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Bipolar (Spectrum) Disorder and Mood Stabilization: Standing at the Crossroads?

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Key Words
Bipolar disorder · Hypomania · Agitated depression · Depressive mixed state · Mood stabilizer · Mood stabilization

Abstract
Diagnosis and treatment of bipolar disorder has long been a neglected discipline. Recent years have shown an upsurge in bipolar research. When compared to major depressive disorder, bipolar research still remains limited and more expert based than evidence based. In bipolar diagnosis the focus is shifting from classic mania to bipolar depression and hypomania. There is a search for bipolar signatures in symptoms and course of major depressive episodes. The criteria for hypomania are softened, leading to a bipolar prevalence that now equals that of major depressive disorder. Anti-epileptics and atypical antipsychotics have joined lithium in the treatment of bipolar disorder. Fortunately, mood stabilization has become the core issue in bipolar disorder treatment. In contrast with recent trends in the diagnosis of bipolar disorder, treatment research remains more focused on classic mania than depression or hypomania. This leaves the clinician with the difficult task of diagnosing 'new bipolar patients' for whom no definite evidence-based treatment is available. An important efficacy-effectiveness gap further compromises the translation of the evidence base on bipolar disorder treatment into clinical practice. The recent upsurge of research on bipolar disorder is to be applauded, but further research is needed: for bipolar disorder in general, and for bipolar depression and the long-term treatment specifically. Given the complexity of the disorder and the many clinical uncertainties, effectiveness studies should be installed.

Introduction

Bipolar disorder has become a clinical and health-economic challenge for the 21st century [1]: a highly prevalent disorder, often misdiagnosed, with poor symptomatic and psychosocial outcome even after treatment has been initialized, thereby being an important socio-economic burden. Although conservative rates of 1–1.6% lifetime prevalence were reported in former studies on bipolar disorder [2, 3], a re-analysis of the US National Epidemiological Catchment Area database found a 6.4% lifetime prevalence for bipolar (spectrum) disorders [4]. This increased prevalence was fully accounted for by the inclusion of subthreshold cases: 5.1% lifetime prevalence versus 1.3% for threshold manic or hypomanic episodes.

Most bipolar disorder patients are 'hidden': not diagnosed at all or falsely diagnosed as suffering from unipolar disorder. In a community survey of Hirschfeld et al. [5], only 20% of individuals with positive screens for bipolar

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disorder had previously received a diagnosis of bipolar disorder. Thirty-one percent had been given the diagnosis of unipolar depression, whereas 49% had received no such diagnosis at all. In this survey the Mood Disorder Questionnaire was used. It was developed as a screening instrument for bipolar spectrum disorders and has shown a generally good sensitivity and specificity with regard to research diagnostic interviews in validation studies, both in clinical and non-clinical samples [6, 7]. Similar results were found in a clinical sample of hospitalized bipolar disorder patients: 40% of cases were previously misdiagnosed as being unipolar [8]. A period of 7.5 ± 9.8 years elapsed in this group before a diagnosis of bipolar disorder was made. Patients and physicians both seem responsible for this delay in diagnosis and subsequent treatment. In a recent survey among members of manic-depressive support groups, only 36% of patients had sought help within 1 year after the onset of symptoms [9]. Sixty-nine percent reported misdiagnoses, with a mean of 3.5 other diagnoses and 4 physicians before receiving an accurate diagnosis of bipolar disorder. Although healthcare professionals were mainly blamed for this untimely diagnosis, patients substantially underreported their manic (and to a lesser extent depressive) symptoms to their care providers. It is disquieting that these problems of misdiagnosis and troubled pathway of care were not significantly different from the results of a similar survey, done 8 years earlier [10].

Furthermore, bipolar disorder shows a severe and chronic course, even after treatment has been initialized. Symptoms fluctuate within the full range of affective symptom severity and polarity. About half of the time, bipolar disorder patients are symptomatically ill (syndromal, subsyndromal and minor affective symptoms), with depressive symptoms predominating over manic, hypomanic or mixed symptoms [11, 12]. Psychosocial outcome is jeopardized throughout the bipolar spectrum: increased marital disruption, health service utilization, need for welfare and disability benefits, and suicidal behaviour [13]. Not surprisingly and although very conservative prevalence rates were used for calculation, the World Health Organization identified bipolar disorder as the fifth leading cause of years of life lived with disability in the world among people aged 15–44 years [14].

This challenge of bipolar disorder is now answered by an upsurge of interest in diagnosis and treatment. New diagnostic categories, treatment options and guidelines are being developed. This paper does not intend to cover these developments exhaustively. It rather takes a closer look at the origin of this current upsurge of interest. Critical issues concerning the introduction of the bipolar spectrum and mood-stabilizing agents into clinical practice are discussed. How were these new bipolar disorder patients previously diagnosed? Is there such a thing as a mood stabilizer? Finally, where does it leave the patient? How are these recent developments translated into clinical practice? Although this paper is not a systematic review, extensive Medline searches were performed for the various topics. From the papers that were found, references were then looked at for other relevant papers. For one section in particular, 'Bipolar disorder – an upswing in research', a more comprehensive and methodological Medline search was done, which will be discussed in more detail.

