 1970s there have been 25 cross-sectional comparative studies of unipolar and bipolar depression (Mitchell and Malhi, 2004). While often individually too small, the results of these studies have been consistent enough to merit a consensus view. Thus, in 3 large cross-sectionally rated data sets containing almost 1000 depressed unipolar patients and 83 bipolar patients, bipolar depressed patients were more likely to manifest objective psychomotor slowing and pathological guilt and showed, in addition (Mitchell et al., 2001), an increased frequency of atypical depressive symptoms such as hypersomnia and past psychotic depressive episodes. Psychomotor agitation was not a distinguishing characteristic. However, these studies did not identify a point of rarity in the distribution of characteristics of bipolar as compared to unipolar depression, simply that there are features statistically more likely to be associated with one than the other. This in itself implies an underlying dimensional rather than categorical difference to be likely. The most characteristic symptoms are psychomotor retardation, hypersomnia, hyperphagia, weight gain, leaden paralysis, lability of mood, psychotic features, worthlessness, low self esteem and social withdrawal. The most characteristic features in the course of illness were an earlier onset, shorter duration of episodes, more episodes prior to the index presentation and a family history positive for bipolar disorder. Those features most likely to be associated with unipolar depression included higher activity levels, initial insomnia, appetite loss/weight loss and somatic complaints. The course of the illness correspondingly showed age of onset to be later, a longer duration of episodes, fewer episodes prior to the index presentation and family history tended to be negative for bipolar disorder. The limitations of the studies are the samples, which are often based on clinical presentation, potential confounding variables such as age, gender and the use of medication, and multiple testing across data sets with many variables.

There have been several longitudinal studies of the characteristics when depressed of converters from recurrent unipolar depression to bipolar depression: these subjects are obviously of particular interest for the current argument. One percent of hospitalized depressives later convert from unipolar depression to bipolar depression every year (Angst and Preisig, 1995). The predictors of this change relate to the differential characteristics described in the preceding paragraph; that is, onset of depression under age 25, hypersomnia, family history of bipolar disorder, antidepressant associated manic symptoms and postpartum depression. In the NIMH 11 year follow up (Coryell et al., 1995) those who switched to bipolar I disorder were more likely to have been psychotically depressed or in hospital at the index episode, showed greater psychic anxiety, poor concentration, social withdrawal and feelings of inadequacy.

These data have been summarised for the International Society for Bipolar Disorders Diagnostic Guidelines Taskforce on bipolar depression (Ghaemi et al., 2008; Mitchell et al., 2008). The proposal is that a categorical distinction between bipolar and unipolar depression, based on cross-sectional features, is currently not supportable. Instead, a probabilistic approach is more likely to be informative for future studies. All patients are required to meet DSM-IV-TR or ICD criteria for a major depressive episode. The differences in symptoms are shown in Table 1. Some clinical features have low diagnostic specificity such as worthlessness and low self esteem. At present, it is unclear how to threshold any difference: however, secondary analysis of individual patient data from all drug studies should allow the proposal to be developed.

Bipolar II depression has been rarely compared with unipolar depression (Brugue et al., 2008). Benazzi (2002–2003) reported increased prevalence of atypical depressive features such as hypersomnia and hyperphasia and non-euphoric "hypomanic features" of distractibility, racing thoughts, irritability and talkativeness. Rates of psychomotor retardation did not differ. There is currently some controversy over the position of agitated depression as a putative 'mixed state'. This has been described by Benazzi et al. in a personal outpatient sample where 20% had 'agitated depression'. This was conceptualised as a depressive mixed state or unrecognised bipolar mixed state on the basis of high rates of non-euphoric hypomanic symptoms as described above and a family history of bipolar II disorder (not bipolar I disorder). There is

Table 1 A proposed "probabilistic" approach to the diagnosis of bipolar I depression in a person experiencing a major depressive episode with no clear prior episodes of mania (Mitchell et al., 2008)

The greater likelihood of the diagnosis of bipolar I depression should be considered if ≥*x* of the following features are present [a]:	The greater likelihood of the diagnosis of unipolar depression should be considered if ≥*x* of the following features are present [a]:
1. Symptomatology and mental state signs	
Hypersomnia and/or increased daytime napping	Initial insomnia/reduced sleep
Hyperphagia and/or increased weight	Appetite and/or weight loss
Other "atypical" depressive symptoms such as "leaden paralysis"	
Psychomotor retardation	Normal or increased activity levels
Psychotic features and/or pathological guilt	Somatic complaints
Lability of mood/manic symptoms	
2. Course of illness	
Early onset of first depression (?<25 years) [a]	Later onset of first depression (? >25 years) [a]
Multiple prior episodes of depression (≥5 episodes) [a]	Long duration of current episode (>6 months) [a]
3. Family history	
Positive family history of bipolar disorder	Negative family history of bipolar disorder

[a] Confirmation of the specific numbers to be used requires further study and consideration.

concern about the validity of the concept because of its focus on non-euphoric hypomanic symptoms. It ignores the phenomenological difference in content in favour of the similarity in form between hypomania and depression: for example grandiosity/disinhibition versus mental disturbance/guilt. Moreover, it is clear that bipolar I depression is characterised more by psychomotor retardation rather than agitation.

Additional areas of uncertainty include the relationship between anxiety and bipolar disorder. Anxiety has been reported as more common during unipolar than bipolar depressive episodes in a number of clinical cohort studies (Vieta et al., 2007). However, as an apparent paradox, anxiety disorders are usually stated to be more commonly co-morbid with bipolar disorder than with unipolar disorder. The problem may lie more in the methodological bias in clinical cohorts. Moreover, scales most commonly employed in symptomatic assessments of depression or mania in bipolar disorder frequently do not include a total of more than three items on anxiety. A recent survey of 10,000 respondents in Australia suggests that 52% of bipolar disorder patients had at least one co-morbid anxiety disorder over 12 months which, while much higher than the general population, was not higher than those with unipolar depression. The most common disorders were panic, social phobia, GAD, OCD and PTSD (Mitchell et al., 2004). Similar rates of co-morbidity were seen in the US replication survey (Kessler et al., 2005) for bipolar I and bipolar II disorders. Since anxiety is so common in bipolar populations, RCT inclusion criteria need to accept co-morbid anxiety disorders where these are not dominating the mental state at recruitment to a study. In addition, measurement of anxiety outcomes should be included in most studies of bipolar disorder.

