EDITORIAL

Treatment Guidelines in Bipolar Disorders and the Importance of Proper Clinical Trial Design

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A working group led by Dr. Konstantinos Fountoulakis developed the first International College of Neuropsychopharmacology (CINP) clinical guidelines for the treatment of Bipolar Disorders in adult patients. Their work is very thoroughly described in four separate papers (parts) included in this issue of the journal. The first article is Background and Methods of the Development of Guidelines (Fountoulakis et al., 2017d); part 2 is Review, Grading of the Evidence, and a Precise Algorithm (Fountoulakis et al., 2017c); part 3 is The Clinical Guidelines (Fountoulakis et al., 2017a); and Part 4 is Unmet Needs in the Treatment of Bipolar Disorder and Recommendations for Future Research (Fountoulakis et al., 2017b).

The background section provides a very comprehensive historical review of bipolar disorder going back 5000 years, including its natural course of illness, phenomenology, and development of treatments.

The CINP guidelines are unique, as they include additional recommendations for specific clinical characteristics such as agitation, predominant polarity, mixed features, and rapid cycling course. Furthermore, guidelines are also provided for nonpharmacological treatments.

The authors clearly describe their approach on grading articles from the scientific literature, and methods for the development of guidelines. The guidelines were developed by an evidence-based consensus approach primarily based on placebo or active comparator randomized controlled trials (RCTs) but also taking into consideration posthoc analysis reports, related meta-analyses, and other treatment guidelines as well as the research and clinical expert opinion of the authors utilizing a Delphi method to reach final decisions.

The PRISMA method was used in the literature search (Fountoulakis et al., 2017d). The authors based their recommendations on 569 articles containing RCTs, reviews, posthoc secondary analyses or meta-analyses, and 57 publications on treatment guidelines. The authors searched MEDLINE (http://clinicaltrials.gov and http://www.clinicalstudyresults.org) as well as web pages of pharmaceutical companies with compounds used in bipolar disorder up to March 25, 2016.

The authors provide a critical analysis of the existing treatment grading methods that led them to determine that there was no optimal method to grade treatments for bipolar disorder, therefore creating their own grading system. Their methodology provides 32 different levels of recommendations, starting with the optimal: “At least 1 positive 2 active arm RCT vs placebo exists, plus positive 1 active arm RCTs, and no negative RCTs.” Lower level scenarios take into account posthoc reports, meta-analyses, and failed trials. Different scenarios are ranked appropriately, as a different weight is given to the absence of evidence than to the presence of negative data.

A 5-level composite treatment recommendation was created that combines efficacy and safety/tolerability, which is a thoughtful approach. An important and reasonable consideration made by the group was to give a higher weight for safety than for efficacy. For instance, a level 1 recommendation requires level 1 for safety/tolerability but can include level 1 or 2 for efficacy. This can lead to treatments of superior efficacy but lower tolerability being ranked lower; level 5 is reserved for “not recommended.”

Guidelines are provided for each of the major phases of bipolar disorder; a novel approach is emphasizing the importance of considering the maintenance phase when treatments are recommended during the acute phases.

Comparisons with recommendations of other bipolar disorder treatment guidelines (NICE, CANMAT/ISBD, WFSBP, and BAP) will be helpful to the reader.

Part 4, Needs in the Treatment of Bipolar Disorder and Recommendations for Future Research, is particularly thoughtful. The authors highlight the need to merge guidelines of all phases into a single guideline taking into consideration the course and staging of the condition. Furthermore, the authors
emphasize that current treatment guidelines encourage the fragmentation of bipolar disorder into phases resulting in the lack of an overall longitudinal therapeutic strategy. They also mention other areas of need for more evidence-based treatments, including use of combinations treatment and treatments for specific conditions such as mixed features or rapid cycling course.

The Value of Optimal Methodology in the Evaluation of Clinical Trial Results

The authors address a number of research design issues that need to be considered in the future development of treatment guidelines in bipolar disorder. A key point raised by the workgroup is the importance of the release of raw clinical trial data from industry to the scientific community. The value of this issue can be exemplified by a recent development of novel analyses of exiting longitudinal data such as the Multi-Outcome Analysis of Treatments that provides more pragmatic information for clinicians and investigators in guiding maintenance treatment decisions in bipolar disorder (Bowden et al., 2016; Tohen et al., 2016). The development of this methodology was possible as 3 major pharmaceutical companies provided the raw data to independent academic investigators who obtained a grant from NIMH (RC1MH088431, MTohen [PI]). The methodology is now available to the public (www.moatsoftware.com; https://delta.uthscsa.edu/moat).

Another important issue raised in the guidelines is the need to develop uniform clinical trial standards including uniform results of outcomes to be reported. The authors provide helpful appendices with recommendations. To address this issue, The International Society for Bipolar Disorders recently proposed a uniform nomenclature for the definition of commonly used outcomes such as recovery, relapse, and remission (Tohen et al., 2009). In terms of suggested outcomes, the guidelines appropriately highlight the need to focus more on functional rather than symptomatic outcomes, an issue that has been raised in the literature (Dion et al. 1988; Goetz et al. 2007; Tohen et al. 1990, 2003).

An important recommendation by the workgroup is the need to report results on individual items in symptom rating scales in addition to overall results, which no doubt provides a better understanding of the specific benefits of a treatment; for example, in a patient with bipolar depression, the improvement of insomnia due to somnolence does not have the same value as the improvement of depressed mood.

The authors recommend statistical analyses of side effects; however, this has the potential to be misleading. With some exceptions (Zajecka et al., 2003), the sample size of the vast majority of clinical trials is determined by a power analysis to detect a difference (if one exists) for efficacy but not for safety (Tohen, 2013). Lack of proper sample size estimation can lead to a type II error where, due to a small size, the results fail to show that there is a difference in safety of a treatment compared with placebo when in reality there is a difference. Such a finding can lead to the dangerous conclusion that a treatment is safe when in reality it may not be.

Adequate sample size estimation is also essential in the interpretation of comparative studies of active treatments. Low statistical power due to a small sample size can lead to a type II error that concludes that two treatments are equally effective when in reality one is more effective than the other (Tohen, 2008, 2015).

In the interpretation of clinical trials, issues that need to be taken into account include potential observation bias (Tohen, 1992), the duration of the observation time for maintenance studies (Tohen, 2015), the selection of the patient population (Baldessarini et al., 2008; Tohen, 2012), and factors that lead to placebo response (Yildiz et al., 2007). Another potential source of bias that needs to be considered is funding source (Paul and Tohen, 2007; Tohen, 2007).

An area that in general receives little attention in treatment guidelines are cultural issues or differences in efficacy or tolerability across global populations to specific treatments (Gallo and Tohen, 2010; Tohen, 2014). Considering that CINP is a global organization, for its next version it should consider addressing this important issue as well as expanding the geographical diversity of the authors, as currently only Western Europe and Canada are represented with the omission of any authors from developing countries or East Asia.

Another important issue highlighted by the authors is the need to have more effectiveness studies. Treatment guidelines in general do not consider effectiveness comparison studies. An example of a well-designed effectiveness study is a recent head-to-head study comparing quetiapine vs lithium in the treatment of all phases in bipolar disorder under usual and customary clinical care conditions (Nierenberg et al., 2016).

In summary, CINP should be commended for the product of this distinguished group of experts that provides clinicians worldwide an opportunity to make evidence-based treatment decisions in the treatment of bipolar disorder that hopefully will result in improving the lives of those who suffer from this devastating condition.

Statement of Interest


References

REVIEW

The International College of Neuropsychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 1: Background and Methods of the Development of Guidelines

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Abstract

Background: This paper includes a short description of the important clinical aspects of Bipolar Disorder with emphasis on issues that are important for the therapeutic considerations, including mixed and psychotic features, predominant polarity, and rapid cycling as well as comorbidity.

Methods: The workgroup performed a review and critical analysis of the literature concerning grading methods and methods for the development of guidelines.

Results: The workgroup arrived at a consensus to base the development of the guideline on randomized controlled trials and related meta-analyses alone in order to follow a strict evidence-based approach. A critical analysis of the existing methods for the grading of treatment options was followed by the development of a new grading method to arrive at efficacy and recommendation levels after the analysis of 32 distinct scenarios of available data for a given treatment option.

Conclusion: The current paper reports details on the design, method, and process for the development of CINP guidelines for the treatment of Bipolar Disorder. The rationale and the method with which all data and opinions are combined in order to produce an evidence-based operationalized but also user-friendly guideline and a specific algorithm are described in detail in this paper.

Keywords: Bipolar Disorder; anticonvulsants; antidepressants; antipsychotics; evidence-based guidelines; lithium; mania; bipolar depression; mood stabilizers; treatment
Introduction

General Background, Disclosure, and Aim

Treatment guidelines are becoming an ever more important part of medical reality, especially since the translation of research findings to everyday clinical practice is becoming increasingly difficult with the accumulation of complex and often conflicting research findings that are thereafter also included in metaanalysis. Guidelines aim to assist clinicians but also policymakers to arrive at decisions concerning the treatment and care of patients. They set the standard of care and training for health professionals and they also identify priority areas for further research, since they are based primarily on the available evidence, but also in areas where evidence is not available, on expert opinion (Fountoulakis, 2015i).

In the field of Bipolar Disorder (BD), accumulated knowledge is often complex, confusing, and in many instances contrasts with the beliefs and practices that appear to have been set in stone in psychiatric culture and training for the last few decades.

To fulfil this need for expert translation of research findings into clinical practice for the benefit of patients, the International College of Neuropsychopharmacology (CINP) launched an effort to critically appraise the literature and provide guidance to clinicians in the form of a precise treatment algorithm. It is hoped that this algorithm for the treatment of BD will help the clinician to follow the state-of-the-art evidence, thus enabling their clinical practice to be based on an informed decision-making process. This guideline has been commissioned by the CINP, and the workgroup consisted of experts with extensive research and clinical experience in the field of BDs. There was no funding from any source for the development of the guidelines and the activities of the workgroup.

All the members of the workgroup were psychiatrists who are in active clinical practice and were selected according to their expertise and with the aim to cover a multitude of some different cultures. All of them were involved in research and other academic activities, and therefore it is is possible that through such activities some contributors have received income related to medicines discussed in this guideline. All conflicts of interest are mentioned at the end of this paper, which is the introductory paper to the CINP BD guidelines. It should also be noted that some drugs recommended in the guideline may not be available in all countries, and labelling and dosing might vary.

The aim of the current endeavor was to develop a guideline and precise algorithm for treatment of BD in adults for use in primary and secondary care. Children, adolescents, and the elderly are not the focus of this guidance. The guideline and algorithm have been developed after a complete review of the literature and with the use of stringent criteria. Both the guideline and the precise algorithm try to balance research vs clinical wisdom but give primacy to the available evidence.

To comply with the journal’s word limit for manuscripts and for easy readability, the CINP guidelines have been organized and presented as a series of 4 distinct papers. This paper is the first of this series and will cover the general background of the guideline and algorithm, that is, the historical perspective and general clinical and treatment issues followed for the development of the guideline and the algorithm. The second paper summarizes, classifies, and grades the treatment data on BD while the third paper includes the guideline and the treatment algorithm themselves. The fourth and final paper addresses the unmet needs and areas that should be the focus of attention and specific research in the future.

Historical Perspective

Depression and bipolarity were mentioned in Eber’s papyrus in ancient Egypt around 3000 BC (Okasha and Okasha, 2000) and in the Hippocratic texts. Plato (424–348 BC) and Aristotle (384–322 BC) further elaborated on the concept and Aristotle was the first to describe accurately the affections of desire, anger, fear, courage, envy, joy, hatred, and pity. Later, Galen (131–201 AD), Themison of Laodicea (1st century BC) and Aretaeus of Cappadocia (2nd century AD) as well as Arab scholars and especially Avicenna (980–1037) further elaborated on the concept of mood disorders (Fountoulakis, 2015b).

Jean-Philippe Esquirol (1772–1840) was the first to clearly point out that melancholia was a disorder of the mood with “partial insanity” (monomania) and used the word “hippomania.” Finally, Jean-Pierre Faitre (1794–1870) and Jules Gabriel Francois Baillarger (1809–1890) established the connection between depression and mania and gave it the name of “folie circulaire” or “folie à double forme,” but it was Emil Kraepelin (1856–1926) who established manic-depressive illness as a distinct nosological entity and separated it from schizophrenia on the basis of heredity, longitudinal follow-up, and a supposed favorable outcome (Kraepelin, 1921). His pupil Wilhelm Weygandt (1870–1939) published the first textbook on mixed clinical states (Weygandt, 1899). Following a similar line of thinking, and in spite of some major objections to the Kraepelian approach, Karl Jaspers (1883–1969) described aspects of mixed depressive states that he named “querulant mania,” “nagging depression,” or “wailing melancholia” (Jaspers, 1913), while Eugene Bleuler coined the term “affective illness” and by this he broadened the concept of manic-depression.

In 1957 Karl Leonhard (1902–1988) proposed that the term “bipolar disorder” should replace manic-depression, and he also made a distinction between monopolar (unipolar depression) and bipolar illness (Leonhard, 1957a, 1957b; Leonhard, 1979).

In 1870, Silas Weir Mitchell (1829–1914) was the first to recommend lithium as an anticonvulsant, hypnotic, and as medication for “general nervousness” (Mitchell, 1870, 1877). In 1871, William Alexander Hammond (1828–1900) was probably the first to prescribe a modern and effective psychotropic agent, and this was lithium (Mitchell and Hadzi-Pavlovic, 2000). Carl Lange (1834–1900) and Frederik Lange (1842–1907) had used lithium in the treatment of depression since 1886 (Lenox and Watson, 1994). However, in spite of encouraging results, by the turn of the 20th century, the “brain gut” theory of mood disorders disappeared as a medical entity and the use of lithium in psychiatry was abandoned.

In 1949 John Cade (1912–1980) reported positive results from the treatment of 10 acutely manic patients (Cade, 1949, 2000); however, 2 years later he reported the first death caused by lithium toxicity in a patient whose bipolar illness otherwise responded extremely well to treatment. Later, Mogens Schou (1918–2005) undertook a randomized controlled trial of lithium in mania (Schou et al., 1954; Bech, 2006), and eventually the efficacy of lithium during the maintenance phase was established (Gershon and Yuwiler, 1960; Baastrup, 1964; Baastrup and Schou, 1967; Angst et al., 1969, 1970; Baastrup et al., 1970; Schou et al., 1970; Johnstone et al., 1988; Schioldann, 1999; Mitchell and Hadzi-Pavlovic, 2000; Bech, 2006; Schioldann, 2006; Schioldann, 2011).

Valproate was introduced in 1966 as an anticonvulsant (Lambert et al., 1966) and later carbamazepine (Okuma et al., 1979) followed. Neuroleptics were introduced by Jean Delay...

There were several reports in the 1970s suggesting that in bipolar depression the use of antidepressants might induce mania, mixed episodes, and rapid cycling (Wehr and Goodwin, 1987; Wehr et al., 1988). In 1994 the first detailed operational treatment guidelines were published by the American Psychiatric Association and after 2000, systematic industry-sponsored studies of second generation antipsychotics and haloperidol were performed. Also, during this period the first meta-analytic studies emerged, and the evidence-based medicine principles gained ground in treatment recommendations.

**Clinical Description**

While the basic conception of BD suggested that it is characterized by the alternation of manic and depressive episodes with a return to the premorbid level of functioning between the episodes and to favorable outcome compared with schizophrenia (Kraepelin, 1921), today we know that this is not always the case (Tohen et al., 1990; Grande et al., 2016). Not only BD is a much more complex disorder than this, but also the outcome varies. The most prominent clinical facets are shown in Table 1 (Fountoulakis, 2015a, 2015c, 2015d, 2015e, 2015j, 2015n).

The fact that often the correct diagnosis is made only after 8 to 10 years has passed because the first episode is psychotic-like or depressive and the correct diagnosis can be made only after a manic or a mixed episode emerges (Angst, 2007) is especially problematic. It has been estimated that more than one-half of hospitalized patients originally manifesting a depressive episode will turn out to be bipolar in the next 20 years (Angst et al., 2005a). It is of utmost importance for both clinicians and researchers to create a biographical chart with the patient's course over time and including any important event in the developmental history of the patient and emphasizing the main events and hallmarks of his/her life and his/her full psychiatric and medical history. Such a chart clarifies both the diagnosis and the course of the disease and also the response to therapeutic interventions, since any delay in the proper diagnosis also delays proper treatment (Altamura et al., 2010; Drancourt et al., 2013).

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<th>Table 1. List of the Multiple Clinical Aspects of Manic-Depressive Illness</th>
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<td>1. Manic episodes</td>
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<td>2. Depressive episodes</td>
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<td>3. Mixed episodes</td>
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<td>4. Subthreshold manic symptoms</td>
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<td>5. Subthreshold depressive symptoms</td>
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<td>6. ‘Mixed’ states and ‘roughening’</td>
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<td>7. Mood lability/cyclothymia/‘personality-like’ behavior</td>
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<td>8. Predominant polarity</td>
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<td>9. Frequency of episodes/rapid cycling</td>
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<td>10. Psychotic features</td>
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<td>11. Neurocognitive disorder</td>
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<td>12. Functional deficit and disability</td>
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<td>13. Drug/alcohol abuse</td>
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<td>14. Comorbid anxiety and other mental disorders</td>
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<td>15. Self-destructive behavior and suicidality</td>
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In terms of individual symptoms, fatigue and psychomotor retardation dominate the clinical picture in 75% of patients during acute bipolar depression. Irritability is present in almost 75% of patients (Winokur et al., 1969), delusions are present in 12 to 66% (Winokur et al., 1969; Carlson and Strober, 1978; Rosenthal et al., 1980; Black and Nasrallah, 1989), and hallucinations in 8 to 50% (Winokur et al., 1969; Carlson and Strober, 1978; Rosenthal et al., 1980; Black and Nasrallah, 1989; Baethge et al., 2005). Psychotic features seem to constitute a stable trait that tends to repeat itself across episodes (Helms and Smith, 1983; Nelson et al., 1984; Aronson et al., 1988a, 1988b). Depending of the study sample composition, changes in appetite for food are seen in almost all patients (Winokur et al., 1969), with one-fourth manifesting overeating and one-fourth losing significant weight (Casper et al., 1985). Almost all bipolar depressed patients experience some kind of sleep problem (Winokur et al., 1969; Casper et al., 1985). A subgroup of bipolar depressed patients (up to 25%) often exhibit excessive sleep and have difficulty getting up in the morning (Winokur et al., 1969). Decreased sexual desire is seen in more than 75% of patients (Winokur et al., 1969; Casper et al., 1985) and concerns both sexes. Approximately two-thirds of bipolar depressed patients present with multiple physical pains and complaints (e.g., headache, epigastric pain, precordial distress, etc.) in the absence of any physical illness, especially in primary care (Winokur et al., 1969).

Euphoria is observed in 30 of 97% of acutely manic patients (Clayton and Pitts, 1965; Winokur et al., 1969; Beigel and Murphy, 1971; Carlson and Goodwin, 1973; Taylor and Abrams, 1973; Winokur and Tsuang, 1975; Abrams and Taylor, 1976; Leff et al., 1976; Loudon et al., 1977; Taylor and Abrams, 1977; Cassidy et al., 1998a), while unrestrained and expansive mood is seen in 44 to 66% (Taylor and Abrams, 1973, 1977; Loudon et al., 1977). Patients are dissatisfied and intolerant and the vast majority manifest mood lability and instability (42 to 95%) (Winokur et al., 1969; Carlson and Goodwin, 1973; Abrams and Taylor, 1976; Loudon et al., 1977; Taylor and Abrams, 1977; Cassidy et al., 1998a). Irritability is also very frequent (51–100%) (Winokur et al., 1969; Carlson and Goodwin, 1973; Taylor and Abrams, 1973, 1977; Winokur and Tsuang, 1975; Abrams and Taylor, 1976; Loudon et al., 1977; Cassidy et al., 1998a; Serretti and Olgiati, 2005). However, even significant depressive symptoms are experienced by as many as 29 to 100% of acutely manic patients (Winokur et al., 1969; Beigel and Murphy, 1971; Kotin and Goodwin, 1972; Carlson and Goodwin, 1973; Murphy and Beigel, 1974; Loudon et al., 1977; Prien et al., 1988; Cassidy et al., 1998a; Bauer et al., 2005).

Accelerated psychomotor activity is observed in the vast majority of patients (56–100%) (Winokur et al., 1969; Carlson and Goodwin, 1973; Taylor and Abrams, 1973; Abrams and Taylor, 1976; Leff et al., 1976; Loudon et al., 1977; Carlson and Strober, 1978; Cassidy et al., 1998a, 1988b; Cassidy et al., 1998a; Serretti and Olgiati, 2005) and pressured speech in almost all patients (Clayton and Pitts, 1965; Winokur et al., 1969; Carlson and Goodwin, 1973; Taylor and Abrams, 1973; Abrams and Taylor, 1976; Leff et al., 1976; Loudon et al., 1977; Carlson and Strober, 1978; Cassidy et al., 1998b; Serretti and Olgiati, 2005); hypersexuality is present in 25 to 80% of patients with 23 to 33% of them having significant sexual exposure (Allison and Wilson, 1960; Clayton and Pitts, 1965; Winokur et al., 1969; Carlson and Goodwin, 1973; Taylor and Abrams, 1973, 1977; Abrams and Taylor, 1976; Leff et al., 1976; Loudon et al., 1977; Carlson and Strober, 1978). Decreased need for sleep (hyposomnia) is present in 63 to 100% of patients (Clayton and Pitts, 1965; Winokur et al., 1969; Leff et al., 1976; Loudon et al., 1977; Carlson and Strober, 1978).
Cassidy et al., 1998b; Serretti and Olgiati, 2005) and psychotic features in 33 to 96% of patients (Winokur et al., 1969; Carlson and Strober, 1978; Rosenthal et al., 1980; Black and Nasrallah, 1989).

Overall, psychotic features are so common that acute mania should be considered primarily a psychotic state (Koukopoulos, 2006). Delusions are present in 24 to 96% of manic patients, and it is interesting that persecutory ideas are equally frequent with delusions of grandiose (Bowman and Raymond, 1932; Rennie, 1942; Astrup et al., 1959; Clayton and Pitts, 1965; Winokur et al., 1969; Beigel and Murphy, 1971; Carlson and Goodwin, 1973; Taylor and Abrams, 1973, 1977; Murphy and Beigel, 1974; Abrams and Taylor, 1976; Leff et al., 1976; Loudon et al., 1977; Carlson and Strober, 1978; Rosenthal et al., 1980; Winokur, 1984; Black and Nasrallah, 1989; Serretti et al., 2002; Keck et al., 2003; Goodwin and Jamison, 2007). Hallucinations are less frequent and present in 13 to 66% of cases; they can either be congruent or noncongruent, with auditory, visual, and olfactory ones being almost equally frequent (Lange, 1922; Bowman and Raymond, 1932; Astrup et al., 1959; Winokur et al., 1969; Taylor and Abrams, 1973, 1977; Abrams and Taylor, 1976; Carlson and Strober, 1978; Rosenthal et al., 1980; Winokur, 1984; Black and Nasrallah, 1989; Serretti et al., 2002; Keck et al., 2003; Goodwin and Jamison, 2007).

Psychotic symptoms in BD are predictable of a more detriment course, including a higher rate of rehospitalizations (Caetano et al., 2006; Ozyildirim et al., 2010).

Almost one-third of acutely manic patients are “confused” and 46 to 75% are violent (Carlson and Goodwin, 1973; Taylor and Abrams, 1973, 1977; Abrams and Taylor, 1976; Cassidy et al., 1998b). The term confused refers to manic disorganization and not to organic drop in the level of consciousness. As many as 14 to 56% of patients manifest severe regression, catatonia, posturing, and negativism, often making differential diagnosis from schizophrenia difficult (Lange, 1922; Carlson and Goodwin, 1973; Taylor and Abrams, 1973, 1977; Carlson and Strober, 1978; Abrams and Taylor, 1981; Brauning et al., 1998; Kruger et al., 2003), and 10 to 20% have fecal incontinence (Taylor and Abrams, 1973, 1977; Abrams and Taylor, 1976). A summary of the frequencies of appearance of various symptoms during the two different acute phases of the illness is shown in Table 2.

Formally, those episodes with manic symptoms but less pronounced in terms of severity and with a shorter duration are labeled hypomanic. Hypomania is much more common than mania (Angst, 1998), but its recognition is mostly achieved mainly by interviewing significant others and not the patient. Hypomanic episodes cause mild or no impairment at all, and on the contrary, in some cases, they may even contribute to success in business, leadership roles, and the arts. Psychotic symptoms are less frequent (around 20%) in comparison to full-blown manic episodes, but they do occur (Mazzarini et al., 2010).

Mixed episodes are defined as the coexistence of both depressive and manic symptoms; however, the term was abandoned with DSM-5, which includes mixed features as a specifier only. The DSM-5 demands the presence of a full-blown episode of either pole together with at least 3 symptoms of the opposite pole being present in order to allow the label of “mixed features” specifier.

It is reported that in 69.6% of cases the course resembles that of a recurrent episodic illness, while in 25% of cases there is a chronic course without clear remissions between episodes. In only 5.4% is there a single episode of mania. Suicidal ideation is present in 78.6% of patients at some time in their life. Only around 5% of BD patients have chronic mania (Akiskal, 2000).

Karl Leonhard was the first to report the presence of a predominant polarity with 17.9% of patients having a manic- and 25.6% having a depressive-predominant polarity (Leonhard, 1963). The concept was further formulated by Jules Angst (1978) and Carlo Perris (Perris and d’Elia, 1966a, 1966b) and has recently been utilized for long-term prognosis and to assist clinicians in long-term therapeutic design (Quittin et al., 1986; Judd et al., 2003; Colom et al., 2006). The most reliable definition of predominant polarity demands that at least two-thirds of episodes belong to one of the poles (Colom et al., 2006; Rosa et al., 2008; Garcia-Lopez et al., 2009; Mazzarini et al., 2009; Tohen et al., 2009; Vieta et al., 2009; Nivoli et al., 2011; Baldessarini et al., 2012; Pacchiarotti et al., 2013a; Carvalho et al., 2014a, 2014b).

Somewhere between 15% and 50% of BD patients are reported to manifest some type of seasonal variation of symptomaticity (Hunt et al., 1992; Faedda et al., 1993; Goikolea et al., 2007; Shand et al., 2011). Two opposing seasonal variations have been described: fall-winter depression with or without spring-summer mania or hypomania; and spring-summer depression with or without fall-winter mania or hypomania (Faedda et al., 1993). Most studies support the first subtype (Walter, 1977; Parker and Walter, 1982; Mulder et al., 1990; Peck, 1990; Parton and Lonqvist, 1996; Clarke et al., 1999; Lee et al., 2007; Murray et al., 2011).

The concept of rapid cycling appeared for the first time in the 70s in a landmark paper by Dunner and Fieve (1974). In general the classic rapid-cycling includes cycles with duration of weeks to months. Ultra-rapid cycling is reported when mood cycling has frequency of weeks to days, and ultradian cycling when there is significant mood variation within a 24-hours period (Kramlinger and Post, 1996). Other terms include ultra-ultra rapid and ultradian rapid and refer to weekly or daily cycling, which is not uncommon in BD patients (Kramlinger and Post, 1996). Most studies suggest a 5 to 33.3% up-to-1-year prevalence

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<tr>
<th>Symptom</th>
<th>Manic</th>
<th>Depressive</th>
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<tr>
<td>Euphoria</td>
<td>30–97%</td>
<td>100%</td>
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<tr>
<td>Expansive mood</td>
<td>44–66</td>
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<tr>
<td>Depressive symptoms</td>
<td>29–100%</td>
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<tr>
<td>Mood lability</td>
<td>42–95%</td>
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<tr>
<td>Irritability</td>
<td>51–100%</td>
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<tr>
<td>Psychomotor retardation</td>
<td>56–100%</td>
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<tr>
<td>Psychomotor acceleration</td>
<td>100%</td>
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<tr>
<td>Pressured speech</td>
<td>12–66%</td>
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<td>Psychotic features</td>
<td>33–96%</td>
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<td>Delusions</td>
<td>24–96%</td>
<td>12–66%</td>
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<tr>
<td>Hallucinations</td>
<td>13–66%</td>
<td>8–50%</td>
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<td>Weight loss</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>25%</td>
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</tr>
<tr>
<td>Hyposomnia</td>
<td>63–100%</td>
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<tr>
<td>Oversleeping</td>
<td>25%</td>
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<tr>
<td>Loss of libido</td>
<td>25%</td>
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</tr>
<tr>
<td>Hypersexuality</td>
<td>25–80%</td>
<td></td>
</tr>
<tr>
<td>Significant sexual exposure</td>
<td>23–33%</td>
<td></td>
</tr>
<tr>
<td>Confused</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Violent</td>
<td>46–75%</td>
<td></td>
</tr>
<tr>
<td>Regression, catatonia etc.</td>
<td>14–56%</td>
<td>20–25%</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>10–20%</td>
<td></td>
</tr>
<tr>
<td>Physical complains</td>
<td>66%</td>
<td></td>
</tr>
</tbody>
</table>

| Table 2. Summary of the Frequencies of Appearance of Various Symptoms during the Two Different Acute Phases of BD |
In terms of neurocognitive function, the literature suggests that the neurocognitive deficit in BD patients concerns almost all domains and phases of the illness with only a few exceptions. Its magnitude is at the severe range during the acute episodes and at the medium range during euthymia, while the origin of the deficit remains unclear. In terms of neurocognitive function, BD patients do quantitatively better than patients with schizophrenia, but the qualitative pattern of the deficit is similar in the 2 disorders. There are no clear differences between BD subtypes. The deficit is present early in the course of the disorder. At least in some patients it might emerge before the onset of the first mood episode, and in the majority of patients it progresses probably in relationship with the manifestation of psychotic symptoms. The verbal memory and executive function deficits probably constitute endophenotypes, while the role of medication as a causative factor is limited (Tsitsipas and Fountoulakis, 2015; Cullen et al., 2016).

Finally, in contrast to the original conceptualization of BD by Emil Kraepelin a century ago, unfortunately it seems that only a minority of BD patients achieve complete functional recovery (Goldberg et al., 1995a, 1995b; Keck et al., 1998; Strakowski et al., 1998; Daban et al., 2006; Martinez-Aran et al., 2007; Mur et al., 2007).

**Classification**

ICD and DSM include BD as a diagnostic entity but with significant differences between them (Fountoulakis, 2015b). It is important to note that almost all the research literature follows the DSM classification, while almost all countries worldwide have the obligation to use the ICD in their official documents, including hospital records, etc. The ICD-10-CM helps to bridge these 2 different classification systems for administration purposes. In ICD-10 (WHO, 1992, 1994), BD is included in the chapter on mood (affective) disorders (F30-F39). While in previous editions of the DSM, both unipolar and bipolar disorders were grouped under the chapter on mood disorders, on the contrary in DSM-5 (American Psychiatric Association, 2013), BDs were separated from unipolar depression. The “bipolar” chapter includes BD and cyclothymic disorder, while the “depression” chapter includes disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), and premenstrual dysphoric disorder. Both chapters include “unspecified,” “other,” and “due to” categories.

Another important difference between the 2 classification systems is that ICD requires the presence of at least 2 episodes of pathological disturbance of mood while DSM does not. DSM recognizes the presence of 2 subtypes of BD, that is, of BD-I (BD with manic episodes) and BD-II (BD with hypomanic but not manic episodes). BD-II is not part of the ICD-10 diagnostic list, which accepts hypomania as a diagnostic entity (F30.0), but it is considered simply a low-severity mania.

In ICD-10 a mixed affective episode (F38.0) is defined as an affective episode of at least 2 weeks duration that is characterized by either a mixture or a rapid alternation (usually within a few hours) of hypomanic, manic, and depressive symptoms. In DSM-5 a radical change was the abolishment of the concept of mixed episodes. In previous versions of the DSM, mixed episodes were defined as the coexistence of full-blown manic and depressive episodes simultaneously. Although such a coexistence is rather rare, almost one-third of patients recruited in pharmaceutical trials of acute mania were diagnosed as mixed. Thus there exists ample data, although neither properly analyzed nor published. Instead of the diagnosis of mixed episodes, DSM-5 introduced the mixed features specifier concept. According to this, a mood episode (either manic or depressed) has mixed features if at least 3 criteria of the opposite pole (from a specific list) coexist. It is important to note that according to DSM-5, mixed features can also be attributed to a unipolar major depressive episode without changing the diagnosis to BD.

Another important change in the DSM-5 is the introduction of the anxious distress specifier, which demands the presence of at least 2 criteria from a list of 5 (tension, restlessness, concentration difficulties, worry, fear of losing control).

The ICD-10 classification accepts the presence of “somatic syndrome,” which seems analogous but it is not identical to “melancholic features” of DSM-5 (Fountoulakis et al., 1999). The atypical features, rapid cycling, and anxious distress are described in DSM-5 but not in ICD-10. Also, ICD-10 does not differentiate psychotic symptoms into mood congruent vs mood incongruent. The other specifiers, catatonia, peripartum onset, and seasonal pattern, are not included in the ICD-10 either. It is also important to note that ICD-10 recognizes catatonia only in the frame of schizophrenia, while DSM-5 uses this specifier also in affective disorders.

There is an issue concerning the diagnosis of cases with subthreshold manic symptoms or long-lasting hyperthymia. While the traditional bipolar vs unipolar distinction is widely used and adopted by classification systems, it is doubtful whether it can capture the essence of the huge heterogeneity observed in mood disorders and their dynamic nature with frequent switches and changes in the clinical profile. The greatest disadvantage of both classification systems is that they perform better (and focus) when interepisodic remission is present; instead, the everyday real-life patient is more likely to suffer from a chronic disorder with residual and mixed symptoms. The term spectrum was first used in psychiatry in 1968 for the schizophrenia spectrum (Kety et al., 1968).

The proposed mood spectrum models unify categorical classification, which is essential, with a dimensional view, which is true to nature; both are needed and both are empirically testable. Today the term bipolar spectrum is mainly used in 2 complementary senses: (1) a spectrum of severity, which embraces psychotic and nonpsychotic major and minor BDs (including bipolar dysthymia, recurrent brief and minor depressions), cyclothymic disorders, hypomania and, at its broadest, even borderline disorders and cyclothymic temperament; (2) a proportional mood spectrum, which considers the 2 components, mania and depression, on the level of major and minor mood disorders. This proportional model is an extension of Kleist’s concept of BD as a combination of the 2 monopolar disorders of depression and mania (Kleist, 1937). Thus these 2 approaches to spectrum reflect 2 distinct continua: from normal to pathological and from unipolar to bipolar.

An important part of the bipolar spectrum is cyclothymic disorder, which is considered to be an attenuated form of BD. Their behavior is characterized by the alternation of extremes (Akiskal et al., 1977). Depending on the threshold of traits used in determining the presence of hyperthymia, cyclothymic patients may constitute 10 to 20% of those with major depressive disorder. Also, cyclothymia is often a prodromal of BD (Akiskal et al., 1979). Another important part of the bipolar spectrum are those patients who experience an antidepressant-induced switch.
Thus, many patients with so-called unipolar depression are actually pseudounipolar. Some authors suggest that a significant part of the literature consists mostly of expert opinion overemphasizing various links between bipolar and unipolar mood disorders and personality disorders (Paris et al., 2007; Patten and Paris, 2008). Recently, the first solid international epidemiological data in support of the bipolar spectrum have been published (Merikangas et al., 2007, 2011; Angst et al., 2010). According to these authors there is a direct association between increasingly restrictive definitions of BD and indicators of clinical severity, including symptom severity, role impairment, comorbidity, suicidality, and treatment. For example, the proportion of mood episodes rated as clinically severe increased from 42.5% for subthreshold BD to 68.8% for BD-II to 74.5% for BD-I. However, since clinical diagnosis and severity share confounding factors and definitions overlap, it is also important to note that these studies also showed that the proportion of cases reporting severe role impairment ranged from 46.3% for subthreshold BD to 57.1% for BD-I (Merikangas et al., 2011).

On the basis of both epidemiological data and clinical wisdom, a limited number of models reflecting the structure of the bipolar spectrum have been proposed. The first effort was a dimensional concept (from normal to pathological) proposed by Kretschmer in 1921 for schizophrenia (schizothymic-schizoid-schizophrenic) and for affective disorders (cyclothymic temperament-cycloid ‘psychopathy’-manic-depressive disorder). Bleuler suggested a similar concept in 1922. In 1977 Akiskal proposed a cyclothymic-bipolar spectrum (Akiskal et al., 1977). A simple model system was introduced in 1978 by Jules Angst (1978; Angst et al., 1978), who used the the following codes: M for severe mania, D for severe depression (unipolar depression), m for less severe mania (hypomania), and d for less severe depression. In 1981 Gerald Klerman suggested a manic spectrum (Klerman, 1981, 1987) and in the late 1990s Akiskal proposed 6 subtypes, some of which are further subdivided according to their unique clinical features. A summary of his proposed subtype schema is as follows (Akiskal and Pinto, 1999; Akiskal and Benazzi, 2005; Ng et al., 2007; Fountoulakis, 2008).

Epidemiology

In the last few decades there has been an increasing interest in psychiatric epidemiology. For BD, a point that plays a major role in the estimation of the prevalence rates is the definition of hypomania and of mixed, irritable, or dysphoric forms of manic episodes. This is further complicated by the presence of inaccurate recall and the low sensitivity of the interview instruments concerning subthreshold symptomatology and nonclassical clinical pictures (Kessler et al., 1997a).

A number of important studies exist and provide important but inconclusive information. The Amish study (Egeland and Hostetter, 1983; Egeland et al., 1983; Hostetter et al., 1983) reported similar prevalence rates between unipolar depression and bipolar illness and also similar rates between genders. It is impressive that 79% of patients with BD-I were previously diagnosed as suffering from schizophrenia. The Epidemiological Catchment Area study (ECA) (Eaton et al., 1981; Regier et al., 1984, 1988, 1993; Bourdon et al., 1992) reported a lifetime prevalence of 0.8% for BD-I (0.3–1.2%) and an annual prevalence of 0.6% (0.2–1%) with similar prevalence for males and females. The annual incidence was 0.4% (0.1–0.6%) of cases, which corresponds to approximately 3.2 (0.8–4.8) per 100,000 residents. The median age at onset was 18 years. A reanalysis of the ECA data with the addition of subthreshold bipolarity produced a total lifetime prevalence of 6.4% with 0.5% being a lifetime prevalence of BD-II (Judd and Akiskal, 2003). The National Comorbidity Survey (NCS) (Kessler et al., 1993, 1994a, 1994b, 1995, 1996, 1997b; Blazer et al., 1994; Wittchen et al., 1994; Warner et al., 1995; Kendler et al., 1996; Magee et al., 1996) reported a lifetime prevalence of 1.7% for BD-I and an annual prevalence of 1.3% with similar prevalence for males and females. The median age at onset was 21 years. The NCS-R (Kessler et al., 2004, 2005a, 2005b, 2012a, 2012b; Kessler and Merikangas, 2004; Merikangas et al., 2007; Angst et al., 2010; Nierenberg et al., 2010) reported a lifetime prevalence of 1.0% for BD-I and an annual prevalence of 0.6% with again similar prevalence for males and females. The median age at onset was 19 years. For BD-II the lifetime prevalence was 1.1% and the annual prevalence was 0.8% with similar prevalence for males and females. The median age at onset was 20 years. There was a small difference between males and females in the BD-II rates, with female rates being slightly higher. The Cross National Collaboration Group study included data from 7 countries (US, Canada, Puerto Rico, Germany, Taiwan, South Korea and New Zealand) (Weissman et al., 1996) and reported variable rates for different countries, but overall the rates seemed moderately consistent cross-nationally. The Zurich study (Angst et al., 1984, 2005b; Wicki and Angst, 1991) reported an annual prevalence of BD-I of 0.7% and a lifetime prevalence for the bipolar spectrum of 5.5%. The Nottingham study (Brewin et al., 1997) reported the 2-year incidence rate reported for BD was 0.005%, which corresponds to an annual incidence of 2.5/100,000. The Netherlands study (Bijl et al., 2002; Regeer et al., 2002; ten Have et al., 2002) suggested a lifetime prevalence of BD equal to 2.0%. The annual incidence was equal to 2.7/100,000. There was no significant difference between males and females. The Australian National Survey reported the year prevalence of euphoric BD (combined BD-I and BD-II) was 0.5% (Mitchell et al., 2004). The Butajira study from Ethiopia reported a lifetime prevalence of BD-I disorder of 0.5%, with the rate being 0.6% for males and 0.3% for females. The mean age of cases was 29.5 years, with no significant sex difference. The mean age of first recognition of illness was 22 years. There was no significant sex difference in the age at onset of manic or depressive phases (Negash et al., 2005). A more recent cross-sectional, face-to-face, household survey in 11 countries in the Americas, Europe, and Asia reported that the lifetime prevalence was 0.6% for BD-I and 0.4% for BD-II, while the year prevalence was 0.4% and 0.3%, respectively (Merikangas et al., 2011). A few studies report on the epidemiology of bipolar spectrum and suggest that in the adult population the lifetime prevalence of the bipolar spectrum is between 3 and 8.3% (Weissman and Myers, 1978; Angst et al., 1984, 2005b; Oliver and Simmons, 1985; Wicki and Angst, 1991; Heun and Maier, 1993; Angst, 1998; Szadoczky et al., 1998; Hirschfeld et al., 2003a, 2003b; Judd and Akiskal, 2003; Moreno and Andrade, 2005; Faravelli et al., 2006; Kessler et al., 2006).