Bipolar Disorder – An Upswing in Research

Research in bipolar disorder is claimed to have been a neglected discipline, a 'scientific orphan' [1, 15]. However, in recent years bipolar disorder has received increasing attention from clinicians, researchers and society as a whole. This upsurge of interest is exemplified by the appearance of the first issue of *Bipolar Disorders* (a peer-reviewed publication specializing in bipolar disorders) in September 1999 [16], 1999 also being the beginning of the publication of all but two of the Medline-cited guidelines for treating bipolar disorder in adults (Medline search with bipolar disorder as MeSH term, search restricted to major topic headings only, practice guideline as publication type) [17–27].

In order to have a closer look at these recent changes, we performed a bibliometric study focusing on bipolar disorder. Research activities in bipolar and depressive disorder were compared. Our bibliometric study thereby differed from an earlier study of Clement et al. [15] in which research activity was looked at in bipolar disorder and schizophrenia. The search was done using the Medline database and covered the last 15 years (1990–2004). Bipolar disorder and depressive disorder were used as MeSH terms. By restricting the search to major topic headings only, we tried to exclude irrelevant publications as much as possible. The primary aim was to quantify the publication activity with regard to bipolar disorder and to compare it with that of depressive disorder. A secondary aim was to examine the nature of publication activity by focusing on the type of publications: reviews, clinical trials (CT) and randomized controlled trials (RCT). Due to the relative selectivity of involved publication types (more directed towards treatment), this further search was made

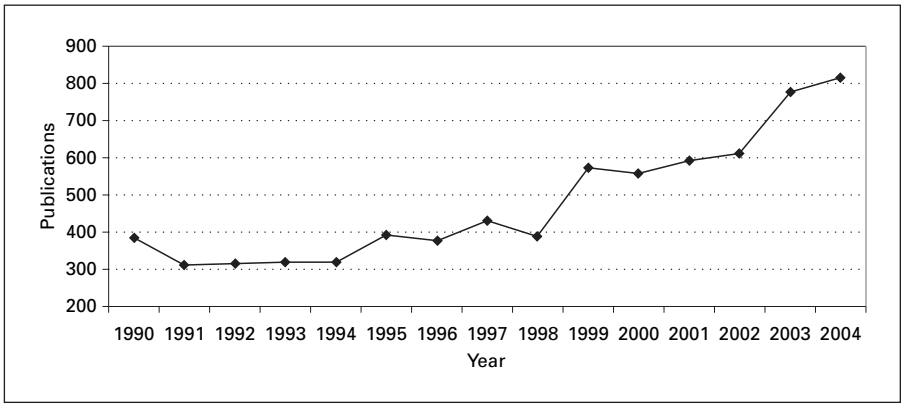

Fig. 1. Publication activity in bipolar disorder (1990–2004). Medline search, bipolar disorder used as MeSH term, search restricted to major topic headings only.

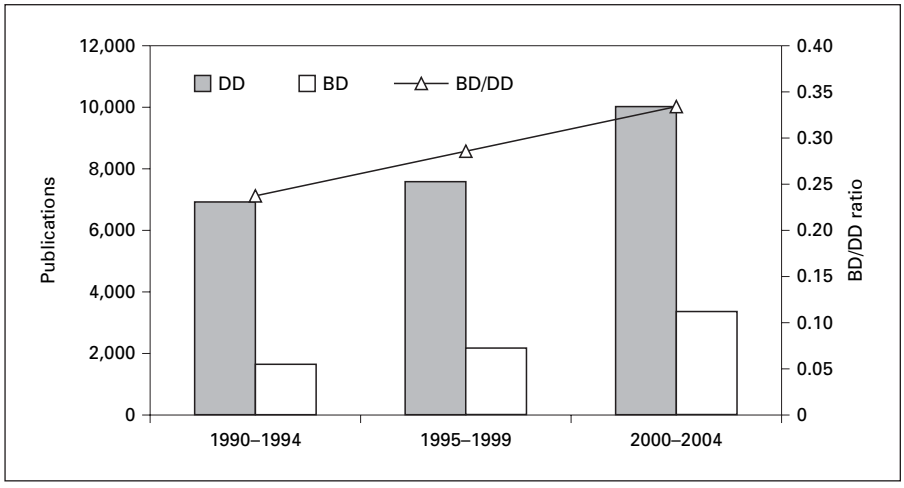

Fig. 2. Research activity of bipolar disorder and depressive disorder: absolute number of publications and ratio (bipolar disorder: depressive disorder). Medline search, bipolar disorder and depressive disorder used as MeSH terms, search restricted to major topic headings only. BD = Bipolar disorder; DD = depressive disorder.

for the subheading 'drug therapy' only. This selection was also in line with the focus of the paper on new pharmacological treatment options in bipolar disorder.