In fact, bipolar disorder has elevated co-morbidity rates with virtually all psychopathological conditions/disorders and suicide: some recognition of this in trials is necessary (Kessler et al., 2005). Exclusion of some patients will make cohorts more homogeneous: where subjects with co-morbidity are included, their psychopathology should be measured.

2.5. The use of rating scales in bipolar depression

If changes in depressive symptoms with treatment are to be captured faithfully, scales have to measure them. The emphasis in the development of the best known severity rating scales such as the Hamilton Depression rating Scale (HAM-D) and the Montgomery Asberg Depression rating Scale MADRS was upon the detection of change and response to treatments for unipolar depression. The HAM-D is almost universally employed to measure illness severity despite many limitations, the most important being perhaps that many scale items are poor contributors to the measurement of depression severity (Bagby et al., 2004). In addition, neither the HAM-D nor the MADRS adequately address a number of features apparently more common in bipolar depression such as hypersomnia, mood lability and observer rated psychomotor disturbance. Nevertheless, in the last few years there have been several successful studies of patients with bipolar I disorder recruited during a major depressive episode, using the MADRS as primary outcome (see section 5.2). Entry to such studies has required a minimum HAM-D or MADRS total score and a maximum restrictive score on the Young mania rating scale of less than 12. While this may already seem to impose exacting criteria it does not capture for many clinicians the complexity of bipolar depression. Accordingly while it may be necessary to keep the MADRS conventional end point in the treatment of depression it seems desirable to include multidimensional assessments of mood in any trial looking at bipolar depression. In the first instance this is likely to be a hypothesis generating exercise but it may eventually generate scales more appropriate to bipolar depression (such as the Bipolar Depression Rating Scale (Berk et al., 2007)) given its unusual, if not unique, characteristics.

Another approach to this is the Multidimensional Assessment of Thymic States (MAThyS) scale which supposes several dimensions which range from inhibition on the one

hand to acceleration on the other in domains either of emotional reactivity, speed of thought and action, motivation and perception. Taking into account all bipolar mood states, using the MAThyS it is possible to show a clustering into 3 groups, a group in which inhibition predominates in all domains, another in which excitation predominates in all domains and a third which is a mixture of both. Cluster 1 best characterises major depressive episodes without any agitation, cluster 2 is characteristic of hypomanic or manic states and cluster 3 represents a broad spectrum of mixed states (Henry et al., 2007a). Using the same scale in bipolar patients presenting with depression as defined by the DSM-IV, a cluster analysis revealed two types of depressive states. One group which had a low score, is characterised by an inhibition in all dimensions, whereas the other group is characterised by an over-activation. Emotional reactivity is the most relevant dimension for discriminating these two types of depression and showing that bipolar depressive states are not homogeneous (Henry et al., 2007b). The use of such continuous scales might allow prediction of treatment response in heterogeneous patient groups.

Finally, some measure of psychosocial functioning should be introduced in clinical trials to ensure that psychometric and clinical benefits effectively translate into "real world" outcomes. While most available instruments are neither very user-friendly nor sensitive to change, the ISBD Task Force has developed the FAST (Functioning Assessment Short Scale), which has been validated in several languages and for bipolar disorder in particular (Rosa et al., 2007). These scales might be particularly useful in long-term, maintenance trials.

3. Treatment studies in bipolar depression

Bipolar disorder without depressive disorder has been found to be very rare. Moreover, the long-term course is dominated by depressive rather than hypo(manic) symptoms. Recent prospective surveys suggest that patients with bipolar disorder seen in clinic samples are euthymic for only about 50% of the time (Judd et al., 2002; Kupka et al., 2007). Of the rest of the time most of it is spent depressed, with a more modest fraction (approximately 12%) in states of mood elevation. Prospective data collection, as in the Stanley Foundation Bipolar Network study, appears more likely accurately to detect hypomania (Kupka et al., 2007). These statistics define both the primary burden of the disease and the challenge to develop and improve treatments.

3.1. Antidepressants

It remains a widespread assumption that data on antidepressants studied in unipolar depression can be extrapolated to major depressive episodes in the context of a bipolar illness course. This rests on the foregoing evidence that major depressive episodes share much else in common in the two illness courses. However, this assumption has discouraged regulatory studies in bipolar depression. Hence, the data on which to base a pragmatic judgement remains very limited and confined to comparisons between the response rates for unipolar and bipolar disorders to the same or similar treatments across different studies. Response rates (active treatment minus placebo) in unipolar depression can be confidently said to lie between 14% and 22%, depending upon age, on the basis of many placebo-controlled trials (Hazell et al., 2002). For bipolar depression, the response rate reported in a meta-analysis published in 2004, was comparable at 24%: but the total numbers of patients randomized was under 700 and the antidepressants considered were a heterogeneous group (Gijsman et al., 2004). This average effect was determined for the majority of cases on a background of co-medication to prevent mania. Nevertheless subsequent studies have tended to find a lower treatment response.

Thus, the largest independent study (STEP-BD) was resoundingly negative for antidepressants added to a variety of other treatments (Sachs et al., 2007). In an earlier example (Nemeroff et al., 2001), the effect of the lithium level was retrospectively determined to be significant in determining the response to added placebo: this implied an important contribution from the lithium acting as an antidepressant in its own right. Effect sizes in studies to date are greater when studies are conducted in the absence of mood stabilisers such as lithium. However, not all antimanic co-medication has prevented detection of an antidepressant treatment effect, as in the case of olanzapine (Tohen et al., 2003). It might be expected that interaction with other medications would depend upon their individual capacity to relieve depressive symptoms. A further observation is that effect sizes show a progressive decrease from earlier to later published studies, similar, but more extreme, to that seen with unipolar depression (Walsh et al., 2002). This inflation of placebo responding suggests that the nature of the samples studied over time may have changed. Experts speculate that one important contributor to the problem of inflated placebo response is the commercialization of patient recruitment by Clinical Research Organisations, instead of recruiting clinically well defined patients from research settings.

Whether this should be regarded simply as a technical issue – co-medications may obscure assay sensitivity in placebo-controlled trials – or whether it has the important practical implication that combined treatment with an antidepressants and a mood stabiliser is an ineffective clinical strategy remains to be established. In summary, there is currently insufficient data to know if the expected effect size is comparable to that seen in the much larger data sets for unipolar depression, especially when antidepressants are used with mood stabilisers. The evidence that we have includes studies with different classes of antidepressants, different methodologies and the strong probability that concomitant effective treatment with mood stabilisers may reduce or abolish the size of the effects that could be observed. Independent monotherapy trials in bipolar depression are desirable for individual compounds as well as studies clarifying whether combinations confer advantage over monotherapy.