Overall and according to the WHO, BD affected an estimated 29.5 million persons worldwide in 2004 (WHO, 2008). The available data suggest that the life prevalence of BD-I is around 1%, with probably a similar rate concerning BD-II. The full bipolar spectrum probably has lifetime prevalence around 5%. There are no striking differences between genders. However, these figures should be considered as only indicative, since important discrepancies exist among studies and countries, as mentioned above. The rather small difference between annual and lifetime rates suggests that BD is both an episodic but also a chronic mental disorder with high recurrence rates.
The various studies from around the world suggest that the age at onset is late adolescence or early adulthood, around the age of 18 to 20 years, but also they suggest that approximately one-fourth of BD patients have the onset before the age of 13 (Perlis et al., 2004; Post et al., 2008; Stringaris et al., 2010; Merikangas et al., 2012), and among other things this suggests caution in the use of stimulants for the treatment of children with ADHD and worse overall outcome (Agnew-Blais and Danese, 2016).

Staging

After the introduction of operationalized diagnostic criteria for all contemporary classification systems, the need to define and rate seriousness, progression, changes in physiology, and damage made and the extent and the specific characteristics of the disease emerged. Staging is the term that defines this procedure (Fountoulakis, 2015a). The field in medicine where staging is most successful and enjoys great importance is that of clinical oncology. Since 1993 there were many attempts to arrive at a staging model for psychiatry (Fava and Kellner, 1993; Yung and McGorry, 1996, 2007; McGorry et al., 2006, 2007, 2010; McGorry, 2007, 2010b; Vieta et al., 2011; Cosci and Fava, 2013). The concept of staging if and when applied has a number of implications. Almost by definition it suggests that early stages are easier to treat, while later stages are rather refractory to treatment. Thus these later stages might need the application of treatment options with more adverse events, higher risk, and less overall benefit (Post et al., 2010) or some kind of palliative care should be considered.

The earliest research contribution to the effort of staging BD was the description of the stages of mania in the early 1970s when Carlson and Goodwin not only described discrete stages in the development and course of acute mania, but also they described a rollback phenomenon that is the clinical condition improves by manifesting the same stages but at a reverse order (Carlson and Goodwin, 1973). Up to n, 5 major staging models have been proposed for BD (Berk et al., 2007a, 2007b; Kapczinski et al., 2009; Post, 2010; Post et al., 2012; Cosci and Fava, 2013; Frank et al., 2014). Although there is some support for the proposed staging models, the research base is thin, the heterogeneity of the data is significant, and the studies include small sample sizes. A number of vicious logical cycles could be in place. Most of the data are cross-sectional (Kapczinski et al., 2014), and the need for a transdiagnostic and longitudinal research approach is prominent (Lin et al., 2013).

The data so far support the presence of an asymptomatic at-risk phase and a nonspecific prodromal phase. This prodromal phase seems to be common for a number of mental disorders, and prediction is extremely difficult on the basis of current knowledge. The literature is also supportive of the presence of an early stage of the full-blown illness, during which the episodes are well defined and there are no or very few inter-episode residual symptoms, good response to treatment, and little disability. It also supports the presence of a late stage that is associated with a more chronic and refractory disease, probably with depressive predominant polarity, psychotic features, and significant disability. It is disappointing that there is little research on the treatment effect at late stages (Berk et al., 2012), with only a few exceptions (Torrent et al., 2013). The use of biomarkers might, in the near future, facilitate the validation of staging systems and their therapeutic utility (Vieta, 2015).

Therapeutic Issues

The treatment of BD is complex (Fountoulakis, 2008) and for several decades the treatment of BD was theoretically based on the concept of mood stabilizers. This term was originally used during the 1950s to refer to a combination of amphetamine and a barbiturate to treat patients with neurotic instability but not patients with BD. The term mood normalizer was proposed by Mogens Schou for lithium (Schou, 1963), but eventually the stabilizer concept prevailed, probably because the focus of research with lithium was on the long-term prophylaxis.

During the last decade, however, there was a plethora of data, mainly because of the introduction of atypical antipsychotics as possible treatment options. However, this gave the chance also for older substances to be tested under rigorously defined research conditions. These studies revealed that the treatment could be more complex than previously believed and several issues exist. The clinician should be aware of many specific indications, contraindications, details, and traps (Fountoulakis et al., 2005, 2007a, 2007b, 2008, 2015a; Gonda et al., 2009).

The concept of mood stabilizers is disputed, since the data do not support an equally wide efficacy for different compounds like lithium, valproate, or carbamazepine to warrant such a label. On the contrary, there are negative data concerning specific areas, while our knowledge is quite limited concerning other areas. One particular problem, which only recently has been acknowledged, is that probably some facets of the disorder are refractory to treatment. Another important problem is that not only is the evidence limited concerning the treatment of specific facets and issues of BD (Fountoulakis, 2010; Fountoulakis et al., 2012, 2013), but also continued scientific training and reading is inadequate. Thus, research findings are not making it to everyday clinical practice. Focused educational intervention might be necessary to change this attitude. Part of this problem is reflected in the common practice among clinicians to use medication on the basis of a class effect. This means that they consider that a whole class of medications possesses a specific action. This class effect is often considered in combination with a syndromal approach, which means that irrespective of the nosological entity, a specific kind of symptoms respond to a specific class of medication.

For example, according to this combined approach all antipsychotics are equally effective against psychotic symptoms irrespective of disorder diagnosis, and the same holds for all antidepressants against depressive symptoms. This is the most commonly used approach in everyday clinical practice and has a huge impact on public mental health. Its significant advantage is that it provides the clinician with fast and simple rules to determine treatment. On the other hand, its greatest problem is that this approach has been proven false, especially in the case of BD where it is specifically combined with a very broad mood stabilizers concept (Fountoulakis et al., 2011). The extent to which this truly influences the everyday clinical practice worldwide is unknown but is probably significant. The extent to which this concept influences the outcome of BD is similarly unknown, although theoretically a more evidence-based approach should improve the overall outcome of BD patients.

It is important to note that with the introduction of the second-generation antipsychotics, antipsychotics became a cornerstone for the treatment of BP also according to treatment guidelines. On the contrary, a number of studies showed that the usefulness of antidepressants that were traditionally seen in Europe as a meaningful treatment option for bipolar depression is questionable (Pacchiarotti et al., 2013b). Additionally, the maintenance/long-term treatment became more complex, since it has proven that agents previously considered to be mood stabilizers were essentially more effective for one pole than the other (Popovic et al., 2012). This is definitely a fast-moving field,
and it is certainly difficult for a clinician to follow new findings and incorporate them into his or her everyday clinical practice.

On the other hand, the data on the usefulness of psychosocial interventions are limited, and their value against specific symptoms and problems remains unknown (Fountoulakis et al., 2009; Reinares et al., 2014).

One very special issue is agitation and its treatment. There is a significant number of published papers on the pharmacological (Citrome, 2004; Battaglia, 2005; Nordstrom and Allen, 2007; Nordstrom et al., 2012) but also on the nonpharmacological treatment of agitation (Marder, 2006; Amann et al., 2013), while recently a consensus paper on how to treat agitation in BD patients has been published (Garriga et al., 2016).

Special Issues

Since BD is characterized by phases that respond to a completely different way to treatment, it is of outmost importance to define phases of treatment and comorbidity (Fountoulakis, 2015f; Vrublevska and Fountoulakis, 2015).

It is relatively easy to define acute either manic/hypomanic or depressive episodes. However the terms continuation and maintenance are often interchangeably used in the terminology of RCTs and thus create significant confusion (Frank et al., 1991; Ghaemi et al., 2004). Continuation treatment lasts up to 12 months, and the duration depends on an estimate of when the episode would have remitted spontaneously. On the other hand, maintenance treatment starts after remission and thus after continuation and covers several years. Although a strict definition demands at least 2 months of sustained recovery for the patient to be considered in remission (American Psychiatric Association, 2000), the reality is that only a minority of patients in RCTs achieve complete remission. This makes the use of terms (relapse vs recurrence and continuation vs maintenance) problematic. In the nomenclature of RCTs, the terms relapse and maintenance are preferred. The FDA policy is to accept data, based on patients in remission for <2 months, thus adding to the continuation vs maintenance confusion of definitions (Calabrese et al., 2006).

The term relapse is also problematic in BD. A narrow definition suggests that relapses are of the same polarity with the index episode, and they tend to occur within the first months of improvement. However with a polymorphic disease like BD, it might be inappropriate not to include in relapses the early emergence of an episode of the opposite pole. It is important to note that licensing authorities accept the latter approach.

The acute episode after which BD patients are enrolled into maintenance trials is called the index episode. To date, most maintenance trials follow an enriched design, that is, only patients who have remitted under the investigation agent during the acute phase are enrolled into the double blind maintenance phase. This design has interesting consequences, since it biases the sample both towards a specific predominant polarity and also towards a favorable response to the specific agent (Cipriani et al., 2014). These 2 comments constitute important limitations in the generalizability of the results and make very difficult the translation of research findings into the everyday clinical practice in the case of patients who, rather than continued on the same medication, are switched to another one during the maintenance phase (Grande et al., 2014).

Economic Considerations

It is very difficult to calculate the true economic cost of a polymorphic disorder like BD. The cost includes direct spending due to hospitalizations and medication, cost of supporting infrastructure of the various National Health Systems, somatic comorbidity, indirect and out-of-pocket costs, as well as the absenteeism from work and premature death (Fountoulakis, 2015g).

For the UK the total cost has been estimated to be £2.055 billion in 1999/2000 prices (Das Gupta and Guest, 2002). It is interesting that 86% of this cost was the result of productivity loss and unemployment, while only 10% was cost related with NHS services. Medication costs in primary care were approximately £8.5 million, corresponding to 0.4% of total cost and 4.3% of NHS cost. A more recent study showed that the NHS cost has been doubled, with medication costs rising disproportionally and reaching £25.2 million, that is 7.4% of NHS cost (Young et al., 2011). In the US, the cost of medication was rather very low during the 1990s and reached 2% of the total cost after 2000, but the exact figure is unknown (Wyatt and Henter, 1995; Begley et al., 2001; McCrone et al., 2008; Dilsaver, 2011). In Germany the total annual cost was calculated to be 5.8 million euros, with 98% being due to productivity loss (Runge and Grunze, 2004). Similar estimations come from other areas of the world, with the calculations basing on different prevalence rates and health systems and societal structures (Hakkaart-van Roijen et al., 2004; Fisher et al., 2007; Ekman et al., 2013).

It is clear that the cost of medication treatment constitutes a very small percentage of the total cost of BD (Hidalgo-Mazzei et al., 2015). Medication treatment is, however, the intervention with the greatest impact on the course of the illness and the intervention that makes possible other actions to exist by resolving acute episodes in a reliable way. Furthermore, it decreases the long-term impairment and improves insight and collaboration by the side of the patient. Nevertheless, it also seems clear that medication cost is disproportionally rising, at least in some places of the world and for periods of time, and this constitutes an additional factor of concern. One should be very careful, because a small reduction in medication costs as a consequence of giving priority to cheaper agents and disregarding clinical data could easily result in a significant and disproportional increase in the total cost of the disease.

The CINP workgroup decided not to take medication cost or availability of medication into consideration. It chose to rely exclusively on clinical data, leaving the cost and availability issues to local and national groups who would like to implement the CINP guidelines in a specific country or region and would be obliged to take into consideration also the local sociopolitical and economic environment.

Methodology

The workgroup decided after consensus to follow the following methodology for the development of the treatment algorithm with the steps listed below:

a) Defining the sources of data and choosing which to use
b) Development of a grading method
c) Search of the literature
d) Grading of the data
e) Defining the clinical parameters to take into consideration
f) Development of a precise treatment algorithm
g) Development of the clinical guideline

Defining the Sources of Data and Choosing Whom to Use

Randomized Controlled Trials (RCTs)

This type of study constitutes the main source of evidence. Without them it is impossible to say whether an agent or
method possesses efficacy or not, since it is impossible to control for confounding variables any other way. Randomization of patients to parallel treatment arms, including placebo, allows one to attribute confidently observed differences in efficacy between these arms to the effects of the treatments (McAlister et al., 1999a, 1999b; Pocock and Elbourne, 2000).

However, with BD there is an important problem. Because of ethical, practical, and most often economic limitations, it is not always possible to apply the RCT method across all facets and issues of BD. For many of them, data are available only on the basis of posthoc analyses or secondary outcomes. Another major limitation is that this kind of study is very expensive, and thus most of them are industry sponsored with the objective to obtaining the label for the specific product. Although such trials follow the regulatory agencies’ design, they have limitations on generalizability. Also it is well known that only a small minority of highly selected patients is eligible to enter these studies, and thus the generalizability of results is problematic. The study duration is often relatively short and this is true also for maintenance trials, in part because the existence of a placebo arm carries a high attrition rate.

An important pitfall concerns the actual results of the RCT, which often are different from those published. It is not unusual that when a trial is negative on the basis of its primary outcome, a publication is done on the basis of positive secondary outcomes. This is essentially misleading, but fortunately it is a phenomenon that has been less frequent during the recent years.

Meta-Analysis

Meta-analysis is a technique that combines data (not simply pooled) from several trials and returns a specific quantitative answer to a specific question that usually is which treatment is superior in comparison with others or placebo. Sometimes but not always it also provides an absolute estimate of the treatment effect size.

There are a number of significant limitations for the meta-analytic methods (Huf et al., 2011a, 2011b). There is a need for the studies included in the meta-analysis to be similar in design and with sufficient information being available. Meta-analytic studies often violate this rule and include a diverse group of trials in the analysis (e.g., studies of monotherapy and combination treatment, fixed and flexible dosage studies, etc.) with unknown consequences (Fountoulakis et al., 2014).

Common problems of meta-analyses include small sample sizes, inadequate power, study heterogeneity, lack of extractable data, lack of interchangeable measurement instruments and definitions of outcomes, and other differences in the design of studies whose data are utilized. Negative trials are often not published and this poses an important limitation to the meta-analytic approach. Today the trials sponsored by official foundations can be traced in trial repositories. However, their detailed results are unlikely to be retrieved and even if they are retrieved, they have not undergone the essential peer review process (which adds credibility) like those published, and their quality could be questionable.

The question whether it is appropriate to use data from the largest possible number of disparate studies vs the need for including data only from essentially identical studies is a matter of debate and has also been discussed specifically concerning acute mania trials where these different approaches gave conflicting results (Yildiz et al., 2010; Cipriani et al., 2011). Practically, all meta-analytical studies utilize compromises to deal with the above problems and limitations. These compromises might have profound effects on the validity and generalizability of their results (Noble, 2006; Mismetti et al., 2007; Huf et al., 2011b).

Some authors consider meta-analysis to be on the top of the evidence-based pyramid of data sources. This approach suggests that its results are superior to the results of the RCTs, and subsequently it is meant that a positive meta-analysis is superior to a number of negative RCTs even in the case of the absence of any positive RCTs. However, the authors of the current paper consider that in most cases meta-analysis has a lower evidence level than RCTs and therefore graded it below them, primarily because of a significant number of limitations and drawbacks that often make the results of meta-analysis equivocal.

Open Trials

Open trials do not utilize the double blind design and they are not placebo controlled. Therefore they are easier to conduct, their number and size are greater, and the quality of patients enrolled is closer to that seen in the real world. Their great limitation is that their open nature induces significant bias, and thus they are by no means considered to be even close to being the gold standard or a reliable source of evidence data. Their role should be considered complementary. It is not unusual that treatment modalities with many positive open trials fail in RCTs, with topiramate in BD being a striking example (Suppes, 2002).

Review and Opinion Papers

Review and opinion papers mainly constitute educational tools, which attempt to translate the research findings into ready-to-use tools for the everyday clinical practice. They are extremely useful for the average clinician; however, they usually echo the opinion of the author, and thus they might contain significant bias. Their overall reliability and validity is questionable and only a few add significantly to our understanding by critically analyzing the existing data. Their ever-increasing number in the literature might constitute a problem, since they often obscure research findings by reproducing widely established biases and misconceptions. This is an important problem especially in the field of BD treatment.

Sources to Include

The authors decided by consensus to include only RCTs and meta-analyses in the development of the current treatment algorithm, since they have the highest validity for judgment. The authors reserved the privilege to judge and use the second and third source on an individual basis and according to their research and clinical experience for the latter steps of the algorithm where a Delphi method to arrive at decisions was utilized.

Development of a Grading Method

The authors decided to develop a grading method for the evaluation of available data concerning the treatment of BD. Such methods have existed since the early 1980s (Fletcher and Spitzer, 1980), but the de novo development of such a method was judged to be absolutely necessary, because the existing grading methods were not sufficiently appropriate for use in this particular set of data. In the frame of this process, the most widely accepted grading methods were studied, and their advantages and disadvantages were identified and taken into consideration in relationship to the specific needs of the current study. All grading methods include a method to assess the quality of data and a method to arrive at recommendations on the basis of the extent to which we can be confident that the desirable effects of an intervention outweigh the undesirable effects. The values
and preferences factor as well, but the cost was not taken into consideration by the workgroup.

Starting in 1992, 5 steps were developed to summarize the process of individual-level decision making and they were published in 2005 (Dawes et al., 2005). They include:

a. The formulation of a precise and answerable question and avoiding uncertainty and vague statements (Richardson et al., 1995; Schlosser et al., 2007).
b. The performance of a systematic search and retrieval of the evidence available (Rosenberg et al., 1998).
c. The critical review and classification of the retrieved evidence with the recognition of the presence of systematic errors, various types of bias, confounders, reliability and validity issues, etc. The clinical significance and the generalizability of the results should also be taken into account (Parkes et al., 2001; Horsley et al., 2011).
d. Application of results in practice.
e. Evaluation of performance (Jametvedt et al., 2003, 2006a, 2006b; Ivers et al., 2012).

It is important to assess the quality of the evidence that comes from the sources described above. The quality assessment is based on the strength of their freedom from the various biases that beset medical research. In this frame, triple-blind, placebo-controlled trials with allocation concealment and complete follow-up involving a homogeneous patient population and medical condition should be considered to constitute the highest grade, while case reports should be considered to constitute the lowest grade. Expert opinion should not be considered to be a source of evidence, although it could be a valuable tool for the development of guidelines (Tonelli, 1999).

Until recently there were a number of grading systems for assessing the quality of evidence that were developed by different organizations. One of them is the U.S. Preventive Services Task Force (U.S. Preventive Services Task Force, 1989; Sherman et al., 2011) and another system is the Oxford (UK) Center for Evidence Based Medicine Levels of Evidence, which also is useful for the grading of diagnostic tests, prognostic markers, or harm (Oxford (UK) Center for Evidence Based Medicine Levels of Evidence Working Group) and constituted the basis for the use of the BCLC staging system for diagnosing and monitoring hepatocellular carcinoma in Canada (Paul et al., 2012). Another method to grade data is the Patient Outcomes Research Team (PORT) method (Lehman and Steinwachs, 1998), which has been used by the World Federation of Societies of Biological Psychiatry for the development of the WFSBP guidelines (Grunze et al., 2002, 2003, 2004). In 1992 the Agency for Health Care Policy and Research and the National Institute of Mental Health established a PORT for Schizophrenia at the University of Maryland School of Medicine and the Johns Hopkins University School of Public Health. The PORT investigators adopted the criteria on levels of evidence used for development of the Agency for Health Care Policy and Research Depression Guidelines.

The most detailed and precise modern method seems to be the GRADE method (short for Grading of Recommendations Assessment, Development and Evaluation) for the development of guidelines (Guyatt et al., 2008b; Jaeschke et al., 2008), which clearly separates quality of evidence from level of recommendation and suggests it is necessary to include a clear question that should include all 4 components of clinical management (patients, an intervention, a comparison, and the outcomes of interest) (Oxman and Guyatt, 1988) and to grade the outcomes into those who are critical for the decision making and those who are not (Schunemann et al., 2006). In this frame, the assessment of the quality of evidence is important, since it reflects the confidence whether the effect is adequate to support recommendations. The determinants of quality are study limitations, inconsistency of results, indirectness of evidence, imprecision, and reporting bias (Guyatt et al., 2010a, 2011b, 2011c, 2011d, 2011e, 2013). There is some option to upgrade the quality when the effect size is very high (Guyatt et al., 2011f). The GRADE method provides guidance to grade the data from a variety of sources (Guyatt et al., 2008a), but it is not sensitive for datasets that focus solely on RCTs like the dataset of the current workgroup. According to the GRADE grading system, all the data included in the current effort to develop guidelines are of high quality. From the limitations recognized by the GRADE (lack of allocation concealment, lack of blinding, large losses to follow-up, failure to adhere to an intention to treat analysis, and stopping early for benefit failure to report outcomes), only large losses to follow-up and stopping early for benefit or failure to report outcomes could be applicable to the current study. A comparison of all the grading methods is shown in Table 3.

Table 3. Comparative Presentation of Different Grading Methods

<table>
<thead>
<tr>
<th>USPSTF</th>
<th>OCEBM</th>
<th>GRADE</th>
<th>PORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I: Evidence obtained from at least one properly designed randomized controlled trial. Level II-1: Evidence obtained from well-designed controlled trials without randomization.</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>High quality</td>
<td>Level A: Good research-based evidence, with some expert opinion, to support the recommendation</td>
</tr>
<tr>
<td>Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group. Level II-3: Evidence obtained from multiple time series designs with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Medium quality</td>
<td>Level B: Fair research-based evidence, with substantial expert opinion, to support the recommendation</td>
</tr>
<tr>
<td></td>
<td>Nonrandomized controlled cohort/ follow-up study</td>
<td>Low quality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case-series, case-control studies, or historically controlled studies</td>
<td>Very low quality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mechanism-based reasoning</td>
<td></td>
<td>Level C: Recommendation based primarily on expert opinion, with minimal research-based evidence, but significant clinical experience</td>
</tr>
</tbody>
</table>
The recommendation methods constitute a step forward and are determined by the balance of risk vs benefit of the intervention and the level of evidence on which this information is based. A comparison of the recommendation methods of the U.S. Preventive Services Task Force uses (Sherman et al., 2011) that utilizes a 5-levels system and the GRADE system that has only 2 categories concerning recommendations and characterizes them as strong (conditional) and weak (discretionary) (Guyatt et al., 2008b, 2008c) and also considers cost (Brunetti et al., 2013) is shown in Table 4.

As defined previously, only RCTs were taken into consideration, a fact that puts all the data at the highest grading according to all systems. However, the workgroup was concerned about a number of issues, including inconsistency of results between RCTs, conflicting results between RCTs and meta-analyses, issues explored only on the basis of secondary outcomes, etc. After recognizing all these sources of problematic quality, 32 individual scenarios were identified and are listed in Table 5. Afterwards they were ranked after consensus and grouped into levels. Two solutions were proposed. The ranking the 4- and 5-levels solution, and the final grading system are shown in Table 6. The description of the grading and the recommendation systems are shown in Table 7.

At this point it is important to note that the absence of evidence is not identical with the presence of negative data.

Table 4. Comparative Presentation of Recommendation Methods

<table>
<thead>
<tr>
<th>USPSTF</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A: Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks.</td>
<td>Strong</td>
</tr>
<tr>
<td>Level B: At least fair scientific evidence suggests that the benefits of the clinical service outweighs the potential risks.</td>
<td>Weak</td>
</tr>
<tr>
<td>Level C: At least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations.</td>
<td></td>
</tr>
<tr>
<td>Level D: At least fair scientific evidence suggests that the risks of the clinical service outweighs potential benefits.</td>
<td></td>
</tr>
<tr>
<td>Level I: Scientific evidence is lacking, of poor quality, or conflicting, such that the risk versus benefit balance cannot be assessed.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation for the Development of Guidelines; OCEBM, Oxford (UK) Center for Evidence Based Medicine; PORT, Patient Outcomes Research Team; USPSTF, U.S. Preventive Services Task Force.

Table 5. The 32 Different Scenarios That Were Identified, Listed, and Graded

<table>
<thead>
<tr>
<th>Primary Outcome Scenarios</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. At least 1 positive 2-active arm RCTs vs placebo exist, plus positive 1 active arm RCTs. No negative RCTs</td>
<td></td>
</tr>
<tr>
<td>2. At least 2 positive RCTs vs placebo exist. No negative RCTs</td>
<td></td>
</tr>
<tr>
<td>3. One positive RCT vs placebo exists. No negative RCTs</td>
<td></td>
</tr>
<tr>
<td>4. Some positive plus some negative RCTs vs placebo. Positive all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>5. Some positive plus some negative RCTs vs placebo. Mixed results from meta-analyses</td>
<td></td>
</tr>
<tr>
<td>6. Some positive plus some negative RCTs vs placebo. Negative all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>7. More positive but some negative RCTs vs placebo. Positive all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>8. More positive but some negative RCTs vs placebo. Mixed results from meta-analyses</td>
<td></td>
</tr>
<tr>
<td>9. More positive but some negative RCTs vs placebo. Negative all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>10. More negative but some positive RCTs vs placebo. Positive all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>11. More negative but some positive RCTs vs placebo. Mixed results from meta-analyses</td>
<td></td>
</tr>
<tr>
<td>12. More negative but some positive RCTs vs placebo. Negative all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>13. Only 1 negative trial exists vs placebo</td>
<td></td>
</tr>
<tr>
<td>14. Only negative trials exist vs placebo. Meta analyses all negative</td>
<td></td>
</tr>
<tr>
<td>15. Only negative trials exist vs placebo. Meta analyses all positive</td>
<td></td>
</tr>
<tr>
<td>16. Only negative trials exist vs placebo. Meta analyses mixed</td>
<td></td>
</tr>
<tr>
<td>Posthoc scenarios</td>
<td></td>
</tr>
<tr>
<td>17. Only 1 positive from posthoc analyses vs placebo</td>
<td></td>
</tr>
<tr>
<td>18. At least 2 positive from posthoc analyses vs placebo</td>
<td></td>
</tr>
<tr>
<td>19. Only 1 negative from posthoc analyses vs placebo</td>
<td></td>
</tr>
<tr>
<td>20. At least 2 negative from posthoc analyses vs placebo. Positive all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>21. At least 2 negative from posthoc analyses vs placebo. Negative all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>22. At least 2 negative from posthoc analyses vs placebo. mixed meta-analyses</td>
<td></td>
</tr>
<tr>
<td>23. More negative than positive from posthoc analyses vs placebo. Positive all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>24. More negative than positive from posthoc analyses vs placebo. Negative all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>25. More negative than positive from posthoc analyses vs placebo. mixed meta-analyses</td>
<td></td>
</tr>
<tr>
<td>26. More positive than negative from posthoc analyses vs placebo. Positive all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>27. More positive than negative from posthoc analyses vs placebo. Negative all meta-analyses</td>
<td></td>
</tr>
<tr>
<td>28. More positive than negative from posthoc analyses vs placebo. mixed meta-analyses</td>
<td></td>
</tr>
<tr>
<td>Other scenarios</td>
<td></td>
</tr>
<tr>
<td>29. Only 1 failed trial, no other data</td>
<td></td>
</tr>
<tr>
<td>30. At least 2 failed trials, no other data</td>
<td></td>
</tr>
<tr>
<td>31. Only prematurely terminated trials</td>
<td></td>
</tr>
<tr>
<td>32. Although trials exist, the data are not available in a way to arrive at reliable conclusions</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. The Ranking, the 4- and 5-levels Solution, and the Final Grading System for the 32 Different Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Rank</th>
<th>5-Grade</th>
<th>4-Grade</th>
<th>Grade system</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 positive 2-active arm RCTs vs placebo exist, plus positive 1 active arm RCTs. No negative RCTs.</td>
<td>1</td>
<td>A</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>At least 2 positive RCTs vs placebo exist. No negative RCTs</td>
<td>2</td>
<td>A</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>One positive RCT vs placebo exists. No negative RCTs</td>
<td>3</td>
<td>B</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>More positive but some negative RCTs vs placebo. Positive all meta-analyses</td>
<td>4</td>
<td>B</td>
<td>B</td>
<td>2</td>
</tr>
<tr>
<td>Some positive plus some negative RCTs vs placebo. Positive all meta-analyses</td>
<td>5</td>
<td>B</td>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>More negative but some positive RCTs vs placebo. Positive all meta-analyses</td>
<td>6</td>
<td>C</td>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>Only negative trials exist vs placebo. Meta analyses all positive</td>
<td>7</td>
<td>D</td>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>At least 2 positive from posthoc analyses vs placebo</td>
<td>8</td>
<td>D</td>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>Only 1 positive from posthoc analyses vs placebo</td>
<td>9</td>
<td>E</td>
<td>C</td>
<td>3</td>
</tr>
<tr>
<td>Some positive plus some negative RCTs vs placebo. Mixed results from meta-analyses</td>
<td>10</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>More positive but some negative RCTs vs placebo. Mixed results from meta-analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More positive than negative from posthoc analyses vs placebo. Positive all meta-analyses</td>
<td>11</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>At least 2 negative from posthoc analyses vs placebo. Positive all meta-analyses</td>
<td>12</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>More positive than negative from posthoc analyses vs placebo. Mixed meta-analyses</td>
<td>13</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>Only negative trials exist vs placebo. Meta analyses mixed</td>
<td>14</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>At least 2 negative from posthoc analyses vs placebo. Mixed meta-analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More negative than positive from posthoc analyses vs placebo. Mixed meta-analyses</td>
<td>15</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>Some positive plus some negative RCTs vs placebo. Negative all meta-analyses</td>
<td>16</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>More positive but some negative RCTs vs placebo. Negative all meta-analyses</td>
<td>17</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>More negative but some positive RCTs vs placebo. Negative all meta-analyses</td>
<td>18</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>Only 1 negative trial exists vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only negative trials exist vs placebo. Meta analyses all negative</td>
<td>19</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>Only 1 negative from posthoc analyses vs placebo</td>
<td>20</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>At least 2 negative from posthoc analyses vs placebo. Negative all meta-analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More negative than positive from posthoc analyses vs placebo. Negative all meta-analyses</td>
<td>21</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>More positive than negative from posthoc analyses vs placebo. Negative all meta-analyses</td>
<td>22</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>Only prematurely terminated trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Although trials exist, the data are not available in a way to arrive at reliable conclusions</td>
<td>23</td>
<td>E</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>Only 1 failed trial, no other data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 2 failed trials, no other data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All treatment agents were graded also in terms of safety and tolerability. All combination options were graded at best with 2, since they put the patient at a higher risk for manifesting adverse events.

Search of the Literature

The workgroup decided that the PRISMA method (Hopewell et al., 2008; Liberati et al., 2009; Moher et al., 2009a, 2009b) should be followed in the search of the literature, which will include 3 kinds of papers:

i. RCTs (placebo controlled as well as clinical trials with an active comparator with the compounds used as monotherapy or add-on therapy).
ii. Posthoc analyses of RCTs
iii. Meta-analyses and review papers
iv. Treatment guidelines papers

The search strategies will include:

1. To locate RCTs, the combination of the words ‘bipolar,’ ‘manic,’ ‘mania,’ ‘manic depression,’ and ‘manic depressive’ and ‘randomized’ will be used.
2. Webpages containing lists of clinical trials will be scanned. These sites include http://clinicaltrials.gov and http://www.clinicalstudyresults.org as well as the official sites of all the pharmaceutical companies with products used for the treatment of BD.

3. Relevant review articles will be scanned and their reference lists will be utilized.
4. The MEDLINE will be searched with the combination of keywords ‘guidelines’ or ‘algorithms’ with ‘mania,’ ‘manic,’ ‘bipolar,’ ‘manic-depressive,’ or ‘manic depression.’
5. The treatment guidelines will also be scanned and their reference lists will be utilized.
6. Only papers in English language will be included.

Additionally, an unstructured search of the literature will be performed concerning the adverse events and other safety issues of treatment options.

The workgroup considered the fact that it is difficult to locate unpublished studies, especially old ones, and even more difficult to retrieve their results. Thus it was decided that the focus should be put mainly on published studies which are definitely peer reviewed, are of higher quality, and provide more details than meeting abstracts or report sheets. However, whenever an unpublished trial should be located, it is mentioned in the specific part of the manuscript. The authors decided not to seek for additional information concerning unpublished trials from manufacturers, because this might increase the retrieval bias.

Grading of the Data

The grading of the data will follow their retrieval and will be done according to the method developed and described in the
current paper. The grading will be included in the second paper concerning the CINP guidelines for BD

**Defining the Clinical Parameters to Take into Consideration**

In the real-world setting, the therapist encounters patients with specific clinical features that often determine the choice of treatment on the basis of clinical experience and wisdom rather than evidence. These features include the so-called core manic and core depressive features, psychotic features, anxiety, the co-occurrence of manic and depressive symptoms in a variety of combinations that often do not correspond to concepts accepted by modern classification systems, agitation, and rapid cycling. It is interesting to address the complete constellation of symptoms instead of a specific group. The problem is that the data often focus on the second rather than the first option. It is important also to consider the predominant polarity and subtype of BD (BD-I vs BD-II), the personal history of the patient, and more specifically previous response or refractoriness to treatment and adverse events (including switch).

The data will be scanned concerning the treatment of all the above conditions and modifiers and relevant conclusions will be made concerning whether they can be used as clinical cues for the selection of appropriate treatment.

**Development of a Precise Algorithm**

The development of a precise algorithm for experimental reasons will be the first task. This algorithm will be based exclusively on the evidence and will be the next step after the data and the interventions have been graded in terms of recommendation. This algorithm will be based on the data in a narrow and strict sense and might provide with very precise but limited treatment options for the everyday clinical practice. There will be no trade between the evidence-based approach and clinical utility; the first will be absolutely dominant. This algorithm will reflect the exact state of the art concerning hard data but will lack any clinical wisdom, and it is expected that its application in everyday clinical practice will be problematic. Therefore it should be considered as experimental, and clinicians who will wish to apply it in their clinical practice should do so by taking into consideration these advantages and disadvantages. The algorithm will be included in the second paper concerning the CINP guidelines for BD, and it will be accompanied by a detailed table with the grading recommendation of all available interventions during all the phases of BD and in relevance with the presence of specific clinical features.

At a later time point a software application will be developed by the CINP to assist with the use of the algorithm.

**Development of the Clinical Guideline**

The development of the guideline will follow after the data and the interventions have been graded and the precise algorithm has been developed. The guideline will be included in the third paper concerning the CINP guidelines for BD. The workgroup decided after consensus on the following rules for the development of the guidelines:

1. Overall the guideline should be based on existing research hard evidence, but also it should make sense for the everyday clinical practice and should be user friendly. Although their nature will be based on the evidence-based approach, this should not go too far concerning the interpretation of the research findings and the potential clinical implications.

**Table 7. Summary of the Method for the Grading of the Data and Recommendation as Decided by the Workgroup on the Basis of Both Efficacy and Safety Tolerability**

<table>
<thead>
<tr>
<th>Grading on Basis of Efficacy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Good research-based evidence, supported by at least 2 placebo controlled studies of sufficient magnitude and good quality.</td>
</tr>
<tr>
<td>Level 2</td>
<td>Fair research-based evidence, from one randomised, double-blind placebo controlled trial.</td>
</tr>
<tr>
<td>Level 3</td>
<td>Some evidence from comparative studies without placebo arm or from posthoc analyses.</td>
</tr>
<tr>
<td>Level 4</td>
<td>Inconclusive data or poor quality of RCT’s</td>
</tr>
<tr>
<td>Level 5</td>
<td>Negative data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grading on the basis of safety and tolerability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Very good tolerability, few side effects which are not enduring, they do not cause significant distress and are not life-threatening and they do not compromise the overall somatic health of the patient</td>
</tr>
<tr>
<td>Level 2</td>
<td>Moderate tolerability, many side effects which could be enduring, and cause significant distress but they are not life-threatening although they could compromise the overall somatic health of the patient. Agents with very good overall tolerability but with rare life-threatening adverse events, could be classified here only if the lethality risk can be essentially considered to be negligible with the application of procedures and protocols (e.g., laboratory testing, titration schedules, etc.)</td>
</tr>
<tr>
<td>Level 3</td>
<td>Poor tolerability, many side effects which are enduring, cause significant distress, compromise the overall somatic health of the patient or are life-threatening. Agents with moderate overall tolerability and rare life-threatening adverse events should be classified here even in cases the lethality risk can be essentially considered to be negligible with the application of procedures and protocols (e.g., laboratory testing, titration schedules, etc.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations for treatment (combination of efficacy and safety/tolerability)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Level 1 or 2 for efficacy and 1 or safety/tolerability</td>
</tr>
<tr>
<td>Level 2</td>
<td>Level 1 or 2 for efficacy and 2 for safety/tolerability</td>
</tr>
<tr>
<td>Level 3</td>
<td>Level 1 or 2 for efficacy and 1 or safety/tolerability</td>
</tr>
<tr>
<td>Level 4</td>
<td>Level 4 for efficacy or 3 for safety/tolerability</td>
</tr>
<tr>
<td>Level 5</td>
<td>Level 5 for efficacy (not recommended)</td>
</tr>
</tbody>
</table>
ii. Agents and treatment modalities with proven efficacy across all 3 phases of the illness (acute mania, acute bipolar depression, and maintenance phase concerning the prevention of both manic and depressive episodes) should be given priority.

iii. No economic and availability issues will be taken into consideration. National bodies that might wish to utilize the CINP guidelines could add such analyses tailored to the specific country or region.

Discussion

The current paper sets the frame for the development of the CINP treatment guidelines for BD. It contains all the background information, including important clinical features, staging methods, and important treatment issues and details. It also elaborates on the methodology to be used and describes the development of a grading system that will be suitable for use with the kind of data under consideration.