First, a clear upswing of publications on bipolar disorder was found, with a marked increase starting in 1999 (fig. 1). Second and despite this recent increase, there is still a dearth of publications on bipolar disorder when compared to depressive disorder. However, the ratio (bipolar disorder:depressive disorder) is growing (fig. 2). Third, bipolar disorder publications on drug therapy are characterized by an overrepresentation of reviews versus RCT or CT (table 1; fig. 3). The relative numbers of RCT and CT versus reviews are different from those seen in depressive disorder. Over the study period 1990–2004, the ratios CT:review and RCT:review for bipolar disorder were 0.77 and 0.38, respectively, versus 1.37 and 0.85 for depressive disorder. Even the absolute and recent increase in bipolar disorder publications is still more accounted for by reviews than by CT or RCT. The influence of a potential overlap in publications between bipolar and depressive disorder on these analyses was looked at in subsequent and more restricted searches: analysis for depressive disorder excluding bipolar disorder and vice versa. Similar results (not presented in this paper, but available upon request) were found.

The consistency of these findings (differential quantity and nature of publications) over time and type of search method give support for making some tentative conclusions. First, although there is still a dearth of research on bipolar disorder when compared to depressive disorder, bipolar disorder is catching up with a marked increase at the end of the nineties. This hinge moment coincides with the appearance of the anticonvulsants and atypical antipsychotics in the treatment of bipolar disorder. Second, publications on drug therapy for bipolar disorder and depressive disorder differ substantially in the type of publications. Reviews are overrepresented in bipolar disorder when compared to depressive disorder. As to research activity on bipolar disorder, this could be interpreted as being more clinician based or expert based than evidence

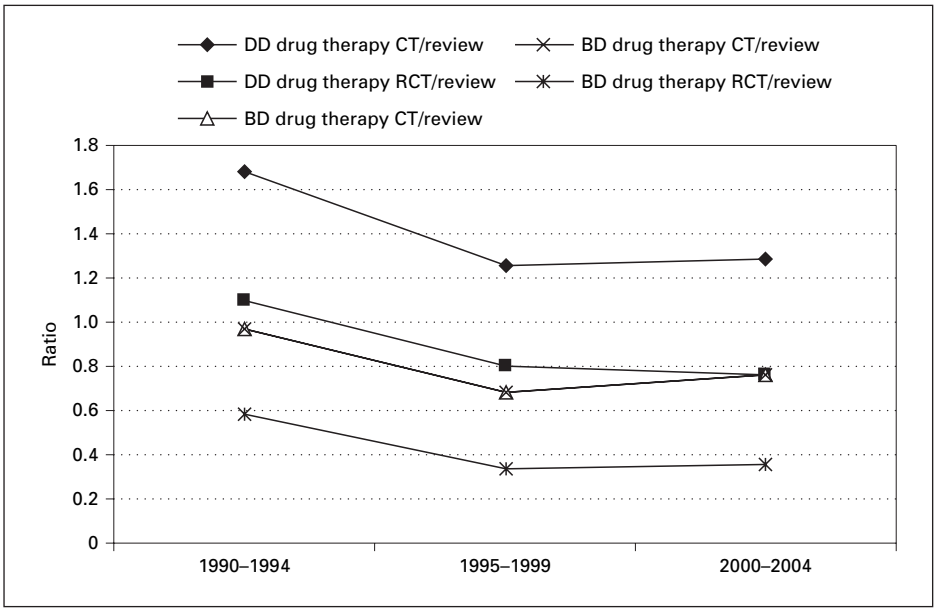

Fig. 3. Nature of publications on drug therapy in depressive and bipolar disorder: ratio CT:review and RCT:review. Medline search, bipolar disorder and depressive disorder used as MeSH terms, search restricted to major topic headings only and subheading 'drug therapy'; CT, RCT and review used as publication types. DD = Depressive disorder; BD = bipolar disorder.

Table 1. Drug therapy in depressive (DD) and bipolar disorder (BD): number and type of publications

	1990–1994	1995–1999	2000–2004
DD drug therapy	1,616	1,948	2,450
DD drug therapy review	306	477	546
DD drug therapy CT	515	598	704
DD drug therapy RCT	336	380	417
BD drug therapy	410	601	1,042
BD drug therapy review	77	146	293
BD drug therapy CT	75	100	222
BD drug therapy RCT	45	49	103

Medline search, bipolar disorder and depressive disorder used as MeSH terms, search restricted to major topic headings only and subheading 'drug therapy'; CT, RCT and review used as publication types.

based. This disparity may be explained by the inherent difficulties of short-term and long-term efficacy trials in bipolar disorder: high rates of protocol non-completion and non-specific responses, the extremely labile and rapidly changing nature of the condition, the complexity of the clinical picture (manic and depressive symptoms are commonly intermixed) and the complexity of its treatment (combination treatment is more a rule than an exception) [28–30]. Given the limited evidence base, physicians are in need of reviews to guide their clinical decisions.

Bipolar (Spectrum) Disorder – Extended Diagnosis

Past research has focused mainly on bipolar I disorder, with mania as its hallmark. Bipolar II disorder (with hypomania), cyclothymia and bipolar disorder not otherwise specified have been relatively neglected [31–33]. The introduction of the bipolar spectrum disorder concept has extended these bipolar boundaries [34–36]. In its broadest and dimensional sense, the bipolar spectrum may encompass any disorder characterized by unstable mood and behaviour, and any recurrent cycling psychiatric disturbance [37].