Bipolar II data for treatment with antidepressants is almost non-existent: there is probably a need to define antidepressant efficacy in this group. The probability of the switch to hypomania may be lower (Altshuler et al., 2006) but also be of relatively less clinical significance than a manic switch would be. Bipolar II disorder has been satisfactorily investigated in recent treatment studies with

secondary analysis of treatment effects after stratification (see below).

3.2. Switching to hypomania or mania

It is an obvious clinical fact that, sometimes, patients with bipolar disorder taking antidepressants for a depressive episode may switch into hypomania or mania. This is sometimes unthinkingly described as an antidepressant induced switch to mania rather than simply an association between treatment and manic switch, which might occur in any case as a result of the natural course of the illness and/or recovery from depression (as well as during treatment by other classes of medication). Comparative data that allow a judgement about the relative likelihood of switch under different antidepressant treatments has been very meagre. An analysis of the data bases from pharmaceutical companies in 1994 (Peet, 1994) suggested that SSRIs were no more likely to cause switch than placebo, whereas tricyclics increased the risk by about 3-fold. This was confirmed by meta-analysis of published bipolar depression trials (Gijsman et al., 2004), although the length of these acute studies was quite short. There have been a number of identified possible risk factors for switch, none of which has been replicated in subsequent studies (Visser and van der Mast, 2005). Studies of an adequate size are still needed to decide the issue and for the moment there is little to be recommended other than clinical vigilance and life charting to decide treatment in individual cases.

The randomized blinded study of bipolar I and II depressed patients in STEP-BD reported no evidence of differences in mood destabilisation or switching between patients treated with mood stabiliser plus either paroxetine or bupropion versus those treated with mood stabiliser alone for 16 weeks (Sachs et al., 2007). Recent prospective data from the Stanley Foundation Bipolar Network suggests that treatment with venlafaxine, even when added to a mood stabiliser, is associated with an increased switch to mania (Post et al., 2006). Events compared to those seen while taking sertraline or bupropion only occurred after nearly 10 weeks of treatment and were associated with treatment response. Switch appears to occur earlier in bipolar I patients (Altshuler et al., 2006). The finding of higher switch rates in the earlier meta-analysis (Gijsman et al., 2004) was for tricyclic antidepressants relative to SSRIs, MAOI and buproprion. The similar findings for venlafaxine (Post et al., 2006; Vieta et al., 2002) suggest that the combination of serotonin and norepinephrine re-uptake inhibition is a particularly potent pharmacological combination for switch.

The limitations of studies hitherto have often been related particularly to the unclear definition of a switch. At its simplest this could simply be a switch from a resolving depression to pure hypomania. In most studies it is unclear whether such patients are drug responders, switchers or both. Other uncertainties are the possibility of a switch into a mixed state without response of the depressive episode, an increase in agitation or an apparent worsening of depression. In addition there has been little attempt to discriminate between mania and hypomania or to determine whether or not the outcomes are necessarily deleterious. To capture a switch event, studies should include scales to define the phenomenology of the event (e.g. hypomania or mania), its severity and functional impact. These may be best applied shortly after the clinical decision that switch is occurring. Finally, it is unclear how much later a (hypo)manic episode can follow response and remission of depression and still be called a switch. An interval of a few days or even weeks appears reasonable: to accept an interval of months appears less so.

Spontaneous mania is apparently more severe in some case series (Stoll et al., 1994). It is very desirable that this be established by careful clinical follow up for a wider range of cases. Of the existing treatment studies, most patients received co-medication with an antimanic agent and then rates of switch are low (Gijsman et al., 2004). Switch rates will be highly influenced by the inclusion in clinical samples of rapid cyclers, and indeed such patients accounted for the main effect in the Stanley Foundation Bipolar Network study (Post et al., 2006).

There is an overall paucity of randomized studies. There is a good deal of methodological variation and in particular the frequent concomitant medication with mood stabilisers that may confound the effects being studied (efficacy or switch). There has usually been insufficient data to assess entry severity requirements and little attempt to formalise a placebo run-in. There has been some lack of clarity as to whether switch counted towards response or remission rates and the definition of switch itself differed from clinical diagnosis to definitions using the YMRS. At present, monotherapy with antidepressants is probably more effective than placebo although the effect size is not established. If there is indeed an effect it appears to be diminished by concomitant medication whatever that may be, although individual drug data is very limited. The manic switch is higher on tricyclic antidepressants (TCAs) or venlafaxine than on SSRIs or bupropion which may imply a noradrenergic involvement in the effect. The length of trial needed to show efficacy is at least 6 weeks but in the absence of comparative data 8–10 weeks may well be better. This is particularly the case in studies designed to measure switch rates. There is currently little evidence for efficacy in relapse prevention but also little evidence of harm if in combination with an antimanic treatment like lithium. The perhaps questionable assumption that there is an increased risk of switch has been an important additional deterrent to placebo trials of antidepressants as monotherapy in bipolar depression.

The assumption that antidepressants can also induce a rapid cycling illness course is based almost exclusively on naturalistic observation (Ghaemi et al., 2003). There is some limited evidence for cyclical acceleration after taking antidepressants in individual cases (Wehr and Goodwin, 1979) but the shortage of controlled information is striking and limits the confidence with which any conclusions can be reached.

In the long term, there is little data on continuation treatment with antidepressants. The early Prien study (Prien et al., 1988) showed that monotherapy with imipramine was less effective in preventing relapse than treatment with lithium alone or lithium plus imipramine over a 30 month follow up period. The main risk appeared to be manic relapse. Another early study failed to demonstrate an advantage of adding imipramine to lithium, although

depressive relapses were too few to power the study adequately (Quitkin et al., 1981).

3.3. Proposal for definitions of switch as opposed to recurrence

The distinction between relapse (or switch) and recurrence may have meaning in bipolar disorder and a terminology based on that employed in unipolar disorder (Frank et al., 1991) is provided here for discussion (Fig. 1). The definition of switch, as a change of polarity within the recovery (relapse) phase) captures the way the word is used. However, the relapse/recurrence distinction poses difficulties, even in unipolar disorder. First, it is difficult in practice to define the correct periods of time in which to distinguish relapse from recurrence. Secondly, many patients have partial remission — is a worsening then a relapse or a recurrence? Finally the relapse/recurrence distinction should imply a different risk for the two phases. If it were bimodal, then this would strongly support the relapse (high risk) versus recurrence (lower risk) distinction. But, in fact the probability of a new episode simply reduces over time following return to euthymia. The formulation would also, only ever fit episodic illness and not continuous (rapid) cycling.