The overall aim of the workgroup was to push guidelines one step further by evaluating the available data in depth and also by identifying clinical issues that need specific interventions that could be supported by the data. A significant contribution is expected to be the precise experimental algorithm that will constitute an option for further study.

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Statement of Interest

K.N.F. has received grants and served as consultant, advisor, or CME speaker for the following entities: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Pfizer, the Pfizer Foundation, Sanofi-Aventis, Servier, Shire, and others.

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H.G. within the last 3 years received grant/research support from: NIHR UK, MRC UK, NTW, and NHS Foundation Trust; receipt of honoraria or consultation fees from: Gedeon-Richter, Lundbeck, and Hofmann-LaRoche; and participated in a company-sponsored speaker’s bureau at BMS, Ferrer, Janssen-Cilag, Otsuka, Lundbeck, and Pfizer.

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The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 2: Review, Grading of the Evidence, and a Precise Algorithm

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Abstract

Background: The current paper includes a systematic search of the literature, a detailed presentation of the results, and a grading of treatment options in terms of efficacy and tolerability/safety.

Material and Methods: The PRISMA method was used in the literature search with the combination of the words ‘bipolar,’ ‘manic,’ ‘mania,’ ‘manic depression,’ and ‘manic depressive’ with ‘randomized,’ and ‘algorithms’ with ‘mania,’ ‘manic,’ ‘bipolar,’ ‘manic-depressive,’ or ‘manic depression.’ Relevant web pages and review articles were also reviewed.

Results: The current report is based on the analysis of 57 guideline papers and 531 published papers related to RCTs, reviews, posthoc, or meta-analysis papers to March 25, 2016. The specific treatment options for acute mania, mixed episodes, acute bipolar depression, maintenance phase, psychotic and mixed features, anxiety, and rapid cycling were evaluated with regards to efficacy. Existing treatment guidelines were also reviewed. Finally, Tables reflecting efficacy and recommendation levels were created that led to the development of a precise algorithm that still has to prove its feasibility in everyday clinical practice.

Conclusions: A systematic literature search was conducted on the pharmacological treatment of bipolar disorder to identify all relevant random controlled trials pertaining to all aspects of bipolar disorder and graded the data according to a predetermined
method to develop a precise treatment algorithm for management of various phases of bipolar disorder. It is important to note that the some of the recommendations in the treatment algorithm were based on the secondary outcome data from posthoc analyses.

**Keywords:** bipolar disorder, anticonvulsants, antidepressants, antipsychotics, evidence-based guidelines, lithium, mania, bipolar depression, mood stabilizers, treatment, clinical trials

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**Introduction**

The current paper is the second in the series of The International College of Neuro-Psychopharmacology papers concerning the development of a precise algorithm and clinical guidelines for the treatment of bipolar disorder (BD) in adults for use in primary and secondary care. It includes a systematic search of the literature and a detailed presentation of the results concerning placebo-controlled randomized trials for all phases and aspects of BD. It also includes the grading of treatment options in terms of efficacy and tolerability/safety as well as a precise algorithm that still has to prove its feasibility in everyday clinical practice.

**Materials and Methods**

As described in the first paper concerning the CINP treatment guidelines for BD, the workgroup decided that the PRISMA method (Hopewell et al., 2008; Liberati et al., 2009; Moher et al., 2009) should be followed in the search of the literature. The method included the search for 3 kinds of papers:

a. Randomized controlled trials (RCTs; placebo controlled as well as clinical trials with an active comparator with the compounds used as monotherapy or add-on therapy).

b. Posthoc analyses of RCTs.

c. Meta-analyses and review papers.

d. Treatment guidelines papers.

For this purpose, MEDLINE was searched to March 25, 2016 with the following search strategies:

1. To locate RCTs, the combination of the words ‘bipolar,’ ‘manic,’ ‘mania,’ ‘manic depression,’ and ‘manic depressive’ and ‘randomized’ was used.

2. Web pages containing lists of clinical trials were scanned. These sites included http://clinicaltrials.gov and http://www.clinicalstudyresults.org as well as the official sites of all the pharmaceutical companies with products used for the treatment of BP.

3. Relevant review articles were scanned and their reference lists were utilized (Srisurapanont et al., 1995; Yatham et al., 1997; Davis et al., 1999; Burgess et al., 2001; Macritchie et al., 2001, 2003; Bech, 2002, 2006; Rendell et al., 2003; Gijsman et al., 2004; Fountoulakis et al., 2005; Gao et al., 2005; Cipriani et al., 2006a, 2006b, 2011; Rendell et al., 2006; Smith et al., 2007; Fountoulakis et al., 2008, 2012, 2015a, 2015b, 2015c; Fountoulakis et al., 2008a, 2009b, 2012a, 2012d; Fountoulakis and Viesta, 2008; Yildiz et al., 2010; Nivoli et al., 2011; Tarr et al., 2011; Nivoli et al., 2012).

4. The MEDLINE was searched with the combination of keywords ‘guidelines’ or ‘algorithm’ with ‘mania,’ ‘manic,’ ‘bipolar,’ ‘manic-depressive,’ or ‘manic depression.’

5. The treatment guidelines were also scanned and their reference lists were utilized.

It is difficult to locate unpublished studies, especially old ones, and even more difficult to retrieve their results. Thus, the main focus of this paper was on published studies that would have been peer-reviewed, are typically of higher quality, and provide more details than meeting abstracts or conference reports. However, whenever an unpublished trial was located, it is mentioned in that specific part of the manuscript. The authors decided not to seek additional information concerning unpublished trials from manufacturers as this might increase the retrieval bias.

Eventually the efficacy data were graded on the basis of a method developed by the authors and described in the first paper of the CINP guidelines for BD, that is also shown in Table 1. Agents were graded on the basis of safety and tolerability, and these grades are also shown in Table 1.

The PRISMA chart of the search process is shown in Figure 1 concerning RCTs and in Figure 2 concerning guidelines. Ultimately the current report was based on the analysis of 57 papers related to guidelines and 569 published papers concerning RCTs or other relevant papers (reviews, posthoc, or meta-analyses).

**Efficacy Data**

**Acute Mania**

The data on monotherapy and combination treatment for acute mania are shown in Table 2. As well, the table also includes grading of efficacy data for various features of mania such as psychotic features, mixed features, agitation, etc., most of that was based on the posthoc analyses of RCTs.

**Monotherapy**

Lithium. The first study investigating the efficacy of lithium against acute mania was conducted in 1971, but it did not follow a methodology that is accepted today as scientific standard (Stokes et al., 1971). Since then 4 placebo-controlled RCTs using modern clinical trial methodology starting in 1994 have been published. All of them utilized a period of 3 weeks vs placebo, and if a comparator was included, there was an extension phase without placebo (Bowden et al., 1994, 2005b; Kushner et al., 2009; Keck et al., 2009).

Overall there are 5 RCTs supporting the efficacy of lithium in comparison with placebo in acutely manic or mixed BD patients. All 5 are positive and the results are consistent. The overall response rate suggests a rough number needed to treat (NNT) around 5 to 6. The therapeutic effect appears after 7 days of treatment, that is, later in comparison with antipsychotics. There are limited data about the effect of lithium on the core symptoms of mania, but there are some suggestive of an effect on psychotic features (Bowden et al., 2005b). Its effect specifically on mixed episodes is unknown, and a posthoc analysis (Swann et al., 1997) of one of these RCTs (Bowden et al., 1994) confirmed the efficacy of lithium only in classic manic but not mixed patients albeit the number of mixed patients was too small to allow firm conclusion.
It exerts a therapeutic effect on manic-psychotic symptoms, but probably there is no therapeutic effect on concomitant depressive symptoms. The drop-out rate in these trials was comparable with placebo with probably more patients on placebo withdrawing from the study because of lack of efficacy, while side effects were the more common reasons for withdrawal in patients taking lithium. The most common adverse events with lithium were nausea, vomiting, dizziness, headache, insomnia, asthenia, constipation, diarrhea, tremor, and weight gain.

Antiepileptics. Valproate—Limited data concerning the efficacy of valproate in acute mania exist from earlier studies (Emrich et al., 1980, 1981; McElroy et al., 1989). The first study with modern methodology on the efficacy and safety of valproate in the treatment of acute mania was published in 1991 (Pope et al., 1991). Since then 3 positive (Pope et al., 1991; Bowden et al., 1994, 2006) and 2 failed RCTs (Tohen et al., 2008b; Hirschfeld et al., 2010) were published. Another study on a heterogeneous sample consisting of bipolar spectrum disorder patients was negative (McElroy et al., 2010a). A posthoc analysis of one of the RCTs (Bowden et al., 1994) did not find any preferential effect for divalproex in classic vs mixed manic patients (Swann et al., 1997). Overall the data support the usefulness of valproate against acute mania, although a number of issues need clarification. Its effect on psychotic symptoms is unknown and there seems to be no effect on concomitant depressive symptoms. The NNT for response is probably around 10 and the therapeutic effect is present after 5 to 15 days. Although the dosages utilized in these studies were higher than those usually used in everyday clinical practice (15–30 mg/kg/d), they hardly achieved the target serum concentrations (50–100 microg/mL).

The most frequent adverse events were somnolence, nausea, dizziness, asthenia, constipation, twitching, and vomiting.

Carbamazepine—The earlier studies demonstrating the efficacy of carbamazepine in acute mania were published in the 1980s (Ballenger and Post, 1980; Post et al., 1987). Three large clinical trials using modern methodology have been published since 2000, all of that have confirmed the efficacy of carbamazepine (Weisler et al., 2004, 2005; Zhang et al., 2007).

Thus, the data concerning the efficacy and safety of carbamazepine at dosages 400 to 1600 mg/d and a mean plasma level of 8.9 μg/mL are robust. The reported NNT is approximately 5 for response, that starts around week 2. It is unknown whether carbamazepine has a beneficial effect on the core manic symptoms, in mixed patients, or against psychotic symptoms. There seems to be a beneficial effect on concomitant depressive symptoms only in mixed patients but not in manic patients (Weisler et al., 2005). The most frequent adverse events related to carbamazepine treatment were dizziness, nausea, somnolence, and an increase in total cholesterol that was composed of increases in both high-density and low-density lipoproteins.

Other antiepileptics—There is one negative (BIA-2093–203) and one fixed-dosage failed (BIA-2093–204) trial for eslicarbazepine (Robertson et al., 2010). Three unpublished RCTs (NCT00107926, NCT00107939, and NCT00099229) concerning the racemic mixture licarbazepine were also negative. There are 2 unpublished negative trials concerning lamotrigine in treating acute manic episodes (SCAA2008/GW609 and SCAA2009/GW610) (Goldsmith et al., 2003). Four trials con-

### Table 1. The Method for the Grading of Data on the Basis of Efficacy and Tolerability

<table>
<thead>
<tr>
<th>Grading on Basis of Efficacy</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendations for treatment (combination of efficacy and safety/tolerability)</td>
<td>Level 1 or 2 for efficacy and 1 for safety/tolerability</td>
<td>Level 1 or 2 for efficacy and 2 for safety/tolerability</td>
<td>Level 3 for efficacy and 1 or 2 for safety/tolerability</td>
<td>Level 4 for efficacy or 3 for safety/tolerability</td>
<td>Level 5 for efficacy (not recommended)</td>
</tr>
</tbody>
</table>
Concerning topiramate were all negative (Kushner et al., 2006). One small RCT evaluated the efficacy and safety of lamotrigine and gabapentin monotherapy vs placebo in 31 patients with refractory bipolar and unipolar mood disorders. Although lamotrigine differed significantly from placebo, gabapentin did not (Frye et al., 2000). Thus the data are negative for all other antiepileptics except for valproic acid and carbamazepine, that suggests that there is no class effect concerning antiepileptics in the treatment of BD (Rosa et al., 2009; Fountoulakis et al., 2011b).

Antipsychotics. The earlier studies on antipsychotics supported the efficacy of chlorpromazine (Klein, 1967) and suggested that antipsychotics acted more rapidly, although lithium was more globally effective (Shopsin et al., 1975).

Haloperidol—The efficacy and safety of haloperidol (up to 30 mg/d) was studied in 5 RCTs and all were positive (McIntyre et al., 2005; Smulevich et al., 2005; Young et al., 2009; Vieta et al., 2010a; Katagiri et al., 2012). The results suggest a NNT roughly equal to 5 to 8 for response. The therapeutic effect is apparent as early as day 4 (Goikolea et al., 2013a). However it is important to note that there is a signal for the induction of depression in the short term (Goikolea et al., 2013b). One study reported no effect on the core symptoms of mania. However, although haloperidol

Figure 1. PRISMA flowchart for RCTs literature search.
might be particularly efficacious in psychotic patients, its effect on mixed patients is unknown. Adverse events most commonly reported with haloperidol treatment were somnolence, extrapyramidal symptoms (EPS), weight gain, and constipation.

Olanzapine—There are 6 positive trials supporting the efficacy of olanzapine (5–20 mg/d) for the treatment of manic or mixed episodes and concomitant psychotic features (Tohen et al., 1999, 2000, 2008b; McIntyre et al., 2009a, 2010b; Katagiri et al., 2012). The NNT is approximately around 5 for response (defined as a 50% drop in Young Mania Rating Scale [YMRS]). Olanzapine seems to have a beneficial effect on the core symptoms of mania and on psychotic symptoms, treats mixed patients as well as rapid cycling, possibly improves coexisting depressive symptoms, and response occurs as early as days 2 to 7. Olanzapine does not seem to induce a switch to depression. The most common adverse events related with olanzapine treatment were somnolence, dizziness, dry mouth, thirst, and weight gain. EPS occur but at a lower rate than with haloperidol.

Quetiapine—There exist 4 positive studies supporting the efficacy of quetiapine up to 800 mg/d for the treatment of acute mania (Bowden et al., 2005b; McIntyre et al., 2005; Vieta et al., 2010b; Cutler et al., 2011). Quetiapine does not seem to induce depression; on the contrary there is a clear beneficial effect on concomitant depressive symptoms. However, there is some doubt concerning its efficacy against mixed episodes (such patients were excluded in most quetiapine trials), concomitant psychotic features, and in rapid cycling patients. The NNT is around 4 to 6 for response. The most common adverse events associated with quetiapine treatment were somnolence, dizziness, dry mouth, thirst, and weight gain. EPS occur but at a lower rate than with haloperidol.

Aripiprazole—There are 5 positive (Keck et al., 2003b, 2009; Sachs et al., 2006; Young et al., 2009; Kanba et al., 2014) and one negative fixed dosage study (El Mallakh et al., 2010) concerning the efficacy of aripiprazole 15 to 30 mg/d for the treatment of acute manic and mixed episodes. One study was not completed and reported no results. Again the effect on the core symptoms of mania is unknown. There is a significant effect in mixed and rapid cycling patients, and it also treats concomitant positive psychotic features and agitation. Aripiprazole does not seem to induce depression, but it does not seem to have any effect on concomitant depressive symptoms either. The NNT is approximately around 5 to 10 for response. Nausea, dyspepsia, somnolence, anxiety, vomiting, insomnia, light-headedness, constipation, and akathisia were the most common adverse events. There were no significant effects on body weight, serum prolactin, or QTc prolongation.

Risperidone—The efficacy of risperidone 1 to 6 mg/d for the treatment of acute manic and mixed episodes is supported by 3 positive studies (Hirschfeld et al., 2004; Khanna et al., 2005; Smulevich et al., 2005). The therapeutic effect is evident from day 3 onwards. It seems also effective in the treatment of positive psychotic symptoms and agitation and concomitant depressive symptoms. The NNT is approximately around 3 to 5 for response. It is unknown whether risperidone has an effect on the core symptoms of mania or whether it is beneficial for rapid cycling patients. It does not seem to induce a switch to depression. Somnolence, dyspepsia, nausea, and EPS were the most common adverse events.

Ziprasidone—Three positive studies (Keck et al., 2003a; Potkin et al., 2005; Vieta et al., 2010a) support the efficacy of ziprasidone 80 to 160 mg/d for the treatment of acute manic and mixed episodes. It has a treatment effect on the core symptoms of mania and on concomitant positive psychotic symptoms. It does not seem to have any significant effect on depressive symptoms, but it also does not seem to induce a switch to depression. Its effect
Table 2. Acute Mania/Mixed Treatment Phase, Grading on Basis of Efficacy (Treatment Phase up to 12 Weeks)

<table>
<thead>
<tr>
<th>Agent/modality (alphabetical order)</th>
<th>Acute Manic Episodes</th>
<th>Combination with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect start day</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2–4</td>
<td>1</td>
</tr>
<tr>
<td>Asenapine</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Loxapine inhalant</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lithium</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Palipiramate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Risperidone</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TMS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Topiramate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Valproate</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Verapamil</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: -, no data; Cbz, carbamazepine; ECT, electroconvulsive therapy; FGA, first generation antipsychotic; Lam, lamotrigine; Li, lithium; MS, mood stabilizer; TMS, transcranial magnetic stimulation; Val, valproate.

The treatment options are rated according to the rating system shown in Table 1.

in rapid cycling patients is unknown. The NNT is approximately 6 for response. The most common adverse events with ziprasidone treatment were EPS, somnolence, dizziness, anxiety, and dyspepsia. There were no significant effects on body weight or serum lipids. There was a small and clinically not significant QTC prolongation reported.

Asenapine—Three positive trials (McIntyre et al., 2009a, 2010b; Landbloom et al., 2016) support the efficacy of asenapine 10 to 20 mg/d for the treatment of acute manic and mixed episodes with efficacy as early as day 2. It is unknown whether it has a treatment effect on the core symptoms of mania, and while in one of the studies a positive effect on the total Positive and Negative Symptoms Scale (PANSS) score is reported, the specific effect on concomitant positive or negative psychotic features is unknown. Also unknown is the efficacy in rapid cycling patients. The data are equivocal concerning the effect on depressive symptoms, but also it does not seem to induce depression. The NNT is between 6 and 12 for response. The most common adverse events related with asenapine treatment were EPS, somnolence, dizziness, sedation, fatigue, oral hypesthesia, dry mouth, weight gain, and EPS.

Paliperidone—Two studies (Vieta et al., 2010b; Berwaerts et al., 2012b) provide support for the efficacy of 12 mg/d of paliperidone ER for the treatment of acute manic and mixed episodes, while the data for lower dosages is conflicting. Paliperidone is effective as early as day 2. It is not reported whether it has a treatment effect on the core symptoms of mania, positive psychotic symptoms, and depression and the effect in rapid cycling patients is unknown. It is unclear whether paliperidone ER can induce switches to depression. The most common adverse events related with paliperidone ER treatment were headache, somnolence, EPS, and prolactin elevation.

Cariprazine—Three studies (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015) confirmed the efficacy of cariprazine (3–12 mg daily) vs placebo in the treatment of acute manic or mixed episodes. The NNT for response or remission is approximately 4 to 7. Cariprazine is reported to improve the core symptoms of mania but had no effect on the Montgomery Asberg Depression Rating Scale (MADRS). It improves the total PANSS but the specific effect on the PANSS positive subscale is unknown. Its efficacy in mixed and rapid cycling patients is unknown.
Other agents and treatment modalities. Overall, the data for tamoxifen are positive; however, the total patient sample is still small (Zarate et al., 2007; Yildiz et al., 2008). One NIMH-sponsored clinical trial (NCT00026585) has not reported results yet. One small 3-week study was negative for verapamil (Janicak et al., 1998). The data concerning repetitive Transcranial Magnetic Stimulation (rTMS) are conflicting. There are two RCTs, one negative (Kaptan et al., 2003) and one positive (Praharaj et al., 2009).

Summary of monotherapy trials for acute mania. Overall there are sufficient data in the literature to support the general efficacy of a number of agents in the treatment of acute mania; however, many details remain to be explored concerning many of the agents. Lithium, valproate, carbamazepine, haloperidol, olanzapine, quetiapine, aripiprazole, risperidone, ziprasidone, azenapine, paliperidone, cariprazine, and probably tamoxifen are efficacious in the treatment of acute manic episodes. It should be mentioned that haloperidol probably induces depression. It is unsatisfactory that there are no controlled data concerning the usefulness of electroconvulsive treatment (ECT).

A significant problem for the everyday clinical practice is that the average clinician often utilizes the so-called “class effect” to easily navigate among therapeutic options. However, what needs to be stressed is that while antipsychotics seem to possess a class effect specific to the treatment of acute mania (possibly an antidepressive effect; Brugue and Vieta, 2007), there is no such effect in anticonvulsants concerning any phase of BD (Rosa et al., 2009; Fountoulakis et al., 2011b).

Comparison of Agents

Lithium vs others. In 2 studies comparing lithium with valproate, the 2 agents were found to be equivalent. There was a tendency of valproate to manifest fewer adverse events and dropouts, but its signal for efficacy in RCTs might be driven by its effect in patients with mixed features (Freeman et al., 1992; Bowden et al., 1994). A similar finding restricting the efficacy of carbamazepine to an undefined subgroup of patients in contrast to a wider efficacy of lithium was reported by another study as well (Lerer et al., 1987). Overall the efficacy was similar to carbamazepine but with fewer adverse events (Okuma et al., 1990; Small et al., 1991). There has been a comparison of carbamazepine with lamotrigine that should be considered to be a failed study (Chim et al., 2000). It should be noted however that lamotrigine is not an effective antimanic agent.

The comparison of lithium to chlorpromazine suggested that although chlorpromazine acts faster and might be more efficacious in more agitated patients, this might be due to sedation alone, while lithium has again a broader effect on the core manic symptomatology (Platman, 1970; Frien et al., 1972; Shopsin et al., 1975). In contrast, the comparison of haloperidol and lithium suggested that haloperidol had a stronger and more rapid effect, especially on behavior and motor activity but without sedation, while lithium acted more evenly and comprehensively on the entire range of manic symptomatology (Shopsin et al., 1975; Garfinkel et al., 1980).

Lithium was found to have equal efficacy to carbamazepine (Lerer et al., 1987; Okuma et al., 1990; Small et al., 1991), olanzapine (Berk et al., 1999; Niufan et al., 2008; Shafti, 2010), quetiapine (Bowden et al., 2005b; Li et al., 2008), and aripiprazole (Keck et al., 2009). In severely psychotic patients, it seems inferior to haloperidol (Shopsin et al., 1975; Garfinkel et al., 1980). Overall, lithium has a wider antimanic effect than valproate and carbamazepine but a weaker effect on psychotic symptoms and a slower onset of action in comparison with antipsychotics. Overall, lithium demonstrated a more favorable adverse effect profile in comparison with all other agents except aripiprazole and valproate.

Valproate vs others. In comparison with lithium, valproate was less efficacious and with a tendency to cause fewer adverse events and dropouts, but its efficacy might be restricted to that specific group of patients with mixed features (Freeman et al., 1992; Bowden et al., 1994). In one small study, it was superior to carbamazepine and had a faster onset of action (Vasudev et al., 2000). In another study, it was superior to oxcarbazepine but with more frequent adverse events (Kakkar et al., 2009). It might be less efficacious in comparison with olanzapine and with a slower onset of action, but also with fewer adverse events (Tohen et al., 2002a, 2008b; Zajecka et al., 2002).

Carbamazepine vs others. Carbamazepine was reported to be equally effective in comparison with lithium but with a higher rate of adverse events. Its efficacy appeared somewhat restricted to an undefined subgroup of patients in contrast to a broader spectrum of efficacy of lithium (Lerer et al., 1987; Okuma et al., 1990; Small et al., 1991). In another study carbamazepine was inferior to valproate and had a slower onset of action (Vasudev et al., 2000). In 2 other studies carbamazepine was found equal to chlorpromazine but with fewer adverse events (Okuma et al., 1979) and equal to haloperidol but with a slower onset of action (Brown et al., 1989).

Other antiepileptics. There is one study on lamotrigine vs lithium that should be considered as failed probably because it was underpowered (Chim et al., 2000). In another study, oxcarbazepine was found to be inferior to valproate but with fewer adverse events (Kakkar et al., 2009).

Haloperidol vs others. The comparison of haloperidol with lithium suggested that haloperidol is more efficacious in severely psychotic patients and exerts its effect earlier, especially on behavior and motor activity but without sedation, while lithium acted more evenly and comprehensively on the entire range of manic symptomatology (Shopsin et al., 1975; Garfinkel et al., 1980). Haloperidol was found equally effective to carbamazepine but with a faster onset of action (Brown et al., 1989). Haloperidol had a faster onset of action than olanzapine but with more dropouts, and olanzapine was superior in the nonpsychotic patients. Both agents were equally effective in reducing the HDRS score in mixed patients and in patients with higher depressive scores. Switch to depression occurred significantly more rapidly with haloperidol than with olanzapine. More EPS were reported with haloperidol and more weight gain with olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Haloperidol was reported to be overall superior to quetiapine and more efficacious in psychotic patients. In contrast to quetiapine it had no effect on depressive symptoms. Haloperidol-treated patients had more dropouts and more EPS (McIntyre et al., 2005). It was reported as not superior to aripiprazole and did not improve the depressive symptoms measured with the MADRS. In comparison with aripiprazole, more haloperidol-treated patients switched to depression, more dropped out, and EPSs were more frequent with haloperidol (Vieta et al., 2005b; Young et al., 2009). Haloperidol was found similarly efficacious to risperidone (Segal et al., 1998; Smulevich et al., 2005) and superior to ziprasidone but also with more dropouts and adverse events (Vieta et al., 2010a). The comparison of 25 mg/d vs 5 mg/d haloperidol revealed that the higher haloperidol dosage produced greater improvement than did the low dose but with more side effects (Chou et al., 1999).
In summary, haloperidol was similar in efficacy as carbamazepine (Brown et al., 1989) and olanzapine (Tohen et al., 2003b; Katagiri et al., 2012), risperidone (Segal et al., 1998; Smulevich et al., 2005), and aripiprazole (Vieta et al., 2005b; Young et al., 2009). It was found to be superior to quetiapine (McIntyre et al., 2005) and ziprasidone (Vieta et al., 2010a) and in severely psychotic patients to lithium (Shopsin et al., 1975; Garfinkel et al., 1980). It acted faster in comparison with lithium (Shopsin et al., 1975; Garfinkel et al., 1980), carbamazepine (Brown et al., 1989), and olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Overall it demonstrated superior efficacy in psychotic patients but less improvement (if any) on depressive symptoms. It also showed more adverse events (especially EPS), switching to depression and dropouts more than the comparators.

Olanzapine vs others. Olanzapine was reported to be equally effective to lithium but with more adverse events, mainly weight gain (Berk et al., 1999; Niufan et al., 2008; Shafiti, 2010). It might be superior and faster acting in comparison with valproate (although this could be a function of dosage) but again with more adverse events (Tohen et al., 2002a, 2008b; Zajecka et al., 2002). It was found to be similar in efficacy to haloperidol but with a slower onset of action and fewer dropouts. The data suggest that during the acute phase both agents were equally effective in reducing the HDRS score in mixed patients and in patients with higher depressive scores. More EPSs were registered with haloperidol and more weight gain with olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Olanzapine was found superior to asenapine in manic and mixed patients and also significantly improved the MADRS score, that asenapine did not. Olanzapine-treated patients had more weight gain (McIntyre et al., 2009a, 2010b).

Olanzapine was found to have similar efficacy as risperidone in patients without psychotic features in terms of YMRS, HAM-D, and MADRS change. The 2 agents were also equal in the subgroup of rapid cycling patients. Fewer olanzapine-treated patients dropped out of the head-to-head comparison but there was more weight gain in the olanzapine group (Perlis et al., 2006b). Finally, an unpublished study of olanzapine vs ziprasidone (NCT00329108) was stopped prematurely due to poor recruitment (2009).

Quetiapine vs others. Quetiapine is reported to be comparable with lithium but with more dropouts and adverse events (Bowden et al., 2005b; Li et al., 2008). Also it is reported to be inferior to haloperidol, with fewer dropouts and less frequent EPS, and also less efficacious in psychotic patients. In contrast to haloperidol it had an effect on depressive symptoms (McIntyre et al., 2005).

Quetiapine is reported to be equal to paliperidone and both agents had a similar effect in manic and mixed patients. Body weight increase was more frequent in the quetiapine group, but more patients with paliperidone switched to depression (Vieta et al., 2010b).

Other antipsychotics. Chlorpromazine was found equal to pimozide with faster action, probably due to its greater sedative effect. Sedation was the side effect most frequent with chlorpromazine and EPS were more frequent with pimozide (Cookson et al., 1981).

The following studies have already been reported and discussed above; however, it is important to consider them again from a reverse angle. Risperidone was found equal to haloperidol (Segal et al., 1998; Smulevich et al., 2005) and olanzapine (Perlis et al., 2006b). Aripiprazole was found equal to lithium (Keck et al., 2009) and haloperidol (Vieta et al., 2005b; Young et al., 2009). Asenapine was found inferior to olanzapine (McIntyre et al., 2009a, 2010b) and paliperidone equal to quetiapine (Vieta et al., 2010b). There is one unpublished study comparing ziprasidone with olanzapine that did not report any results (2009) and another one finding it inferior to haloperidol (Vieta et al., 2010a). Finally, there are 2 studies comparing chlorpromazine with lithium (Flatman, 1970; Prien et al., 1972) and one with carbamazepine (Okuma et al., 1979), suggesting equal efficacy.

Summary of the comparison of agents. Overall, comparison studies suggest that the greater the efficacy the more frequent the adverse events are. Although there are no sufficient data to support a big difference between agents, it seems that antipsychotics and lithium are more efficacious than valproate and carbamazepine unless a loading strategy for these anticonvulsants is applied. Also it seems clear that antipsychotics act earlier in comparison with the other compounds. The effect on depressive symptoms is unclear, but it seems that haloperidol-treated patients might switch more often to depression.

Earlier studies suggested that lithium could be specifically useful against the more “classic” cases of euphoric mania, while antiepileptics might have a better efficacy for patients with mixed features and those with comorbidity. This is not supported by more recent data (Fountoulakis et al., 2012b). A factor that could have affected the results is the so-called lithium-discontinuation-related refractoriness (Post et al., 1992), because of that patients enrolled in RCTs could constitute a sample more refractory to lithium treatment than expected. However, the assumption for the existence of lithium-discontinuation-related refractoriness is not supported by studies reporting that even when samples enriched for lithium refractoriness were used, no inferiority of lithium to the other agent was documented (Bowden et al., 1994). Also a recent meta-analysis of all published cases concluded that there is not sufficient data to support such a concept (de Vries et al., 2013).

Combination and Add-On Treatment

Several studies examined the efficacy and safety of agents given not as monotherapy but combined treatments. The study samples range from patients being refractory to an initial treatment to drug-naive patients. In the first instance, an agent is used as adjunct or add-on therapy on a preexisting treatment to that the patient has shown unsatisfactory response. In the second instance the study tests a combination treatment against monotherapy and both agents are initiated simultaneously. Although essentially both designs provide information on how to treat patients with an unsatisfactory response to monotherapy, the conclusions and the generalizability might differ.

Combination Treatment

Adding valproate to First Generation Antipsychotics (FGAs; haloperidol or perazine in this study) produced higher response rates in manic patients (70% vs 46%) compared with FGA plus placebo (Muller-Oerlinghausen et al., 2000). Similarly, combination of lithium (600–1800 mg/d) and quetiapine XR (400–800 mg/d) was superior to quetiapine plus placebo (Bourin et al., 2014) in treating acute mania. Three studies that reported on combinations of mood stabilizing agents with haloperidol vs haloperidol monotherapy are equivocal as the outcome depended on the haloperidol dosage (Garfinkel et al., 1980; Klein et al., 1984; Chou et al., 1999).

Other studies reported on the efficacy of an antipsychotic agent and a mood stabilizer in comparison with mood stabilizer alone. In general, antipsychotic and carbamazepine combination is not superior to carbamazepine alone, primarily due to
the effect of carbamazepine inducing the metabolism of antipsychotics in the combination group, thus resulting in lower plasma levels of antipsychotics. One 6-week international trial of olanzapine (10–30 mg/d) vs placebo add on to carbamazepine (400–1200 mg/d) was negative. In the olanzapine group, however, the triglyceride levels were significantly higher and potentially clinically significant weight gain occurred more frequently. Furthermore, carbamazepine significantly reduced olanzapine serum concentrations (Tohen et al., 2008a). Similarly, in another study, carbamazepine significantly reduced olanzapine levels of risperidone (Yatham et al., 2003) that contributed to the negative findings of this study on the primary efficacy measure.

Overall the data on the combination of lithium with other agents support the conclusion that the combinations of lithium with haloperidol, lorazepam, carbamazepine, tamoxifen, and allopurinol are superior to lithium alone, but not the combination of lithium plus ziprasidone or dipyridamole. Most of these combinations had more adverse events in comparison with monotherapy (Garfinkel et al., 1980; Lenox et al., 1992; Small et al., 1995; Weisler et al., 2003; Bowden, 2005; Machado-Vieira et al., 2008; Amrollahi et al., 2010). Adding allopurinol to treatment as usual was not more effective compared with treatment as usual (Weiser et al., 2014). On the contrary, positive results were reported by the addition of 400 mg/d celecoxib on valproate in nonrapid cycling and nonpsychotic patients (Arabzadeh et al., 2015) but negative when added on ECT (Kargar et al., 2015).

A number of trials investigated the combination of an atypical antipsychotic or other agents with addition of an agent on top of lithium or valproate, since these 2 constituted the backbone of the treatment of BD for decades. Overall the data are in support of combining lithium or valproate with asenapine, olanzapine, risperidone, haloperidol, and tamoxifen but negative concerning gabapentin and medroxyprogesterone (Pande et al., 2000; Sachs et al., 2002; Yatham et al., 2003; Kulkarni et al., 2006; Szegedi et al., 2012; Kulkarni et al., 2014; Xu et al., 2015b). The addition of folic acid to valproate has equivocal support (Behzadi et al., 2009) and the addition of omega-3 fatty acids has negative data (Chiu et al., 2005). Adding the herbal agent Free and Easy Wanderer Plus (FEWP) on carbamazepine was not better than carbamazepine alone, but it was in comparison with placebo while carbamazepine monotherapy was not. Technically it does not support the use of FEWP in acute mania, but a number of other interpretations also exist, for example that adding FEWP compensates for the drop in carbamazepine levels (Zhang et al., 2007). However, that study did not define an a-priori primary outcome and therefore its quality is low. Finally, one study suggested that the valnoctamide plus risperidone combination was more effective than risperidone alone (Bersudsky et al., 2010).

In summary, there are few but still important data suggesting that specific combinations are superior to monotherapy in nonrefractory or otherwise selected samples, although it is difficult to assess the quality of many study samples. Despite the very small number of trials and the problems with the data quality, one could generalize that the combination of an antipsychotic plus lithium or valproate is superior to lithium or valproate alone, with the caveat of greater side-effect burden. Tamoxifen and probably allopurinol are also valuable agents to use in combination with mood stabilizers.

Add-On Treatment

In patients refractory to haloperidol treatment, the addition of phenytoin has been shown to be beneficial (Mishory et al., 2000). In patients refractory to lithium, adding 600 to 1200 mg/d carbamazepine or oxcarbazepine improved the outcome (Jurjua et al., 2009), but that study was of poor quality, questionable phase of the disorder and outcome, and without any a-priory defined primary outcome. Adding lovastatin on lithium was negative (Ghanizadeh et al., 2014).

In patients refractory to lithium, valproate, or carbamazepine, it is beneficial to add haloperidol, olanzapine, quetiapine, aripiprazole, or asenapine (Szegedi et al., 2012) (Sachs et al., 2002, 2004; Tohen et al., 2002b; Yatham et al., 2007; Vieta et al., 2008b) but not ziprasidone, topiramate, risperidone, or paliperidone (Roy Chengappa et al., 2006; Berwaerts et al., 2011; Sachs et al., 2012a, 2012b; Moosavi et al., 2014). One study that used a mixed population with some patients entering after a minimum of 2 weeks of mood stabilizer therapy, and others starting a mood stabilizer and risperidone in parallel, provided inconclusive data for risperidone (Yatham et al., 2003) as the results were likely confounded by the effects of carbamazepine on serum levels of risperidone. Allopurinol was not beneficial in patients refractory to lithium, valproic acid, carbamazepine, or atypical antipsychotic medications (Fan et al., 2012), although there are some data suggesting a beneficial effect on patients refractory to valproate (Jahangard et al., 2014). Adding the melatonin agonist ramelteon was also not efficacious in patients refractory to treatment as usual (McElroy et al., 2010b). There is only one sham-controlled trial of ECT as adjunctive treatment to chlormpromazine (600 mg/d) in 30 acutely manic patients. That study supported the efficacy of ECT with a faster rate of improvement (Sikdar et al., 1994).

A recent placebo-controlled 4-week RCT in 180 acutely manic patients supported the efficacy and safety of the purinergic agents allopurinol (600 mg/d) and dipyridamole (200 mg/d) as adjunctive to lithium in acute bipolar mania (Machado-Vieira et al., 2008). Folic acid was also found to be useful as an adjunct to valproate in treating acute mania (Behzadi et al., 2009). There is one 5-week trial from Israel on 32 recently admitted manic inpatients that compared valnoctamide (600–1200 mg/d; n=15) vs placebo (n=17) on top of risperidone (1–6 mg/d). All medications were started at day 1. In all efficacy measures the valnoctamide plus risperidone combination was more effective than risperidone plus placebo from week 3 to week 5. Valnoctamide is an anticonvulsant analogue of valproate that does not undergo biotransformation to the corresponding free acid, and in mice it has been shown to be distinctly less teratogenic than valproate (Bersudsky et al., 2010). A pilot 8-week study in 21 acutely manic outpatients on the usefulness of adjunctive ramelteon in acute mania/mixed states failed (McElroy et al., 2010b), while another 2 on the cholinesterase inhibitor donepezil were negative (Eden Evins et al., 2006a; Chen et al., 2013).

Overall, the data in partial responders or refractory patients support the addition of specific antipsychotics to lithium or valproate and also the use of allopurinol and the combination of lithium with carbamazepine or maybe oxcarbazepine.

Posthoc Analyses and Meta-Analytic Studies

A very important posthoc analysis of individual patient data reported that patients with impaired insight (as measured with the use of item 11 of the YMRS) responded better; therefore treatment should be initiated immediately and the therapist should not wait until the patient gains sufficient insight (Welten et al., 2016).

Overall, posthoc and meta-analytic studies confirm the efficacy of specific agents vs placebo (Emilien et al., 1996; Yatham et al., 2004; Perlis et al., 2006a; Scherl et al., 2007; Tamayo et al., 2010) and also confirm the superiority of antipsychotics vs lithium, valproate, and carbamazepine both in terms of faster onset of action but also in terms of the overall outcome in the short-term treatment of acute mania. However, they also confirm that this higher efficacy comes with the cost of more frequent adverse events, mainly EPS, weight gain, and somnolence (Correll et al., 2010; Tarr et al., 2010). These conclusions should be received with
caution, taking into consideration both the limitations of meta-analytical methods and the frequent conflicting results.