A first subset of patients in whom bipolar spectrum diagnosis can now be made are patients formerly labelled with borderline personality disorder, attention deficit disorder, bulimia nervosa and substance abuse [37, 38]. However, most of the new bipolar disorder patients have until now been classified into major depressive disorder (MDD), a second and from a clinical point of view most important subset. When reviewing the literature, this unipolar-to-bipolar metamorphosis is done in three ways. Firstly, there is a search for bipolar signatures in purely depressive episodes (major depressive episode, MDE) or during the course of MDD. Secondly, the presence of broader manic symptoms in MDE (without fulfilling the criteria of a mixed episode as defined in DSM-IV) is looked at in depressive mixed episode, agitated depression and depression with anger. These different presentations of MDE are now given the bipolar label. Thirdly, a

greater detection and loosening of the criteria for hypomania have made the bipolar spectrum as prevalent as the unipolar spectrum.

Depressive Episode – Looking for Bipolar Signatures in Course and Symptoms

When symptomatically ill, patients with bipolar I and II disorder spend most of their time with depressive symptoms, more than with manic or hypomanic symptoms: 31.9 versus 9.3% for bipolar I disorder, and 50.3 versus 1.3% for bipolar II disorder, respectively [11, 12]. About 60% of both groups will experience a depressive episode as their first lifetime-affective episode [13]. Furthermore, manic symptoms are more often underreported to physicians than depressive symptoms [9], and current hypomanic symptoms, not interfering with normal functioning, will not be mentioned at all. Lack of insight, during the acute manic episode and even when manic symptoms have improved, may be responsible for this underreporting [39–41]. Thereby, meeting a bipolar patient is more likely during a depressive episode than during a manic or hypomanic episode. The question then arises which signs in course and symptoms may suggest a bipolar origin of apparently unipolar disorder patients. Earlier age of onset, a greater number of episodes, a relatively acute onset and abatement of symptoms are all cited as being indicative of bipolar depression [42, 43]. Although DSM-IV-R criteria [44] assume a common bipolar and unipolar symptomatology, recent studies have given proof for symptomatic differences between unipolar and bipolar depression [45, 46]. Mitchell et al. [45] compared 39 bipolar I with 39 unipolar disorder patients during a depressive episode. No differences were found in severity. Bipolar disorder patients were more likely to demonstrate a characteristic admixture of psychomotor-retarded melancholic and atypical depressive features, and to have had more previous psychotic episodes. Specifically, bipolar disorder patients had more frequent and/or severe symptoms of worthlessness, anticipatory anhedonia, subjective restlessness, hypersomnia and leaden paralysis. Objectively they showed more psychomotor retardation, but no more agitation. Benazzi [46] compared consecutive unipolar and bipolar II depressed outpatients. Besides lower age, lower age of onset, longer duration of illness, more recurrences, more family history of bipolar II disorder and more depressive mixed state, bipolar II disorder patients had significantly more atypical features (53 vs. 24%). Furthermore, atypical unipolar and early-onset unipolar disorder patients were highly similar to bipolar disorder patients in terms of age of onset or atypical features, respectively, recurrences, depressive mixed state and family history bipolar II disorder.

The importance of depressive symptoms, course of illness and response to treatment in diagnosing bipolar disorder is taken to a final step by Ghaemi et al. [47, 48]. A definition of bipolar spectrum disorder is postulated in which (hypo)manic symptoms are no longer required and a diagnosis of bipolar disorder can be made solely based upon a combination of family history of bipolar disorder, hyperthymic personality, and depressive features in symptoms and course: recurrent MDE, early age of onset, atypical features, brief MDE, psychotic MDE, postpartum depression, antidepressant-induced (hypo)mania, antidepressant wear-off, lack of response to ≥ 3 adequate antidepressant treatment trials. In a recent study, Ghaemi et al. [49] looked at these 'bipolar validators' in consecutively treated bipolar and unipolar disorder patients. After adjusting for correlations and interactions between predictors, the most powerful predictors for bipolar disorder were brief MDE, early age of onset, antidepressant-induced mania, postpartum depression and atypical features.

From Depressive Mixed State to Agitated Depression and Depression with Anger

Detection of (hypo)manic symptoms in depressive episodes is a second wave in the unipolar-to-bipolar metamorphosis. Mainly, this is done in three ways: the concept of depressive mixed states, the re-appraisal of agitated depression and the focus on anger (or irritability) in depression.

Depressive mixed state (DMS) is an MDE accompanied by some manic symptoms, but not fulfilling the criteria of a mixed episode as defined in DSM-IV-R. Its origin goes back to early classic authors such as Kraepelin [50], and DMS is now reintroduced as belonging to the bipolar spectrum [51–53]. Sato et al. [51] reported on the frequency of manic symptoms in depressed unipolar and bipolar disorder inpatients, and evaluated the validity of DMS as bipolar spectrum. The frequency of manic symptoms (flight of idea, logorrhoea, aggression, excessive social contact, increased drive, irritability, racing thoughts and distractability) was significantly higher in depressive patients with bipolar I and II than unipolar disorder: 23, 20 and 9%, respectively. DMS (defined as having 2 or more of these manic symptoms) had more similarities with bipolar than with unipolar depression in clinical variables such as family history of bipolar disorder and age at onset. In this sample of depressed inpatients, the inclusion of depressive mixed state into the bipolar spectrum doubled