3.4. Anticonvulsants and bipolar depression

The impact of treatment with anticonvulsants on depression remains somewhat uncertain. Indeed, anticonvulsants as a class do not appear to have a single predictable action in bipolar disorder. The initial evidence suggesting a particular impact of anticonvulsants on depressive symptoms in patients was indirect. Thus, Bowden showed, in a secondary analysis of a seminal acute study in mania (Bowden, 1995), a greater impact from valproate (as divalproex) than lithium in those patients with mixed mania, compared to those with pure mania. In other words there appeared to be an advantage for depressive symptoms coexistent with manic symptoms in responsiveness to an anticonvulsant. Further analysis of the maintenance trial comparing divalproex, lithium and placebo showed that those patients showing early discontinuation for depression were more common in the placebo and lithium groups. This tendency was even more striking when the outcome was identified to be the prescribing of SSRI's as a rescue treatment. In those circumstances just 10% of divalproex treated patients required SSRI's, compared to 45% of those on placebo and almost 30% of those on lithium (Gyulai et al., 2003). These results are limited by the small numbers involved and the post hoc nature of the analysis. There has been a single preliminary acute study of bipolar depression as an index episode using depakote, when it was numerically superior to placebo (Thase and Sachs, 2000). Nevertheless, the effects of valproate on mania have remained more convincing.

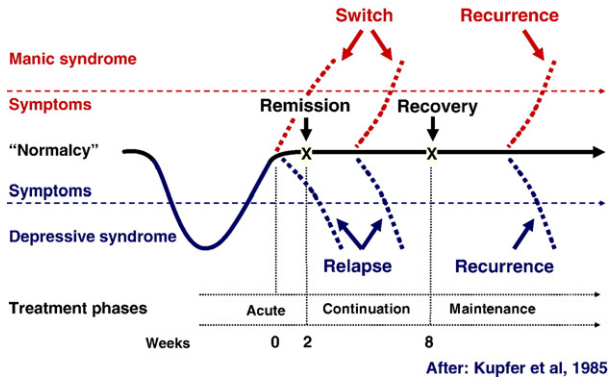

Figure 1 Suggestions for definitions in bipolar disorder.

In contrast, evidence for an anticonvulsant having antidepressant properties (and limited antimanic potential) comes from studies of lamotrigine (Calabrese et al., 1999; Calabrese et al., 2000). In fact, all the acute studies conducted by the product's pharmaceutical company in the investigation of lamotrigine were individually negative on the primary outcome, but showed, nevertheless a consistent positive direction of effect. In other words, they showed a numerical advantage to treatment with lamotrigine against placebo in each individual trial without statistical significance (Goldsmith et al., 2003). In addition there is one positive study in bipolar depression in which lamotrigine was more effective than placebo as add-on to ongoing treatment with lithium (van der Loos et al., in submission). Meta-analysis is consistent with a homogeneous weak effect, that individual trials were under-powered to detect (Geddes et al., 2008).

The likely reasons for these results are instructive. First, because of the requirement to taper up the dose slowly to minimize the risk of dermatological problems, there is an inherent disadvantage for lamotrigine in acute treatment studies compared to placebo: an increased time for patients to drop out of studies due to lack of treatment response in the active arm. Secondly, lamotrigine has almost no adverse effects at the doses used in the acute studies that might bias patients or investigators towards the active treatment: hence assay sensitivity needs to be optimal to detect treatment effects. A recent independent meta-analysis of all the individual patient data, provided by the company, suggests that if a division of index cases is made by severity, those patients with HAM-D scores of over 24 at entry showed a highly statistically discriminable effect compared to placebo, whereas those with lower scores on the Hamilton rating scales showed no difference between drug and placebo. A component of STEP-BD trial in the adjunctive treatment of resistant patients with bipolar depression suggested a role for lamotrigine (Nierenberg et al., 2006): there was a 24% response rate to lamotrigine compared to only 5% with risperidone.

The investigation of maintenance treatment with lamotrigine compared with lithium and placebo showed an effect against depression in studies where patients entered either from a manic episode or a depressive episode. Thus, patients with either mania or depression were treated to recovery by any means necessary in the open phase of the study, while lamotrigine was tapered up to a therapeutic dose. This allows no confidence that there has been an initial acute response to lamotrigine per se. If the purpose of such trials is to prove maintenance of effect, then subsequent randomisation to lamotrigine monotherapy or placebo cannot prove that a 'response' has been maintained. Nevertheless, the design of the study allowed an estimate of lamotrigine's capacity to prevent recurrence compared to placebo. Therefore positive findings seem to many authorities to represent a convincing effect on the risk of further illness and support the addition of

lamotrigine during or after the resolution of a depressive or manic episode to prevent further depressive relapse.

3.5. Atypical antipsychotics and bipolar depression

There has been increased recent interest in the capacity to treat bipolar depression with atypical antipsychotics. The possible mechanism of action for this effect is uncertain and the usual assumption is that it is via an action either on $5HT_2A$ receptors acting as antagonists to modulate dopamine levels but other mechanisms such as H1 antagonism are common with some antidepressants, and may be involved as well (Brugue and Vieta, 2007). Antidepressant effects might then be mediated by facilitating dopamine actions in reward pathways that may be related to depression. Bipolar disorder, since it shows more consistent evidence of retardation etc. and other symptoms may more closely involve dopamine than does unipolar disorder. It could form the basis for dimensional differences between bipolar and unipolar depression. However these rationalisations are post hoc and most of what we know has been driven by empirical investigation by companies looking for an increased indication for their compounds.

The first observation was that olanzapine, either alone or in combination with fluoxetine, was superior to placebo in an 8 week study in bipolar depression (Tohen et al., 2003). The olanzapine only effect was modest in size and failed to modify core symptoms of depression such as sadness, impaired concentration, lassitude, and pessimistic or suicidal thoughts. Instead olanzapine monotherapy had effects primarily on attention, reduced sleep and reduced appetite as individual items of the MADRS. Somewhat in contrast, two studies of quetiapine of more or less identical design show significant efficacy for quetiapine at a dose of 600 and 300 mg compared with placebo in 8 weeks' treatment of bipolar I and bipolar II disorders (Calabrese et al., 2005; Thase et al., 2006). All items on the MADRS change significantly under quetiapine treatment and significant, clear cut effects were seen at one week with both doses of quetiapine. Effect size was somewhat smaller in the bipolar II patients mainly because of a smaller active treatment response rather than different placebo response. Sub-analyses of the pooled data set demonstrated effects in rapid cyclers and an absence of switch compared to placebo. Prospective safety data within the 8 week treatment period demonstrated that, in both olanzapine and quetiapine trials, the atypical antipsychotic was associated with significant increases in weight and deleterious changes in metabolic parameters.