Haloperidol might be the fastest acting of all (Goikolea et al., 2013a) but also the most likely one to induce depression (Goikolea et al., 2013b). Olanzapine was efficacious against mixed episodes, depressive symptoms, and psychotic features as well as in rapid cycling patients (Baker et al., 2002; Baldessarini et al., 2003b; Chengappa et al., 2003; Suppes et al., 2005, 2008b). Quetiapine was proven efficacious for all YMRS individual items, depressive symptoms, and also against psychotic features (Vieta et al., 2005a). Risperidone vs placebo caused higher remission rate and the drop-out rate because lack of efficacy was lower, while the drop-out rate because of adverse events was similar to that of placebo (Gopal et al., 2005). Asenapine was efficacious against depressive symptoms (Szegedi et al., 2011) and mixed episodes (Azorin et al., 2013; McIntyre et al., 2013) and has an effect on the core symptoms of mania (Cazorla et al., 2013). Aripiprazole had no effect in patients aged >55 years but was effective against psychotic symptoms (Suppes et al., 2008b; Fountoulakis et al., 2009a; Sayyaparaju et al., 2014). Aripiprazole, lithium, and haloperidol overall are not efficacious against concomitant depressive features (Ostacher et al., 2015b). Ziprasidone was efficacious against dysphoric mania (Ketter et al., 2010; Stahl et al., 2010). The data of oxcarbazepine appear to be insufficient (Vasudev et al., 2011). A posthoc analysis of a lithium study (Bowden et al., 1994) confirmed the efficacy of lithium in classic manic but not mixed patients (Swann et al., 1997), while another posthoc study confirmed the lack of efficacy of eslicarbazepine although there seems to be some signal in the secondary outcomes (Grunze et al., 2015).

Meta-analytic studies also suggest that combination treatment is superior to monotherapy at the cost of more frequent adverse events; however, these meta-analyses do not distinguish between add-on and combination studies and populations (Scherk et al., 2007; Smith et al., 2007; Tarr et al., 2011; Ogawa et al., 2014). One meta-analysis reported that studies outside the United States had higher effect size and the baseline YMRS predicted the outcome (Tarr et al., 2011), probably because of a mathematical structural coupling effect (Fountoulakis and Kontis, 2012). Year of study publication was not associated with YMRS score change. Furthermore, the study size, number of study sites, YMRS score required for study entry, inclusion of patients with mixed mania or treatment resistance, and inclusion of inpatients vs outpatients had no significant influence on the outcome (Tarr et al., 2011).

Two recent meta-analyses attempted to rank antimanic agents according to efficacy. The first one utilized the method of multiple-treatments meta-analysis and reported that the ranking in terms of efficacy was haloperidol, risperidone, olanzapine, lithium, quetiapine, aripiprazole, carbamazepine, asenapine, valproate, and ziprasidone. According to that meta-analysis, overall, antipsychotics were significantly more effective than mood stabilizers; however, the results of that analysis do not fully support such a conclusion (Cipriani et al., 2011). This meta-analysis has been criticized both concerning the overall methodology but also concerning the incomplete list of RCTs that was utilized (Fountoulakis and Siamouli, 2012). A more balanced meta-analysis confirmed that the response to antipsychotics was greater and more rapid in comparison with lithium, valproate, or carbamazepine, but it did not confirm any difference between haloperidol and second generation antipsychotics (Yildiz et al., 2010).

A more recent network meta-analysis did not support the superiority of any agent vs another except for risperidone vs aripiprazole and valproate (Yildiz et al., 2015). A meta-analysis that pooled data from 9 randomized, double-blind, placebo-controlled, acute studies of ziprasidone reported that the discontinuation rate due to adverse events or 7% or greater weight gain between ziprasidone and placebo was not significant for all psychiatric conditions. In acute mania the risk for akathisia with ziprasidone had a number needed to harm (NNH) = 12, the risk for overall EPS had a NNH = 12, and the reported somnolence had NNH = 7 (Gao et al., 2013). Finally, a recent network meta-analysis reported that aripiprazole, olanzapine, quetiapine, risperidone, and valproate had less all-cause discontinuation rates than placebo and that there is a similar efficacy profile for haloperidol, second-generation antipsychotics, and mood stabilizers (Yildiz et al., 2014) while a meta-analysis of combination studies confirmed the higher rate of adverse events in comparison with monotherapy (Gallig et al., 2015).

The analysis of the data concerning the usefulness of the cholinesterase inhibitors galantamine and donepezil as well as the glutamate receptor antagonist memantine was negative (Veronese et al., 2016).

Acute Bipolar Depression

Bipolar depression is not well studied, and the common practice among clinicians is to extrapolate the clinical data and wisdom from the treatment of unipolar to bipolar depression. However, the clinical trials that examined the efficacy of various agents have raised questions about the validity of such strategy.

The agents are listed below in a historical sequence with lithium and anticonvulsants first, then antidepressants, and finally with antipsychotics on the basis of the year of the first study they were investigated.

The data on monotherapy and combination treatment for acute bipolar depression and its special characteristics are shown in Table 3.

Monotherapy

Lithium. The earlier studies on the efficacy of lithium against bipolar depression provided some positive data but are difficult to interpret (Goodwin et al., 1969, 1972; Greenspan et al., 1970; Stokes et al., 1971; Noyes and Dempsey, 1974; Noyes et al., 1974; Baron et al., 1975; Mendels, 1976; Donnelly et al., 1978; Srisurapanont et al., 1995). There is only one modern and rigorously conducted RCT (EMBOLDEN I) and it was negative for lithium while positive for quetiapine. While in this particular study the mean lithium serum levels were 0.61 mEq/l, with 34.9% of patients having levels <0.6 mEq/l, a posthoc analysis reported that the results were negative also in patients with lithium levels >0.8 mEq/l and also in patients who completed the study. Furthermore, lithium level did not correlate with change in depression rating scores (Young et al., 2010).

Antiepileptics. Valproate—There are 3 small positive trials (Davis et al., 2005; Ghaemi et al., 2007; Muzina et al., 2010) and one failed (Sachs et al., 2001), that is not published and can be assessed only through 2 meta-analytic papers (Bond et al., 2010; Smith et al., 2010). Taken together, these studies suggest that there are some data (though somewhat inconsistent and not sufficient), coming from small trials supporting the efficacy of valproate (titrated up to 2500 mg/d) in bipolar depression, especially in BD-I patients and on the core symptoms of depression. There is possibly some efficacy against concomitant anxiety.

Carbamazepine—The old, small withdrawal studies concerning carbamazepine efficacy against bipolar depression were positive (Ballenger and Post, 1980; Post et al., 1983, 1986) but also suggested that plasma levels do not correlate with the treatment effect.
Table 3. Acute Depression Treatment Phase, Grading on Basis of Efficacy (Treatment Phase up to 12 Weeks)

<table>
<thead>
<tr>
<th>Agent/modality (alphabetical order)</th>
<th>Monotherapy</th>
<th>Combination</th>
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<tr>
<td></td>
<td>Overall</td>
<td>BD-I</td>
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<tr>
<td>Agomelatine</td>
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<td>Aripiprazole</td>
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<td>Armadonil</td>
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<td>Bupropion</td>
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<tr>
<td>Carbamazepine</td>
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<td>Celecoxib</td>
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<td>Donepezil</td>
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<td>Escitalopram</td>
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<td>FEWP</td>
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<td>Gabapentin</td>
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<td>Imipramine</td>
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<td>Ketamine</td>
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<td>Lamotrigine</td>
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<tr>
<td>Levetiracetam</td>
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<tr>
<td>Levothyroxine (L-T4)</td>
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<tr>
<td>Lisdexamfitamine</td>
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<td>Lithium</td>
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<tr>
<td>L-sulpiride</td>
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<td>Lurasidone</td>
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<td>Memantine</td>
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<td>Modafinil</td>
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<td>OFC</td>
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<td>Olanzapine</td>
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<td>Oxcarbazepine</td>
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<td>Paroxetine</td>
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<td>Phenelzine</td>
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<td>Pioglitazone</td>
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<td>Quetiapine</td>
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<td>Risperidone</td>
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<td>TMS</td>
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<td>Tranylcypromine</td>
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<td>Valproate</td>
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<td>Venlafaxine</td>
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<tr>
<td>Ziprasidone</td>
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</tbody>
</table>

Abbreviations: -, no data; Cbz, carbamazepine; ECT, electroconvulsive therapy; FEWP, Free and Easy Wanderer Plus; Lam, lamotrigine; Li, lithium; MS, Mood Stabilizer; OFC, Olanzapine Fluoxetine Combination; TMS, transcranial magnetic stimulation; Val, valproate.

The treatment options are rated according to the rating system shown in Table 1.

A more recent 12-week double-blind, randomized, placebo-controlled study from China had equivocal results (Zhang et al., 2007). Lamotrigine—There are 5 trials that investigated the efficacy and safety of lamotrigine in the treatment of acute bipolar depression (SCA100223/NCT00274677, SCA30924/NCT0056277, SCA40910, SCAA2010, and SCAB2001). One included BD-I patients alone and one a mixed population of BD-I and BD-II patients. All were negative concerning the primary outcome (Calabrese et al., 1999; Goldsmith et al., 2003; Ostacher et al., 2008), although in one study lamotrigine separated from placebo on MADRS, an important secondary outcome measure (Calabrese et al., 1999). A small double-blind, randomized study with crossover series of three 6-week monotherapy evaluations in a mixed unipolar-bipolar population reported that lamotrigine was superior to placebo (Frye et al., 2000). Overall the data are negative concerning the efficacy of lamotrigine in acute bipolar depression, although the presence of a weak signal cannot be ruled out.

**Antidepressant Monotherapy**

Despite the fact that antidepressants have established efficacy in unipolar depression, that defines them as a class of drugs that includes different kinds of molecules, such a “class effect” does not appear to be present for bipolar depression (Fountoulakis et al., 2011b). Although the data are problematic, the use of antidepressants is neither encouraged nor prohibited by all treatment algorithms, that however consistently advise the concomitant use of an antimanic agent. The current view is that antidepressant monotherapy should not be used in bipolar depression (Vieta, 2014). Older placebo-controlled studies were mostly positive but difficult to judge on the basis of modern criteria and understanding of methodology.

An early study reported superiority of tranylcypromine vs placebo in anergically depressed patients and suggested that...
Tranylcypromine could be efficacious against bipolar depression since anergic depression most typically occurs in BD and in pseudounipolar affective illnesses (Himmelhoch et al., 1982). However, the methodology of this study has been criticized.

The first trial reported that fluoxetine and imipramine were efficacious vs placebo, but the interpretation of the results of this study is complicated by the concomitant use of lithium, especially in the fluoxetine group (Cohn et al., 1989). A second small trial was negative for fluoxetine and olanzapine monotherapy and also for the olanzapine-fluoxetine combination (OFC) (Amsterdam and Shults, 2005a). Another small placebo-controlled, cross-over study lasting 9 months in 10 BD-II depressed patients suggested that escitalopram might be better than placebo as monotherapy for depression and without worsening of illness course (Parker et al., 2006). The only properly conducted study on a sample of adequate size was an international trial on 740 patients with bipolar depression (both BD-I and BD-II). This study was negative for paroxetine 20 mg/d while it was positive for quetiapine. However, paroxetine produced a significant improvement in anxiety in terms of change of HAM-A scale score from baseline but was not efficacious concerning depressive symptoms in any subgroup of patients. The most frequent adverse events were dry mouth, sedation, headache, insomnia, and nausea with paroxetine treatment (McElroy et al., 2010c).

In conclusion, given that the efficacy data are conflicting along with concerns about manic/hypomanic switch, the use of antidepressant monotherapy is strongly discouraged.

**Antipsychotics**

Olanzapine. An international trial supported the superiority of olanzapine (5–20 mg/d) vs placebo in the treatment of bipolar depression. However, olanzapine monotherapy was proven inferior to OFC and furthermore, the analysis of individual MADRS items suggested that in contrast with OFC, olanzapine monotherapy had no effect on the core symptoms of depression (Tohen et al., 2003c). Also, a further small study was underpowered and negative (Amsterdam and Shults, 2005a). Another small study was positive (Wang et al., 2014). It is important to note that to demonstrate a true antidepressive effect, an effect on the “core items” of depression should be demonstrated (Bech, 2001; Lecrubier and Bech, 2007). To answer this question, another trial was conducted and the results again suggested that olanzapine (5–20 mg/d) was superior to placebo, but again no effect of olanzapine was observed on the core depressive symptoms according to LOCF analysis but surprisingly MMRM analysis showed a significant effect on core symptoms (Tohen et al., 2012). Overall, while olanzapine separated from placebo in 2 large clinical trials of bipolar depression, the data concerning its efficacy on the core symptoms of depression are equivocal.

Quetiapine. Overall, there are 6 studies concerning the efficacy of quetiapine in bipolar depression. All of them were positive. Quetiapine IR or XR is reported to be efficacious at dosages of both 300 and 600 mg/d. It is important to note that quetiapine had a similar efficacy in BD-I and BD-II patients as well as in rapid cycling, and it significantly improved all the MADRS items corresponding to the core symptoms of depression and also improved concomitant anxiety (Calabrese et al., 2005b; Thase et al., 2006; McElroy et al., 2010c; Suppes et al., 2010; Young et al., 2010; Li et al., 2016).

Aripiprazole. Two identically designed, 8-week, multicentre, randomized, double-blind, placebo-controlled studies (CN138-096 and CN138-146) to evaluate the efficacy and safety of aripiprazole monotherapy in depressed BD-I outpatients without psychotic features were both negative for aripiprazole (Thase et al., 2008). It has been argued that the failure of these 2 trials was due to the “catching up” of the placebo group after week 6 rather than because of a lack of efficacy of aripiprazole; however, at endpoint the placebo response in terms of MADRS score change in the aripiprazole studies (-10.6 and -11.5) was similar to what was observed also in the quetiapine studies (from -10.3 to -11.9), while the aripiprazole response (-11.9 and -12.3) was clearly lower to the response observed with quetiapine (from -15.4 to -17.4). Another confounding factor in these studies was that transient use of hypnotics was permitted but not after 4 weeks into the trial.

Ziprasidone. There are 2 negative trials (NCT00141271 and NCT00284264) concerning ziprasidone, that were published in a single paper (Lombardo et al., 2012). The placebo responses in these trials were >50%, that might have contributed to negative results. One trial of ziprasidone in bipolar spectrum depressed patients was negative (Patkar et al., 2015).

Lurasidone. One 6-week trial in bipolar depressed patients without psychotic features reported that lurasidone (20–60 mg/d or 80–120 mg/d) was superior to placebo. Lurasidone had an effect on the core symptoms of depression. Both lurasidone groups also experienced significant improvements compared with placebo in anxiety symptoms and in patient-reported measures of quality of life and functional impairment (Loebel et al., 2014a). As this was a 6-week study, and having in mind the negative findings at endpoint (week 8) for aripiprazole while the data was positive at week 6, one might be cautious concerning the interpretation of the lurasidone data. However, the magnitude of improvement and the absolute values of lurasidone and placebo-induced change in the MADRS score argue in favor of lurasidone.

Other agents and treatment options. There is a small number of early studies on very small samples concerning the α2-adrenergic agonist clonidine, the α2-adrenergic antagonist idoxozan, and Thyrotropin-releasing hormone (Kastin et al., 1972; Jimerson et al., 1980; Osman et al., 1989). A trial concerning the usefulness of ECT has been announced (Kessler et al., 2010), but its results have not been published until now. Three other uncontrolled trials suggested that bipolar depressives respond to ECT, and conflicting results exist as to whether unipolar or bipolar depression respond better although probably to a lesser extent in comparison with unipolars (Dalry et al., 2001; Medda et al., 2009; Baille et al., 2010). A recent study showed ECT to be superior to a pharmacotherapy algorithm (Schoeyen et al., 2015). There is one negative study of rTMS (Nahas et al., 2003). There is a small positive study on the usefulness of cranial electrotherapy stimulation in BD-II depression (McClure et al., 2015).

**Comparison of Treatment Options**

Since only a limited number of options for the treatment of bipolar depression exist, comparison studies are limited and often they compare agents with unproven efficacy. Some early studies were too small and are problematic concerning their methodology (Coppen et al., 1972; Kessell and Holt, 1975; Aberg-Wistedt, 1982). Overall the comparison data are sparse and they suggest antidepressants are equal in efficacy but with a different adverse events profile (Baumhacker et al., 1989; Cohn et al., 1989; Himmelhoch et al., 1991; Grossman et al., 1999; Amsterdam and Garcia-Espana, 2000; Silverstone, 2001; Vieta et al., 2002). Clozapine might be more efficacious than imipramine in refractory BD depressed patients (Thase et al., 1992).
However, the efficacy of antidepressants should be considered in combination with the negative monotherapy data for paroxetine. The frequent use of concomitant mood stabilizers as “background” medication complicates the interpretation of results. OFC is superior to olanzapine alone (Tohen et al., 2003c) and to lamotrigine (Brown et al., 2006) and has an effect on the core symptoms of depression. The comparison of paroxetine with venlafaxine suggests a higher switching risk for patients treated with venlafaxine (Vieta et al., 2002). The relatively higher risk of treatment emergent affective switches with venlafaxine compared with sertraline or bupropion has also been reported (Post et al., 2006). However, a more recent study reported that venlafaxine was equal to lithium and without any increase in the switch rate (Lorenzo-Luaces et al., 2016).

Combination and add-on treatment. Combination treatment—There is one trial in BD-I depressed patients that suggested that the OFC (6 and 25, 6 and 50, or 12 and 50 mg/d) was superior both to olanzapine monotherapy and to placebo. The OFC arm was relatively small (only 86 patients) and this was one of the limitations of the study. The analysis of individual MADRS items suggested that OFC had an effect on the core symptoms of depression. In comparison with placebo and olanzapine, the OFC arm also had a lower number of inpatients, less frequent psychotic features, more rapid cycling (that may translate in higher rates of “spontaneous remission”), and lower number of centers. All these could translate into better response and limit interpretation (Tohen et al., 2003c). Another small study was negative but also underpowered to detect any treatment effect (Amsterdam and Suls, 2005a). A second study from the United States (STEP-BD) utilized a combination treatment by adding paroxetine or bupropion or placebo to a mood stabilizer. The results suggested that the 2 antidepressant arms did not perform significantly better than placebo on top of a mood stabilizer after 26 weeks in terms of recovery rates or transient remission. The switch rates were similar as was the drop-out rate (Sachs et al., 2007), and neither response to treatment nor switching were dose dependent (Tada et al., 2015). The third trial was a 12-week double-blind, randomized, placebo-controlled study from China that reported that carbamazepine plus the herbal FEWP (36 g/d) was superior to carbamazepine alone and to placebo, but the quality of this study is considered to be low because there was no a-priori defined primary outcome (Zhang et al., 2007).

In a small study, 21 patients with acute BD-II depression, being on therapeutic levels of lithium or valproate, were randomly assigned to treatment with the dopamine D2/D3 antagonist pramipexole (n = 10) or placebo (n = 11) for 6 weeks. All subjects except for one in each group completed the study. There was a superiority of pramipexole in terms of response (60% vs 9%; P = .02). One subject on pramipexole and 2 on placebo developed hypomanic symptoms (Zarate et al., 2004). Another small study randomized 17 BD depressed patients to receive adjunctive inositol or placebo for 6 weeks on lithium or valproate. The results were numerically in favor of inositol in terms of response rates (44% vs 0%; P = .053) (Eden Evins et al., 2006b).

Add-on treatment—Overall, the data suggest that in bipolar depressed patients who experience depression while under lithium treatment, it is appropriate to add lamotrigine (van der Loos et al., 2009, 2010, 2011), the D2 antagonist L-sulpiride (Bocchetta et al., 1993), or maybe oxcarbazepine (Jurjena et al., 2009) but not imipramine (Nemeroff et al., 2001). The data on adding paroxetine and amitriptyline are equivocal (Bocchetta et al., 1993; Bauer et al., 1999a; Pilhatsch et al., 2010; van der Loos et al., 2010). Imipramine and venlafaxine might pose the patients at an increased risk of switching to the opposite pole without any visible therapeutic benefit in comparison with other antidepressants (Nemeroff et al., 2001; Vieta et al., 2002).

In BD patients experiencing depression during treatment with lithium or valproate, ketamine or lurasidone could be added. Lurasidone also improves anxiety and ketamine improves suicidality in these patients. Response to a single ketamine infusion appears within minutes but does not last more than 3 to 4 days (Young et al., 2000; Diazgranados et al., 2010; Zarate et al., 2012; Loebel et al., 2014b; Xu et al., 2015a). However, there is one unpublished failed study with lurasidone as add-on to lithium or valproate (Suppes et al., 2013; Sanford and Dhillon, 2015). A small placebo-controlled adjunctive study of aripiprazole to lithium and citalopram was negative. However, the study was underpowered and the study sample was too small to detect any differences (Quante et al., 2010).

The data on the options to treat BD patients who experience a depressed episode during treatment with mood stabilizers suggest that it is not appropriate to add zipsrasidine (Sachs et al., 2011), and the data are also negative also concerning bipolar spectrum depressed patients (Patkar et al., 2015). The antiepileptic agent topiramate and leviracetam should be avoided because there is a risk of worsening depression and inducing suicidality (Fountoulakis et al., 2012c; 2015; Siamouli et al., 2014). Imipramine and venlafaxine increased the risk of switching to the opposite pole without any visible therapeutic benefits in comparison with other antidepressants (Sachs et al., 1994, 2011; Post et al., 2001, 2006; Shelton and Stahl, 2004; Schaffer et al., 2006; Alshuler et al., 2009; Saricicek et al., 2010).

The data are negative concerning the addition of memantine to lamotrigine (Anand et al., 2012) or valproate (Lee et al., 2014a, 2014b), ketamine to ECT (Abdallah et al., 2012), lisdexamfetamine to treatment as usual (McElroy et al., 2015), and the melatonergic antidepressant agomelatine to lithium or valproate (Yatham et al., 2016).

Another placebo-controlled study in 85 bipolar depressive patients with adjunctive modafinil (a wake-promoting agent; mean dose 177 mg/d) demonstrated improved outcomes of bipolar depression without switching to mania or hypomania. Both the response and remission rates were significantly higher in the modafinil group (44% and 39%) compared with the placebo group (23% and 18%) (Frye et al., 2007). Although that study did not report a higher risk for manic switches, it has been reported that modafinil could cause subclinical switches (Fountoulakis et al., 2008c). One published study for the treatment of acute BD-I depression with adjunct modafinil (the longer lasting isomer of modafinil; dosage 150 mg/d; n = 128) on lithium, valproate, or olanzapine was positive (Calabrese et al., 2010, 2014). However 2 other studies were reported to be negative (Ostacher, 2014; Ketter et al., 2015). One small study on the efficacy of the antidiabetic agent pioglitazone as add-on to lithium in bipolar patients without diabetes mellitus was positive (Zeinoddini et al., 2015). A trial of celecoxib (400 mg/d) did not support its efficacy as an adjunct in the treatment of depressive or mixed episodes (Nery et al., 2008). One study with add-on pregnenolone (titrated to 500 mg/d) was negative (Brown et al., 2014), while a very small placebo controlled trial without an a-priori defined primary outcome suggested that adding supraphysiologic doses of levothyroxine (L-T4) to a mood stabilizer improves the outcome (Bauer et al., 2016).

Some data support the usefulness of omega-3 fatty acids as adjunctive therapy in bipolar depression but not mania, but the data are conflicting and inconclusive (Stoll et al., 1999; Chiu et al., 2006).
2005; Frangou et al., 2006; Keck et al., 2006b; Frangou et al., 2007; Murphy et al., 2012; Sarris et al., 2012; Sylvia et al., 2013)

Although there is a wide consensus on the usefulness of ECT both against acute mania and acute bipolar depression and in refractory cases, controlled hard data are scant (Loo et al., 2010). A recent study suggests that ECT may be more effective than pharmacotherapy for treatment-resistant bipolar depression (Schoeyen et al., 2015). Another potential tool could be TMS; however, it has been poorly investigated in bipolar depression (Dell’Osso et al., 2009). Sleep deprivation and other noninvasive circadian-related interventions could be useful add-on treatments to accelerate and sustain the antidepressant response (Wu et al., 2009). One study on bright light therapy in bipolar depression was negative (Dauphinais et al., 2012).

### Posthoc, Review, and Meta-Analytic Studies

Posthoc analyses of controlled trials. A posthoc analysis of the OFC and olanzapine data (Tohen et al., 2003c) reported patients with bipolar depression receiving olanzapine or OFC had greater improvement in health-related quality of life than those receiving placebo, and additionally OFC treatment is superior to olanzapine alone (Shi et al., 2004b). A second posthoc analysis of the same data set data reported that the beneficial effect was already present at day 7. A number of alternative methods of analysis of the data (pattern analysis, survival analysis, and mixed-effects regression analysis) confirmed the superiority of both olanzapine and OFC vs placebo (Dube et al., 2007).

A subanalysis of Japanese subpopulation from the second olanzapine study (Tohen et al., 2012) further supported the efficacy of olanzapine in the treatment of bipolar depression (Katagiri et al., 2013). A pooled analysis of the 2 olanzapine studies (Tohen et al., 2003c, 2012) that utilized last observation carried forward data supported the efficacy of olanzapine on the core depressive items (Tohen et al., 2013).

One posthoc analysis included 2 quetiapine trials (Calabrese et al., 2005b; Thase et al., 2006) and confirmed the efficacy of quetiapine as monotherapy, in comparison with placebo, for the treatment of acute depressive episodes in BD-II disorder (Suppes et al., 2008a). Another posthoc analysis of only one of these trials (Calabrese et al., 2005b) concluded that quetiapine significantly improved quality of life from week 4 onwards as well as quality of sleep (Endicott et al., 2007). A further posthoc analysis of the same study reported that the NNT was 5 for both response and remission for quetiapine (600 and 300 mg/d) compared with placebo (Cookson et al., 2007). Another posthoc analysis of these 2 quetiapine trials reported that quetiapine was effective in BD-I depressed patients already from week 1 onwards (Weisler et al., 2008).

One posthoc analysis of pooled data from 2 similarly designed trials who assessed the impact of aripiprazole monotherapy (Thase et al., 2008) reported that at endpoint aripiprazole was not efficacious in the more severely depressed patients (Thase et al., 2012). The posthoc analysis of the 2 negative unpublished ziprasidone monotherapy trials confirmed that ziprasidone did not show superiority over placebo at week 6 in the treatment of bipolar depression and was not efficacious in the more or less severely depressed patients (Lombardo et al., 2012).

A posthoc analysis of a 6-week trial of imipramine, phenelzine or placebo reported that BD-II depressive patients respond in a similar way to unipolar patients (Agosti and Stewart, 2007).

An interesting posthoc analysis of the lurasidone studies developed a mathematical model for the drug and placebo responses and trajectories (Chapel et al., 2016), while a meta-analysis of combination studies confirmed the higher rate of adverse events in comparison with monotherapy (Galling et al., 2015). A third analysis suggested a beneficial effect of lurasidone on functioning that was partially mediated through the improvement of depressive symptoms and partially a direct effect (Rajagopalan et al., 2016).

The meta-analysis of ketamine studies support its efficacy but suggest the data are conflicting as to whether the therapeutic effect extends beyond day 4 and up to day 7 (Lee et al., 2015; Romeo et al., 2015).

### Review and meta-analytic studies.

A review confirmed that lamotrigine had only negative data concerning the primary outcome in acute bipolar depression (Amanol, 2010); however, there was some kind of positive signal in some of the secondary outcomes. The pooling of raw data from the lamotrigine studies found a significant effect in terms of response (HAM-D score, RR = 1.27, 95% CI 1.09–1.47, P = .002) and remission rates (MADRS score, RR = 1.21, 95% CI 1.03–1.42, P = .021). There was a significant change in the MADRS total score from baseline (P = .04) but not in the HAM-D (P = .08). Baseline severity of depression seemed to play a significant role, and lamotrigine was superior to placebo in patients with HAM-D score >24 (RR = 1.47, P = .001) but not in those with HAM-D score ≤24 (RR = 1.07, P = .445). This meta-analysis reported an admixture of contradictory results, with lamotrigine being efficacious according to one outcome but not according to another (e.g., according to MADRS but not to HAM-D and vice versa). Also the interaction by severity was because of a higher response rate in the placebo group in the moderately ill patients, while the response rate to lamotrigine was independent of severity (Geddes et al., 2009).

The efficacy of carbamazepine was supported by 2 other reviews (Sriurapanont et al., 1995; Yatham et al., 1997).

A number of meta-analyses that were published later reported that only quetiapine, OFC, lamotrigine, and to a lesser extend olanzapine monotherapy exert efficacy in the treatment of bipolar depression. They also reported negative results for lamotrigine and aripiprazole, lithium as well as for adjunctive inositol (Cruz et al., 2010; Kemp et al., 2010; Tamayo et al., 2010; Vieta et al., 2010c; De Fruyt et al., 2011, 2012; Gao et al., 2011; Silva et al., 2013; Citrome et al., 2014; Mukai et al., 2014; Suttaji et al., 2014). Also, it was reported that patients who do not respond in the first 2 weeks of treatment are unlikely to respond eventually and would benefit from a change in treatment (Kemp et al., 2010).

Two meta-analyses using identical studies suggested there is some weak efficacy for valproate (Bond et al., 2010; Smith et al., 2010) and one suggested the same for aripiprazole (Fountoulakis et al., 2011a). Another one suggested that treatment with ziprasidone increases the risk for akathisia and reported somnolence that seemed to be dose dependent (Gao et al., 2013). There are 3 meta-analysis with conflicting conclusions concerning the efficacy of antidepressants (Gijssman et al., 2004; Sidor and Macqueen, 2010, 2012; Vazquez et al., 2013) However, it is clear that a class effect is not present concerning antidepressants in bipolar depression (Fountoulakis et al., 2011b). Another meta-analysis suggested that mood stabilizer monotherapy is efficacious but the addition of an antidepressant does not increase efficacy (Van Lieshout and MacQueen, 2010).

One meta-analysis that focused on depressed patients with BD-II reported that quetiapine had compelling evidence supporting its efficacy, while there was some support for the efficacy of lithium, antidepressants, and pramipexole. The data for lamotrigine were equivocal (Swartz and Thase, 2011), while some data suggest the efficacy of stimulants, especially modafinil (Corp et al., 2014), ketamine (Fond et al., 2014; McGirr et al., 2014), and antiinflammatory agents compared with...
conventional therapy alone in the treatment of bipolar depression (Rosenblat et al., 2016).

Two reviews investigated the issue of the treatment of refractory bipolar depression and concluded that the available hard data are extremely scarce and most of the strategies remain essentially experimental; however, there seem to be some that are potentially efficacious and promising (Aan Het Rot et al., 2012; Sienaert et al., 2013).

One meta-analysis compared the efficacy of ECT in unipolar vs bipolar depression and identified 6 relevant studies. It reported a similar rate of response in both disorders (50.9% vs 53.2%) (Diercks et al., 2012).

Finally, a meta-analysis reported that the probability of receiving placebo, baseline illness severity, and trial duration correlate with placebo response rates and/or clinical trial outcome in RCTs of pharmacotherapy for bipolar depression (Nierenberg et al., 2015), while another one was negative concerning the usefulness of galantamine, donepezil, and memantine (Veronese et al., 2016).

Maintenance Treatment

The efficacy data for monotherapy for the maintenance treatment phase are shown in Table 4. The data concerning the combination treatment are shown in Table 5.

Monotherapy

Lithium. There are a number of historic small studies that investigated the usefulness of lithium in the maintenance treatment of BD (Baastrup et al., 1970; Melia, 1970; Small et al., 1971; Cundall et al., 1972; Hullin et al., 1972; Persson, 1972; Prien et al., 1973b; Prien et al., 1973a; Dunner et al., 1976; Fieve et al., 1976; Fyro and Petterson, 1977; Klein et al., 1981; Christodoulou and Lykouras, 1982; Kane et al., 1982; Margo and McMahon, 1982; Mander and Loudon, 1988; Post et al., 1992). All of them reported positive findings; however, a number of drawbacks including the obsolete methodological approach and the utilization of mixed and small samples make the results of these trials difficult to interpret.

Overall, there are 4 randomized placebo controlled studies concerning the efficacy of lithium in the maintenance treatment of BD. One is negative/failed (Bowden et al., 2000) and 3 are positive (Bowden et al., 2003; Calabrese et al., 2003b; Weisler et al., 2011). The fourth is a small discontinuation study (Kafantarlis et al., 2004). Two of the positive studies support the usefulness of lithium in the prevention of manic but not depressive episodes irrespective of the polarity of the index episodes (Bowden et al., 2003; Calabrese et al., 2003b). The third study also supports its usefulness in the prevention of depressive episodes (Weisler et al., 2011). There are no data on the efficacy concerning the prevention of mixed episodes or for rapid cycling patients. It is important to note that the study samples were not enriched for response to lithium. On the contrary, one study had a sample enriched for response to quetiapine (Weisler et al., 2011), while 2 others had samples enriched for lamotrigine (Bowden et al., 2003; Calabrese et al., 2003b), that, however, is not efficacious against acute mania. There are some problems with the design of the studies, especially concerning the magnitude of improvement during the acute treatment phase and the duration the patients were required to be stable before entering the double-blind phase. With a few exceptions, most are essentially relapse prevention, not maintenance studies.

Antiepileptics. Valproate—As mentioned above, there is one properly conducted trial (Bowden et al., 2000) in that valproate was the agent under investigation. Lithium served as active control, and since, as shown above, lithium has proven efficacy during the maintenance phase of BD, this specific trial is best considered to be a failed study and not negative for valproate.

Carbamazepine—Concerning carbamazepine, there is only one small placebo controlled study. Although carbamazepine was effective in 60% of cases relative to 22% in the placebo group, the differences were not significant likely due to lack of power. Further, there were methodological issues with the study design and hence, the data are difficult to interpret (Okuma et al., 1981).

Lamotrigine—Overall there are 3 placebo controlled RCTs concerning the efficacy of lamotrigine in the maintenance treatment of BD. Two of them suggest lamotrigine is efficacious in the prevention of depressive but not manic episodes irrespective of the polarity of the index episodes (Bowden et al., 2003; Calabrese et al., 2003b). There are no data concerning index mixed episodes. The only study in rapid cycling patients was negative concerning the primary outcome (Calabrese et al., 2000). All studies were enriched for tolerability to lamotrigine, but one should keep in mind that lamotrigine is neither efficacious against acute mania nor acute bipolar depression. There were some problems with the design of the studies, particularly concerning the magnitude of improvement during the acute treatment phase and the dura-

<table>
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<tr>
<th>Agent/modality (alphabetical order)</th>
<th>Index episode</th>
<th>Enriched sample</th>
<th>Any episode</th>
<th>Manic</th>
<th>Depressive</th>
</tr>
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</table>

Abbreviations: - , no data; m, mania/mixed; d, depression; m/d, both mania and depression.

The treatment options are rated according to the rating system shown in Table 1. Enriched sample: the sample is enriched on the basis of remission after treatment with the agent under consideration during the acute phase (index episode).
Table 5. Combination treatment during the maintenance phase, grading on basis of efficacy.

<table>
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<th>Agent/modality (alphabetical order)</th>
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<th>Overall</th>
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<th>Depressive</th>
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</tr>
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<td>Ziprasidone</td>
<td>m</td>
<td>yes</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: -, no data; CBT, cognitive behavioral therapy; Cbz, carbamazepine; d, depression; Lam: Lamotrigine; Li: Lithium; m, mania/mixed; m/d, both mania and depression; MS, mood stabilizer; Val, valproate.

The treatment options are rated according to the rating system shown in Table 1. Enriched sample: the sample is enriched on the basis of remission after treatment with the agent under consideration during the acute phase (index episode).

tion the patients were stable before entering the double-blind phase. Essentially they were relapse prevention, not maintenance studies.

Antidepressants. There are 2 small, old negative studies concerning the efficacy of imipramine (Prien et al., 1973a; Kane et al., 1982), while on the contrary, 3 other small studies in BD-II patients provide some support for the usefulness of fluoxetine monotherapy in the prevention of depressive episodes (Amsterdam et al., 1998; Amsterdam and Shults, 2005b, 2010).

Antipsychotics. Olanzapine—Three trials provide support for the efficacy of olanzapine in the prevention of manic, depressive, or mixed episodes in patients with an index manic or mixed episode that responded to olanzapine treatment during the acute phase (Tohen et al., 2006; Berwaerts et al., 2012a; Vieta et al., 2012). There are some data to support the notion that the efficacy of olanzapine is not restricted to those patients who responded to olanzapine during the acute phase. Its long-term effects in rapid cycling patients are unknown.

Aripiprazole—There are 2 trials that support the efficacy of aripiprazole in the prevention of manic but not depressive episodes in BD patients after an index manic or mixed episode who responded to aripiprazole during the acute phase (Keck et al., 2006a; Keck et al., 2007). These 2 trials utilize a methodology that satisfies stringent criteria concerning the definition of “maintenance” treatment.

Quetiapine—There is one published positive study that investigated the efficacy and safety of quetiapine IR monotherapy (300–800 mg/d) as maintenance treatment in BD-I patients compared with switching to placebo or lithium. The time to recurrence of any mood event was significantly longer for both quetiapine and lithium vs placebo. Both quetiapine and lithium significantly increased time to recurrence of both manic and depressive episodes compared with placebo (Weisler et al., 2011). A second study in patients who had recovered from bipolar depression reported that quetiapine prevented depressive but not manic episodes (Young et al., 2014).

Paliperidone—There is one positive study that supports the usefulness of paliperidone in the prevention of manic but not depressive recurrences in patients with index manic or mixed episodes who responded to paliperidone during the acute phase (Berwaerts et al., 2012a).

Risperidone long-acting injectable (RLAI)—Two studies support the efficacy of RLAI in the prevention of manic but not depressive episodes in BD-I patients with a manic or mixed index episode who responded to oral risperidone or RLAI during the acute phase (Quiroz et al., 2010; Vieta et al., 2012).

Conclusion of monotherapy trials. Lithium, olanzapine, quetiapine, aripiprazole, paliperidone, and RLAI are efficacious in the prevention of manic episodes in patients who recovered from an index manic or mixed episode. Olanzapine and quetiapine are also efficacious in the prevention of depressive episodes. Quetiapine was efficacious irrespective of the index episode. Olanzapine was also efficacious in the prevention of mixed episodes. There is a lack of data concerning carbamazepine or valproate.

Lamotrigine is efficacious in the prevention of depressive but not manic episodes irrespective of index episode. It was not efficacious in the prevention of mixed episodes or in rapid cycling patients. The literature does not support the efficacy of imipramine, while, on the contrary, it gives some support for the efficacy of fluoxetine but only in BD-II patients.

All except lithium and olanzapine were proven efficacious only in samples enriched for response or tolerability during the acute phase. Except from the negative data for lamotrigine there are no data concerning rapid cycling patients. Also, except from the data concerning olanzapine, there are no data concerning
specifically the prevention of mixed episodes or the response of patients with an index mixed episode.

**Comparison of Treatments**

**Lithium vs others.** There are a number of studies comparing lithium with carbamazepine (Placidi et al., 1986; Watkins et al., 1987; Lusznat et al., 1988; Stoll et al., 1989; Small et al., 1991; Oxhead et al., 1992; Simhandl et al., 1993; Denicoff et al., 1997; Hartong et al., 2003) including the MAP study (Greil et al., 1997; Greil and Kleindienst, 1999a, 199b; Kleindienst and Greil, 2000, 2002), and overall the data suggested that both agents are comparable in terms of efficacy. There are some data in favor of a superiority of lithium in the treatment of more “classic” patients, but in the rest of patients the 2 agents seem to be comparable. Lithium was also comparable to valproate in terms of prevention of mood episodes (Bowden et al., 2000; Calabrese et al., 2005a) and suicidality (Oquendo et al., 2011) to olanzapine (Tohen et al., 2005) and also to aripiprazole (El-Mallakh et al., 2012).

Furthermore, there was a difference in the clinical profiles of lithium and lamotrigine. As mentioned before, 3 placebo-controlled RCTs suggest that lamotrigine was more efficacious in the prevention of depressive episodes and lithium in the prevention of manic, hypomanic, and mixed episodes (Bowden et al., 2003; Calabrese et al., 2003b).