the ratio bipolar:unipolar, i.e. from 11 to 22%. Benazzi and Akiskal [52] studied the prevalence of DMS in depressed outpatients with MDD and bipolar II disorder. DMS with 3 or more hypomanic symptoms (DMS3) was found significantly more in patients with bipolar II than unipolar disorder: 46.3 versus 7.8%, respectively. Most common intra-episode hypomanic symptoms were irritability, distractability and racing thoughts. A second study [53] confirmed these earlier results. Furthermore, DSM3 was significantly associated with variables distinguishing bipolar from unipolar disorder: younger age at onset, more MDE, more atypical features, and more family history of bipolar II disorder.

The issue of agitated depression is extensively covered in the influential paper of Koukopoulos and Koukopoulos [54]. In their historical review of the concept, the authors proposed diagnostic criteria covering various forms of agitated depression: (a) MDE, (b) at least 2 out of 3 symptoms (motor agitation, psychic agitation or intense inner tension, racing or crowded thoughts). The prevalence of agitated depression, defined as such, was looked at in a recent study of Benazzi et al. [55]. MDE with intense inner tension/irritability and racing/crowded thoughts was found in 38.6% of depressed outpatients. Other common hypomanic symptoms in agitated depression were distractability and more talkativeness. The majority of these patients had a diagnosis of bipolar II disorder. Agitated depression was strongly and significantly associated with external validators for bipolarity (younger age at onset, multiple recurrences, family history of bipolar disorder).

Anger (anger attacks, persistent anger or irritability) has also been linked to bipolar disorder in recent studies. Perlis et al. [56] compared the prevalence and clinical significance of anger attacks in unipolar versus bipolar depression. Anger attacks were significantly more common among depressed patients with bipolar than unipolar-disorder: 62 and 26%, respectively. After adjusting for gender and depression severity, individuals with anger attacks were significantly more likely to have bipolar disorder than MDD. A broader definition of anger (persistent anger, tendency to respond to events with angry outbursts) was used in a study of Benazzi [57]. The prevalence of anger was looked at in consecutive depressed outpatients (MDD and bipolar II disorder). The frequency of depressive episodes with anger was 61.2% in bipolar II disorder patients and 35.6% in unipolar disorder patients. Depression with anger was significantly associated with a diagnosis of bipolar II disorder, younger age at onset, atypical features, depressive mixed state, and family history of bipolar disorder.

Hypomania – From Hard to Soft Criteria

Hypomania according to DSM-IV-R is defined as a sometimes short-lasting elevation of mood, identified by the usual criteria of mania, but without marked impairment in social or occupational functioning. This lack of associated impairment makes hypomania a troublesome disease state for various reasons [32]. First, the patient's experience of hypomania is usually ego-syntonic, is not associated with significant subjective distress, is sometimes associated with improved functioning and productivity, and will therefore not be viewed as needing intervention (by either patient or physician) [58]. Second, diagnosing hypomania does not always result in immediate treatment of the disease state itself but rather in future treatment of the unstable mood and subsequent depressive episodes. This apparent paradox has become more important as the reported prevalence of bipolar II disorder is increasing and almost equals the prevalence of MDD. This higher prevalence is caused by a better detection of hypomania, a different use of stem criteria as well as a decrease in the number and duration of symptoms required for diagnosis. Several of these aspects were looked at by Angst et al. [36] in a 20-year prospective community cohort study of young adults. Besides formal DSM diagnosis, two other concepts of bipolar II disorder were considered: (1) MDE with a hypomanic syndrome (hard criteria) and (2) MDE with hypomanic symptoms only, without consequences (soft criteria). In order to qualify for a strict diagnosis of hypomania (hypomanic syndrome), subjects had to: (1) have euphoria, irritability or overactivity, (2) have themselves experienced problems or received comments from others that something must be wrong with them (consequences), (3) present at least 3 out of 7 signs and symptoms of DSM-IV hypomania. The clinical validity of these concepts was analyzed by family history, course and clinical characteristics. Overactivity was found to be a stem criterion that should be added to euphoric and irritable mood when defining hypomania. Episode length was not withheld as a criterion as long as 3 out of 7 symptoms were present. The two bipolar II subgroups (soft and hard criteria) did not differ from all but one of the validators, whereas they did differ significantly from patients with MDD. The combined prevalence of bipolar II disorder was 11%. By loosening the criteria of hypomania, the ratio depressive disorder:bipolar disorder declined from 9.4 to 1.0. Benazzi and Akiskal [59], using a refined definition of hypomania, determined the prevalence of bipolar II disorder in a selected group of outpatients, presenting spontaneously for treatment of a depressive episode. The minimum duration of ≥ 4 days was

not adhered to, and ≥ 2 days of hypomania was sufficient for diagnosis. An interview was also done with a modified SCID-CV interview. If the patient's answer about 'a period of elevated or irritable mood' was negative, further assessment of hypomanic symptoms was not skipped (as required by the SCID-CV), but the patient was questioned about all the other hypomanic symptoms. Then, once an episode of past hypomanic behaviour was remembered, patients were re-questioned about 'a period of elevated mood'. This approach in depressed outpatients yielded a 61.3% prevalence of bipolar II disorder. By modification of the SCID-CV interview, with more emphasis on hypomanic behaviour when probing for hypomania, a net gain of 16% was achieved compared to a previous study in which a strict SCID-CV was followed [53].