The findings from these studies demonstrate the feasibility of clinical trials in mixed samples of bipolar I and bipolar II disorders in the absence of a concomitant medication and with relatively large numbers. The main limitations will have been the difficulty of blinding when one of the treatments produces significant side effects such as sedation or weight gain: this may be obvious both to participants and to investigators and is a potential source of bias.

The prospective measurement of items of rating scales relating to suicidality, has shown reductions in apparent risk over the treatment interval. There are significant concerns in the case of quetiapine that the minimal effective dose has not been established.

4. Clinical trials design

Acute treatment studies of new treatments for bipolar depression are likely to continue to be necessary against placebo, and appear to have been feasible recently in a number of countries. Mature patients in later stages of bipolar disorder are often on long-term treatments: this makes monotherapy trials in this group very difficult. Younger patients may often be more easily entered into such studies. Most studies have recruited both bipolar I and bipolar II patients and the efficacy results have usually been similar with the two putative DSM-IV sub-types: e.g. for quetiapine (Calabrese et al., 2005; Thase et al., 2006) and lamotrigine (Geddes et al., 2008).

The duration of trials to establish acute efficacy in unipolar depression has often been rather short (6–8 weeks) and will optimize comparison with active and placebo treatment phases while the majority of participants remain in a study. Similar considerations will apply for the choice of primary efficacy end point in bipolar patients. For bipolar depressed patients sufficient continuing time should also be allowed to detect increased rates of switching (and continuing efficacy, of course). The risk of switch seems to increase after 8 weeks so that at least 12 weeks may be necessary to accumulate adequate numbers of events. This is a challenge for placebo-controlled studies. Particular attention is required to the criteria for stopping ineffective treatment.

Comparison with an active comparator is useful to establish assay sensitivity in negative studies, and as a preliminary secondary estimate of relative efficacy of any new compound. The best choice of active comparator for bipolar depression is currently probably quetiapine. However, on the basis of being a longstanding accepted first line treatment for bipolar depression, lithium could also be considered a comparator. Antidepressants appear less likely to be adopted in future studies; there is an absence of a significant body of evidence for their efficacy and the independent negative study already referred to, has diminished their profile further. However, in the absence of any gold standard for treating depression (and hence much international variation in practice), positive two-arm placebo-controlled trials will still be informative.

Medicines to treat bipolar depression will often be required in combination with long-term treatments such as lithium, valproate etc. Co-medication is likely to reduce the apparent efficacy of a new compound. However, trials of new medicines in combination with other long-term treatments may be useful in proof of concept for more severe patients, to guide clinical practice and finally for safety.

Long-term treatment is commonly required in bipolar disorder. Trials to detect maintenance of effect or continued response in bipolar depression should follow a 'relapse prevention' design: i.e. patients are treated in an index episode with the medicine of interest and then randomized to either continue the active treatment or placebo. However, acute withdrawal of active medication

after treatment response might artificially enhance effect size due to withdrawal effects of an active drug. A short taper is usually desirable.

The duration of treatment required to stabilise mood before randomization to drug withdrawal is not established. It is not known whether there is a different biology underlying relapse after 2 weeks mood stability versus 12 weeks mood stability. Longer periods of stabilisation for up to 3 months may appear desirable, but protocol compliance may then be difficult to achieve in practice and so will certainly make studies more difficult and expensive to conduct. The time of withdrawal of the active medicine, after stabilisation has been achieved, may with advantage be varied to increase the blinding of investigators and participants.

The addition of a medicine to other agents during or after the resolution of a depressive or manic episode, and its subsequent investigation as monotherapy against placebo to prevent further relapse (as in the lamotrigine maintenance trials) is clinically informative.

Assay sensitivity is enhanced if the primary outcome in long-term studies is 'time to intervention for a new episode' for discontinuation designs. This outcome also increases patient acceptability since the threshold for intervention during a clinically significant relapse is not artificially high and can reflect clinical practice.

Sample sizes that give adequate power to detect changes in both (hypo)manic and depressive relapse are desirable.

Finally, besides the traditional measures of outcome based on symptom severity rating scales, it would be advisable to include some secondary measures addressing functionality (this might include neuropsychological tests of attention memory and executive function) and quality of life.

Role of the funding source

ECNP fully funded the participation of the committee members.

Contributors

Chairpersons:

Guy M. Goodwin, University Department, Warneford Hospital, Oxford OX3 7JX, UK.

Celso Arango, Unidad de Adolescentes, Hospital General Universitario Gregorio Marañón, CIBER-SAM, Madrid, Spain.

Committee:

Ian Anderson, Neuroscience and Psychiatry Unit, The University of Manchester, Room G809, Stopford Building, Oxford Road, Manchester, M13 7PT.

Charles L. Bowden, Department of Psychiatry, University of Texas Health Science Center, San Antonio, Texas, USA, 78229-3900.

Chantal Henry, INSERM, U 841, IMRB, Department of Genetics, Psychiatry Genetics, Creteil, F-94000, France; University Paris 12, Faculty of Medicine, IFR10, Creteil, Paris, France.

Philip B. Mitchell, School of Psychiatry, University of New South Wales, and Black Dog Institute, Sydney, NSW, Australia.

Willem A. Nolen, Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Eduard Vieta, Bipolar Disorders Program, Institute of Clinical Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBER-SAM, Barcelona, Spain.

Hans-Ulrich Wittchen, Institute of Clinical Psychology, Center of Clinical Epidemiology and Longitudinal Studies, Technische Universitaet, Dresden, Germany.

Rapporteur:

Guy Goodwin.

Conflict of interest

The authors wish to declare the following interests that might be perceived as a possible conflict of interest: Ian Anderson, AstraZeneca, BMS, Janssen-Cilag, Lundbeck, Servier, Wyeth; Celso Arango, AstraZeneca, BMS, Janssen-Cilag, Lilly, Lundbeck, Pfizer, Sanofi-Aventis; Charles L. Bowden, Abbott, BMS, GSK, Jazz, Organon, Repligen, Sanofi-Aventis; Guy Goodwin, AstraZeneca, BMS, Eisai, Lilly, Lundbeck, P1Vital, Sanofi-Aventis, Servier, Wyeth; Chantal Henry, Lilly, Sanofi-Aventis; Philip Mitchell, Alphapharm, AstraZeneca, Janssen-Cilag, Lilly,Lundbeck; W.A. Nolen, Astra Zeneca, Cyberonics, Lilly, GSK, Netherlands Organisation for Health Research and Development, Pfizer, Servier, Stanley Medical Research Institute,Wyeth; Eduard Vieta, AstraZeneca, BMS, GSK, Janssen-Cilag, Lilly, Lundbeck, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Servier; Hans-Ulrich Wittchen, Lilly, Lundbeck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Wyeth.