When compared with antidepressants, the available data suggest that lithium is superior to imipramine for the prevention of depression in BD-I patients episodes (Prien et al., 1973a; Prien et al., 1984) but inferior to fluoxetine in BD-II patients (Amsterdam and Shults, 2010).

A maintenance study reported equal efficacy between venlafaxine and lithium in the prevention of depressive relapses, although there was a tendency of better performance for venlafaxine (Amsterdam et al., 2015).

**Antiepileptics vs others.** The studies comparing valproate with lithium have already been discussed above (Bowden et al., 2000; Calabrese et al., 2005a; Oquendo et al., 2011). Two trials suggested valproate is comparable with olanzapine (Tohen et al., 2003a) and with a similar cost to healthcare system (Zhu et al., 2005). Carbamazepine has been studied only in comparison with lithium, and these studies have been discussed previously in the paragraph concerning lithium (Placidi et al., 1986; Watkins et al., 1987; Lusznat et al., 1988; Small et al., 1991; Oxhead et al., 1992; Simhandl et al., 1993; Denicoff et al., 1997; Greil et al., 1997; Greil and Kleindienst, 1999a; Kleindienst and Greil, 2000, 2002; Hartong et al., 2003).

**Olanzapine vs others.** The comparison of olanzapine with lithium (Tohen et al., 2005) and valproate (Tohen et al., 2003a; Zhu et al., 2005) has been discussed above.

One study that constituted the extension of an acute phase trial suggested that olanzapine is comparable with asenapine (McIntyre et al., 2010a), while another suggested that it is superior to paliperidone ER (Berwaerts et al., 2012a) and to long-acting risperidone (Vieta et al., 2012).

Other comparisons. The comparisons of aripiprazole (El-Mallakh et al., 2012), fluoxetine (Amsterdam and Shults, 2010), imipramine (Prien et al., 1984), and lamotrigine (Bowden et al., 2003; Calabrese et al., 2003b) with lithium, and of asenapine (McIntyre et al., 2010a), paliperidone, and risperidone with olanzapine (Berwaerts et al., 2012a; Vieta et al., 2012) have been discussed previously.

One 25-week RCT comparing the OFC vs lamotrigine in the prevention of bipolar depression reported that bipolar depressive patients who responded to OFC do better on long-term OFC in comparison with spontaneously improved patients on long-term lamotrigine (Brown et al., 2009). The result is difficult to interpret as there was an enrichment of the OFC arm, but not the lamotrigine arm. Finally, one study compared the efficacy of venlafaxine in the prevention of bipolar vs unipolar depression and reported no difference between groups (Amsterdam and Garcia-Espana, 2000).

**Combination and Add-On Treatment**

Combination treatment. There are 3 early studies that investigated the combination of lithium with another agent. The lithium plus imipramine combination was not more efficacious than lithium monotherapy (Kane et al., 1982; Prien et al., 1984) and lithium or carbamazepine monotherapy was not inferior to their combination that, however, was more efficacious in rapid cycling patients (Denicoff et al., 1997). Also the combination of lithium, carbamazepine, or valproate with perphenazine was not better than mood stabilizer monotherapy; on the contrary, combination treatment was associated with a shorter time to depressive relapse, more drop-outs, and increased rates of dysthymia and depressive symptoms (Zarate and Tohen, 2004). Similarly negative were the results for the lithium or valproate combination with olanzapine (Tohen et al., 2004) while, on the contrary, the combination with quetiapine had significant advantages irrespective of index episode, mood stabilizer and rapid cycling status (Vieta et al., 2008a; Suppes et al., 2009). Positive results were also reported for their combination with ziprasidone (Bowden et al., 2010). Results were negative for aripiprazole plus valproate (Woo et al., 2011) or lamotrigine (Carlson et al., 2012).

The OFC was similar to lamotrigine in terms of incidence of relapse, but overall bipolar depressive patients who responded to OFC do better on long-term OFC in comparison with spontaneously improved patients on long-term lamotrigine (Brown et al., 2009). Lamotrigine plus divalproex was not superior to lamotrigine alone concerning the time to depressive episode (Bowden et al., 2012).

The open-label BALANCE study results neither reliably confirmed nor refuted a benefit of valproate/lithium combination therapy compared with lithium monotherapy, but clearly demonstrated that it is superior to valproate alone (Geddes et al., 2010). Another study reported that risperidone or olanzapine adjunctive therapy for 24 weeks is beneficial but continuation of risperidone beyond this period does not reduce the risk of relapse. Whether continuation of olanzapine beyond this period reduces relapse risk remains unclear but the potential benefit needs to be weighed against an increased risk of weight gain (Yatham et al., 2015).

Overall, there is no compelling data that combination treatment in general does better than monotherapy. Patients stabilized on combination treatment might, however, do worse if shifted to monotherapy, and combination treatment with quetiapine or ziprasidone plus a mood stabilizer might work better than a mood stabilizer alone.

**Add-on treatment.** A small study supported the adding of phenytoin to treatment as usual (Mishory et al., 2003) as did another small one for gabapentin (but not on top of antipsychotics) (Vieta et al., 2006). The data are negative for the addition of oxcarbazepine (Vieta et al., 2008c) and equivocal for lamotrigine (van der Loos et al., 2011) to lithium. Negative data were also reported from a trial of adjunctive pramipexole to treatment as usual (TAU) in stabilized BD patients with the aim to improve neurocognition (Burdick et al., 2011), and from a trial of N-acetyl cysteine on TAU in patients after an index episode of bipolar depression (Berk et al., 2012). It is interesting that adjunctive
RLAI on TAU significantly prolongs the time to relapse in rapid cycling patients (Macfadden et al., 2009). Adding aripiprazole to lithium or valproate also supplied positive results (Marcus et al., 2011).

It is reported that patients who respond to treatment with lithium, valproate, or carbamazepine plus antidepressants are more likely to maintain response with continuation of the combined treatment; however, those patients who manifest only a partial acute response are unlikely to further improve when the same treatment is continued (Altshuler et al., 2009). Also, adjunctive asenapine to lithium or valproate was well tolerated for up to 52 weeks, but no efficacy data were reported from that trial (Szegedi et al., 2012).

Two trials investigated the efficacy of adjunctive N-acetyl cysteine (NAC). The first one randomized 75 BD patients during the maintenance phase and reported that NAC treatment caused a significant improvement on the MADRS score in comparison with placebo (P=0.02). Improvements were lost after washout. There was no effect of NAC on time to a mood episode and no significant between-group differences in adverse events (Berk et al., 2008). The second randomized 14 patients (not all of them with high depression scores) and reported a superiority of the NAC group vs placebo in terms of remission (P=0.031) (Magalhaes et al., 2011b). One maintenance study supported the usefulness of ramelteon in the prevention of relapse in BD patients (Norris et al., 2013). Negative results have been reported for the usefulness of memantine in patients on valproate treatment (Lee et al., 2014b).

There are some studies suggesting that there is a role for various nutritional supplements such as n-3 fatty acids, chromium, choline, magnesium, and tryptophan alone or in combination with pharmacotherapies for the treatment of BD, but the data are of low quality (Sylvia et al., 2013).

Posthoc, Reviews, and Meta-Analytic Studies

Posthoc analyses. A number of posthoc analyses exist and attempt to answer questions that the original papers did not address. Posthoc analysis can be informative but can also be a major source of publication bias (Vieta, 2007). A subanalysis of the MAP study reported that lithium was superior in classical BD-I patients and comparable with carbamazepine in the rest. An additional subanalysis including mixed states as an additional nonclassical feature confirmed the results (Greil et al., 1998).

Concerning the usefulness of antidepressants, one posthoc analysis suggested that the discontinuation rate for any reason was lower among patients in the divalproex group taking a selective serotonin re-uptake inhibitor (SSRI) than among patients in the placebo group taking an SSRI (Gyulai et al., 2003b), while the application of 4 different remission criteria suggested that the application of different definitions of remission does not make any significant difference concerning the results (Pae et al., 2012). The addition of an atypical antipsychotic-antimanic agent in some BD patients might help to reduce suicidal ideation (Houston et al., 2006). Olanzapine might be more beneficial if started at an earlier stage of the disease (Ketter et al., 2006), and it is also efficacious in patients with an index mixed episode (Tóhen et al., 2009).

Concerning lithium, it has been reported that only at plasma levels between 0.6 and 1.2 mEq/L it is efficacious in the prevention of both manic and depressive episodes (Nolen and Weisler, 2013). Another posthoc analysis did not confirm its efficacy in the prevention of depressive episodes while it confirmed the efficacy of lamotrigine in the prevention of both manic and depressive episodes irrespective of index episode (Calabrese et al., 2003a; Goodwin et al., 2004). These results still held true when early relapses that occurred in the first 90 or 180 days were excluded from the analysis (Calabrese et al., 2006). The lack of efficacy of lithium in a subgroup of patients might be due to lithium induced thyroid function abnormalities in a subpopulation of patients (Frye et al., 2009). Overall, lamotrigine performed better in comparison with lithium in terms of remission and the persistence of subsyndromal symptoms (Frye et al., 2006). Some positive results for NAC were also suggested by 2 posthoc analyses (Magalhaes et al., 2011a, 2013).

Review and meta-analyses. One review confirmed the efficacy of lithium but reported that there is no definitive evidence as to whether or not lithium has an anti-suicidal effect (Burgess et al., 2001). A more recent meta-analysis confirmed the antisuicidal effect of lithium vs placebo but not its superiority over other agents except carbamazepine (Cipriani et al., 2013). Two other studies support the usefulness of RLAI (Bobo and Shelton, 2010) and of ziprasidone for the maintenance treatment of BD-I disorder in adults as an adjunct to lithium or valproate (Citrome, 2010). Another review identified 4 issues that limit the interpretation of trials (insufficient duration, enriched sample, possible conflation with iatrogenic adverse effects by abrupt medication discontinuation with beneficial effects on treatment, and a low overall completion rate) (Tsai et al., 2011).

Concerning meta-analysis, the first one for carbamazepine failed to prove the prophylactic efficacy (Dardenne et al., 1995). A second one concluded that the data for oxcarbazepine are of very low quality not allowing firm conclusions (Vasudev et al., 2008). A fair number of meta-analyses focused on lithium. One confirmed its efficacy but failed to find sufficient evidence to prove that a lithium-withdrawal relapse phenomenon exists, that is patients relapse soon after stopping lithium and the symptomatology turns refractory to treatment (Davis et al., 1999). Another one supported an anti-suicidal efficacy of lithium (Tondo et al., 2001). Three others confirmed the prophylactic antimanic efficacy of lithium but were equivocal for the prophylactic efficacy against depressive episodes (Burgess et al., 2001; Geddes et al., 2004; Severus et al., 2014).

Furthermore, a number of meta-analytic studies confirmed the prophylactic antimanic efficacy of specific agents and the antidepressant of others. It is important to mention that among other more or less expected results, the antidepressant efficacy of valproate and imipramine was supported (Beynon et al., 2009) as well as of lithium (Popovic et al., 2010), while the prophylactic antidepressant efficacy of olanzapine was questioned (Cipriani et al., 2010). Antipsychotics might be superior to lithium and anticonvulsants but with more adverse effects (Vazquez et al., 2015a, 2015b).

The issue of combination treatment has been the focus of 2 meta-analyses. They both reported negative conclusions for the addition of antidepressants (Ghaemi et al., 2008; Beynon et al., 2009). A third analysis suggested that no monotherapy was associated with a significantly reduced risk for both manic/mixed and depressive relapse, and only quetiapine plus lithium or divalproex was associated with a significantly reduced risk for relapse towards both the manic/mixed and depressive pole (Vieta et al., 2011). This specific meta-analysis also pointed out that the majority of studies included samples enriched for response to a specific agent during the acute phase.

Finally, pharmaco-epidemiological data suggest that valproate and lithium might have a protective effect against any psychiatric hospitalization for patients with BD in a real world setting, while lamotrigine and carbamazepine might exert
protective effects solely against depressive and manic episodes, respectively (Joas et al., 2015).

Treatment of Mixed Episodes

Mixed episodes are no longer accepted as a diagnostic entity by DSM-5; instead “mixed features” is included as a specifier and this creates a degree of confusion for future treatment recommendations, since the 2 concepts differ significantly (Fountoulakis, 2015d). So far, mixed episodes have been combined with pure manic episodes in RCTs and results have been reported together. Only a few papers, usually posthoc analyses, report the results concerning mixed episodes separately. Unfortunately all data on mixed episodes stem from trials of acute mania and only one trial reports on the efficacy of lurasidone in bipolar depressive patients with mixed features. That trial supported the efficacy of lurasidone in those patients for the improvement of both depressive and manic symptoms (McIntyre et al., 2015; Suppes et al., 2015). Another important limitation is that the results reported usually concern only the manic but not the depressive component of the mixed episode (Fountoulakis et al., 2012b). The ranking of the data for the treatment of mixed episodes is shown in Table 6.

Treatment of Acute Mixed Episodes

Aripiprazole and carbamazepine were found efficacious in the treatment of both the manic and the depressive component of acute mixed episodes (Keck et al., 2003b; Weisler et al., 2004, 2005, 2006; Sachs et al., 2006; Suppes et al., 2008b). Ziprasidone was also found to be efficacious against both components, but the definition of mixed states was different from the DSM.

Olanzapine and valproate were reported to be efficacious against mania but the data are inconclusive concerning the depressive component (Tohen et al., 1999, 2000; Baker et al., 2003; Baldessarini et al., 2003b; Shi et al., 2004a; Bowden et al., 2006; Ghaemi et al., 2007; McIntyre et al., 2009b). The posthoc analysis of the 2 bipolar depressive trials suggested that olanzapine was efficacious in those patients with mixed features suggesting an effect also on the depressive component (Tohen et al., 2014). Furthermore, risperidone but not asenapine is reported to be efficacious against the manic component, but no data exist concerning their efficacy on the depressive component (Khanna et al., 2005; McIntyre et al., 2009b). A posthoc analysis suggested that asenapine but not olanzapine improved the quality of life in mixed patients (Michalak et al., 2014), and another 2 suggested that asenapine improved both the manic and depressive component in comparison with placebo and was also found superior to olanzapine concerning the manic but not the depressive component (McIntyre et al., 2013; Berk et al., 2015). However, a more recent trial was negative (Landblom et al., 2016). Paliperidone was efficacious only against the manic component (Vieta et al., 2010c; Berwaerts et al., 2012b). One study for quetiapine was a failed one (Cutler et al., 2011).

The combination of olanzapine olanzapine plus lithium or valproate have positive data concerning both components (Tohen et al., 2002b; Baker et al., 2004; Houston et al., 2006, 2009, 2011). In mixed depression the OFC was comparable with olanzapine and both were superior to placebo, but due to the small number of subjects the report does not permit to derive conclusions (Tohen et al., 2003c; Benazzi et al., 2009). The data concerning the combination of haloperidol or risperidone plus lithium or valproate were negative (Sachs et al., 2002). Overall it seems that second generation antipsychotics (SGAs) are effective in treating acute mixed episodes of BD, with predominant manic symptoms. Their efficacy in treating depressed mixed episodes remains unclear (Muradidharan et al., 2013).

The only trial in patients in bipolar depressive episode with mixed features supported the efficacy of lurasidone in these patients for the improvement of both depressive and manic symptoms (McIntyre et al., 2015; Suppes et al., 2015).

Maintenance Treatment of Mixed Bipolar Episodes

The data so far suggest that olanzapine prolongs time to relapse into any episode in patients with an index mixed episode (Tohen et al., 2006, 2009) while on the contrary, lithium and valproate had negative results in patients with a dysphoric manic index episode (Bowden et al., 2005a). Additionally, the data are in support of the combination of quetiapine plus lithium or valproate (Vieta et al., 2008a; Suppes et al., 2009) but are negative concerning aripiprazole in patients with an index mixed episode (Yatham et al., 2013a).

Table 6. Treatment of Mixed Episodes

<table>
<thead>
<tr>
<th>Agent/modality (alphabetical order)</th>
<th>Monotherapy</th>
<th>Combination with MS</th>
<th>Combination</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Acute Phase</td>
<td>Maintenance Phase</td>
<td></td>
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<tr>
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<td>3</td>
<td>2</td>
</tr>
<tr>
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<td>-</td>
</tr>
<tr>
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<tr>
<td>Celecoxib</td>
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</tr>
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<tr>
<td>Ziprasidone</td>
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</tbody>
</table>

Abbreviations: - no data, Cbz, carbamazepine, Lam, lamotrigine, Li, lithium; MS, mood stabilizer; OFC, olanzapine-fluoxetine combination; Val, valproate.

The treatment options are rated on the basis of efficacy according to the rating system shown in Table 1.
Treatment of Rapid Cycling Patients

The treatment of rapid cycling patients constitutes a challenge. Often their course frustrates the therapist and the evaluation of treatment is difficult because of the rapid switching from one pole to another (Fountoulakis et al., 2013). The ranking of the treatment of rapid cycling patients is shown in Table 7.

Treatment of Acute Episodes in Rapid Cycling Patients

Olanzapine is effective in reducing symptoms of mania and was well tolerated in rapid cycling BD-I patients as shown by a secondary analysis (Sanger et al., 2003). The pooling of data from 2 RCTs reported that improvement of mania with olanzapine was similar in rapid cyclers and non-rapid cyclers. However, rapid cyclers showed an earlier response (Vieta et al., 2004). One trial was also positive concerning aripiprazole in acutely manic rapid cycling patients (Sachs et al., 2006).

Although one study on acute mania in rapid cycling patients was a failed one (Cutler et al., 2011), one a priori planned subanalysis of data from rapid cycling patients with acute BD-I or BD-II depression suggested that quetiapine monotherapy (300–600 mg/d) was effective and well tolerated (Vieta et al., 2007). The posthoc analysis of the rapid cycling subsample of bipolar depressives from the BOLDER study confirmed this (Cookson et al., 2007), and finally the subanalysis of the data from a small number of depressed rapid cycling BD patients again suggested that 300 mg of quetiapine monotherapy was superior to placebo (Suppes et al., 2010).

It seems that lithium has a week but positive effect (Young et al., 2010) and also there are some positive but equivocal data for valproate (Muzina et al., 2010). On the other hand, the data are clearly negative for paroxetine (McElroy et al., 2010c).

The combination of lithium and divalproex was not effective and the further addition of lamotrigine did not seem to add anything in Terms of efficacy (Kemp et al., 2012b).

Relapse Prevention in Rapid Cycling Patients

For the prevention phase, the data so far suggest that divalproex is not more effective than lithium (Calabrese et al., 2005a) and also that the combination of lithium plus divalproex is not better than lithium alone (Kemp et al., 2009). One small study reported that the combination of lithium plus carbamazepine did better than either agent alone (Denicoff et al., 1997). It is interesting that the data are negative for lamotrigine, although in some secondary outcomes there was a beneficial signal especially in BD-II patients (Calabrese et al., 2000). Overall, the widely believed concept among clinicians that divalproex is more effective than lithium in the long-term management of rapid-cycling BD was not supported by a trial on 139 patients (Findling et al., 2005).

One posthoc analysis suggested that aripiprazole was efficacious (Muzina et al., 2008). There are no data on other antipsychotics in monotherapy concerning the maintenance phase. A posthoc analysis reported that rapid cycling patients did less well during the extended observation period than nonrapid cycling patients, regardless of treatment and that overall olanzapine and divalproex appeared comparable (Suppes et al., 2005).

Another study confirmed the efficacy and safety of quetiapine add-on to lithium or divalproex in the prevention of mood episodes in rapid cycling BD-I patients with most recent episode manic/mixed or depressive (Vieta et al., 2008a). There was a North American study with a similar design as the previous one reporting similar results (Suppes et al., 2009). A large controlled trial that evaluated adjunctive maintenance treatment with RLAi on TAU in 240 BD-I patients with at least 4 mood episodes in the 12 months prior to study entry yielded positive results (Macfadden et al., 2009).

The results of the STEP-BD support a role of antidepressants in the development of rapid cycling in a subpopulation of BD patients (Schneck et al., 2008; Ghaemi et al., 2010). A similar conclusion came from earlier randomized controlled study of rapid cycling patients using a double-blind on-off-on-off design with the use of tricyclic antidepressants (Wehr et al., 1988).

Finally, the data are negative concerning the administration of 6 g/d of ethyl-eicosapentanoate as augmentation of treatment with mood stabilizers in rapid cycling patients with bipolar depression (Keck et al., 2006b).

One meta-analysis suggested that lithium is at least partially efficacious in rapid cycling patients (Kupka et al., 2003), another one suggested there is no clear advantage of any treatment option vs the others (Tondo et al., 2003), while a third one proposed that some atypical antipsychotics (especially quetiapine and olanzapine) may be considered as the first-line treatment options (Cruz et al., 2010). The meta-analysis of 20 studies published from 1974 to 2002 comparing subjects with rapid and nonrapid cycling BD reported that in contrast to common beliefs, lithium prophylaxis has at least partial efficacy in a considerable number of rapid cyclers, especially when antidepressants are avoided. Hypothyroidism may be associated with mood destabilization in vulnerable patients (Kupka et al., 2003).

Table 7. Treatment of Rapid Cycling Patients during the Different Phases of BD

<table>
<thead>
<tr>
<th>Agent/modality (alphabetical order)</th>
<th>ACUTE mania</th>
<th>Depression</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>-</td>
<td>-</td>
<td>2 (Li + Cbz)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Lithium</td>
<td>4</td>
<td>3</td>
<td>2 (Li, Li + Cbz)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3</td>
<td>2</td>
<td>2 (Quet+ Val/Li)</td>
</tr>
<tr>
<td>Risperidone, long-acting injectable</td>
<td>-</td>
<td>-</td>
<td>2 (RLAI+TAU)</td>
</tr>
<tr>
<td>Valproate</td>
<td>4</td>
<td>4</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: -, no data; Cbz, carbamazepine; Li, lithium; Quet, quetiapine; RLAi, risperidone long-acting injectable; TAU, treatment as usual; Val, valproate.

The treatment options are rated on the basis of efficacy according to the rating system shown in Table 1.

Treatment of Special Conditions

Treatment of Comorbid Conditions

Comorbidities are common in bipolar patients and often need more elaborated therapeutic interventions (Fountoulakis, 2015e, 2015f, 2015g).

Treatment of comorbid substance abuse disorder (SUD). There are 2 placebo controlled trials suggesting that the combination of valproate and lithium in BD patients with co-occurring alcohol dependence improves both mood and alcohol use symptoms (Salloom et al., 2005, 2007) and that lithium treatment in BD adolescents improves mood and substance use symptoms (Cerullo and Strakowski, 2007). Lithium can be used for the treatment of comorbid substance and polysubstance abuse (Geller et al., 1992, 1998), and quetiapine and risperidone can reduce drug craving.
The ranking of the treatment of comorbid anxiety is shown in Table 3.

Weight gain. Topiramate is not effective in the treatment of BD per se; however, it is unique because of its ability to cause weight loss at dosages of 50 to 200 mg/day. A review reported that more than 70% of patients taking topiramate for a mean duration of 5 months lost a mean of 5 to 6 kilograms (Arnone, 2005). However, topiramate might cause de novo depression and suicidality in some patients, although no completed suicides related to topiramate have been reported (Fountoulakis et al., 2012c).

Treatment of agitation. Probably most clinicians would choose antipsychotics in severely agitated bipolar patients, and this option is supported by a double-blind clinical trial that reported that intramuscular haloperidol (5–10 mg) was equal in efficacy but faster acting in comparison with intramuscular clonazepam (1–2 mg) in agitated mania at 0, 30, and 60 minutes (Chouinard et al., 1993). Similarly, i.m. olanzapine (10 mg, first 2 injections; 5 mg, third injection) was reported to be superior to lorazepam (2 mg, first 2 injections; 1 mg, third injection) for the control of agitation in manic patients. Already 2 hours after the first injection, patients treated with olanzapine showed a significantly greater reduction in scores on all agitation scales compared with patients treated with either placebo or lorazepam (Meehan et al., 2001).

Valproate oral loading of 20 mg/kg/d was reported to be comparable with haloperidol 0.2 mg/kg/d for the treatment of exited manic patients in a single-blind study and the effect was evident within 3 days from starting (McElroy et al., 1996). Overall, valproate loading up to 30 mg/kg/d was reported to be safe and well tolerated (Hirschfeld et al., 1999).

Inhaled loxapine exerted an antiagitation effect at 10 minutes at both the 5- and 10-mg doses and was superior to placebo at all time points measured. For safety reasons it has been recommended that inhaled loxapine should be restricted to a single dose in 24 hours and needs to be subject to a Risk Evaluation and Mitigation Strategy program (Citrome, 2012; Kwentus et al., 2012). In Europe, 2 doses are allowed (the second must be given 2 hours after the initial inhalation) (Popovic et al., 2015).

The issue of agitation with aripiprazole is controversial. As an adverse event it is not reported in the dataset and on the contrary, aripiprazole is a recommended evidence-based treatment against agitation associated with schizophrenia or bipolar mania (Sanford and Scott, 2008; Gonzalez et al., 2013; Citrome et al., 2016). However, it has been reported under naturalistic conditions (Di Lorenzo et al., 2007) and especially in vulnerable populations such as elderly patients (Coley et al., 2009). Agitation has also been described when initiating aripiprazole in patients after prolonged treatment with potent D2 blocking agents that may result in an upregulation of postsynaptic dopamine receptors (Lea et al., 2007). However, a major obstacle for a fair estimate of the rate of agitation with aripiprazole is that akathisia can easily be mistaken as agitation (Thomas et al., 2015), especially by less experienced raters.

Treatment of Neurocognitive Deficits
The presence of a significant neurocognitive deficit in BD patients has been solidly shown and it concerns all phases of the disorder, including periods of euthymia (Titsiapa and Fountoulakis, 2015). Galantamine may have specific benefits for episodic memory, but not processing speed, in patients with cognitive impairment as part of BD (Ghaemi et al., 2009). One study reported that pramipexole...
may improve neurocognition in euthymic patients only (Burdick et al., 2012) while the data are negative for NAC (Dean et al., 2012).

Adjuvant intranasal insulin (40 IU q.i.d.; n = 34) had a beneficial effect on executive function but not on the other neurocognitive measures in euthymic patients (McIntyre et al., 2012a). Also adjuvant mifepristone, which is a synthetic steroid, at 600 mg/d improved spatial working memory in BD depressed patients, and this was evident also 7 weeks after the cessation of treatment (Watson et al., 2012).

ECT was reported to produce an improvement in neurocognitive function similar to that of algorithm-based pharmacological treatment (Kessler et al., 2014).

Suicide
There is much discussion concerning the potential antisuicidal efficacy of specific drugs and especially of lithium. However, almost all the data come from studies of naturalistic and epidemiological nature and no controlled studies exist.

There is only one posthoc analysis that investigated suicidality in BD-I patients during treatment with olanzapine in combination with lithium or divalproex. In mixed patients with residual suicidality, suicidal thoughts were associated with somatic discomfort, agitation, depression, and psychosis. It seems that combination therapy with olanzapine plus lithium (n = 36) vs lithium alone (n = 22) significantly reduced the score in the suicidal item of the HAM-D by 58% vs 29% (P <.05) within 1 week and all associated symptoms within 2 weeks by averages of 31% vs 12% (P <.05) (Houston et al., 2006). The analysis of pharmaco-epidemiological data suggests that treatment with lithium but not with valproate is associated with lower suicidality (Goodwin et al., 2003; Song et al., 2015).

Nonbiological Treatment Options
There are some but overall limited data concerning the usefulness of specific adjunctive psychotherapies (Reinares et al., 2014; Mizio et al., 2015). Research so far has focused on acute depression and the maintenance phase but not on acute mania. These studies suffer from the same limitations and methodological problems as all psychotherapy trials do. There is no universally accepted standardized method to conduct this kind of study and blinding and the nature of the control intervention are unresolved limitations. The grading of these treatment options is shown in Table 8.

Cognitive-Behavioral Therapy (CBT)
The overall data for the long-term efficacy of CBT either as monotherapy or as add on to psychoeducation and in comparison with TAU are negative concerning relapse prevention. However, there are some positive results for the acute depressive phase in BD (Ball et al., 2006; Scott et al., 2006; Zaretsky et al., 2008; Costa et al., 2011; Gomes et al., 2011; Meyer and Hautzinger, 2012; Gonzalez Isasi et al., 2014). A posthoc analysis suggested that CBT could be more effective than TAU in patients with <12 previous episodes, but less effective in those with more episodes (Scott et al., 2006). In BD patients with insomnia, CBT for insomnia was superior to psychoeducation concerning manic relapses (Harvey et al., 2015).

Psychoeducation
The data on adjunctive psychoeducation suggest that in comparison with TAU or nonspecific intervention, it prevents relapse to both poles if administered to patients in clinical remission (Perry et al., 1999; Colom et al., 2003, 2009; Lobban et al., 2010; de Barros et al., 2013) but it has no effect on biological rhythms (Cardoso Tde et al., 2015). Again a posthoc analysis suggested that patients with more than 7 episodes did not show significant improvement with group psychoeducation for time to recurrence, and those with more than 14 episodes did not benefit from the treatment in terms of time spent ill (Colom et al., 2010). A systematic review confirmed the above (Bond and Anderson, 2015).

Interpersonal and Social Rhythm Therapy (IPSRT)
Overall there are no convincing data on the usefulness of IPSRT during the maintenance phase of BD; however, there are some data suggesting that if applied early and particularly already during the acute phase, it might prolong the time to relapse (Frank et al., 2005, 2008; Swartz et al., 2012; Inder et al., 2015).

Family Focus Treatment
Overall the literature supports the idea that interventions that focus on families and caregivers exert a beneficial impact especially on family members, but the effect on the patients themselves is controversial and uncontrolled. Probably it improves issues like treatment adherence and family dynamics (Miklowitz et al., 2000, 2003; Rea et al., 2003; Reinares et al., 2004, 2008; D’Souza et al., 2010).

Intensive Psychosocial Intervention
“Intensive” psychotherapy is another option but it is of unknown efficacy with limited research support (Miklowitz et al., 2007a, 2007b). The term refers to up to 30 sessions of CBT, IPSRT, or family focus treatment within 9 months.

Cognitive Remediation and Functional Remediation
The data are positive in improving functioning, that is the critical endpoint, but mostly negative concerning cognitive outcomes
when using cognitive remediation techniques as add on to TAU in BD patients (Martinez-Aran et al., 2011; Lahera et al., 2013; Torrent et al., 2013), although a more recent posthoc analysis was promising (Sole et al., 2014).

**Mindfulness-Based Interventions (MBCT)**

Overall the data do not support a beneficial effect of MBCT on the core symptoms of BD but also suggest that MBCT could be useful in the reduction of anxiety in BD patients. So far there are no data supporting its efficacy in the prevention of recurrences (Williams et al., 2008; Ives-Deliperi et al., 2013; Perich et al., 2013a, 2013b).

**Internet-Based Interventions**

There is only one randomized trial that compared a completely Internet-based preventive program for BD, adjunctive to usual pharmacological management vs a control intervention. The results suggested no differences between treatment groups (Barnes et al., 2015). The design of the study precludes deriving general conclusions for the efficacy of web-based approaches. Another study that combined psychoeducation with mobile phone technology did not show any benefit vs paper and pencil method, however this could mean that a mobile phone approach could be an important alternative without compromising the outcome (Depp et al., 2015).

**Safety Issues With Pharmacotherapy of BD**

A comprehensive grading of all agents in terms of their safety and tolerability profile is shown in Table 9.

**Lithium**

Lithium has a narrow therapeutic window concerning its dosage and plasma levels (recommended plasma level 0.6–1.2 mmol/l), and laboratory testing and thorough investigation before starting lithium treatment (ECG; kidney function etc.) is necessary. Unfortunately this often delays the initiation of treatment. Adverse events are more frequent with higher doses, while “rebound mania” has been described upon withdrawal. The most frequent adverse events include neurological, endocrinological (more often from the thyroid), cardiovascular, renal, gastrointestinal, hematological, and dermatological manifestations, and lithium intoxication is not rare. In clinical practice patients often complain of sedation and tremor and sometimes a decline in creative thinking (Shaw et al., 1986; Engelsmann et al., 1988; Stoll et al., 1996). A general negative impact of lithium on neurocognitive function has been reported (Karniol et al., 1978; Kropf and Muller-Oerlinghausen, 1979; Reus et al., 1979; Squire et al., 1980; Connelly et al., 1982; Lund et al., 1982; Shaw et al., 1987; Engelsmann et al., 1988; Maarbjerg et al., 1988; Kocsis et al., 1993; Kessing, 1998; Honig et al., 1999; Bora et al., 2007; Senturk et al., 2007; Goldberg, 2008). It seems that there is a complex relationship between lithium treatment, female gender, hypothyroidism, and rapid cycling (Cowdry et al., 1983; Bauer and Whybrow, 1990; Bauer et al., 1990; Czyliu et al., 2003a; Fountoulakis et al., 2008b). While most authors argue that lithium is neuroprotective, a neurotoxic effect is also possible in the long term, even at therapeutic levels, especially in combination with antipsychotics (Fountoulakis et al., 2008b). Comprehensive guidelines concerning lithium treatment and optimal therapeutic serum levels are available and should be applied (Malhi et al., 2011), and a recent review provides up-to-date information on its safety (Murru et al., 2015).

**Antiepileptics**

The recommended therapeutic valproate serum concentration is 50 to 150 mg/mL. It is not recommended to be used in women of childbearing age because of the high frequency of unplanned pregnancies in bipolar females and the relatively high teratogenicity of valproate. Other potential acute side effects are weight gain and hair loss. Its use has been associated with polycystic ovary syndrome (PCOS). It is to be noted however, that similar to epilepsy, there is an association between PCOS and major psychiatric disorders, including BD. An increased risk can also be demonstrated in their siblings suggestive of shared familial factors between PCOS and psychiatric disorders (Cesta et al., 2016).

The typical dosage of carbamazepine in the treatment of acute mania is 600 to 1800 mg/d (serum concentration 4–12 mg/ mL). After several weeks under carbamazepine, an induction of hepatic enzymes (CYP 3A4) occurs and the drug levels drop and may require additional upward dose titration (Bertilsson and Tomson, 1986). The dosage-related adverse effects include double or blurred vision, dizziness, sedation, ataxia, vertigo, gastrointestinal disturbances, cognitive impairment, hematological effects, and Stevens-Johnson syndrome including its related dermatologic effects (Tohen et al., 1991, 1995; Blackburn et al., 1996).

The most significant drawback of lamotrigine treatment is the need to initiate it at 25 mg/d for 2 weeks, then 50 mg/d for another 2 weeks and then by increments of 25 to 50 mg/d thereafter to avoid a moderately high incidence of rash (Seo et al., 2010). Carbamazepine decreases lamotrigine concentrations by approximately 50%, and in combination therapy, lamotrigine can be started with higher dosages and faster titration. Vice versa, when combined with valproate a slower titration scheme is needed for lamotrigine, carbamazepine induces the metabolism of other agents as well, for example, risperidone (Ono et al., 2002).

It is also important to note the adverse effects of topiramate because although it is not used in the treatment of BD per se, it is often administered in BD patients in order to lose weight or to treat a comorbid substance abuse disorder. It is reported that topiramate impairs attention, verbal memory, psychomotor speed, and word-finding even at very low dosages (25–50 mg/d). This impairment is reversible after discontinuation of the drug (Salinsky et al., 2005; Goldberg, 2008).

An important recent development was the safety warning by the FDA after a meta analysis that suggested that antiepileptics might double the suicidal risk (FDA, 2008). The field remains uncertain, with some reports and authors supporting the FDA warning (Nilsson et al., 2002; Mula and Sander, 2007; Gibbons et al., 2009; Andersohn et al., 2010; Arana et al., 2010; Olesen et al., 2010; Patorno et al., 2010; VanCott et al., 2010; Zienna et al., 2010; Wen et al., 2011; Fountoulakis et al., 2012c; Pugh et al., 2012; Siamouli et al., 2014). It is important to note that suicidality data came from the registration of adverse events rather than from systematically collected data (Hesdorffer and Kanner, 2009). However, it seems clear that topiramate, lamotrigine, and levetiracetam are related to increased suicidality in nonpsychiatric patients and this should be the focus of further research.

**Antipsychotics**

The adverse effects of FGAs include EPS, tardive dyskinesia, and hyperprolactinaemia and the life-threatening but rather rare
Table 9. Grading of Treatment Options According to Safety Issues (According to the System Shown in Table 1)

<table>
<thead>
<tr>
<th>Agent/modality (alphabetical order)</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agomelatine</td>
<td>2</td>
<td>Liver enzymes induction</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>2</td>
<td>Swelling of mouth and lips, severe skin rashes, infections, eye irritation, hepatitis, appetite and weight loss, and painful or bloody urination</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Armodafinil/modafinil</td>
<td>2</td>
<td>Stimulant, risk for abuse</td>
</tr>
<tr>
<td>Asenapine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>2</td>
<td>Hepatic enzymes induction, many adverse effects</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>3</td>
<td>Potentially lethal agranulocytosis, metabolic syndrome</td>
</tr>
<tr>
<td>Donepezil</td>
<td>1</td>
<td>Not preferred by patients, mild cognitive problems</td>
</tr>
<tr>
<td>ECT</td>
<td>2</td>
<td>Not preferred by patients, mild cognitive problems</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>FEWP</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2</td>
<td>EPS, Tardive dyskinesia, neuroleptic malignant syndrome, switch risk</td>
</tr>
<tr>
<td>Imipramine</td>
<td>2</td>
<td>Cardiac side effects, many adverse effects, switch risk</td>
</tr>
<tr>
<td>Ketamine</td>
<td>3</td>
<td>Stimulant</td>
</tr>
<tr>
<td>L-sulpiride</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2</td>
<td>Good overall tolerability but potentially lethal skin reaction that can be avoided by slow titration</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>3</td>
<td>Induction of suicidality</td>
</tr>
<tr>
<td>Levotyroxine (L-T4)</td>
<td>2</td>
<td>Mild cardiovascular, skin and bone adverse effects</td>
</tr>
<tr>
<td>Licarbazepine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>3</td>
<td>High risk for abuse and dependence</td>
</tr>
<tr>
<td>Lithium</td>
<td>2</td>
<td>Many adverse effects, weight gain, toxicity</td>
</tr>
<tr>
<td>Loxapine inhalant</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>N-acetyl cysteine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Modafinil</td>
<td>2</td>
<td>Stimulant, risk for abuse</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>2</td>
<td>Switch risk, EPS, tardive dyskinesia, neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>2</td>
<td>Many adverse effects</td>
</tr>
<tr>
<td>Phenelzin</td>
<td>2</td>
<td>Many adverse effects</td>
</tr>
<tr>
<td>Pimozide</td>
<td>2</td>
<td>EPS, tardive dyskinesia, neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>2</td>
<td>Not recommended in patients with diabetes mellitus type I and in liver disease. Absolute contraindication in heart failure patients</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>2</td>
<td>Adverse effects include the induction of problematic behaviours and psychotic symptoms</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>2</td>
<td>Not well studied</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RLAI</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>3</td>
<td>Deep vein thrombosis, cognitive disorder</td>
</tr>
<tr>
<td>TMS</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>3</td>
<td>Induction of depression and suicidality</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>2</td>
<td>Many adverse effects</td>
</tr>
<tr>
<td>Valproate</td>
<td>1</td>
<td>Cautious use in women of childbearing age</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>2</td>
<td>Switch risk</td>
</tr>
<tr>
<td>Verapamil</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>2</td>
<td>QTc prolongation, patients should undergo cardiologic examination before receiving ziprasidone</td>
</tr>
</tbody>
</table>

Abbreviations: ECT, electroconvulsive therapy; EPS, extrapyramidal signs; FEWP, Free and Easy Wanderer Plus; RLAI, risperidone long-acting injectable; TMS, transcranial magnetic stimulation.
neuroleptic malignant syndrome, while the most frequent side effects of chlorpromazine are EPS, tardive dyskinesia, postural hypotension, and hepatotoxicity.