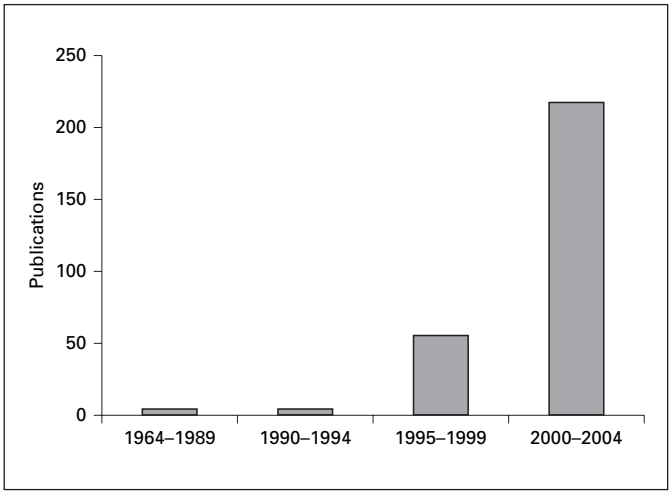

Fig. 4. Publication activity regarding 'mood stabilizer' between 1964 and 2004. Medline search, 'mood stabilizer' as search term.

Mood Stabilizers – The Risk of Overpromising and Underdelivering

Anti-epileptics (divalproex, carbamazepine, lamotrigine) and atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) have joined lithium in the treatment of bipolar disorder. The term 'mood stabilizer' is now prominently used as a common denominator for these distinct agents and thereby seems to be the therapeutic counterpart of the upsurge in bipolar disorder diagnosis. Despite its popularity some critical issues merit further attention.

First, the origin of the term is quite recent. For many years lithium was the only agent widely used for bipolar disorder and thereby synonymous with the concept of mood stabilizer and mood stabilization. The need for a distinct term only came when other agents (divalproex, carbamazepine) showed mood-stabilizing properties and when it was recognized that some agents used in bipolar disorder (e.g. antidepressants and typical neuroleptic agents) could worsen the course of the illness [60–62]. In a Medline search of the term 'mood stabilizer' (search term), only 10 papers are found between 1964 and 1994. This contrasts sharply with 218 publications in the period of 2000–2004 (fig. 4).

Second, although the term 'mood stabilizer' is commonly used in the marketing of the newer drugs, it is not officially recognized by the US Food and Drug Administration. There is no real consensus among investigators and many definitions can be applied [61, 63–65]. The most comprehensive definition requires (1) efficacy in acute affective symptoms, (2) efficacy in psychotic symptoms, (3) efficacy in behavioural symptoms, (4) efficacy in cognitive symptoms and (5) efficacy in preventing manic, mixed and depressive episodes. Ideally, eradication of interepisode subsyndromal symptoms and mood lability should also be included. Obviously, this definition of a magic mood-stabilizing bullet is not met by any of the existing compounds, and development of such a compound does not seem likely. The triple option of (1) efficacy in acute mania, (2) efficacy in acute depression and (3) efficacy in preventing manic and depressive episodes, is a more down-to-earth and lithium-inspired definition. A double option is then (1) efficacy in acute mania or acute depression and (2) efficacy in preventing affective episodes. Another definition was proposed by Ghaemi [61]: efficacy in 2 of 3 phases of bipolar illness (acute mania, acute depression, prophylaxis of mania and depression). In the least restrictive and uniphasic way, mood stabilizer is defined by efficacy in at least one phase of the illness without exacerbating another phase. All these definitions disproportionately value the efficacy in acute mania or depression, and seem to ignore that treating the longer course of the illness is the main issue. In contrast and as an answer to this neglect, Harris et al. [60, 66] have formulated a more radical definition of mood stabilizer: agents, which show prophylactic efficacy, while evidence of efficacy in the acute phase is not needed. When applying this definition to the evidence base of bipolar disorder treatment, as presented in the latest review of Bauer and Mitchner [63], only lithium and to a lesser extent lamotrigine are really mood stabilizers.

Third, none of the new agents has been specifically designed for mood-stabilizing purposes. They are distinct products and most have a primarily proven antipsychotic or anti-epileptic effect. Their mood-stabilizing properties have only been shown secondarily: first in bipolar mania or depression, second in prophylactic treatment. New nomenclatures (mood stabilizer, mood stabilizers from below, mood stabilizers from above) could then be seen as artifices [67]. Different mechanisms of action are being covered up by a common denominator. Furthermore, research should look for functional differences between these distinct agents. Functional differences, based upon different mechanisms of action, may be overlooked when they are evaluated by the broad category of mood stabilization.