Acknowledgement

This consensus meeting was conducted under the auspices of the European College of Neuropsychopharmacology.

References

Altshuler, L.L., Suppes, T., Black, D.O., Nolen, W.A., Leverich, G., Keck Jr., P.E., Frye, M.A., Kupka, R., McElroy, S.L., Grunze, H., Kitchen, C.M., Post, R., 2006. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. Am. J. Psychiatry 163, 313–315.

Angst, J., 2007. The bipolar spectrum. Br. J. Psychiatry 190, 189–191.

Angst, J., Preisig, M., 1995. Course of a clinical cohort of unipolar, bipolar and schizoaffective patients. Results of a prospective study from 1959 to 1985. Schweiz. Arch. Neurol. Psychiatr. 146, 5–16.

Angst, J., Sellaro, R., 2000. Historical perspectives and natural history of bipolar disorder. Biol.Psychiatry 48, 445–457.

Angst, J., Gamma, A., Benazzi, F., Ajdacic, V., Eich, D., Rossler, W., 2003. Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. J. Affect. Disord. 73, 133–146.

Bagby, R.M., Ryder, A.G., Schuller, D.R., Marshall, M.B., 2004. The Hamilton depression rating scale: has the gold standard become a lead weight? Am. J. Psychiatry 161, 2163–2177.

Berk, M., Malhi, G.S., Cahill, C., Carman, A.C., Hadzi-Pavlovic, D., Hawkins, M.T., Tohen, M., Mitchell, P.B., 2007. The bipolar depression rating scale (BDRS): its development, validation and utility. Bipolar Disord. 9, 571–579.

Birmaher, B., Axelson, D., 2006. Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. Dev. Psychopathol. 18, 1023–1035.

Birmaher, B., Axelson, D., Strober, M., Gill, M.K., Valeri, S., Chiappetta, L., Ryan, N., Leonard, H., Hunt, J., Iyengar, S., Keller, M., 2006. Clinical course of children and adolescents with bipolar spectrum disorders. Arch. Gen. Psychiatry 63, 175–183.

Blader, J.C., Carlson, G.A., 2007. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. Biol. Psychiatry 62, 107–114.

Bowden, C.L., 1995. Predictors of response to divalproex and lithium. J. Clin. Psychiatry 56 (Suppl 3), 25–30.

Brugue, E., Vieta, E., 2007. Atypical antipsychotics in bipolar depression: Neurobiological basis and clinical implications. Prog. Neuropsychopharmacol. Biol. Psychiatry 31, 275–282.

Brugue, E., Colom, F., Sanchez-Moreno, J., Cruz, N., Vieta, E., 2008. Depression subtypes in bipolar I and II disorders. Psychopathology 41, 111–114.

Calabrese, J.R., Bowden, C.L., Sachs, G.S., Ascher, J.A., Monaghan, E., Rudd, G.D., 1999. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J. Clin. Psychiatry 60, 79–88.

Calabrese, J.R., Suppes, T., Bowden, C.L., Sachs, G.S., Swann, A.C., McElroy, S.L., Kusumakar, V., Ascher, J.A., Earl, N.L., Greene, P.L., Monaghan, E.T., 2000. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. J. Clin. Psychiatry 61, 841–850.

Calabrese, J.R., Keck Jr., P.E., Macfadden, W., Minkwitz, M., Ketter, T.A., Weisler, R.H., Cutler, A.J., McCoy, R., Wilson, E., Mullen, J., 2005. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am. J. Psychiatry 162, 1351–1360.

Cassano, G.B., Rucci, P., Frank, E., Fagiolini, A., Dell'osso, L., Shear, M.K., Kupfer, D.J., 2004. The mood spectrum in unipolar and bipolar disorder: arguments for a unitary approach. Am. J. Psychiatry 161, 1264–1269.

Castro-Fornieles, J., Parellada, M., Gonzalez-Pinto, A., Moreno, D., Graell, M., Baeza, I., Otero, S., Soutullo, C.A., Crespo-Facorro, B., Ruiz-Sancho, A., Desco, M., Rojas-Corrales, O., Patino, A., Carrasco-Marin, E., Arango, C., 2007. The child and adolescent first-episode psychosis study (CAFEPS): design and baseline results. Schizophr. Res. 91, 226–237.

Coryell, W., Endicott, J., Maser, J.D., Keller, M.B., Leon, A.C., Akiskal, H.S., 1995. Long-term stability of polarity distinctions in the affective disorders. Am. J. Psychiatry 152, 385–390.

Costello, E.J., Pine, D.S., Hammen, C., March, J.S., Plotsky, P.M., Weissman, M.M., Biederman, J., Goldsmith, H.H., Kaufman, J., Lewinsohn, P.M., Hellander, M., Hoagwood, K., Koretz, D.S., Nelson, C.A., Leckman, J.F., 2002. Development and natural history of mood disorders. Biol. Psychiatry 52, 529–542.

Duffy, A., 2007. Does bipolar disorder exist in children? A selected review. Can. J. Psychiatry 52, 409–417.

Fraguas, D., de Castro, M.J., Medina, O., Parellada, M., Moreno, D., Graell, M., Merchan-Naranjo, J., Arango, C., 2007. Does diagnostic classification of early-onset psychosis change over follow-up? Child Psychiatry Hum. Dev. 139, 137–145.

Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W., Rush, A.J., Weissman, M.M., 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch. Gen. Psychiatry 48, 851–855.

Geddes, J.R., Calabrese, J., Goodwin, G.M., 2008. Lamotrigine for acute treatment of bipolar depression: an independent meta-analysis and meta-regression of individual patient data from 5 randomized trials. Br. J. Psychiatry (in submission).

Geller, B., Tillman, R., 2005. Prepubertal and early adolescent bipolar I disorder: review of diagnostic validation by Robins and Guze criteria. J. Clin. Psychiatry 66 (Suppl 7), 21–28.

Geller, B., Zimerman, B., Williams, M., DelBello, M.P., Frazier, J., Beringer, L., 2002. Phenomenology of prepubertal and early adolescent bipolar disorder: examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. J. Child Adolesc. Psychopharmacol. 12, 3–9.