On the other hand, the most significant problem with some of the SGAs is weight gain, hyperlipidaemia, and diabetes mellitus. The treatment of these somatic conditions is difficult and the methods proposed have produced rather unsatisfactory results so far. Hyperprolactinemia and EPS are the most frequent adverse effects with amisulpride. Akathisia and EPS are the adverse effects most often reported with aripiprazole.

Concerning olanzapine, the most frequent adverse effects include dry mouth, weight gain, increased appetite, diabetes mellitus and metabolic syndrome, and somnolence. The main adverse effects of quetiapine are persistent sedation and weight gain, however, to a lower extent than olanzapine. Maybe the XR formulation of quetiapine induces less sedation in comparison with the IR formulation (Riesenborg et al., 2012). The main side effects of risperidone are dose-related EPS, weight gain, sedation, and hyperprolactinemia. Somnolence, akathisia, and EPS as well as a significant QTc prolongation are the main adverse effects of ziprasidone treatment; however, ziprasidone is not associated with the metabolic syndrome (Kemp et al., 2012a).

Reports on antipsychotics concerning adverse effects on neurocognition are rare and conflicting (Holmes et al., 2008; Goldberg and Chengappa, 2009; Pan et al., 2011). There are data suggesting that an executive function deficit is correlated with years of exposure to antipsychotic drugs (Zubieta et al., 2001). This latter finding could reflect either the toxic effect of chronic psychosis, the toxic effect of long-term medication, or both. Current antipsychotic treatment in BD patients is reported to relate to worse performance in sustained attention and visuomotor speed, across all executive function tests as well as in semantic fluency, verbal learning, and recognition memory, even when studies were controlled for differences in clinical features (King, 1994; Altshuler et al., 2004; Frangou et al., 2005; Jamrozinski et al., 2009).

### Antidepressants

There is a number of different adverse effects caused by antidepressants. Most of them are not severe and may cause significant burden to the patients but usually improve with time (NHS, 2014).

The adverse effects of SSRIs and serotonin and norepinephrine re-uptake inhibitors include agitation, shakiness, anxiety or feeling of being sick, indigestion, stomach aches, diarrhoea or constipation, loss of appetite, dizziness, insomnia and other sleep disorders, or, on the contrary, hypersomnia and sedation, headache, loss of libido, weight gain, excessive sweating, hyponatraemia (especially in the elderly), and sexual dysfunction. The adverse effects of tricyclic antidepressants include: dry mouth, blurred vision, constipation, dysuria, drowsiness, dizziness, weight gain, excessive sweating, and heart rhythm problems. A rare but potentially life-threatening adverse event is the serotonin syndrome whose symptoms include confusion, agitation, muscle twitching, sweating, shivering, and diarrhea. Rare but serious cases may manifest with very high fever, epileptic fits, arrhythmia, and coma. All classes of antidepressants have been linked to an increased risk of developing type 2 diabetes, but the causality is uncertain.

There is a warning issued by the FDA (black box warning) concerning the risk of suicidality in pediatric patients taking SSRIs for depression (Libby et al., 2007), and a number of papers suggest that antidepressants are related to an increased risk for suicidal behavior (Rouillon et al., 1991; Khan et al., 2000, 2001, 2003; Luoma et al., 2002; Baldessarini et al., 2003a; Healy, 2003) but not for completed suicide (Whittington et al., 2004). This might constitute one of the most interesting paradoxes of our contemporary psychiatry, since antidepressants prevent suicidal behavior among severely ill, frequently suicidal “real life” unipolar depressives but may provoke such behavior sometimes in less severe, actually non-suicidal unipolar depressives (Leon et al., 1999; Angst et al., 2002; Verevianian et al., 2004; Simon et al., 2006; Gibbons et al., 2007). It has been suggested that antidepressants induce suicidality essentially only in pseudo-unipolar patients (Akiskal and Benazzi, 2005; Rihmer and Akiskal, 2006; Perlis et al., 2007b), while the data from the STAR-D trial suggest the presence of a genetic vulnerability predisposing to the manifestation of new suicidal ideation after antidepressant treatment (Laje et al., 2007; Perlis et al., 2007a, 2007b).

### Switching to the Opposite Pole

It is widely accepted among psychiatrists that both antidepressants and SGAs can induce a mood switch to the opposite pole, or a chronic, dysphoric, mixed, or irritable state in BD patients and may accelerate episode frequency and/or may cause other forms of course destabilization in patients with BD. However, hard evidence is limited and the bulk of evidence comes from chart reviews and retrospective and open studies. A comprehensive summary of the risk to induce switching for all agents during the 3 phases of treatment is shown in Table 10.

The literature suggests that without the concomitant use of an antimanic agent the switch rate to mania or hypomania is around 20 to 40% (Bottleder et al., 2001, 2004; Goldberg and Truman, 2003), while with the concomitant use of an antimanic

<table>
<thead>
<tr>
<th>Table 10. Risk of Various Agents to Induce the Opposite Mood Pole (Switch Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent/modality (alphabetical order)</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Asenapine</td>
</tr>
<tr>
<td>Bupropion</td>
</tr>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>ECT</td>
</tr>
<tr>
<td>Escitalopram</td>
</tr>
<tr>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Impiramine</td>
</tr>
<tr>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>OFC</td>
</tr>
<tr>
<td>Olanzapine</td>
</tr>
<tr>
<td>Paliperidone</td>
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<tr>
<td>Paroxetine</td>
</tr>
<tr>
<td>Perphenazine</td>
</tr>
<tr>
<td>Quetiapine</td>
</tr>
<tr>
<td>RLAI</td>
</tr>
<tr>
<td>Sertraline</td>
</tr>
<tr>
<td>Valproate</td>
</tr>
<tr>
<td>Venlafaxine</td>
</tr>
<tr>
<td>Ziprasidone</td>
</tr>
</tbody>
</table>

Abbreviations: -, no data, ECT, electroconvulsive therapy; OFC, olanzapine-fluoxetine combination; RLAI, risperidone long-acting injectable.

The treatment options are rated in an analogous way to the rating system shown in Table 1 as “efficacy to induce the opposite pole.”
More recent reports suggest that switching is exclusively related to antidepressant monotherapy, while the concomitant use of an antimanic agent has a robust protective effect (Viktorin et al., 2014). The results of the STEP-BD support the potentially harmful role of antidepressants in the long-term course of BD (Truman et al., 2007; El-Mallakh et al., 2008, 2015). According to that study switching to the opposite pole was not dose dependent (Tada et al., 2015). However, a number of larger RCTs reported negative data concerning switching with paroxetine and bupropion (Sachs et al., 2007), fluoxetine, even as monotherapy in BD-II patients (Amsterdam et al., 2004), and citalopram (Schaffer et al., 2006). There are some data suggesting a higher risk of switching while on treatment with venlafaxine (Amsterdam and Garcia-Espana, 2000; Vieta et al., 2002, 2009; Leverich et al., 2006; Post et al., 2006) and imipramine (Himmelhoch et al., 1991; Nemeroff et al., 2001; Silverstone, 2001), but a more recent study reported that venlafaxine was equal to lithium and without any increase in the switch rate (Lorenzo-Luaces et al., 2016). It is important to mention that switching to mania or hypomania during treatment of comorbid OCD (White et al., 1986; Steiner, 1991; Vieta and Bernardo, 1992; Rihmer et al., 1996; Perugi et al., 2002) or panic disorder with antidepressants have been reported (Pecknold and Fleury, 1986; Sholomskas, 1990).

The switch risk is probably as high as 18.2% in the short term and 35.6% during the continuation phase (Post et al., 2003) and is higher in BD-I patients in comparison with BD-II (14.2% vs 7.1% in acute trials and 23.4% vs 13.9% in maintenance studies). The rates of switching in unipolar patients are lower than those of bipolar (1.5% in acute trials and 6.0% in maintenance studies) (Bond et al., 2008; Tondo et al., 2010).

| Table 11. Levels of Recommendation Concerning Monotherapy in Acute Mania and Recommended Dosages for Medication Options |
|---------------------------------|-----------------|-----------------|
| **Agent/modality** | **Recommendation level** | **Recommended dosage (mg/d)** |
| Aripiprazole | 1 | 15–30 mg/d |
| Asenapine | 1 | 10–20 mg/d |
| Cariprazine | 1 | 3–12 mg/d |
| Paliperidone | 1 | 3–12 mg/d |
| Quetiapine | 1 | 400–800 mg/d |
| Risperidone | 1 | 2–6 mg/d |
| Valproate | 1 | 1200–3000 mg/d (loading dose 20–30 mg/kg body weight; serum level 75–150 mg) |
| Carbamazepine | 2 | 600–1200 mg/d (serum level 4–15 mg/L) |
| Haloperidol | 2 | 5–20 mg/d |
| Lithium | 2 | 600–1200 mg/d (serum level 0.8–1.3 mmol) |
| Olanzapine | 2 | 10–20 mg/d |
| ECT | 3 | |
| Oxcarbazepine | 4 | 900–1800 mg/d |
| Chlorpromazine | 4 | 300–1000 mg/d |
| Pimozide | 4 | 2–6 mg/d |
| Tamoxifen | 4 | 40–80 mg/d |
| Ziprasidone | 5 | 80–160 mg/d |
| Escitalopram | 5 | |
| Gabapentin | 5 | |
| Lamotrigine | 5 | |
| Licarbazepine | 5 | |
| TMS | 5 | |
| Topiramate | 5 | |
| Verapamil | 5 | |

Abbreviations: ECT, electroconvulsive therapy; NR, not recommended; TMS, transcranial magnetic stimulation.

| Table 12. Recommendation levels for combination treatment for acute mania |
|---------------------------------------------|-----------------|-----------------|-----------------|
| **Agent/modality** | **MS** | **Li** | **Val** | **Cbz** | **FGAs** |
| Asenapine | 1 | - | - | - | - |
| Haloperidol | 2 | 2 | 2 | 2 | - |
| Olanzapine | 2 | - | 2 | 5 | - |
| Aripiprazole | 2 | - | - | - | - |
| Medroxyprogesterone | 5 | - | - | - | - |
| Citalopram | 3 | 3 | - | - | - |
| Risperidone | 3 | - | 5 | - | - |
| Tamoxifen | 4 | 4 | - | - | - |
| Allopurinol | 5 | 2 | - | - | - |
| Paliperidone | 5 | - | - | - | - |
| Ziprasidone | 5 | - | - | - | - |
| Gabapentin | 5 | - | - | - | - |
| Topiramate | 5 | - | - | - | - |
| Lamotrigine | - | - | - | - | - |
| Lithium | - | - | - | 2 | - |
| Oxcarbazepine | - | 4 | - | - | - |
| Valproate | - | - | - | - | 2 |

Abbreviations: Cbz, carbamazepine; FGA, first generation antipsychotic; Li, lithium; MS, mood stabilizer; Val, valproate.

agent the rate is reduced to 14% or below (Nemeroff et al., 2001; Post et al., 2001, 2006; Harel and Levkovitz, 2008; Licht et al., 2008; Tondo et al., 2010). More recent reports suggest that switching

| Table 13. Recommendation Levels for Monotherapy in Rapid Cycling Patients in an Acute Manic Episode |
|---------------------------------------------|-----------------|-----------------|-----------------|
| **Agent/modality** | **Recommendation level** | **Concomitant Depressive symptoms** | **Psychotic symptoms** |
| Quetiapine | 3 | 3 | 3 |
| Risperidone | 3 | 3 | 3 |
| Aripiprazole | 3 | 3 | 3 |
| Asenapine | 5 | 3 | - |
| Olanzapine | 2 | 3 | 3 |
| Carbamazepine | 2 | 5 | - |
| Haloperidol | 2 | 5 | 3 |
| Lithium | 2 | 5 | 3 |
| Tamoxifen | 4 | 5 | 4 |
| Valproate | 1 | 5 | - |
| Ziprasidone | 2 | 5 | 3 |

| Table 14. Recommendation Levels for Monotherapy in Patients in an Acute Manic Episode and the Specific Effect on Concomitant Depressive Symptoms (Mixed Features) and Psychotic Features |
|---------------------------------------------|-----------------|-----------------|-----------------|
| **Agent/modality** | **Therapeutic effect on** | **Overall on manic episode** | **Concomitant Depressive symptoms** | **Psychotic symptoms** |
| Quetiapine | | | |
| Risperidone | | | |
| Aripiprazole | | | |
| Asenapine | | | |
| Olanzapine | | | |
| Carbamazepine | | | |
| Haloperidol | | | |
| Lithium | | | |
| Tamoxifen | | | |
| Valproate | | | |
| Ziprasidone | | | |
Haloperidol and perphenazine treatment have been associated with the development of dysphoria and depression, although the data are inconclusive for haloperidol (Tohen et al., 2003b; Zarate and Tohen, 2004). On the contrary, SGAs do not appear to induce depression, while some authors suggest they possess a mild protective property against switching (Tohen et al., 2003c; Amsterdam and Shults, 2005a; Calabrese et al., 2005b; Keck et al., 2005; Thase et al., 2006; Benazzi et al., 2009). A recent meta-analysis reported that treating acute mania with SGAs is associated with a 42% lower risk of switch to depression than with haloperidol. Nevertheless, caution should be taken when considering this to be a class effect, as only olanzapine, quetiapine, and ziprasidone may show these advantages (Goikolea et al., 2013b).

Overall there are no data to suggest a generalized and class effect for antidepressants or FGAs concerning the induction of an affective switch. There are negative data concerning all SSRIs and SGAs studied and positive data only concerning venlafaxine, imipramine, and perphenazine. Some authors believe that at least the switch risk and perhaps also the risk for rapid cycling and new-onset suicidality have been overinterpreted (Grunze, 2008), and thus the issue of switching is still open and further research is needed. Also negative for the presence of a treatment-induced switch are the longitudinal data of Jules Angst (Angst, 1985). For a safe use of antidepressants in BD, clinicians may follow the recommendations of the International Society for Bipolar Disorders Task Force (Pacchiarotti et al., 2013).

### Review of Existing Guidelines for BD

A number of treatment guidelines were identified and their reference lists were utilized (APA, 1994, 1995, 2002; Suppes et al., 1995, 2001, 2002, 2003; Frances et al., 1996; 1997; AACAP, 1997; Goodwin et al., 1997, 2003, 2009, 2016; Jobson, 1997; Kusumakar et al., 1997; McClellan and Werry, 1997; Gilbert et al., 1998; Barreira et al., 1999; Bauer et al., 1999b; Rush et al., 1999, 2003; Dennehy, 2000; Goldberg, 2000; Sachs et al., 2000; Allen et al., 2001; Montgomery, 2001; Grunze et al., 2002, 2003, 2004, 2009, 2010, 2011, 2013; Licht et al., 2003; Hirschfeld, 2005; Yatham et al., 2005, 2006, 2008, 2009, 2013b, 2013c; National Collaborating Centre for Mental Health, 2006; O’Dowd, 2006; Nolen et al., 2008; Jon et al., 2009; Ng et al., 2009; Beaulieu et al., 2012; Bond et al., 2012; McIntyre et al., 2012b; Rosenbluth et al., 2012; Schaffer et al., 2012; Mohammad and Osser, 2014; Malhi et al., 2015; Ostacher et al., 2015a; Woo et al., 2015). An additional source was the National Institute of Clinical Excellence (NICE) guideline concerning BD (NICE, 2014), while the latest version of the guidelines of the British Association of Psychopharmacology (Goodwin et al., 2016) were included, although they were published after the date of last literature search.

A description of the most important and most recent guidelines (after 2005) will be included in the text that follows. In Tables 17, 21, and 25 there is a detailed description of difference between the current CINP guidelines and previously developed guidelines by other bodies.

### American Psychiatric Association Treatment Guidelines for BD

In 2008 the APA developed a draft of new guidelines after a thorough review of the literature. However, they were never published because of unresolved issues pertaining to the conflict of interest.

### The Canadian Network for Mood and Anxiety Treatments and International Society on Bipolar Disorder Guidelines

The most recent 2013 version of the Canadian Network for Mood and Anxiety Treatments and International Society on Bipolar Disorder guidelines (Yatham et al., 2013c) suggests that for the treatment of acute manic episodes the first line recommendation is monotherapy with lithium, divalproex, divalproex ER, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, or paliperidone ER, and adjunctive therapy with risperidone, quetiapine, olanzapine, aripiprazole, asenapine on lithium, or divalproex. The second line includes monotherapy with carbamazepine, carbamazepine ER, ECT, or haloperidol and combination therapy with lithium plus divalproex. The third line of treatment includes monotherapy with chlorpromazine, clozapine, oxcarbazepine, tamoxifen, or cariprazine and combination therapy with lithium or divalproex plus haloperidol, lithium plus carbamazepine, or adjunctive tamoxifen. They do not recommend monotherapy with gabapentin, topiramate, lamotrigine, verapamil, or tiagabine and combination therapy with risperidone or olanzapine plus carbamazepine.

---

**Table 15. Recommendation Levels for Monotherapy and Combination Treatment in Patients in a DSM-IV-TR Mixed Episode and the Specific Effect on the Manic and the Depressive Component**

<table>
<thead>
<tr>
<th>Agent/modality</th>
<th>Monotherapy</th>
<th>Combination with MS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Manic component</td>
<td>Depressive component</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Asenapine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Valproate</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Risperidone</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>OFC</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Lithium</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: MS, mood stabilizer; OFC, olanzapine-fluoxetine combination.
<table>
<thead>
<tr>
<th>Step</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>Discontinue treatment with antidepressants</td>
<td>Olanzapine or lithium monotherapy</td>
<td>Combination treatment of lithium or valproate with quetiapine, or risperidone.</td>
<td>Apply ECT on top of pharmacological treatment.</td>
<td>Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist, ECT if not applied earlier</td>
</tr>
<tr>
<td>Rapid cycling</td>
<td>Start with aripiprazole or quetiapine monotherapy. In nonpsychotic cases valproate is also an option Take into consideration the previous history of psychotic features.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonrapid cycling with psychotic features</td>
<td>Start with aripiprazole, cariprazine, paliperidone, quetiapine, or risperidone monotherapy.</td>
<td>Monotherapy with haloperidol, lithium, olanzapine or ziprasidone or combination treatment of lithium or valproate with aripiprazole, haloperidol or olanzapine. Lithium combinations with allopurinol* is also an option. Another combination is valproate plus an FGA.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonrapid cycling without psychotic features</td>
<td>All options that are suitable in the presence of psychotic features and also valproate and asenapine monotherapy are a choice. Take into consideration the previous history of psychotic features.</td>
<td>All options that are suitable in the presence of psychotic features and also monotherapy with carbamazepine or valproate plus celecoxib* are an option Take into consideration the previous history of psychotic features.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed Features</td>
<td>Start with quetiapine or risperidone monotherapy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other cases</td>
<td>If the patient is already under one of the above ‘first step’ monotherapy or under combination therapy of any kind and response is unsatisfactory, switch into another ‘first step’ monotherapy.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
In case the personal history of the patient suggests this is not an option, proceed to next step and switch to the closest second step treatment option.

Mixed episode

Start with combination of olanzapine plus valproate or maybe lithium

Monotherapy with olanzapine, aripiprazole, or carbamazepine.

Valproate or OFC or ziprasidone monotherapy.

**Abbreviations:** CBT, cognitive behavioral treatment; Cbz, carbamazepine; ECT, electroconvulsive therapy; IPSRT, InterPersonal and Social Rhythms Therapy; Lam, lamotrigine; Li, lithium; MS, mood stabilizer; OFC, olanzapine fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.

* No wide clinical experience.

Table 16. Comparison of the Detailed Algorithm to Previously Developed Guidelines for Acute Mania

<table>
<thead>
<tr>
<th>Step</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
</tr>
</thead>
<tbody>
<tr>
<td>In case the personal history of the patient suggests this is not an option, proceed to next step and switch to the closest second step treatment option.</td>
<td>Proceed to next step</td>
<td>Start with combination of olanzapine plus valproate or maybe lithium</td>
<td>Monotherapy with olanzapine, aripiprazole, or carbamazepine.</td>
<td>Valproate or OFC or ziprasidone monotherapy.</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CINP, 2016; WFSBP, 2013.**

**Table 17. Comparison of the Detailed Algorithm to Previously Developed Guidelines for Acute Mania**

<table>
<thead>
<tr>
<th></th>
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</thead>
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<tr>
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<td>-</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1</td>
<td>3</td>
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<td>1</td>
</tr>
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<td>Risperidone</td>
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<td>Olanzapine</td>
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<td>3</td>
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<tr>
<td>Ziprasidone</td>
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<td>ECT</td>
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<tr>
<td>Licarbazepine</td>
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<tr>
<td>rTMS</td>
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<tr>
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<td>4</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leviracetam</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Abbreviations:** ECT, electroconvulsive treatment; NR, not recommended; rTMS, repetitive Transcranial Magnetic Stimulation.

The grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options.

Numbers correspond to steps not to efficacy ranking.

* NICE and BAP ordering is on the basis of line of treatment.

* Step 2 in the WFSBP guideline would be a combination of 2 grade “1” recommended medication, or switch from one grade “1” medication to another.
Table 18. Level of Recommendation Concerning Monotherapy in Acute Bipolar Depression, in Comorbid Conditions and Rapid Cycling Patients, and Recommended Dosages for Medication Options

<table>
<thead>
<tr>
<th>Agent/modality</th>
<th>Overall</th>
<th>BD-I</th>
<th>BD-II</th>
<th>Depressive core</th>
<th>Comorbid anxiety</th>
<th>Rapid cycling</th>
<th>Recommended dosage (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>300–600 mg/d</td>
</tr>
<tr>
<td>Lithium</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5–20 mg/d</td>
</tr>
<tr>
<td>OFC</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>6 + 25; 6 + 50; 12 + 50 mg/d</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>2</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20–80 mg/d</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2</td>
<td>4</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>5–20 mg/d</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>300–800 mg/d</td>
</tr>
<tr>
<td>Valproate</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>500–2500 mg/d (50–100 mcg/mL)</td>
</tr>
<tr>
<td>Arpiprazole</td>
<td>3</td>
<td>-</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>5–30 mg/d</td>
</tr>
<tr>
<td>Imipramine</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75–300 mg/d</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>50–200 mg/d</td>
</tr>
<tr>
<td>Phencelzine</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15–90 mg/d</td>
</tr>
<tr>
<td>Lithium</td>
<td>4</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>5</td>
<td>3</td>
<td>600–1800 mg/d</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20–30 mg/d</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75–225 mg/d</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>20 mg/d</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rTMS</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Risperidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not recommended; OFC, olanzapine–fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation.

Table 19. Level of Recommendation Concerning Combination Treatment in Acute Bipolar Depression

<table>
<thead>
<tr>
<th>Agent/modality</th>
<th>MS</th>
<th>Cbz</th>
<th>Lam</th>
<th>Li</th>
<th>Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Modafinil</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ketamine</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Bupropion</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Levotheroxine (L-T4)</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Risperidone</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lithium</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Memantine</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FEWP</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>L-sulpiride</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Arpiprazole</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Imipramine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: Cbz, carbamazepine; FEWP, Free and Easy Wanderer Plus (herbal agent); Lam, lamotrigine; MS, mood stabilizer; Val, valproate.

For the treatment of acute BD-I depression as first line option they recommend monotherapy with lithium, lamotrigine, quetiapine, or quetiapine XR and combination therapy with lithium or divalproex or olanzapine plus an SSRI, lithium plus divalproex and lithium, or divalproex plus bupropion. The second line includes monotherapy with divalproex or lamotrigine and combination therapy with quetiapine plus an SSRI, adjunction

modafinil, and lithium or divalproex plus lamotrigine or lurasidone. The third line includes monotherapy with carbamazepine, olanzapine, or ECT or combination therapy with lithium plus carbamazepine or pramipexole, lithium or divalproex plus venlafaxine, lithium plus MAOI, lithium or divalproex or atypical antipsychotic plus a TCA, lithium or divalproex or carbamazepine plus an SSRI plus lamotrigine, and quetiapine plus lamotrigine. They do not recommend monotherapy with gabapentin, aripiprazole, or ziprasidone and combination therapy with adjunctive ziprasidone or levetiracetam.

For the maintenance treatment, the first line recommendation includes monotherapy with lithium, lamotrigine, divalproex, olanzapine, quetiapine, risperidone LAI, and aripiprazole and adjunctive therapy with quetiapine, risperidone LAI, aripiprazole, or or ziprasidone on lithium or divalproex. The second line monotherapy includes carbamazepine and paliperidone ER and combination therapy with lithium plus divalproex or carbamazepine, lithium or divalproex plus olanzapine, risperidone or lamotrigine, and olanzapine plus fluoxetine. The third line monotherapy includes asenapine and the adjunctive therapy includes phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepine, gabapentin, and asenapine. They do not recommend monotherapy with gabapentin, topiramate, or antidepressants and adjunctive therapy with fluphenixol.

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of BD

The latest WFSBP guidelines utilized a modified version of the PORT method to grade the data concerning efficacy (Grunze et al., 2009, 2010, 2013) and afterwards utilized a secondary classification to include also safety and tolerability.

For the treatment of acute mania, as first choice agents are ranked aripiprazole, valproate, risperidone, and ziprasidone. As second choice, olanzapine, quetiapine, asenapine,
carbamazepine, haloperidol, and lithium were recommended. The third choice includes chlorpromazine, paliperidone, phe
- nytoin, pimozide, and tamoxifen. The fourth includes ami
- sulpride, clonazepam, clozapine, levetiracetam, lorazepam, nimodipine, oxcarbazepine, retigabine, zonisamide, zotepine, and ECT. The fifth and final choice includes verapamil. With 
the utilization of this classification, the WFSBP suggests that concerning the treatment of acute mania the first step includes

### Table 20. Precise Algorithm to Treat Acute Bipolar Depressive Episodes on the Basis of Specific Clinical Characteristics

<table>
<thead>
<tr>
<th>Steps</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Start with quetiapine or lurasidone</td>
<td>Add a mood stabilizer on lurasidone, modafinil or pramipexole</td>
<td>Valproate, aripiprazole, imipramine, phenelzin, carbamazepine, or OFC</td>
<td>Tranlycypromine or lithium monotherapy</td>
<td>ECT or various combinations of medication according to anecdotal knowledge or the personal experience of the therapist</td>
</tr>
<tr>
<td>Rapid cycling</td>
<td>Never consider CBT as monotherapy</td>
<td>If BD-I start with valproate, in BD-II with lithium</td>
<td>Lithium plus lamotrigine, or pioglitazone*</td>
<td>Venlafaxine preferably in combination with an antimanic agent</td>
<td></td>
</tr>
<tr>
<td>No rapid cycling</td>
<td>If BD-II start with escitalopram or fluoxetine monotherapy</td>
<td></td>
<td>Olanzapine monotherapy or OFC</td>
<td>Amiodafin or ketamine on a mood stabilizer</td>
<td></td>
</tr>
<tr>
<td>Comorbid anxiety</td>
<td>Add paroxetine, quetiapine, valproate or lurasidone and consider Mindfulness based interventions as add-on to these agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavioral treatment; Cbz, carbamazepine; ECT, electroconvulsive therapy; FEWP, Free and Easy Wanderer Plus (herbal agent); IPSRT, InterPersonal and Social Rhythms Therapy; Lam, lamotrigine; Li, lithium; MS, mood stabilizer OFC, olanzapine-fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.

* No wide clinical experience.

### Table 21. Comparison of the Precise Algorithm to Previously Developed Guidelines for Acute Bipolar Depression Concerning Monotherapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>OFC</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Imipramine</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>3</td>
<td>1</td>
<td>1</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>Valproate</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lithium</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tranlycypromine</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>ECT</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>NR</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leviracetam</td>
<td>-</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L-thyroxine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Risperidone</td>
<td>-</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rTMS</td>
<td>NR</td>
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</tr>
<tr>
<td>Ziprasidone</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: ECT, electroconvulsive treatment; NR, not recommended; OFC, olanzapine-fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation.

The grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options. Numbers correspond to steps not to efficacy ranking.

1 WFSBP: Recommendation only reflects monotherapy not considering evidence derived from combination treatment (except OFC).
2 NICE and BAP ordering is on the basis of line of treatment.
3 Against BD-II depression.

NICE ordering is on the basis of line of treatment.
monotherapy with first choice agents. The second step would be switching to another first-choice agent or combine 2 first choice agents. Similarly the third step includes combination of 2 first-choice agents. The fourth and fifth steps include combinations of agents essentially according to the judgement of the therapist.

For the treatment of acute bipolar depression, the WFSBP guidelines suggest that first choice agent is only quetiapine, while the next-best option includes olanzapine, fluoxetine, lamotrigine, valproate, OFC, lithium plus lamotrigine, adjunc-
tive modafinil, NAC on lithium or valproate, and FEWP plus carbamazepine. A variety of combinations are proposed as next steps.

For the treatment during the maintenance phase the guidance is more complex and on the basis of the available data the WFSBP guidelines suggest the use of aripiprazole, lamotrigine, lithium, quetiapine, olanzapine, and risperidone, but they note that not all of them prevent both mania and depression. They also note the problems because of the metabolic syndrome induced by some of these agents when used for prolonged periods of time. They also suggest the avoidance of typical antipsychotics because of the risk to induce tardive dyskinesia.

### British Association for Psychopharmacology

The 2016 British Association for Psychopharmacology guidelines for the treatment of BD (Goodwin et al., 2016) recommend for acute mania antidopaminergic agents, lithium, or valproate. For acute bipolar depression they recommend quetiapine, olanzapine, olanzapine plus fluoxetine, antidepressants, lurasidone, and lamotrigine as combination. It also recommends family focused therapy, IPSRT, and CBT as add-on to medication but also CBT as monotherapy as an extrapolation of unipolar depression studies. For the maintenance phase they recommend lithium (for mania, depression, and suicide), dopamine antagonists, and partial agonists as well as valproate (mainly for mania), lamotrigine (for depression), and family focused therapy, CBT, and IPSRT as add-on to medication.

### The UK NICE Treatment Guidelines for BD

Concerning acute mania, the 2014 NICE (NICE, 2014) guidelines recommend the use of olanzapine, risperidone, quetiapine, or haloperidol. If the patient does not respond it is recommended to change to another antipsychotic, and the choice should be made also on the basis of previous response if it exists. If the patient is already under treatment with lithium or valproate then the recommendation is to increase dosage to the highest permitted, and reassessment should follow before the changing of medication. If an antidepressant is in place, it should be discontinued. The second step includes combination of lithium or valproate plus an antipsychotic and the third step demands hospitalization. The NICE warns against the use of gabapentin, lamotrigine, and topiramate in acute mania.
For acute bipolar depression, the NICE recommends olanzapine, OFC, quetiapine, lamotrigine, lithium, and valproate. If the patient is already under treatment with lithium or valproate then the recommendation is to increase the dosage to the highest permitted, and reassessment should follow before the changing of medication. The next step includes combination of lithium or valproate plus quetiapine or OFC. The third step includes lithium plus lamotrigine or olanzapine and valproate plus lamotrigine. The NICE warns against the use of gabapentin and topiramate.

During the maintenance phase, the NICE guidelines recommend as first line treatment the continuation of the treatment the patient received during the acute phase and led to the resolution of the symptoms. Irrespective of predominant polarity the continuation of this treatment should be done for at least 3 to 6 months. In case the patient does not wish to follow this, it is recommended to change treatment to lithium, olanzapine, quetiapine, valproate, or lithium plus valproate. Again, NICE warns against the use of gabapentin and topiramate.

The procedure and the interpretation of evidence as presented in the NICE guidelines have been criticized (Jauhar et al., 2016).

**Efficacy, Recommendation Level, and Precise Treatment Algorithm**

The detailed table of the efficacy level for all treatment options during all phases and against specific features of BD is shown in web appendix 1. The detailed table of the recommendation level for all treatment options during all phases and against specific features of BD is shown in web appendix 2. Add-on and combination data were merged for the sake of simplicity. Additionally, the detailed precise algorithm that was developed is shown in web appendix 3.

The levels of recommendation concerning monotherapy in acute mania and recommended dosages for medication options are shown in Table 11, while the recommendation levels for combination treatment are shown in Table 12. Recommendation levels concerning treatment options for rapid cycling patients are shown in Table 13 and the effects on concomitant depressive and psychotic features are shown in Table 14. The recommendation levels for monotherapy and combination treatment in patients with a DSM-IV-TR mixed episode and the specific effects on the manic and the depressive component are shown in Table 15 (provided here for academic reasons).

The chart of the algorithm for acute mania/hypomania on the basis of strict evidence and by taking into consideration specific clinical features is shown in Table 16. The comparison of this algorithm to previously developed guidelines for acute mania is shown in Table 17.

The levels of recommendation concerning monotherapy in acute bipolar depression, in comorbid conditions, and rapid cycling patients and recommended dosages for medication options are shown in Table 18, while the levels of recommendation concerning combination treatment are shown in Table 19.

The chart of the algorithm for acute bipolar depression is shown in Table 20. The comparison of this algorithm to previously developed guidelines for acute bipolar depression is shown in Table 21.

The levels of recommendation concerning monotherapy during the maintenance phase and in relationship to index episode, composition of the sample, presence of rapid cycling, and the efficacy in the prevention of manic, mixed, or depressive episodes as well as recommended dosages are shown in Table 22, while the levels of recommendation concerning combination treatment during the maintenance phase are shown in Table 23.

The chart of the algorithm for the maintenance phase is shown in Table 24. The comparison of this algorithm to previously developed guidelines for the maintenance phase is shown in Table 25.

Overall the algorithm consists of the stepwise approach in Tables 16, 20, and 24 and in web appendix 3. However, a more fundamental approach would be to utilize web appendix 2 that includes a table with the recommendation levels by clinical indication for all the treatment options. The utilization of this table could be more precise and accurate in comparison with the stepwise description. Until then, the clinician can handle the table in a manual way. First he or she should decide on the phase of the disorder (acute manic vs mixed vs depressive episode vs maintenance phase). Then he or she should choose the combination of the clinical features under the specific phase and finally he or she will identify that treatment options best fit the clinical syndrome. For example, if the patient is in an acute manic episode with some accompanying depressive symptoms (mixed features) and psychotic symptoms and his or her history suggests he or she is also in a rapid cycling, then the only agents that treats all these conditions are olanzapine and quetiapine followed by lithium that is second choice. If the patient is BD-II in a depressive episode with anxiety, then the only suitable agent is quetiapine. Of course such an algorithm might be too restrictive; however, the clinician can use the table to produce combinations of treatment options to satisfy all clinical needs on the basis on research data.

**Discussion**

The current paper represents a systematic search of the literature on the treatment of BD. By using an established approach we identified all relevant RCTs pertaining to all faces and special issues of BD and graded the data according to a predetermined method. Finally, a recommendation level was assigned to all treatment options depending on the clinical situation.

It was interesting to see that except for rare cases, the concept of mood stabilizers is not supported by the available data, especially for those agents traditionally considered as such.

It is obvious that, by far, the body of evidence originates from RCTs that were conducted with agents that have been launched in the last 2 decades. This constitutes a significant bias in the literature, and one should be cautious in the way that the accumulated clinical experience concerning those agents and treatment modalities with poor evidence-based support should also be taken into account.

A low grade of evidence for these old and poorly studied agents and modalities (e.g., carbamazepine, clozapine, ECT, etc.) does not necessarily mean a lower effectiveness and safety in comparison with other drugs, but it still implies that the clinicians should be cautious in their application in patients with BD. Yet it is irrational to use different standards; on the one hand to study carefully and seek flaws in the design of major RCTs and on the other hand to accept a wide recommendation of agents with poor evidence-based support because of historical reasons. The authors of the current paper spent much time and effort to grade the agents on the basis of quantitative but also qualitative characteristics of the data available. This effort resulted in the development of a precise algorithm on the basis of a reproducible methodology.

Also, the results on those areas of interest that are not targeted as primary outcomes are reported in a non-systematic way and therefore the grading of evidence is lower. Unfortunately these areas constitute the overwhelming clinical picture of BD.

As with many other guidelines, the inherent limitations of the literature as well as the unavoidable subjectivity of experts when
Table 24. Precise Algorithm to Treatment during the Maintenance Phase for BD on the Basis of Specific Clinical Characteristics

<table>
<thead>
<tr>
<th>Step</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive predominant polarity or No predominant polarity</td>
<td>Quetiapine or olanzapine monotherapy</td>
<td>Add fluoxetine or lamotrigine</td>
<td>Add N-acetylcysteine</td>
<td>If depressive episodes keep emerging add an agent with proven efficacy against acute bipolar depression no matter whether it has proven maintenance efficacy. Consider adding venlafaxine or lithium plus lamotrigine.</td>
<td>Consider any combinations from steps 1–4 that have not been tried. Consider maintenance ECT. Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist. Consider IPSRT as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider IPSRT as monotherapy.</td>
</tr>
<tr>
<td>Manic predominant polarity</td>
<td>Start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine or risperidone (including RLAI) monotherapy</td>
<td>Add lithium on the first step option</td>
<td>If manic episodes keep emerging add RLAI on current treatment if not already in place</td>
<td>If manic episodes keep emerging add an agent that has proven efficacy against acute mania no matter whether it has proven maintenance efficacy. Consider haloperidol or lithium plus lamotrigine.</td>
<td>Consider IPSRT as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider IPSRT as monotherapy.</td>
</tr>
<tr>
<td>Mixed episodes are frequent</td>
<td>Olanzapine or aripiprazole plus a mood stabilizer</td>
<td>Add valproate, carbamazepine, or lamotrigine on second step treatment</td>
<td>Proceed to next step</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid cycling</td>
<td>Lithium monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>Consider CBT or psychoeducation as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider CBT or psychoeducation as monotherapy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavioral treatment; CBz, carbamazepine; ECT, electroconvulsive therapy; IPSRT, InterPersonal and Social Rhythms Therapy; Lam, lamotrigine; Li, lithium; MS, mood stabilizer.

Table 25. Comparison of the Precise Algorithm to Previously Developed Guidelines for Maintenance Phase Concerning Monotherapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Lithium</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>RLAI</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>OFC</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Valproate</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ECT</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>5</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Continue most recent episode treatment</td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>-</td>
<td>3</td>
<td>NR</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Asenapine</td>
<td>-</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>-</td>
<td>4</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>Topiramate</td>
<td>-</td>
<td>4</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: ECT, electroconvulsive treatment; NR, not recommended; OFC, olanzapine-fluoxetine combination; RLAI, Risperidone Long-Acting Injectable. The grading is not uniform; instead it reflects the grading utilized by individual guidelines and the Table aims only to give an image of how different guidelines prioritize treatment options. Numbers correspond to steps not to efficacy ranking. Recommendation grades and subsequent positioning could be either based on efficacy in the prevention of mania, depression or any episode. Thus, numbers do not reflect the sequence of treatment in an individual patient. NICE and BAP ordering is on the basis of line of treatment.
making a recommendation (even when based on evidence) should be taken seriously into consideration by the clinicians when reading the current paper. Also negative results (level 5) should be taken very seriously into consideration, as they should be considered to be scientifically stronger in comparison with positive ones.

Further limitations include the heterogeneity of the RCTs that served as basis for the recommendations and the lack of trials assessing specific subpopulations, following the rules of stratified medicine (Schumann et al., 2014), or applying staging methods to psychopharmacology (Grande et al., 2015), in search of more precision when treating individual patients (Vieta, 2015). However, these CINP guidelines represent the most up-to-date effort to condense the current knowledge on the management of BD from an international perspective.