Fourth, mood stabilizer is a popular and easy-to-sell concept, but fails to describe the difficult clinical task of treating bipolar disorder patients. In this chronic and cyclic disease, the clinician is faced with the ongoing challenge of keeping the patient symptom free and preventing the affective pendulum from swinging too far toward mania or depression [68]. For many patients mood stabilization is only achieved with the combination of drugs: a cocktail of drugs with some mood/psycho-stabilizing properties instead of a unique mood stabilizer [69–71].

Mood Stabilizers and Bipolar (Spectrum) Disorder – What Is in It for the Patient?

Translation into clinical practice should be the ultimate issue in this upsurge of research, diagnosis and treatment of bipolar disorder. Multiple caveats should here be mentioned: these concern both bipolar disorder in general and bipolar spectrum disorder more specifically.

The limited evidence base of bipolar disorder is undermined by an important efficacy-effectiveness gap. Many factors contribute to this disparity between the performance of an intervention in the controlled environment of an experimental study and its performance in clinical practice [72]. First, due to enrolment practices (e.g. selection of patients that can provide informed consent and are able to comply with study requirements), less severely ill patients are recruited. This could explain the high placebo responses seen in recent trials for acute mania [73]. During a 4-week, randomized, double-blind, parallel study, olanzapine demonstrated significantly greater efficacy than placebo in the treatment of acute bipolar mania [74]. However, response (defined as at least a 50% improvement from baseline to endpoint in the Young Mania Rating Scale, Y-MRS) was as high as 43% in placebo-treated patients (versus 65% in olanzapine-treated patients). Second, concomitant medication (apart from study medication and benzodiazepines) is prohibited in most studies, and controlled combination studies in bipolar disorder are uncommon [75]. This contrasts sharply with clinical practice in which combination treatment is more a rule than an exception. Third, the primary efficacy measures of most short-term clinical trials present a far too optimistic view of improvement, not seen in clinical practice. Efficacy is often measured as a mean change in rating scale score, or the proportion of patients showing a 50% or greater decrease in initial score. Many of these 'responders' remain significantly ill, and will need more time or combination treatment for complete symptomatic recovery. The magnitude of this problem was shown by Chengappa et al. [76], in a re-analysis of the results of two short-term, randomized, double-blind trials of olanzapine versus placebo for treating acute bipolar mania. Various efficacy measures were used: response ($\geq$50% decrease from baseline to endpoint in total Y-MRS score), euthymia (an endpoint Y-MRS score $\leq$12) and remission (an endpoint total Y-MRS score $\leq$7, an endpoint total Hamilton Depression Rating Scale score $\leq$7, and an endpoint Clinical Global Impression Scale – Bipolar Version overall severity score $\leq$2). The rates of response, euthymia and remission of olanzapine versus placebo were: 55 versus 29.5%, 50 versus 27%, and 18 versus 7%, respectively. Due to its short duration, this analysis could not assess the problem of sustained improvement and functional recovery: how many of the remitted patients remain in remission during a longer follow-up, and how many patients return to their baseline functional status? The importance of these phenomena in the clinical course of bipolar illness has recently been described by Tohen et al. [77] who followed 166 bipolar patients 2–4 years after their first hospitalization (for a manic or mixed episode). Although all but 2% of the patients experienced syndromal recovery, 28% remained symptomatic (Y-MRS score >5 or Hamilton Depression Rating Scale Score >8), 57% did not achieve functional recovery, and 57% switched or had a new illness episode.

There is a huge disparity between the current development of new diagnostics, with special consideration of bipolar depression and hypomania, and research that still focuses on the treatment of classic mania and bipolar I disorder. In bipolar I or II disorder the ratio of time spent with depressive versus manic symptoms is 3.4 and 38.7, respectively [11, 12]. However, bipolar depression remains understudied. In the review of Bauer and Mitchner

[63], 48 class A trials examining the efficacy of agents in the treatment of acute manic symptoms in bipolar disorder were found, including 2,352 patients. For the treatment of acute depressive symptoms only 16 trials were withheld, including 637 patients. This leads to a ratio depression versus mania of 1:3 (for class A trials) and 1:4 (for the number of studied patients).

Although atypical features, early age at onset, depressive mixed state, agitated depression and depression with anger are found to belong to the bipolar spectrum, treatment implications are less clear. There is no consensus that these features are predictive of poor outcome during acute treatment with antidepressants [78], and research on the use of mood stabilizers (like lamotrigine or atypical antipsychotics) in this soft bipolar spectrum is just starting. In light of the great bipolar II prevalence [33], the lack of research on bipolar II disorder is even more problematic [79].

Discussion

Bipolar disorder is no longer a neglected discipline or scientific orphan. There is a marked upswing of research, reflected in increased publication activity. When compared with depressive disorder, this publication activity is still limited. Publications on drug treatment are more clinician based or expert based than evidence based. Opinion leaders and experts have the important and difficult task of translating the evidence-based efficacy into clinical effectiveness and to answer questions for which no evidence-based answers exist. However, this also puts bipolar disorder at risk of being too influenced by experts and opinions. Often reviews will not differ in the evidence that is reviewed, but in the story that connects the evidence, the story or opinion thereby being more important than the facts. An example of this latter phenomenon is the current controversy surrounding the treatment of bipolar depression, with European and American experts pleading for or cautioning against the use of antidepressants [80, 81], leaving clinicians with too many choices and perhaps the false postmodern impression that no choice is worthwhile to choose for. This makes bipolar disorder even more vulnerable to publication bias, pharmaceutical propaganda or disease mongering [82, 83].