Geller, B., Tillman, R., Craney, J.L., Bolhofner, K., 2004. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch. Gen. Psychiatry 61, 459–467.

Ghaemi, S.N., Martin, A., 2007. Defining the boundaries of childhood bipolar disorder. Am. J. Psychiatry 164, 185–188.

Ghaemi, S.N., Hsu, D.J., Soldani, F., Goodwin, F.K., 2003. Antidepressants in bipolar disorder: the case for caution. Bipolar Disord. 5, 421–433.

Ghaemi, S.N., Bauer, M., Cassidy, F., Malhi, G.S., Mitchell, P., Phelps, J., Vieta, E., Youngstrom, E., 2008. Diagnostic guidelines for bipolar disorder: a summary of the International Society for Bipolar Disorders Diagnostic Guidelines Task Force Report. Bipolar Disord. 10, 117–128.

Gijsman, H.J., Geddes, J.R., Rendell, J.M., Nolen, W.A., Goodwin, G.M., 2004. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am. J. Psychiatry 161, 1537–1547.

Goldsmith, D.R., Wagstaff, A.J., Ibbotson, T., Perry, C.M., 2003. Lamotrigine: a review of its use in bipolar disorder. Drugs 63, 2029–2050.

Gyulai, L., Bowden, C.L., McElroy, S.L., Calabrese, J.R., Petty, F., Swann, A.C., Chou, J.C., Wassef, A., Risch, C.S., Hirschfeld, R.M., Nemeroff, C.B., Keck Jr., P.E., Evans, D.L., Wozniak, P.J., 2003. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 28, 1374–1382.

Hazell, P., O'Connell, D., Heathcote, D., Henry, D., 2002. Tricyclic drugs for depression in children and adolescents. Cochrane Database Syst. Rev. CD002317.

Hazell, P.L., Carr, V., Lewin, T.J., Sly, K., 2003. Manic symptoms in young males with ADHD predict functioning but not diagnosis after 6 years. J. Am. Acad. Child Adolesc. Psychiatry 42, 552–560.

Henry, C., M'Bailara, K., Desage, A., Gard, S., Misdrahi, D., Vieta, E., 2007a. Towards a reconceptualization of mixed states, based on an emotional-reactivity dimensional model. J. Affect. Disord. 101, 35–41.

Henry, C., M'Bailara, K., Poinsot, R., Casteret, A.A., Sorbara, F., Leboyer, M., Vieta, E., 2007b. Evidence for two types of bipolar depression using a dimensional approach. Psychother. Psychosom. 76, 325–331.

Hirschfeld, R.M., Calabrese, J.R., Weissman, M.M., Reed, M., Davies, M.A., Frye, M.A., Keck Jr., P.E., Lewis, L., McElroy, S.L., McNulty, J.P., Wagner, K.D., 2003. Screening for bipolar disorder in the community. J. Clin. Psychiatry 64, 53–59.

Hollis, C., 2000. Adult outcomes of child- and adolescent-onset schizophrenia: diagnostic stability and predictive validity. Am. J. Psychiatry 157, 1652–1659.

Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A., Leon, A.C., Rice, J.A., Keller, M.B., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch. Gen. Psychiatry 59, 530–537.

Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Arch. Gen. Psychiatry 62, 617–627.

Kraepelin, E., 1913. Lectures on Clinical Psychiatry. Bailliere, Tindall & Cox, London.

Kraepelin, E., Robertson, G.M., 1921. Manic–Depressive Insanity and Paranoia. E. & S. Livingstone, Edinburgh.

Kupka, R.W., Altshuler, L.L., Nolen, W.A., Suppes, T., Luckenbaugh, D.A., Leverich, G.S., Frye, M.A., Keck Jr., P.E., McElroy, S.L., Grunze, H., Post, R.M., 2007. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. Bipolar Disord. 9, 531–535.

Laita, P., Cifuentes, A., Doll, A., Llorente, C., Cortes, I., Parellada, M., Moreno, D., Ruiz-Sancho, A., Graell, M., Arango, C., 2007. Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents. J. Child Adolesc. Psychopharmacol. 17, 487–502.

Leboyer, M., Henry, C., Paillere-Martinot, M.L., Bellivier, F., 2005. Age at onset in bipolar affective disorders: a review. Bipolar Disord. 7, 111–118.

Leibenluft, E., Cohen, P., Gorrindo, T., Brook, J.S., Pine, D.S., 2006. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. J. Child Adolesc. Psychopharmacol. 16, 456–466.

Lewinsohn, P.M., Klein, D.N., Seeley, J.R., 1995. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J. Am. Acad. Child Adolesc. Psychiatry 34, 454–463.

Merikangas, K.R., Akiskal, H.S., Angst, J., Greenberg, P.E., Hirschfeld, R.M., Petukhova, M., Kessler, R.C., 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch. Gen. Psychiatry 64, 543–552.

Meyer, T.D., Hammelstein, P., Nilsson, L.G., Skeppar, P., Adolfsson, R., Angst, J., 2007. The Hypomania Checklist (HCL-32): its factorial structure and association to indices of impairment in German and Swedish nonclinical samples. Compr. Psychiatry 48, 79–87.

Mitchell, P.B., Malhi, G.S., 2004. Bipolar depression: phenomenological overview and clinical characteristics. Bipolar Disord. 6, 530–539.

Mitchell, P.B., Slade, T., Andrews, G., 2004. Twelve-month prevalence and disability of DSM-TV bipolar disorder in an Australian general population survey. Psychol. Med. 34, 777–785.

Mitchell, P.B., Wilhelm, K., Parker, G., Austin, M.P., Rutgers, P., Malhi, G.S., 2001. The clinical features of bipolar depression: A comparison with matched major depressive disorder patients. J. Clin. Psychiatry 62, 212–216.

Mitchell, P.B., Goodwin, G.M., Johnson, G.F., Hirschfeld, R.M.A., 2008. Diagnostic guidelines for bipolar depression: a probabilistic approach. Bipolar Disord. 10, 144–152.

Montgomery, D.B., 2001. ECNP Consensus Meeting March 2000 Nice: guidelines for investigating efficacy in bipolar disorder. European College of Neuropsychopharmacology. Eur. Neuropsychopharmacol. 11, 79–88.

Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A.B., Olfson, M., 2007. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch. Gen. Psychiatry 64, 1032–1039.