Statement of Interest

K.N.F. has received grants and served as consultant, advisor, or CME speaker for the following entities: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Pfizer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Pfizer, the Pfizer Foundation, Sanofi-Aventis, Servier, Shire, and others.

E.Y. has received grants and served as consultant, advisor, or CME speaker for the following entities: Allergan, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lilly, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIEMAT), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute.

A.H.Y. is employed by King’s College London, is Honorary Consultant SLaM (NHS UK), has paid lectures by and participated in advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders, and has no share holdings in pharmaceutical companies. He was lead investigator for Embolden Study (AZ), BCI Neuropsychiatry Study, and Aripiprazole Mania Study; investigator-initiated studies from AZ, Eli Lilly, Lundbeck, and Wyeth; and has received grant funding (past and present) from NIH-BRC (UK); NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UCB-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); and NIHR (UK).

H.G. within the last 3 years received grant/research support from NIHR UK, MRC UK, and NWT NHS Foundation Trust and receipt of honoraria or consultation fees from Gedeon-Richter, Lundbeck, and Hofmann-LaRoche and participated in a company-sponsored speaker’s bureau for BMS, Ferrer, Janssen-Cilag, Otsuka, Lundbeck, and Pfizer.

L.Y. has been on speaker/advisory boards for or has received research grants from Alkermes, Allergan, AstraZeneca, Bristol Myers Squibb, CANMAT, CIHR, Eli Lilly, Forest, GlaxoSmithKline, Intas, Janssen, the Michael Smith Foundation for Health Research, Pfizer, Servier, Sumitomo Dainippon, Sunovion, and the Stanley Foundation.

S.K. within the last 3 years received grants/research support, consulting fees, and honoraria from Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Eli Lilly, Janssen, KRKA-Pharma, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, and Servier.

H.J.M. received honoraria for lectures or for advisory activities or received grants by the following pharmaceutical companies: Lundbeck, Servier, Schwabe, and Bayer. He was president or in the executive board of the following organizations: CINP, ECNP, WFSBP, and EPA and chairman of the WPA-section on Pharmacopsychiatry.

P.B. has received research grants and honoraria for participation in advisory boards from and/or gave presentations to: Allergan, Astra Zeneca, Bristol Myers Squibb, Canadian Institute for Health Research, Eli Lilly, Lundbeck, Janssen, Ontario Brain Institute, Meda-Valeant, Merck, Otsuka, Pierre Fabre Medicaments, Pfizer, Shire, Sunovion, and Takeda.

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REVIEW

The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 3: The Clinical Guidelines

Konstantinos N. Fountoulakis, MD; Heinz Grunze, MD; Eduard Vieta, MD; Allan Young, MD; Lakshmi Yatham, MD; Pierre Blier, MD; Siegfried Kasper, MD; Hans Jurgen Moeller, MD

Abstract

Background: The current paper introduces the actual International College of Neuro-Psychopharmacology clinical guidelines for the treatment of bipolar disorder.

Concept and structure of the guidelines: The current clinical guidelines are based on evidence-based data, but they also intend to be clinically useful, while a rigid algorithm was developed on the basis of firm evidence alone. Monotherapy was prioritized over combination therapy. There are separate recommendations for each of the major phases of bipolar disorder expressed as a 5-step algorithm.

Discussion: The current International College of Neuro-Psychopharmacology clinical guidelines for the treatment of bipolar disorder are the most up-to-date guidance and are as evidence based as possible. They also include recommendations concerning the use of psychotherapeutic interventions, again on the basis of available evidence. This adherence of the workgroup to the evidence in a clinically oriented way helped to clarify the role of specific antidepressants and traditional agents like lithium, valproate, or carbamazepine. The additional focus on specific clinical characteristics, including predominant polarity, mixed features, and rapid cycling, is also a novel approach. Many issues need further studies, data are sparse and insufficient, and many questions remain unanswered. The most important and still unmet need is to merge all the guidelines that concern different phases of the illness into a single one and in this way consider BD as a single unified disorder, which is the real world fact. However, to date the research data do not permit such a unified approach.

Keywords: bipolar disorder, anticonvulsants, antidepressants, antipsychotics, evidence-based guidelines, lithium, mania, bipolar depression, mood stabilizers, treatment, clinical trials
Introduction

The current paper is the third in the series of The International College of Neuro-Psychopharmacology (CINP) papers concerning the development of clinical guidelines for the treatment of bipolar disorder (BD) in adults in primary and secondary care. This guideline is the first on the treatment of BD that is developed by the CINP and concerns the treatment of adult patients with BDr-I or II, with mixed features, rapid cycling, and psychotic features but not children, adolescents, or the elderly. It is designed for use mainly by psychiatrists in secondary care, but it might be also useful in primary care settings. The current guidelines were developed by a group of experts in the field after a systematic and comprehensive review of the literature and thus they are as evidence based as possible but also suitable for use in everyday clinical practice of busy clinicians. No analysis of cost or other issues other than efficacy and safety/tolerability were taken into consideration when developing these guidelines.

During the last few decades there were important developments both in our understanding of BD but also in its treatment (Fountoulakis, 2015a, 2015b, 2015c, 2015d, 2015e, 2015f). In many instances the accumulation of new knowledge challenged old beliefs that dominated the psychiatric academic thinking and practice for decades. It is hoped that these guidelines will assist clinicians, patients and their families, and society in general to benefit from the advances in research and translate them into everyday clinical practice. It should be made clear, however, that guidelines are not a substitute for professional knowledge and clinical judgement, and therefore their use is at the discretion of the clinician after taking into consideration the unique characteristics and needs of the specific patient. It is important to have in mind that this guideline does not override the responsibility of the therapist to arrive at the appropriate decisions, especially since the final choice of treatment will demand the consent and acceptance of the patient and his caretakers and family.

When considering the recommendations of these clinical guidelines, it is important to remember that treatment and care of psychiatric patients is best done within a multidisciplinary setting that engages both the patient and his or her family in the treatment plan. Such setting should also provide advice concerning any direct or indirect effects the disorder has on the lives of the patient and his or her family members.

All members of the workgroup made formal declarations of interest that are included at the end of all the published papers of this series. Eleven members oversaw the analysis and synthesis of research data and the development of the guideline, and all statements and recommendations in this guideline have been agreed upon by the whole workgroup.

The clinical guidelines that are included in the current paper are as much evidence based as possible and by this, they put an even stronger emphasis on evidence than other expert consensus guidelines. However, clinical wisdom and practical issues helped to shape the guidelines in a user-friendly way.

The CINP workgroup developed a precise algorithm and a detailed guideline that are both included in the 2nd paper of this series, while the current paper includes the simpler clinical guideline.

Details on efficacy and recommendation levels for each treatment modality are included in the 2nd paper of this series, which is also included in the current issue of the journal.

Existing Evidence for the Treatment of BD

As shown and discussed in detail in the previous manuscripts of the CINP BD guidelines, there are a significant number of studies that have reported original data or results of posthoc analyses and meta-analyses for the treatment of acute mania, and these studies/analyses have addressed monotherapy, combination or add-on treatments as well as the comparison of some of these treatment options. Unfortunately, the literature is rather limited for acute bipolar depression and the maintenance phase in terms of monotherapy, combination treatment, and comparison of agents as well as posthoc and meta-analyses. There is also limited literature on the treatment of mixed episodes, rapid cycling patients, comorbid conditions, and special issues. In addition to the data from the clinical trials, the workgroup took into consideration recommendations from the existing guidelines, with specific emphasis on those developed during the last 10 years.

Concept and Structure of the Clinical Guidelines

As mentioned before, the current guidelines are based on hard data and were intended to be as evidence based as possible while recognizing that there is not enough evidence available for all phases and facets of BD and that guidelines should be user friendly to be used widely in everyday clinical practice. When developing the guidelines, monotherapy was given priority over combination therapy when data were sufficient to do so. The guidelines give separate recommendations for each of the major phases of BD, that is, acute mania, acute bipolar depression, and the maintenance phase. It is strongly recommended that the clinician when applying the recommendations for the acute phase keeps the long-term treatment needs in mind.

One of the major challenges was the issue of mixed episodes vs mixed features, as DSM-IV-TR and DSM-5 have a different approach (Vieta and Valenti, 2013). Controlled studies use DSM-IV-TR definitions, while at the same time most countries have the obligation to use ICD-10 for clinical purposes. To make things even more complex, the data suggest that mixed features respond to treatment in a different way than mixed episodes do (according to DSM-IV-TR definition).

Another challenge was the use of the term “mood stabilizer.” Although there is controversy on the true meaning of the term given the findings from recent randomized controlled trials, the term is retained in the phrasing of the guidelines when it is impossible to avoid it, since a number of studies utilize it and do not differentiate between the agents that had been used. When used in the guidelines, the term usually refers to lithium, valproate, and in some instances to carbamazepine and lamotrigine.

Clinical Guidelines to Treat Bipolar Disorder

General Guidelines

The first priority when dealing with a BD patient is the assessment of risks to the patient or others, and whether there is a need for immediate hospitalization, even involuntary. It is important to provide a tranquil environment with reduced stimuli for patients in an acute manic or hypomanic episode. Both the patient and the family should be advised that all important decisions including family matters, professional issues, and finances should be postponed until the resolution of the acute symptomatology. On the other hand, during an acute depressive or mixed episode, the patients are at a higher risk to commit suicide, and every measure to protect the life of the patient should be taken.
Establishing a therapeutic alliance with the patient and his/her family and caregivers is of utmost importance, although it could be difficult especially during periods of acute mania and in the presence of psychotic features. Involuntary admission might be unavoidable when the health and the life of the patient or others might be at risk; however, the dignity, human rights, and personal space of the patient should be respected, as law dictates.

As soon as this is feasible, a full physical examination of the patient should be conducted, including laboratory testing. Women should also be assessed for polycystic ovary syndrome (PCOS). The physical examination and laboratory testing should be repeated according to local guidance and the clinical judgement of the therapist especially in response to changes in the clinical picture. It is advisable to repeat laboratory testing after 1 month and every 3 to 6 months thereafter, also depending on the medications prescribed.

Similar to epilepsy, there is an association between PCOS and major psychiatric disorders, including BD. An increased risk can also be demonstrated in their siblings suggestive of shared familial factors between PCOS and psychiatric disorders. Obesity as well as the use of valproate could be another risk factor connecting mental disorders with PCOS (Cesta et al., 2016).

Whenever possible patients should participate in decision making concerning the treatment plan. Psychoeducational interventions will be beneficial for such involvement. Such participation in decision making usually improves adherence and collaboration with the therapist, thus leading to a better outcome. Close collaboration between the patient, his/her family, and the therapist may improve identification of periods with a high risk of relapse and timely adjustments of treatment to reduce the intensity and duration of an emerging acute episode.

The acute treatment should be tailored to the individual patient needs and specific clinical characteristics in terms of medication choice and dosage according to the recommendations made by the guidelines. The dosage should be titrated according to clinical judgement and eventually be raised to the highest recommended and tolerated dose to maximize the chances for treatment response. Therapeutic drug monitoring may be a helpful tool in selected, nonresponsive patients.

Decreased need for sleep is a common symptom of mania and difficulty to fall asleep is a frequent symptom of depression. Further, sleep disturbance can destabilize the course of BD and can also be an early warning sign of impending relapse of mood episodes. Therefore, clinicians need to be particularly vigilant to addressing sleep disturbance in order to aid recovery in those with acute mood episodes and prevent relapse of mood episodes in BD patients during maintenance treatment.

Most clinicians tend to use antipsychotics in manic patients with psychosis, and there is evidence that antipsychotics are equally effective in those with and without psychotic mania. However, the studies have not systematically assessed the efficacy of lithium or other mood stabilizers with regard to whether they work equally well in both populations. Therefore, we recommend using antipsychotics in psychotic manic patients and adding them to those on mood stabilizers that are unresponsive.

The latency until response varies, although in acute mania an observable improvement of symptoms may occur within the first few days, especially with the use of antipsychotics. Response to lithium might take at least a week, while with valproate or carbamazepine it might take longer, but response should be observable within the first 2 weeks. Beyond this manic patients should be considered as nonresponders to the specific agent(s) at the specific dosage(s). For acute bipolar depression and mixed patients response to treatment could take longer and improvement may be more subtle.

The successful treatment of the acute episode should be continued during the adjacent phase, which is called continuation, and may differ from the maintenance phase, although the terms are often interchangeably used.

The position of the CINP guidelines is that the acute phase treatment should be continued with the same medication and at the same dosage for a minimum of 2 months after the achievement of full resolution of manic symptoms (and thus the patient has entered remission) and for at least 6 months if the index episode was bipolar depression. After this period treatment should either be continued or gradually switched to the recommended maintenance treatment. This recommendation was reached through expert consensus on the basis of clinical wisdom, since there are no hard data to rely on. In most patients, maintenance treatment should be kept indefinitely (lifelong) after the diagnosis of BD has been confirmed. Exceptions may be patients after a first and single manic or mixed episode, and those with a history of a very low relapse rate where physical health risks of medication may outweigh benefits. This should be a special issue to deal with during psychoeducational interventions.

As discussed in detail in the specific papers, BD is associated with an increased comorbidity that includes alcohol and substance abuse, anxiety disorders, personality disorders, and higher rates of general medical conditions. The management of these comorbid conditions and especially of those medical conditions that are associated with reduced life expectancy should be considered as high priority.

In essence, BD is a chronic disease with a complex clinical picture, in need of complex and expensive treatments, and associated with high psychiatric and medical comorbidity (Grande et al., 2016). High-quality, intensive care is needed, ideally in the frame of a multidisciplinary team and with step-wise interventions and activities that also extend in the community (Wagner, 1998).

The levels of recommendation concerning monotherapy and combination treatment in acute mania and mixed episodes as well as the recommended dosages of medication are depicted in Table 1. Effects on the manic and the depressive components of mixed episodes are shown separately.

**Clinical Guidelines for the Treatment of Acute Mania/Hypomania**

Patients with acute mania/hypomania should be evaluated immediately upon presentation concerning the risk of violent and dangerous behaviors. Impulsiveness should also be evaluated, since its combination with grandiose thinking might pose the patient at a high risk to hurt herself or himself or others. In potentially or acutely agitated patients, it is important to provide a calming environment with reduced stimuli (Garriga et al., 2016).

Next, rapport with the patient should be established, if possible, to assess the degree of insight and ability to collaborate to receive treatment as well as the need for hospitalization. This should be followed by a thorough physical examination including laboratory testing; however, in many cases it is inevitable to postpone it until the patient is more cooperative.

In the absence of reliable data, hypomania should be treated similarly to full mania, although higher doses may be required for the latter. Besides the specific medication recommendations as depicted in Table 1, there are some general principles that should be obeyed:
Table 1. Level of Recommendation Concerning Monotherapy in Acute Mania/Mixed and Recommended Dosages for Medication Options

<table>
<thead>
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<th>Agent/modality</th>
<th>Acute Mania</th>
<th>Mixed Episode</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mono therapy</td>
<td>Combination</td>
</tr>
<tr>
<td></td>
<td>MS Li Val Cbz FGAs</td>
<td>Manic component</td>
</tr>
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<td>1 2 - - - -</td>
<td>3 3 - -</td>
</tr>
<tr>
<td>Asenapine</td>
<td>1 2 - - - -</td>
<td>3 3 - -</td>
</tr>
<tr>
<td>Cariprazine</td>
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<td>- - - -</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>1 5 - - - -</td>
<td>3 5 - -</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1 2 2 - - -</td>
<td>5 - - -</td>
</tr>
<tr>
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<td>1 2 - 5 - -</td>
<td>3 - 5 5</td>
</tr>
<tr>
<td>Valproate</td>
<td>1 - - - - 2</td>
<td>3 4 - -</td>
</tr>
<tr>
<td>Carbamazepine</td>
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<td>3 3 - -</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2 2 2 2 2 -</td>
<td>- 5 5</td>
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<tr>
<td>Lithium</td>
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<td>- - - -</td>
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<tr>
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<td>ECT</td>
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<td>Pimozide</td>
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<td>Tamoxifen</td>
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<td>Ziprasidone</td>
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<td>OFC</td>
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<td>4 4 - -</td>
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<tr>
<td>Medroxyprogesterone</td>
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</tr>
<tr>
<td>Allopurinol</td>
<td>- 5 2 - - 5</td>
<td>- - - -</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>- - - - - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>5 - - - - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>Gabapentin</td>
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<tr>
<td>Lamotrigine</td>
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<tr>
<td>Licarbazepine</td>
<td>5 - - - - -</td>
<td>- - - -</td>
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<tr>
<td>rTMS</td>
<td>5 - - - - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>Topiramate</td>
<td>5 5 5 - - -</td>
<td>- - - -</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5 - - - - 5</td>
<td>- - - -</td>
</tr>
<tr>
<td>FEWP</td>
<td>- - - - 5 -</td>
<td>- - - -</td>
</tr>
</tbody>
</table>

Abbreviations: -, no data; Cbz, carbamazepine; ECT, Electroconvulsive therapy; FEWP, Free and Easy Wanderer Plus; FGA, first-generation antipsychotic; MS, mood stabilizer; NR, not recommended; OFC, olanzapine-fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.

The grading method including the levels of recommendation are described in detail in the 1st and 2nd papers on CINP treatment guidelines, which are included in the current supplement.

First step:
- Discontinue treatment with antidepressants
- Take into consideration any previous history of psychotic features
- Start with aripiprazole, asenapine, cariprazine, paliperidone, quetiapine, risperidone, or valproate monotherapy
- If the patient is already under one of the above first-step monotherapy or under combination therapy of any kind and response is unsatisfactory, switch to another first-step monotherapy
- If the personal history of the patient suggests that this is not an option, proceed to the next step and switch to the most suitable second-step treatment option based on treatment response and tolerability issues during previous episodes.

Second step:
If the interventions recommended during the first step fail or the response is unsatisfactory, then apply:
- Olanzapine, lithium, carbamazepine, haloperidol, or ziprasidone monotherapy
- Combinations of lithium or valproate plus asenapine, aripiprazole, haloperidol, or olanzapine
- Lithium plus allopurinol
- Valproate plus a first-generation antipsychotic (FGA)
- Valproate plus celecoxib

Third step:
- Combination treatment of lithium or valproate with quetiapine or risperidone

Fourth step:
- Apply ECT on top of pharmacological treatment or switch to oxcarbazepine monotherapy
- The fourth step includes monotherapy with chlorpromazine, pimozide, tamoxifen options are also combination treat-
ments of lithium or valproate plus tamoxifen, or the combination of risperidone plus lithium. In patients with residual manic/hypomanic symptoms, oxcarbazepine addition to lithium may be helpful.

- If a full mixed episode according to DSM-IV criteria is present, then the choice should be olanzapine-fluoxetine combination (OFC) or ziprasidone monotherapy

Fifth step:
- Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist; ECT if not applied earlier

Not recommended:
- Monotherapy with eslicarbazepine, gabapentin, lamotrigine, licarbazepine, rTMS, topiramate, verapamil
- Combination therapy of lithium or valproate plus paliperidone, ziprasidone, gabapentin, topiramate or Free and Easy Wanderer Plus (FEWP) and the combination of allopurinol plus a mood stabilizer (other than lithium) or an FGA (other than chlorpromazine or haloperidol)
- Medroxyprogesterone plus a mood stabilizer
- Valproate is not suitable for women of child bearing age

Note:
* no wide clinical experience

Recommendation of dismissing a treatment option is based on the efficacy and safety of this specific treatment option in acute mania. However, an agent or treatment modality that is otherwise not recommended during the acute phase could be added for specific reasons (e.g., starting with lamotrigine early during mania to prevent future depressive episodes in patients with depressive predominant polarity or topiramate for weight reduction.)

The step-wise algorithm for acute mania/hypomania is shown in Table 2. Comparison of the CINP guidelines to various other previously developed guidelines for acute mania is shown in Table 3.

Clinical Guidelines for the Treatment of Acute Bipolar Depression

The assessment of suicidal and self-harm risk has priority in BD patients with an acute depressive episode. Next, insight and willingness to adhere to the treatment plan as well as the social support network should be evaluated. Based on this information, a decision whether hospitalization (even involuntary) is mandatory should be made. An overview of the study data this clinical guideline is based on is shown in Table 4.

The following stepwise treatment algorithm has been put forward by the task force:

First step:
- Start with quetiapine or lurasidone
- Consider CBT as add-on to medication according to the patient preference and to availability. Never consider CBT as monotherapy

Second step:
- Monotherapy with olanzapine or OFC
- Combination of a mood stabilizer with lurasidone, modafinil, or pramipexole
- Lithium plus lamotrigine or pioglitazone
- Add escitalopram or fluoxetine to ongoing therapy
- For the treatment of comorbid anxiety add paroxetine, quetiapine, valproate, or lurasidone, and consider mindfulness-based interventions as add-on to ongoing therapy

Table 2. Clinical Guideline to Treat Acute Manic and Mixed Episodes

<table>
<thead>
<tr>
<th>Step</th>
<th>Treatment Options</th>
</tr>
</thead>
</table>
| 1st step | Discontinue treatment with antidepressants  
Take into consideration the previous history of psychotic features  
Start with aripiprazole, quetiapine, cariprazine, paliperidone, quetiapine, risperidone, valproate, or asenapine monotherapy  
Consider IPSRT as add-on to medication according to clinical judgement, patient preferences and availability. Never utilize IPSRT as monotherapy |
| 2nd step | Apply  
Olanzapine, lithium, carbamazepine, or haloperidol monotherapy  
Combinations of lithium or valproate plus aripiprazole, haloperidol, olanzapine, quetiapine, or risperidone  
Lithium plus allopurinol or oxcarbazepine  
Valproate plus a FGA  
A mood stabilizer plus medroxyprogesterone  
Valproate plus celecoxib |
| 3rd step | ECT on top of pharmacological treatment  
Oxcarbazepine monotherapy |
| 4th step | Monotherapy with chlorpromazine, pimozide, tamoxifen, or ziprasidone.  
Combination of lithium or valproate plus tamoxifen  
Combination of risperidone plus lithium  
OFC or ziprasidone monotherapy in mixed episodes |
| 5th step | Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist  
ECT if not applied earlier |
| Not recommended | Monotherapy with eslicarbazepine, gabapentin, lamotrigine, licarbazepine, rTMS, topiramate, verapamil, and combination therapy of lithium or valproate plus paliperidone, ziprasidone, gabapentin, topiramate or FEWP and the combination of allopurinol plus a mood stabilizer (other than lithium) or an FGA |

Abbreviations: ECT, electroconvulsive therapy; FEWP, Free and Easy Wanderer Plus; FGA, first-generation antipsychotic; IPSRT, interpersonal and social rhythms therapy; OFC, olanzapine fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation.
Third step:

- Valproate, aripiprazole, imipramine, phenelzine, or lamotrigine monotherapy
- Lithium plus L-sulpiride

Fourth step:

- Start with tranylcypromine or lithium monotherapy
- Venlafaxine in combination with an antimanic agent
- Armodafinil or intravenous ketamine in combination with a mood stabilizer
- Lithium plus fluoxetine or lamotrigine
- Carbamazepine plus FEWP
- Levothyroxine (L-T4) plus a mood stabilizer
- Lithium plus oxcarbazepine

Fifth step:

- ECT
- Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist

Not recommended:

- Monotherapy with donepezil, paroxetine (except for comorbid anxiety), ziprasidone, gabapentin, and TMS
- Combination of any mood stabilizer with agomelatine, paroxetine, ziprasidone, bupropion, celecoxib, levetiracetam, lisdexamfetamine, risperidone, or pregnenolone

Note:

- * no wide clinical experience

Some agents may put the patient at a higher risk to switch (e.g., antidepressants or stimulants) (Pacchiarotti et al., 2013). In spite of the monotherapy recommendation, it is at the therapist’s discretion to add an antimanic agent as a prophylactic measure, since, for most of these agents and contrary to common beliefs, the data are negative or equivocal for switching.

The stepwise algorithm for acute bipolar depression is shown in Table 5. The comparison of the CINP guidelines to other previously developed guidelines for acute bipolar depression is shown in Table 6.

Clinical Guidelines for the Treatment during the Maintenance Phase

It is expected that during the maintenance period, most patients should have full capacity to participate in decisions concerning her/his treatment plan, especially if they have had psychoeducational interventions. Such participation in decision making not only is in accord with social and political ethics, human

Table 3. Comparison of CINP Clinical Guidelines to Other Previously Developed Guidelines for Acute Mania

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Abbreviations: ECT, electroconvulsive treatment NR, not recommended; rTMS, repetitive Transcranial Magnetic Stimulation.
The grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options).

* NICE and BAP ordering is on the basis of line of treatment.
* Step 2 in the WFSBP guideline would be a combination of two grade "1".
Table 4. Level of Recommendation Concerning Monotherapy and Combination Treatment in Acute Bipolar Depression and also for Comorbid Anxiety

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<th>Agent/modality</th>
<th>Monotherapy</th>
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<td>Phenelzine</td>
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</tr>
<tr>
<td>Olanzapine</td>
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<td>4</td>
</tr>
<tr>
<td>Lamotrigine</td>
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<tr>
<td>Tranylcypromine</td>
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<tr>
<td>Venlafaxine</td>
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<tr>
<td>Carbamazepine</td>
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<td>-</td>
</tr>
<tr>
<td>Lithium</td>
<td>5</td>
<td>-</td>
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<tr>
<td>Paroxetine</td>
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<td>5</td>
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<tr>
<td>Gabapentin</td>
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<td>-</td>
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<tr>
<td>rTMS</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>FEWP</td>
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<td>-</td>
</tr>
<tr>
<td>Levothyroxine (L-T4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Modafinil</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Pioglitazone</td>
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<td>Armodafinil</td>
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<tr>
<td>Ketamine</td>
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<td>-</td>
</tr>
<tr>
<td>L-sulpiride</td>
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<td>-</td>
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<td>Oxcarbazepine</td>
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<td>-</td>
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<tr>
<td>Agomelatine</td>
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<td>-</td>
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<tr>
<td>Memantine</td>
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</tr>
<tr>
<td>Levetiracetam</td>
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<td>-</td>
</tr>
<tr>
<td>Bupropion</td>
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<td>-</td>
</tr>
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</tr>
<tr>
<td>Risperidone</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: -, no data; Cbz, carbamazepine; FEWP, Free and Easy Wanderer Plus; Lam, lamotrigine; MS, mood stabilizer; NR, not recommended; OFC, olanzapine-fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.
Recommended dosages for medication options are also shown.

The grading method including the levels of recommendation are described in detail in the 1st and 2nd papers on CINP treatment guidelines, which are included in the current supplement.

rights, and citizen empowerment issues, but usually it also improves adherence and collaboration with the therapist, thus leading to a better outcome. During the maintenance phase it is important to have in mind that at least one-third of BD patients frequently fail to take their medication (Scott and Pope, 2002) as prescribed, and that nonadherence leads to more frequent recurrences, hospitalizations, and sometimes to death by suicide (Muller-Oerlinghausen et al., 1992; Adams and Scott, 2000; Colom et al., 2000).

To enhance treatment adherence it is important to recognize the contributing factors (Sajatovic et al., 2004) and involve both the patient and his/her family in the decision making with psychoeducational support (van Gent and Zwart, 1991; Sajatovic et al., 2004). In this context, the collaboration between the patient and his/her family with the therapist concerning the monitoring of symptoms can lead to the identification of periods with a high risk of relapse, and if necessary to adjustments in treatment or to early targeted interventions to reduce the intensity and duration of an emerging acute episode.

The successful treatment of the acute episode should be perpetuated during the phase that is called continuation and may differ from the maintenance phase, although the terms are often interchangeably used. Maintenance treatment should be kept indefinitely (lifelong) after the diagnosis of BD has been confirmed. Exceptions may be patients after a first and single manic or mixed episode, and those with a history of a very infrequent relapses where physical health risks of medication may outweigh benefits. This should be a special issue to deal with during psychoeducational interventions.

A difficult question is whether it is wise to continue the index medication used for the acute episode. This is an option adopted by many guidelines. The position of the CINP guidelines...
is that the acute-phase treatment should be continued for a minimum of 2 months after the achievement of full resolution of symptoms (and thus the patient has entered remission), and after this period treatment should gradually be changed into the recommended maintenance treatment.

Of utmost importance is the identification of subsyndromal or subthreshold symptoms that are more often of depressive polarity. In case of the presence of these clinical features, the therapist might consider to add on a treatment that is efficacious in acute mania or depression depending on the polarity of

### Table 5. Clinical Guideline to Treat Acute Bipolar Depressive Episodes

<table>
<thead>
<tr>
<th>1st step</th>
<th>2nd step</th>
<th>3rd step</th>
<th>4th step</th>
<th>5th step</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Start with quetiapine, lurasidone, or OFC</td>
<td>• Monotherapy with valproate or lithium</td>
<td>• Aripiprazole, imipramine, or phenelzine monotherapy</td>
<td>• Olanzapine, lamotrigine, tranylcypromine, or carbamazepine monotherapy</td>
<td>• ECT</td>
<td></td>
</tr>
<tr>
<td>• Consider add-on CBT. Never consider CBT as monotherapy</td>
<td>• Combination of a mood stabilizer with lurasidone, modafinil, or pramipexole</td>
<td>• Lithium plus oxcarbazepine or L-sulpiride</td>
<td>• Olanzapine lamotrigine, or carbamazepine monotherapy</td>
<td>• Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lithium plus pioglitazone</td>
<td>• Armadyl or ketamine on a mood stabilizer</td>
<td>• Combination of any mood stabilizer with agomelatine, paroxetine, zonisamide, bupropion, celecoxib, levetiracetam, lisdexamfetamine or risperidone, Memantine plus lamotrigine and lithium plus aripiprazole, donepezil or imipramine. Not recommended also risperidone or zonisamide for the treatment of comorbid anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Carbamazepine plus FEWP</td>
<td>• Lithium plus fluoxetine or lamotrigine</td>
<td>• Venlafaxine preferably in combination with an antimanic agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Add escitalopram or fluoxetine on ongoing therapy</td>
<td></td>
<td>• Aripiprazole, imipramine, or phenelzine monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• For the treatment of comorbid anxiety add paroxetine, quetiapine, valproate, or lurasidone, and consider mindfulness-based interventions as add-on ongoing therapy</td>
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</tr>
</tbody>
</table>

### Table 6. Comparison of the CINP Clinical Guidelines with Other Previously Developed Guidelines for Acute Bipolar Depression

<table>
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</tr>
<tr>
<td>Escitalopram</td>
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<td>-</td>
<td>-</td>
<td>3</td>
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<tr>
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<td>3</td>
<td>-</td>
<td>-</td>
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<tr>
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<tr>
<td>Phenelzine</td>
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<td>-</td>
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<td>5</td>
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<td>3</td>
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<td>-</td>
<td>2</td>
</tr>
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<td>Olanzapine</td>
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<td>1</td>
<td>1</td>
<td>1</td>
</tr>
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<td>Tranylcypromine</td>
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<td>-</td>
<td>-</td>
<td>4</td>
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<tr>
<td>ECT</td>
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<td>4</td>
<td>3</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>NR</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leviracetam</td>
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<td>-</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L-thyroxine</td>
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<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Risperidone</td>
<td>-</td>
<td>-</td>
<td>NR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rTMS</td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>NR</td>
<td>-</td>
<td>NR</td>
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</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavioral treatment; Cbz, carbamazepine; ECT, electroconvulsive therapy; FEWP, Free and Easy Wanderer Plus; IPSRT, interpersonal and social rhythms therapy; Lam, lamotrigine; MS, mood stabilizer; OFC, olanzapine fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.
these subthreshold or subsyndromal symptoms. However, it is obvious that this might lead to polypharmacy with little scientific support. As discussed in detail in the accompanying papers, BD is associated with frequent comorbidity that includes alcohol and substance abuse, anxiety disorders, personality disorders, and higher rates of general medical conditions. The management of these comorbid conditions and especially of those medical conditions that are associated with reduced life expectancy should be considered high priority.

Essentially BD is a chronic disease displaying a complex clinical picture with high psychiatric and medical comorbidity, which demands high-quality intensive and expensive care. A multidisciplinary team approach following an organized step-by-step manner with interventions and activities that also extend in the community is often mandatory (Wagner, 1998).

A number of specific clinical variables with research data supporting their usefulness in the decision-making process should be assessed. These include the predominant polarity, and the presence of psychotic features, mixed episodes, and rapid cycling. Other clinical features might be important (e.g., suicidality); however, there are no hard data to dictate their targeted treatment.

More specifically, first consider whether a predominant polarity is present when starting maintenance treatment (Carvalho et al., 2015). Then consider the possibility to stage the disorder, having in mind that probably the predominant polarity changes into depressive with the progression of the disease. Consider the presence of psychotic symptoms in the course of the disorder. Search for the recurrent emergence of mixed episodes in the past and decide whether the patient should be classified as rapid cycling.

If the treatment during the most recent episode needs to be completely different from the options that are suggested for the maintenance phase in the specific patient, keep it for the continuation phase and gradually taper it against one of the recommended treatments for the maintenance phase. An overview of the data the clinical guideline is based on is shown in Table 7.

First step:
- Take predominant polarity (if evident) into consideration
- Start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine, or risperidone, including Risperidone Long Acting Injectable (RLAI) monotherapy depending on predominant polarity
- Consider CBT or psychoeducation as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider CBT or psychoeducation as monotherapy

Second step:
- Add fluoxetine, lamotrigine, or lithium on the first-step option (depending on predominant polarity)
- Lithium plus carbamazepine
- Quetiapine plus lithium or valproate
- Olanzapine or aripiprazole plus a mood stabilizer

Third step:
Add RLAI, valproate, carbamazepine, or N-acetylcysteine on second-step treatment if not previously used

Fourth step:
- Take into consideration the predominant polarity and add an agent with proven efficacy against the acute phase no matter whether it has proven maintenance efficacy
- Lithium plus lamotrigine
- Consider adding venlafaxine or haloperidol

### Table 7. Level of Recommendation during the Maintenance Phase and the Efficacy in the Prevention of Manic, Mixed, or Depressive Episodes as Well as Recommended Dosages

<table>
<thead>
<tr>
<th>Agent/modalty</th>
<th>Monotherapy</th>
<th>Combination</th>
<th>Recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Manic</td>
<td>depressive</td>
<td>Mixed</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lithium</td>
<td>2</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>4</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Psychoeducation</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Aripiprazole</td>
<td>1</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>RLAI</td>
<td>1</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Paliperidone</td>
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<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Valproate</td>
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<td>-</td>
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<tr>
<td>Carbamazepine</td>
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<td>-</td>
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<td>CBT</td>
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<tr>
<td>N-acetyl cysteine</td>
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<tr>
<td>Memantine</td>
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</tr>
<tr>
<td>Oxcarbazepine</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>Perphenazine</td>
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<td>-</td>
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</tr>
</tbody>
</table>

Abbreviations: CBT, cognitive behavioral therapy; Cbz, carbamazepine; Lam, lamotrigine; MS, mood stabilizer; RLAI, risperidone long acting injection; Val, valproate. The grading method including the levels of recommendation are described in detail in the 1st and 2nd papers on CINP treatment guidelines, which are included in the current supplement.
Fifth step:

- Consider any combinations from steps 1 to 4 that have not been tried
- Consider maintenance ECT
- Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
- Consider Interpersonal and Social Rhythms Therapy (IPSRT) as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider IPSRT or psychoeducation as monotherapy

Not recommended:

- Adding memantine or perphenazine on a mood stabilizer
- Aripiprazole plus lamotrigine or valproate
- Lamotrigine plus valproate
- Lithium plus imipramine or oxcarbazepine

The chart of the guideline for the maintenance phase is shown in Table 8. The comparison of the CINP guidelines to other previously developed guidelines for the maintenance phase is shown in Table 9. It should be noted that there are no adequately controlled trials supporting the efficacy of oxcarbazepine.

Duration of Maintenance Treatment

There are no data concerning the duration of maintenance treatment. As mentioned in the first CINP guidelines paper, in 70% of cases the course resembles that of a recurrent episodic illness, while in 25% of cases there is a chronic course without clear remissions between episodes. In only 5% there is a single episode of mania, and this probably depends on the duration of the follow-up. BD is almost by definition a lifelong disorder, and thus it requires lifelong maintenance treatment or at least close observation and timely interval treatment initiation in selected, reliable patients knowing their early warning signs.

The only medical reasons for stopping maintenance treatment are poor tolerability, safety reasons, and continuous non-adherence. Also in some patients in whom medication does little or no difference, especially during the advanced stages of the disorder, a more palliative type rather than an aggressive maintenance treatment might be preferable. This is a very sensitive issue and it is open to debate.

Many patients will refuse long-term pharmacotherapy, or manifest poor adherence. Psychoeducational interventions have been proven to be efficacious during the earlier stages of the disorder. Since there is lack of knowledge concerning the efficacy of other psychotherapeutic interventions, psychoeducation alone or together with cognitive remediation could be applied to those patients with severe disability and residual symptoms, and to those with poor insight and adherence.

Special Cases and Populations

Agitation

Agitation is most often present during periods of acute manic or mixed episodes, but it is not unusual during periods of depression, especially with mixed depressive states. The presence of agitation acts as a barrier to therapy, prevents the establishment of a therapeutic alliance, and poses a risk to the health and life of the patient and others (Garriga et al., 2016).

It is important to provide a calming environment with reduced stimuli and to make any effort to establish rapport with the patient. In case this fails, then involuntary treatment might be necessary according to local legislation. The evidence-based pharmaceutical interventions recommended are (Chouinard et al., 1993; McElroy et al., 1996; Hirschfeld et al., 1999; Meehan et al., 2001; Citrome, 2012; Kwentus et al., 2012):

- Intramuscular haloperidol (5–10 mg) at 0, 30, and 60 minutes
- Intramuscular olanzapine (10 mg, first 2 injections; 5 mg, third injection)
- Inhaled loxapine 5 mg or 10 mg single dose in 24 hours

Combination of an antipsychotic with

- Clonazepam injections (1–2 mg) at 0, 30, and 60 minutes
- Lorazepam injections (2 mg, first 2 injections; 1 mg, third injection). In case the patient accepts oral therapy and the therapist wishes to avoid injectables, an antipsychotic in monotherapy or in combination with a benzodiazepine could be the choice. Valproate oral loading of 20 to 30 mg/kg/d is also an option

Table 8. Clinical Guideline to Treatment during the Maintenance Phase for Bipolar Disorder

| 1st step | • Start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine, or risperidone (including RLAI) monotherapy
| 1st step | • Consider CBT or psychoeducation as add-on to medication. Never consider CBT or psychoeducation as monotherapy
| 1st step | • Take predominant polarity (if present) into consideration
| 2nd step | • Add fluoxetine or lithium on the first-step option
| 2nd step | • Lithium plus carbamazepine
| 2nd step | • Quetiapine plus lithium or valproate
| 2nd step | • Olanzapine or aripiprazole plus a mood stabilizer
| 3rd step | Add RLAI, valproate, carbamazepine, lamotrigine, or N-acetylcysteine on second-step treatment
| 4th step | Take into consideration the predominant polarity and add an agent with proven efficacy against the acute phase no matter whether it has proven maintenance efficacy.
| 4th step | Consider adding venlafaxine or haloperidol
| 5th step | Consider any combinations from steps 1–4 that have not been tried
| 5th step | Consider maintenance ECT
| 5th step | Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
| Not recommended | Adding memantine or perphenazine on a mood stabilizer, aripiprazole plus lamotrigine or valproate, lamotrigine plus valproate, lithium plus lamotrigine, imipramine, or oxcarbazepine.