Diagnosis of bipolar disorder has made a shift from mania towards depression and hypomania. Features of the course and symptoms in depressed patients are found to be indicative of a bipolar origin: admixture of psychomotor-retarded melancholic and atypical features, atypical features, early age of onset, brief MDE, antidepressant-induced mania, post-partum depression. Manic symptoms are now looked at in depression. This gives rise to a renewed interest in agitated depression, depressive mixed states and depression with anger/irritability: distinct but also overlapping depressive presentations that are now given a bipolar label. Criteria for hypomania are changing, with a different use of stem criteria and a decrease in the number and duration of symptoms. All these changes lead to a dramatic increase in the prevalence of bipolar (spectrum) disorder that now equals that of unipolar disorder. The complexity of a diagnosis of bipolar disorder should be welcomed after the simplicity of the antidepressant era, in which a pharmacocentric view had levelled all diagnostic and therapeutic subtleties. This complexity is further in line with that of clinical practice: the difficulty of treating a patient with serious affective illness. Furthermore, this complexity is not new and goes back to historical authors like Griesinger, Kraepelin and Weygandt [84, 85]. Limitations of this extended-spectrum diagnosis seem twofold. First, increasingly broad definitions could trivialize the core concept of bipolar disorder [86]. By using a spectrum approach, bipolar disorder carries the risk of replacing an antidepressant view of the world by a bipolar one. It may be hoped that current findings of bipolar signatures in depression, depressive mixed states and hypomania will be replicated in further studies and then integrated in the official diagnostic systems. Second, besides diagnostic validity there is the question of diagnostic utility. Although the bipolar validity of depressive mixed states and agitated depression has been shown, the utility of these concepts (i.e. short-term and long-term effectiveness of mood-stabilizing agents in these conditions) needs further proof. Confronted with these new bipolar patients, clinicians are now dealing with too many uncertainties. First, there is the uncertainty or probability of the diagnosis of bipolar disorder. Second, there is the uncertainty of the subsequent treatment (for bipolar disorder in general and bipolar spectrum disorder specifically less evidence-based and more expert-oriented). As with diagnosis, it may be hoped that further studies will take a closer look at the effectiveness of known bipolar disorder treatments in these new bipolar states.

Various mood stabilizers, besides lithium, have expanded the bipolar armamentarium. Mood stabilization is increasingly recognized as the cornerstone of bipolar treatment. This should be applauded in view of the overuse of antidepressants, with the risk of induction of mania, cycle acceleration and treatment failure. Despite its popularity, the term 'mood stabilizer' should not be used loose-

ly, as it could help to order priorities for bipolar treatment [62]. Prevention of future episodes should be the primordial feature of a mood-stabilizing drug [60]. Other properties (e.g. effectiveness in acute mania or depression) are secondary assets. Besides prophylactic treatment, research should focus more on bipolar depression, being more common than mania and less studied. Furthermore, mood stabilizers are all very distinct agents. Not only must their common mood-stabilizing properties be looked at, but also possible drug-specific psychotropic actions [87].

Finally and building upon the former conclusions, further research on bipolar disorder treatment has to close the gap between the limited evidence of efficacy trials, the opinions of experts and the experience of clinicians. Large-scale, randomized, controlled trials are needed, including a heterogeneous group of patients, not excluding the severely ill and rapidly recurrent subgroups, comparing several putative mood-stabilizing agents (one treatment or in combination), assessing an outcome of direct clinical importance and being designed in a way that makes them user friendly for clinicians [29, 30, 88, 89]. Trials that fulfill these requirements are difficult to install and are counter to the approach of most industry-funded efficacy trials (recruiting a homogeneous sample of patients and using primary outcomes of uncertain clinical meaning), designed for regulatory purposes. BALANCE (bipolar affective disorder: lithium/anticonvulsant evaluation), funded by the Stanley Foundation, is an example of how such trials can be installed. After a run-in phase, during which they receive a combination of lithium and valproate for up to 8 weeks, patients will be randomized to receive lithium/valproate as monotherapy or combination treatment, and will be followed up for 2 years [90, 91]. The trial is open to any patient with bipolar disorder who agrees to commence maintenance treatment, but faces clinical uncertainty about the optimal treatment. Primary outcome is the time to hospital admission. Healthcare agencies are probably the best placed to carry out these effectiveness studies. Unfortunately, their funding for research on bipolar disorder has been markedly low in the past. In two papers of Torrey et al. [92, 93], research grants funded by the National Institute of Mental Health were analysed. In 1997 and 1999, research grants for bipolar disorder accounted for only 3.5 and 2.4% of the total grants, respectively. These percentages were substantially lower than those for depressive disorder and schizophrenia: 13.8 and 8.9% for depressive disorder, 11.6 and 8.2% for schizophrenia. It may be hoped that the initiation of the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), examining the longitudinal course of the illness and the effectiveness of current treatments, is a new trend and that similar research on bipolar disorder will be continued in the future [94, 95].

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