Nemeroff, C.B., Evans, D.L., Gyulai, L., Sachs, G.S., Bowden, C.L., Gergel, I.P., Oakes, R., Pitts, C.D., 2001. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am. J. Psychiatry 158, 906–912.

Nierenberg, A.A., Ostacher, M.J., Calabrese, J.R., Ketter, T.A., Marangell, L.B., Miklowitz, D.J., Miyahara, S., Bauer, M.S., Thase, M.E., Wisniewski, S.R., Sachs, G.S., 2006. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. Am. J. Psychiatry 163, 210–216.

Peet, M., 1994. Induction of mania with selective serotonin reuptake inhibitors and tricyclic antidepressants. Br. J. Psychiatry 164, 549–550.

Perlis, R.H., Miyahara, S., Marangell, L.B., Wisniewski, S.R., Ostacher, M., DelBello, M.P., Bowden, C.L., Sachs, G.S., Nierenberg, A.A., 2004. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol. Psychiatry 55, 875–881.

Pfennig, A., Beesd, K., Höfler, M., Lieb, R., Bauer, M., Wittchen, H.-U., 2005. Incidence of hypomania, mania and bipolar depression in the first three decades of life. Biol. Psychiatry 57, 336–342.

Pini, S., de V, Q., Pagnin, D., Pezawas, L., Angst, J., Cassano, G.B., Wittchen, H.U., 2005. Prevalence and burden of bipolar disorders in European countries. Eur. Neuropsychopharmacol. 15, 425–434.

Post, R.M., Altshuler, L.L., Leverich, G.S., Frye, M.A., Nolen, W.A., Kupka, R.W., Suppes, T., McElroy, S., Keck, P.E., Denicoff, K.D., Grunze, H., Walden, J., Kitchen, C.M., Mintz, J., 2006. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br. J. Psychiatry 189, 124–131.

Prien, R.F., Himmelhoch, J.M., Kupfer, D.J., 1988. Treatment of mixed mania. J. Affect. Disord. 15, 9–15.

Quitkin, F.M., Kane, J., Rifkin, A., Ramos-Lorenzi, J.R., Nayak, D.V., 1981. Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients. A double-blind study. Arch. Gen. Psychiatry 38, 902–907.

Reddy, Y.C., Srinath, S., 2000. Juvenile bipolar disorder. Acta Psychiatr. Scand. 102, 162–170.

Reichart, C.G., Nolen, W.A., 2004. Earlier onset of bipolar disorder in children by antidepressants or stimulants? An hypothesis. J. Affect. Disord. 78, 81–84.

Rosa, A.R., Sánchez-Moreno, J., Martinez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2007. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin. Pract. Epidemol. Ment. Health 3, 5.

Sachs, G.S., Nierenberg, A.A., Calabrese, J.R., Marangell, L.B., Wisniewski, S.R., Gyulai, L., Friedman, E.S., Bowden, C.L., Fossey, M.D., Ostacher, M.J., Ketter, T.A., Patel, J., Hauser, P., Rapport, D., Martinez, J.M., Allen, M.H., Miklowitz, D.J., Otto, M.W., Dennehy, E.B., Thase, M.E., 2007. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N. Engl. J. Med. 356, 1711–1722.

Stoll, A.L., Mayer, P.V., Kolbrener, M., Goldstein, E., Suplit, B., Lucier, J., Cohen, B.M., Tohen, M., 1994. Antidepressant-associated mania: a controlled comparison with spontaneous mania. Am. J. Psychiatry 151, 1642–1645.

Thase, M.E., Sachs, G.S., 2000. Bipolar depression: Pharmacotherapy and related therapeutic strategies. Biol. Psychiatry 48, 558–572.

Thase, M.E., Macfadden, W., Weisler, R.H., Chang, W., Paulsson, B., Khan, A., Calabrese, J.R., 2006. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J. Clin. Psychopharmacol. 26, 600–609.

Tohen, M., Vieta, E., Calabrese, J., Ketter, T.A., Sachs, G., Bowden, C., Mitchell, P.B., Centorrino, F., Risser, R., Baker, R.W., Evans, A.R., Beymer, K., Dube, S., Tollefson, G.D., Breier, A., 2003. Efficacy of olanzapine and olanzapine–fluoxetine combination in the treatment of bipolar I depression. Arch. Gen. Psychiatry 60, 1079–1088.

Vieta, E., Phillips, M.L., 2007. Deconstructing bipolar disorder: A critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. Schizophr. Bull. 33, 886–892.

Vieta, E., Martinez-Aran, A., Goikolea, J.M., Torrent, C., Colom, F., Benabarre, A., Reinares, M., 2002. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J. Clin. Psychiatry 63, 508–512.

Vieta, E., Sanchez-Moreno, J., Lahuerta, J., Zaragoza, S., 2007. Subsyndromal depressive symptoms in patients with bipolar and unipolar disorder during clinical remission. J. Affect. Disord. 107, 169–174.

Visser, H.M., van der Mast, R.C., 2005. Bipolar disorder, antidepressants and induction of hypomania or mania. A systematic review. World J. Biol. Psychiatry 6, 231–241.

Wals, M., Hillegers, M.H., Reichart, C.G., Ormel, J., Nolen, W.A., Verhulst, F.C., 2001. Prevalence of psychopathology in children of a bipolar parent. J. Am. Acad. Child Adolesc. Psychiatry 40, 1094–1102.

Walsh, B.T., Seidman, S.N., Sysko, R., Gould, M., 2002. Placebo response in studies of major depression: variable, substantial, and growing. JAMA 287, 1840–1847.

Wehr, T.A., Goodwin, F.K., 1979. Rapid cycling in manic–depressives induced by tricyclic antidepressants. Arch. Gen. Psychiatry 36, 555–559.

Weller, E.B., Weller, R.A., Fristad, M.A., 1995. Bipolar disorder in children: misdiagnosis, underdiagnosis, and future directions. J. Am. Acad. Child Adolesc. Psychiatry 34, 709–714.

Wittchen, H.U., Jacobi, F., 2005. Size and burden of mental disorders in Europe — a critical review and appraisal of 27 studies. Eur. Neuropsychopharmacol. 15, 357–376.

Wittchen, H.U., Mhlig, S., Pezawas, L., 2003. Natural course and burden of bipolar disorders. Int. J. Neuropsychopharmacol. 6, 145–154.

Wozniak, J., Biederman, J., Mundy, E., Mennin, D., Faraone, S.V., 1995. A pilot family study of childhood-onset mania. J. Am. Acad. Child Adolesc. Psychiatry 34, 1577–1583.