Abbreviations: ECT, electroconvulsive therapy; RLAI, risperidone long acting injectable.
Combinations of injectables with oral medication could also be an option depending on availability. In principle benzodiazepines should not be used as monotherapy beyond the acute emergency room setting in BD patients.

Pregnancy, Breast-Feeding, and the Use of Oral Contraceptives
Since around one-half of pregnancies are unplanned (Bergman et al., 1992), the psychoeducation of bipolar females concerning the course of the disorder and issues pertaining to contraceptives, pregnancy, postpartum, and breast-feeding and the effect medication have on the fetus is essential.

Risks (teratogenic effects) and benefits (prevention of recurrence) of medication treatment need to be discussed with the patient and her spouse at the earliest. In principle, maintenance treatment should be paused during pregnancy and especially during the first trimester if possible. This might not always be an option, especially in women with a high risk of recurrence. There are no controlled data on which treatment option is most efficacious and safest, especially in early pregnancy; therefore the general guidelines are in place. If possible pharmacotherapy should be avoided at least during the first trimester, and ECT might be an alternative option in severely ill patients.

If a decision in favor of medication treatment has been made, at least some patients might require higher doses of medication because of physiological changes related to pregnancy. Decrease in dosage might be advisable during the last few weeks before delivery (Altshuler and Hendrick, 1996). The agents with a known teratogenic effect are lithium, valproate, carbamazepine, and lamotrigine in doses >200 mg/d. Valproate and carbamazepine should be avoided in any case; continuation of lithium treatment might be justified in selected patients with their informed consent as the risk of heart malformations has been overestimated in the past (Burt and Rasgon, 2004; Yacobi and Ornoy, 2008). Atypical antipsychotics and lamotrigine monotherapy in doses <200 mg/d are reasonable choices, although the data on their safety during pregnancy are still limited. ECT is always an option; it is relatively safe with no data suggesting any teratogenic effect (Miller, 1994; Walker and Swartz, 1994, Echevarria Moreno et al., 1998; Bhatia et al., 1999; Kasar et al., 2007; Richards, 2007; Bulut et al., 2013; Gahr et al., 2013; Spodniakova et al., 2014; Leiknes et al., 2015). After delivery the most reasonable decision would be to start immediately with maintenance treatment, since the risk for a postpartum recurrence is high and avoid breast-feeding because most pharmacotherapeutic agents are excreted in the milk. Some patients might choose to breastfeed, but this should only be done after a detailed discussion of the risks and benefits, and the infant should be closely and carefully monitored. In this case, it might be better to use medication with short half-lives and to take them after breastfeeding to minimize the exposure of the infant. Unfortunately, the literature on treatment during the postpartum period is limited; therefore, the general guideline should be followed. Divalproex and carbamazepine are considered more compatible with breastfeeding compared with lithium (Austin and Mitchell, 1998; American Academy of Pediatrics Committee on Drugs, 2001; Burt et al., 2001; Ernst and Goldberg, 2002; Burt and Rasgon, 2004; Yonkers et al., 2004; Nice and Luo, 2012).

Management of Somatic Problems in BD Patients
Bipolar patients might present with a variety of somatic problems. The cause of them is variable and difficult to identify, but it includes a general higher risk observed in BD patients, and the sedentary lifestyle as well as the direct effect of medication as additional risk factors.

Increase in appetite, weight gain, and obesity are common problems in BD patients and are associated both with the...
disease and its treatment. Weight gain is perceived by patients and especially by young females to be a distressing side effect, and it frequently leads to poor adherence with treatment. Diabetes mellitus could develop as a consequence of weight gain, but is has been also reported in patients as a direct adverse effect of medication without the mediating effect of weight gain. Those patients with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo a full medical investigation of their individual risk to diabetes, hypertension, and dyslipidaemia before the initiation of treatment and periodically thereafter. During the maintenance phase, all patients should be monitored for symptoms and signs, including polydipsia, polyuria, and polyphagia, and if appropriate a laboratory investigation should be carried out. If necessary, treatment of diabetes and dyslipidaemia should be initiated and medication changes strongly considered.

Severe adverse effects specific to lithium are kidney and thyroid toxicity. Therefore, lithium should be gradually titrated and taken with food to reduce nausea, and plasma creatinine concentrations, Glomerular filtration rate, and thyroid function should be investigated at least once a year.

**Discussion**

The first operational treatment guidelines for BD were those of the American Psychiatric Association in 1994 (APA, 1994). Since then, a significant number of guidelines have been developed and some of them are regularly updated (APA, 1994, 1995, 2002; Suppes et al., 1995, 2001, 2002, 2003; Frances et al., 1996; 1997; AACAP, 1997; Goodwin et al., 1997, 2003, 2009, 2016; Jobson, 1997; Kusumakar et al., 1997; McClellan and Werry, 1997; Gilbert et al., 1998; Barreira et al., 1999; Bauer et al., 1999; Rush et al., 1999; Dennehy, 2000; Goldberg, 2000; Sachs et al., 2000; Allen et al., 2001; Montgomery, 2001; Grenze et al., 2002, 2003, 2004, 2009, 2010, 2013; Licht et al., 2003; Rush et al., 2003; Hirschfeld, 2005; Yatham et al., 2005, 2006, 2008, 2009, 2013a, 2013b; National Collaborating Centre for Mental Health, 2006; O’Dowd, 2006; Nolen et al., 2008; Jon et al., 2009; Ng et al., 2009; Frye et al., 2011; Beaulieu et al., 2012; Bond et al., 2012; McIntyre et al., 2012; Rosenbluth et al., 2012; Schafer et al., 2012; Mohammad and Osser, 2014; NICE, 2014; Malhi et al., 2015; Ostacher et al., 2015; Woo et al., 2015).

It is not surprising that guidelines place emphasis on different kinds of treatments and utilize a different concept of the disorder, since the data are incomplete and subject to varying interpretation. In general, as an approach, treatment guidelines constitute one of the important developments in the field of psychiatry, following the introduction of operationalized diagnostic criteria in the frame of modern classification systems and the promotion of evidence-based medicine (EBM) also in psychiatry. They emerged as an important tool to summarize and appraise the research data and, to the extent this is possible, to standardize treatment on the basis of evidence. They also emerged as a response to the need of many clinicians for algorithms that translate research findings into the everyday clinical practice by organizing information from diverse sources into an easily accessible and reliable format.

Although it is expected that, in principle, the development of algorithms obeys the rules of EBM and is based primarily on research data from studies conducted in a rigorous way, often expert opinion or clinical consensus supersedes the evidence. In the last few years, the consumer opinion as well as economic issues have had increasing strength and importance and may play a significant role in the shaping of steps. The standard approach in the development of algorithms as this has been shaped in the last 20 years is to utilize EBM standards for the earlier steps; however, as algorithms move from earlier to later steps, the evidence becomes more and more insufficient, and in most cases expert opinion or clinical consensus gradually take over. Socioeconomic forces from patient advocates, the industry, and the economic interests of the government and insurance companies exert pressure already from the first step and up to the end of the procedure or interventions.

Eventually, the use of algorithms and guidelines is supposed to bring benefits for the patients in terms of a more favorable overall outcome as it combines efficacy and safety/tolerability. It is also supposed to bring benefits for the health system in general, since the use of algorithms and guidelines facilitates clinical decision making, reduces clinically inappropriate or cost-inefficient clinical practice decisions, provides similar treatment across different settings, and provides a metric to assess patient response and a framework to estimate the cost of treatment (Fountoulakis et al., 2005).

However, there are several potential risks associated with the use of algorithms and guidelines (Rush et al., 1999). The biggest problem is that often the evidence might be insufficient to lead to the development of a reliable algorithm, and the consensus panels whose decisions will cover the gap often express biased opinions. The use of algorithms may increase the costs disproportionately in comparison with benefits, and this poses important ethical dilemmas, especially when efficacy collides with safety and cost. Justified deviations from algorithms may constitute a case for legal action by malpractice lawyers.

The various treatment guidelines generally seem to have a common starting point, best described by the 1994 APA guidelines (APA, 1994), which interestingly seem to reflect the opinion of many clinicians still today. Overall it seems that disagreements are more than agreements even though all treatment guidelines claim to be evidence based. Probably this is because of the different way to approach and utilize the data. The comparison of the current CINP clinical guideline with 3 other guidelines (NICE, CANMAT/ISBD, WFSBP and BAP) is shown in Tables 3, 6, and 9. The current CINP guidelines are the most recent fully updated and fully evidence-based guidelines on the treatment of BD. They also include recommendations concerning the use of psychotherapeutic interventions again on the basis of available evidence. It is of note that the adherence of the workgroup to the evidence in a strict way produced guidelines that somehow differ radically from other previously developed guidelines. These differences include the role of specific antidepressants and the priority in the use of traditional agents like lithium, valproate, or carbamazepine. The focus on specific clinical characteristics, including predominant polarity, mixed features, rapid cycling is also a novel approach, and it has been utilized in the development of the specific algorithm and to a lesser extent in the development of the clinical guidelines. In the past, only predominant polarity had been utilized by the BAP guidelines (Goodwin, 2009).

It is evident that there are many issues that need further study, data are sparse and insufficient, and many questions remain unanswered. The most important and still unmet need is to be able to merge all the guidelines that concern different phases of the illness into a single one and in this way consider BD as a single unified disorder, which is the real world fact. However, to date the research data do not permit such a unified approach. It is also important to note that in spite of the publication of various treatment guidelines, clinicians do not seem to widely adopt any of them. Their impact on clinical practice
is quite limited even in the US. After the publication of the first APA 1994 guidelines, only about 16% of manic patients without psychotic features, 38% with mania with psychotic features, 31% of bipolar depressed with psychotic features, and 17% of bipolar depressed without psychotic features were reported to be treated according to treatment guidelines (Lim et al., 2001).

The pressure to develop guidelines for the treatment of severe and disabling mental disorders becomes stronger and stronger because of the need to provide a standardized, better, and more cost-effective treatment; however, empirical data are not always sufficient and the evaluation of guidelines in the real-world environment does not always support their use, as many times they lead to an increased cost without an impressive improvement in the treatment outcome. But the least these algorithms may achieve is to ensure a minimum quality of treatment and care and the minimum necessary discipline from the side of the therapist. Although the wider utilization of treatment guidelines is a universal need, at the same time the psychiatric community should guard the right of the therapist to make independent decisions concerning treatment on the basis of the individual patient and available scientific data; that means algorithms cannot replace education and training and may not be considered a golden standard of treatment, the deviation from which needs to be justified. Such an extreme position may lead to unnecessary legal complications.

One issue that warrants further study and attention is the fact that not all agents and therapeutic modalities are available in every country and not even within the same country, since sophisticated psychosocial approaches or ECT are often not accessible to the majority of patients. The current guideline did not take into consideration this issue but rather stuck to the body of hard evidence. This might make problematic specific aspects and steps of the guideline in some countries, especially when economic criteria are also implemented.

Concerning the current clinical guidelines, it is obvious that those who will choose to utilize them in their everyday clinical practice should have in mind that evidence-based guidelines like the CINP guidelines are limited by the data that are available. The workgroup hopes that they will constitute a valuable tool to guide the everyday clinical practice for the benefit of the patients, their families, and society, but on the other hand clinicians must exercise caution and make clinical decisions tailored to individual cases on the basis of a specific risk-benefit analysis suitable for the particular patient.

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Statement of Interest

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REVIEW

The International College of Neuropsychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 4: Unmet Needs in the Treatment of Bipolar Disorder and Recommendations for Future Research

Konstantinos N. Fountoulakis, MD; Eduard Vieta, MD; Allan Young, MD; Lakshmi Yatham, MD; Heinz Grunze, MD; Pierre Blier, MD; Hans Jurgen Moeller, MD; Siegfried Kasper, MD

Abstract

Background: The current fourth paper on the International College of Neuropsychopharmacology guidelines for the treatment of bipolar disorder reports on the unmet needs that became apparent after an extensive review of the literature and also serves as a conclusion to the project of the International College of Neuropsychopharmacology workgroup.

Materials and Methods: The systematic review of the literature that was performed to develop the International College of Neuropsychopharmacology guidelines for bipolar disorder identified and classified a number of potential shortcomings.

Results: Problems identified concerned the reliability and validity of the diagnosis of bipolar disorder and especially of bipolar depression. This, in turn, has profound consequences for early detection and correct treatment of the disorder. Another area that needs improvement is the unsatisfactory efficacy and effectiveness of therapeutic options, especially in special populations such as those with mixed features and rapid cycling course. Gender issues and adherence problems constitute an additional challenge. The literature suggests that while treatment providers are concerned more with treatment-related issues, patients and their caregivers worry more about issues pertaining to the availability of services and care, quality of life,
and various types of burden. The workgroup identified additional unmet needs related to the current standard of research in bipolar disorder. These include the fragmentation of bipolar disorder into phases that are handled as being almost absolutely independent from each other, and thus the development of an overall therapeutic strategy on the basis of the existing evidence is very difficult. Trials are not always designed in a way that outcomes cover the most important aspects of bipolar disorder, and often the reporting of the results is biased and unsatisfactory. The data on combination treatments and high dosages are sparse, whereas they are common in real world practice.

Conclusions: The workgroup endorses the full release of raw study data to the scientific community, and the development of uniform clinical trial standards (also including more realistic outcomes) and the reporting of results. The 2 large appendices summarize the results of this systematic review with regard to the areas of lack of knowledge where further focused research is necessary.

Keywords: BD, anticonvulsants, antidepressants, antipsychotics, evidence-based guidelines, lithium, mania, bipolar depression, mood stabilizers, treatment

Background

The first 3 papers of the International College of Neuropsychopharmacology (CINP) guidelines for the treatment of bipolar disorder (BD) consisted of a systematic and exhausting review of the literature concerning the available hard data on treatment options and a description of the major clinical challenges the therapist faces together with the patient and his/her family.

The workgroup developed a precise experimental algorithm and a clinical guideline for the treatment of BD, but it is obvious that these products are far from perfect. In fact there are a significant number of issues and needs that were not addressed due to a lack of evidence-based data. Suboptimal treatment and management, however, puts the patients at a higher risk for an adverse outcome with more residual symptoms and higher disability.

This is of utmost importance, since BD is a rather common and complex mental disorder accompanied by significant morbidity and mortality, including a high rate of suicide, while it is obvious that the treatment needs are not fully met by currently available pharmacotherapies and psychosocial interventions of any kind. The problem is further complicated by the poor adherence to treatment that many patients show and the somatic comorbidities that in some cases are adverse effects of medication.

The current paper is the fourth and last of the initiative to develop CINP guidelines for the treatment of BD and summarizes the experience gained from the whole project. It identifies the unmet needs and makes suggestions for future research and the way of dealing with specific issues in BD.

1. Unmet Needs Identified in the Literature (Summarized in Tables 1 and 2)

Diagnosis

The first and maybe biggest problem in the management of BD is the difficulty in making early correct diagnosis (Lish et al., 1994; Lewis, 2000; Hirschfeld et al., 2003; Morselli et al., 2003). In a majority of patients the first episode is depressive, and thus they receive the diagnosis of unipolar depression and they are mistreated with antidepressant monotherapy (Vieta, 2014). It has been reported that as many as 70% of BD patients failed to receive a correct diagnosis in the 1-year period following the initial episode, and in approximately 35% of them the correct diagnosis has been made only after 10 years had passed (Lish et al., 1994). Additionally, up to 70% of BD patients but especially bipolar spectrum patients often go unrecognized and undisagnosed, and thus remain untreated or inappropriately treated (Hirschfeld et al., 2003; Frye et al., 2004; Ketter, 2010). Since BD patients are most often misdiagnosed as suffering from unipolar depression or some type of personality disorder, they are frequently treated with antidepressants only or an inappropriate type of psychotherapy for prolonged periods of time.

This problem may persist until the day psychiatric diagnosis is not exclusively based on clinical phenotypes but on reliable and valid biological markers that can be utilized for precise diagnostic differentiation and treatment planning. Of all mental disorders, BD is the one that will probably benefit the most from the introduction of reliable and valid biological markers to our diagnostic armamentarium.

Additionally, physical health problems, especially in bipolar spectrum patients, are underrecognized and undertreated (Merikangas et al., 2011). This is probably a consequence of stigma but also of an unhealthy lifestyle, poor treatment adherence, and only irregular contacts with health care services.

Efficacy and Effectiveness of Therapeutic Options

All authors agree that only 2 to 3 agents have some efficacy across all phases, and no single pharmacotherapy is currently achieving remission in a satisfactory proportion of BD patients both across all phases and in the long term. Acute episodes comprise a relatively small time share of the overall illness, but subthreshold or subclinical symptoms dominate the clinical picture for most of the duration of the lives of patients, causing significant impairment, disability, and burden (Judd et al., 2002, 2003; Morgan et al., 2005). Since no single pharmacologic treatment is likely to achieve all therapeutic objectives, combining treatments is usually necessary to achieve an acceptable quality of life (Grande et al., 2016).

The very concept of what constitutes a “mood stabilizer” is under dispute, since there is no agent that is efficacious against all phases and all major clinical features of BD (manic, mixed, and depressive episodes, rapid cycling). Historically, lithium, valproate, and carbamazepine have all been considered to act as mood stabilizers, but today we have to acknowledge that some atypical antipsychotics, namely quetiapine and olanzapine, do also fulfill many criteria of a mood stabilizer. When it comes to clinical usefulness, while antipsychotics may act faster in acute mania and are also definitely efficacious against psychotic features, there are concerns with the safety profile of all agents useful in the treatment of BD, such as metabolic syndrome with antipsychotics, kidney and thyroid issues with lithium.
Almost all the literature concerning the treatment of all phases of BD focuses on reporting changes from baseline in a symptom rating scale and neglects other important aspects, including disability, quality of life, burden, and economic issues. Most researchers agree that currently available treatments are more efficacious in the reduction of symptoms than in the improvement of disability and the overall outcome (Bauer et al., 2001a; Calabrese et al., 2014; Frye et al., 2014; McElroy, 2014). This is especially true concerning bipolar depression, which is a rather refractory mental state with high risk for suicide (Akiskal et al., 1983; Weissman et al., 1984; Frye et al., 2004, 2014) and profound and lasting functional impairment (Bonnin et al., 2015). Residual symptoms may interfere with the ability of the patients to access and benefit from health care but also from the general state welfare (Gerson and Rose, 2012). Particularly in those patients with more severe disability, functional decline, and poor quality of life, the overall burden is further increased by a higher mortality from comorbid medical conditions (McIntyre et al., 2007) and suicide (Morgan et al., 2005). In these cases, the burden is also higher for caregivers, and the increased service utilization leads to a higher overall cost. This is made even worse when discriminatory coverage and reimbursement policies for mental health care are in place as they are in many countries around the world (Charney et al., 2003; Morgan et al., 2005).

It is unfortunate (although the reasons are apparent) that, by far, fewer randomized controlled trials (RCTs) have been conducted on the treatment of acute bipolar depression than for acute mania (Han et al., 2013). The changing composition of the study samples is a developing problem for all RCTs in mental disorders, and it seems that nowadays larger numbers of patients are required to demonstrate a significant effect compared with earlier studies, although the reasons for this are not entirely understood (Sachs, 2003).

Comprehensive managed care comprising of intensive follow-up, psychosocial and psychological treatment, and functional rehabilitation is not easily accessible to patients, even in developed countries. Lack of access to such services probably adversely influences the overall long-term outcome (Morgan et al., 2005; Goossens et al., 2007).

Gender

While it is known that there are gender-specific factors that can influence the treatment and overall management of patients with BD (Leibenluft, 1996; Hendrick et al., 2000; Leibenluft, 2000; Curtis, 2005), little research has been conducted in this area. This is important since unmet needs could differ between males and females (Curtis, 2005; Morgan et al., 2005).

Although the prevalence of BD-I is similar between genders (Morgan et al., 2005), more females suffer from BD-II (Leibenluft, 1996) and depressive predominant polarity (Nivoli et al., 2011). In addition, rapid cycling, mixed episodes, and dysphoric mania but also hypothyroidism and personality disorders might be more prevalent in females (McElroy et al., 1992; Arnold et al., 2000; Judd et al., 2002; Post et al., 2003; Morgan et al., 2005), while suicidality, psychotic features, and hospitalizations are more frequently seen in males (Morgan et al., 2005). There is a greater incidence of a childhood history of sexual abuse among female patients (Hyun et al., 2000), and this is probably true also for adulthood (Coverdale and Turbott, 2000). A history of sexual abuse or the high risk to become a victim might justify nursing the patient in a single-sex environment, although such environments are vanishing. There are some data suggesting a different risk depending on gender comorbid alcohol and substance abuse (Hendrick et al., 2000; Frye et al., 2003). As protective factors, female patients with BD less often stay single or are without children and less frequently live alone. They seem to maintain better global functioning compared with male patients with BD (Morgan et al., 2005).

The most prominent issues with female BD patients are around the reproductive cycle and related physiology. While the influence of the menstrual cycle and menopause on the course of BD is still unclear, there are some research data on the effects of motherhood. It is simply reasonable that in the case of a pregnant patient, multidisciplinary care together with the obstetrician and midwife is mandatory.

The most commonly emerging issues concern unwanted pregnancy (Coverdale et al., 1997). Therefore, bipolar women of childbearing age should receive intense counseling regarding effective contraceptive practice, issues pertaining to interaction of contraceptive pills with medication for BD, and the possible effects of pregnancy and delivery on the course of bipolar illness. Also the treatment options during pregnancy and breast feeding should be discussed along with the psychological and somatic stress of pregnancy and child-rearing, and the effects treatment might have on the fetus depending on the trimester of gestation. Finally, counselling about the genetic risk of BD should be offered also to siblings to enable informed decisions for future pregnancies (Packer, 1992; Cohen et al., 1994). In everyday practice, few patients consider the risks related to pregnancy unacceptable, and these should be guided to use effective contraception, which should be considered together with the medication the patient receives to treat BD. Several drugs, for example carbamazepine, oxcarbazepine, lamotrigine, and topiramate, all increase the clearance rate of oral contraceptives, and thus the doses of oral contraceptive for patients taking these medications need to be adjusted and/or other protective strategies need to be implemented as a standard of care.

According to some studies, pregnancy is associated with a reduced overall risk for psychiatric admission (Kendell et al., 1987) and a lower risk for suicide (Appleby, 1991; Marzuk et al., 1997) and may improve the clinical course of BD (Sharma and Persad, 1995; Grof et al., 2000), but there are also reports of the opposite (Blehar et al., 1998; Freeman et al., 2002). On the other hand, there is a broad consensus that the postpartum period confers the greatest risk for exacerbation of BD (usually within 90 days) (Dunner et al., 1979; Brockington et al., 1981; Davidson and Robertson, 1985; Kendell et al., 1987; Schopf and Rust, 1994; Leibenluft, 1996; Blehar et al., 1998; Freeman et al., 2002).

Besides the issues concerning the reproductive cycle, female patients appear to be at greater risk for a number of medication adverse effects, including weight gain (Fakhoury et al., 2001; Russell and Mackell, 2001) and extreme obesity (McElroy et al., 2002) and decrease in bone mineral density as a result of prolonged hyperprolactinemia (Wieck and Haddad, 2003), which could also cause a hypogonadal state (Smith et al., 2002).

The Therapists’ Point of View

There is not much data concerning the point of view of psychiatrists and of therapists in general on the unmet needs in the treatment of BD patients.

One study reported that psychiatrists in the UK and US consider education and support for patients and families as well as earlier referral to specialist care as the highest ranked needs at entry into care. On the other hand, they thought that during treatment of acute episodes and also during the long-term
Unmet needs: the therapists’ point of view

Gender

• Little research on gender issues
• There are some data suggesting that gender is related to different clinical pictures, adverse events profile and to different outcomes
• Issues related to female physiology and reproduction, especially pregnancy and breast feeding

Unmet needs: the therapists’ point of view

• Clinical research never focuses on the unmet needs as the patients conceive them
• The generalizability of research data to the real-world patient is unknown
• Burden of caregivers of patients

Adherence to treatment

• Psychoeducation is not routinely applied at the earlier stages

Empowerment of service users is not the standard

Table 1. Unmet Needs in the Treatment of BD Patients Identified in the Literature

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Unmet Needs</th>
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<tbody>
<tr>
<td>Early correct diagnosis</td>
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<tr>
<td>Recognition and treatment of somatic health problems</td>
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<tr>
<td>Efficacy and effectiveness of therapeutic options</td>
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<tr>
<td>Only 2–3 agents are efficacious across all phases</td>
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<tr>
<td>The definition of ‘mood stabilizer’ is problematic</td>
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<tr>
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<tr>
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<tr>
<td>Limited data on treatments for acute bipolar depression</td>
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<tr>
<td>Lack of access to specialized care services</td>
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<td>Issues related to female physiology and reproduction, especially pregnancy and breast feeding</td>
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Unmet needs: the patients’ and caregivers’ point of view

• Clinical research never focuses on the unmet needs as the patients conceive them
• The generalizability of research data to the real-world patient is unknown
• Burden of caregivers of patients

Adherence to treatment

• Psychoeducation is not routinely applied at the earlier stages

Empowerment of service users is not the standard

Table 2. Unmet Needs in the Treatment of BD Patients As Identified During the Process of Guideline Development

<table>
<thead>
<tr>
<th>Fragmentation of BD as a disorder</th>
<th>Unmet Needs</th>
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<tr>
<td>Early correct diagnosis</td>
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Unmet needs: the therapists’ point of view

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• Psychoeducation is not routinely applied at the earlier stages

Empowerment of service users is not the standard

Table 3. Recommendations of the Workgroup for Further Research

<table>
<thead>
<tr>
<th>Availability of the raw data</th>
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<tbody>
<tr>
<td>Study design</td>
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<tr>
<td>Study any acute mood episode with the same broad protocol</td>
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<tr>
<td>Anxiety and psychotic symptoms should also be assessed</td>
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<tr>
<td>Assessment of neurocognitive function in long-term studies</td>
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<tr>
<td>Assessment of disability and social and occupational functioning and quality of life</td>
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<tr>
<td>Adequate duration of studies</td>
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<tr>
<td>Separate studies of both enriched and nonenriched samples in maintenance studies</td>
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<tr>
<td>Studies focusing on mixed depression</td>
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Proposed template for a standardized reporting of the results (see appendix)

have been developed to assist them to formulate treatment strategies ranging from a stepped-care approach to supporting caregivers, ranging from basic information and pamphlets to brief training courses and specialized family or caregiver interventions based on need and accessibility (Berk et al., 2011).

The Patients’ and Caregivers’ Point of View

It is well known that different “stakeholders” emphasize different unmet needs, and therefore the point of view of patients and caregivers might vary considerably from the point of view
of mental health professionals (Chengappa and Goodwin, 2005). What may contribute to poor adherence is the fact that clinical research hardly focuses on the unmet needs as the patients perceive them and therefore, at least to some extent, real world needs are not addressed (Bauer, 2002). Even more, it is not known to what extent clinical trials data apply to those patients who are not eligible to be included in standardized controlled research, because they suffer from multiple comorbidities or have shown refractoriness to treatment in the past (Wells, 1999; Bauer et al., 2003b; Simon et al., 2002; Wells et al., 2002; Sachs et al., 2003; Bauer and Mitchner, 2004). There is also profound discrepancy between the interpretation by mental health professionals of the evidence base for treatments in BD and patient perception of the relative effectiveness of different treatment options (Masand and Tracy, 2014).

If the real outcome of mental disease is what patients report concerning their quality of life, research gives a grim picture with patients with severe mental illness reporting dissatisfaction with their social functioning and general health and unmet needs concerning case management services, social and recreational activities, and vocational rehabilitation (Badger et al., 2003). Caregivers of patients with BD may experience a different quality of burden than is seen with other illnesses, and it is definitely more severe compared with the burden of caregivers of patients with unipolar depression. However, there is not enough research data on this issue, which is largely neglected (Reinares et al., 2006). Conceptualizing the burden of a bipolar caregiver in a conventional medical framework may not focus enough on important issues or on cultural and social issues as well as on the objective and subjective aspects of burden. An important fact is that burden to caregivers is associated with caregiver depression, which conversely affects patient recovery by adding stress to the home environment. It is also associated with high levels of expressed emotion, including critical, hostile, or over-involved attitudes. It is reasonable to assume that it is not possible to ameliorate service provision without a better understanding of caregiver burden and the means to measure and target it (Ogilvie et al., 2005).

Adherence to Treatment

Poor treatment adherence is a major problem in mental health care, and especially in BD it is associated with poor outcome (Keck et al., 1996; Bauer et al., 2001a). Depending on definition and setting, it has been reported that between one- and two-thirds of BD patients are noncompliant with treatment (Johnson and McFarland, 1996; Keck et al., 1996; Murru et al., 2013). Adverse events are one of the reasons patients are often unwilling to continue medication treatment for prolonged periods of time. Some might also wish to continue to have the experience of manic or especially of hypomanic episodes, which are particularly pleasant. Psychoeducation and collaborating with patients and caregivers enables patients to be active participants in the management process, and this is believed to improve treatment adherence (Sachs, 2013). It is interesting to note that both patients and their families often seemed to lack a thorough understanding of disease management goals and the need for follow-up care (Lish et al., 1994).

Therefore, there seems to be a clear need for more empowerment of patients and their caregivers. Currently they appear less than optimally informed concerning the need and benefits of continuation treatment and care, with the result of high rates of poor treatment adherence.

2. Unmet Needs Identified by the CINP Guidelines Project

As described and reported in the previous papers of the CINP guidelines, the workgroup synthesized and analyzed the accessible data on the efficacy of existing treatment options for BD. The essential result was a large table of efficacy data for each treatment option across different phases of the illness and considering specific clinical features. The analysis, classification, and tabulation of the results revealed a number of important problems and unmet needs as well as areas that should be the focus of research in the future.

Fragmentation of BD As a Disorder

A major problem of the literature is that it is almost impossible to reliably assemble the available data in a longitudinal treatment strategy that would take into consideration the present phase but also the psychiatric history and possible future development. That is, the data do not consider BD as a single disorder but as separate and literally independent phases. At the guidelines but also the clinical level, it creates a very important dilemma. What should the decision for the maintenance treatment be in case the patient was treated (and responded to) with a treatment with no data concerning the long-term prophylactic treatment, or even worse with negative data concerning the assumed possible future of his or her mental health? For example, a patient has responded favorably to haloperidol during an acute manic episode, but since the patient’s history indicates that the overwhelming majority of the mood episodes were depressive episodes (depressive predominant polarity), it is fair to assume that these episodes will continue to be frequent. In such a case, the therapist is left with a dilemma: should he or she add an agent with proven preventive efficacy against depressive episodes, for example quetiapine, and apply combination treatment, or should he or she change to monotherapy with an agent with proven prophylactic efficacy against both poles? The answer is not apparent and different opinions do exist, especially since almost all maintenance studies include enriched samples, that is samples of patients who responded during the acute phase specifically to the agent under research. Especially in cases of partial or poor response to first line treatment, it is unknown which would be the best next option. Switching might prolong suffering while adjunctive treatment will result in polypharmacy.

Future research should focus on these problems and provide specific answers. Ideally, all treatment options should be tested against all phases and clinical features of BD, and those with broader efficacy should receive priority in the use. Of course safety and tolerability issues might additionally perplex the problem.

Unsatisfactory Design of RCTs

The inclusion of too many scales probably creates severe problems with the completion of RCTs; however, the trials should include those scales that have been proven to be of high importance for everyday clinical practice. In addition, reporting should not only include global measures but inform professionals more specifically which diagnostic features and specifiers of BD responded to a given treatment. However, the total costs of a trial and the feasibility need to be balanced against the research benefits.

In this framework, the design of future clinical trials should take into consideration that outcomes should address issues
like mixed features, anxiety, psychotic symptoms, neurocognitive disorder, and disability. Currently there are few data on mixed features in acute bipolar depression, and almost all data on mixed episodes come from acute mania trials. At the same time, the overall design should keep the effort for the patients and the researchers at a minimum by avoiding unnecessary ratings and making RCTs feasible.

An important concern to mention is the duration of the continuation phase before entering the maintenance phase, which is often unacceptably short. This is sometimes the case for acute phase studies and especially for bipolar depression. Since the aripiprazole studies had positive results at week 6 but negative at endpoint, which was week 8 (Thase et al., 2008), it is reasonable to suggest that the minimum duration for acute bipolar depression studies should be 8 weeks to capture true and lasting improvement. However, this is not always the case, and at least one agent gained approval with a positive study of only 6 weeks duration (Loebel et al., 2014).

While the enriched designs inform about the longer term efficacy of an agent if it was effective for an acute phase, they do not provide information about whether or not they have broader spectrum of prophylactic efficacy (i.e., prophylactic efficacy in patients who responded to other agents during acute phase). While many agents that are effective in acute phase appear to provide benefit during the maintenance phase, it is unknown whether this can be generalized to all agents for the maintenance period.

In acute mania, a study duration of 3 weeks appears not adequate; however, most studies utilized this short duration. Probably the best solution would be to utilize a 12-week design both in acute mania and depression RCTs that may allow for assessing both manic and depressive symptoms that often coexist. The use of placebo is acceptable, but ideally a third arm with a comparator would be more informative for assay sensitivity (Vieta and Cruz, 2012).

Research on substance and alcohol abuse and medical comorbidities should be a specific target of research and probably cannot be incorporated in the frame of the standard RCTs. Large observational studies may be needed to supplement controlled trials.

Focus on More Realistic Outcomes

Almost all the RCTs are industry sponsored, and therefore their primary aim is to obtain labelling for the product. Thus, the primary outcome is always the change in the total score of a scale that measures the symptoms of the acute phase (YMRS, MRS, MADRS, or the HAM-D), while the CGI or the PANSS are included as secondary outcomes. Rates of response and remission are almost always included as secondary outcomes. Relapse into a mood episode is the most usual primary outcome for maintenance studies.

It is very rare that measurements of general impairment, neurocognitive function, social and occupational quality of life, etc. are utilized. Although the currently used outcomes serve the purpose to test whether the agent under consideration is efficacious or not, they fail to capture aspects of treatment that are equally clinically relevant and of high importance for the everyday clinical practice.

Limited Data Concerning Combination Treatment and High Dosages

While in everyday clinical practice polypharmacy is the rule rather than the exception, the research data in support of most combination options are weak or absent. This is also the case with the use of high dosages, which is often everyday clinical practice.

Incomplete Results Reporting

Although the data are often available, the authors and the manufacturers decide not to report them. Examples include the effect of treatment options on the core symptoms of mania or depression and on mixed features, psychotic symptoms, rapid cycling, etc. Often only P values are reported without means and SDs and at other times the opposite happens, thus adding confusion. In many instances, total scale scores with problematic interpretation (e.g., total PANSS score) are reported without a more detailed subanalysis. Sometimes the data are not available for the entire study sample and thus different sample sizes apply for each outcome; however, this is not always made transparent. It is unacceptable that usually in mixed episodes only the effect of the treatment modality on the manic component is reported but the effect on the depressive component is missing.

It is desirable for the raw data to be released and accessible for the scientific community. Much advancement in our knowledge and ability to treat BD patients better may arise not from new and expensive research but from simply exhaustively analyzing existing data. The release of the raw data will also remove publication bias and improve the reliability of conclusions.

Reporting of the Results

The overall impression from the review of the literature is that the results are reported in a nonhomogenous way and although some kind of a template exists, it is not always possible to detect and extract all details. This is a particular problem when extracting data to perform meta-analysis. Important details are often missing, for example, the score on the positive subscale of the PANSS, while others that are less important exist, for example, the PANSS total score. In most instances, a Last Observation Carried Forward approach is utilized while in a minority the Mixed-Effect Model Repeated Measure is used. In some cases the results are reported selectively from either model. Each model/approach has its advantages and disadvantages (Siddiqui et al., 2009). It is also dubious that often different numbers for study samples are found in different publications of the same original study. It is also important that reports fulfil the CONSORT requirements.

3. Recommendations for Future Research Policies (Summarized in Table 3)

Availability of the Raw Data

The wealth of data that has been accumulated but not exhaustively analyzed is huge. The full release of these data will not only provide us with answers to a number of questions but it will also eliminate much of the publication bias that makes conclusions difficult. One of the most important questions that, if not answered, then at least could lead to a much better understanding is which (if any) baseline clinical characteristics predict response to specific treatments.

Since for the vast majority of treatment options the patents have expired, there is no practical reason for the industry to justify the withholding of the data except of a possible loss of face if a previously biased reporting becomes apparent. However, even in the case of those agents still under patent, the benefit for the public health should be considered as more important than any supposed commercial interest. In any case, this should be considered to be a matter of transparency.
Study Design

Future RCTs conducted for licensing purposes will probably need to consider any acute mood episode in a similar way. Since pure episodes of either pole are not the rule but rather the exception and with the “mixed features” specifier in place by the DSM-5, it is important to assess the presence of depressive symptoms in acute mania and manic symptoms in acute bipolar depression. In either case, anxiety and psychotic symptoms should also be assessed. This means that in all RCTs, YMRS or MRS, MADRS or HAM-D, HAM-A, and PANSS need to be included. It is desirable although difficult to include regular assessments of neurocognitive function especially in maintenance studies. For long-term studies, the assessment of disability and especially of social and occupational functioning and quality of life should be mandatory.

Template for a Standardized Reporting of the Results

As already mentioned, there is a need to standardize the reporting of RCT results and make sure that not only all important results are released but also in a manner that adds to our understanding of the treatment of BD and also makes further analysis possible. Such standardization will also increase the reliability of the reports and eliminate the reporting of slightly different results in different articles concerning the same study. A proposed template for the reporting of RCT results is shown in the appendix. The template is laid out for 2 arms (agent vs placebo), and in cases of different design (no placebo or 3-arm design) it should be modified accordingly. It is suggested that both the results according to Last Observation Carried Forward and Mixed-Effect Model Repeated Measure should be reported. Also it seems important to have a standardized list of adverse events and procedure how to capture them, so that it will be easy to compare across studies. The template presented in the appendix is a convenient summary that can be used as a guide as to which results could be of importance and should be reported.

4. Discussion

It is clear that unmet clinical needs exist for all phases of BD. While the review of the literature suggests that early and reliable diagnosis as well as gaps in the education of patients and their families could constitute the biggest unmet needs in the area of BD, the experience from the analysis of the existing evidence identified additional important problems concerning the available knowledge and the way research is carried out.

One important conclusion is that the existing data may already provide answers to a number of clinical questions, including the specific treatment of subgroups of patients. However, relevant analyses have not been carried out and the raw data are not released. Taking full advantage of the data already gathered might have an impact that will have a greater impact in the short term than any new research. There is a pressing need and it is for the benefit of public health that the data should be released and such analyses are carried out.

On the other hand, it is also evident that a standardized design for future RCTs is desirable that reflects the complex clinical picture of BD, with the simultaneous rating of manic, depressive, and psychotic symptoms during all phases of the disorder. The design should be standardized to avoid biases and uncertainties that are frequent because of the current way things are carried out.

A standardized way of reporting the results also seems necessary, since currently only a small and often patchy part of the results is available. It is not unusual that different documents that all report the results of the same trial include slightly different figures. This raises the issue of overall reliability on the current mode of scientific reporting. Besides reporting and appraising the evidence, guidelines should also be educational and promote good practice. The authors hope that the CINP guidelines on BD will have a positive impact on the methodology of future patient-orientated research.

Supplementary Material

For supplementary material accompanying this paper, visit http://www.ijnp.oxfordjournals.org/

Statement of Interest

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