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GUIDELINES

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder

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Abstract

Objectives. These guidelines are based on a first edition that was published in 2004, and have been edited and updated with the available scientific evidence up to October 2012. Their purpose is to supply a systematic overview of all scientific evidence pertaining to the long-term treatment of bipolar disorder in adults. *Methods*. Material used for these guidelines are based on a systematic literature search using various data bases. Their scientific rigor was categorised into six levels of evidence (A–F) and different grades of recommendation to ensure practicability were assigned. *Results*. Maintenance trial designs are complex and changed fundamentally over time; thus, it is not possible to give an overall recommendation for long-term treatment. Different scenarios have to be examined separately: Prevention of mania, depression, or an episode of any polarity, both in acute responders and in patients treated de novo. Treatment might differ in Bipolar II patients or Rapid cyclers, as well as in special subpopulations. We identified several medications preventive against new manic episodes, whereas the current state of research into the prevention of new depressive episodes is less satisfactory. Lithium continues to be the substance with the broadest base of evidence across treatment scenarios. *Conclusions*. Although major advances have been made since the first edition of this guideline in 2004, there are still areas of uncertainty, especially the prevention of depressive episodes and optimal long-term treatment of Bipolar II patients.

Key words: *Bipolar disorder; Maintenance; Prophylaxis; Pharmacotherapy; Antipsychotics*

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Abbreviations: AE, adverse event; AED, antiepileptic drug; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CANMAT, Canadian Network for Mood and Anxiety Treatments, CBT, cognitive behavioural therapy; CE, category of evidence; CGI-BP, Clinical Global Impression – Bipolar; CI, confidence interval; DBS, deep brain stimulation; DDD, defined daily dose; DSM, Diagnostic and Statistical Manual; DSS, Depressive Symptom Scale; ECT, electroconvulsive therapy; EPS, extrapyramidal motor symptoms; ER, extended release; ESRS, Extrapyramidal Symptoms Rating Scale; FE, further evidence; FEW, free and easy wanderer; FDA, US Food and Drug administration; GAS, Global Assessment Scale; HAM-D, Hamilton Rating Scale for Depression; HR, hazard ratio; ICD, International Classification of Diseases; IDS, Inventory of Depressive Symptoms; ISBD, International Society for Bipolar Disorder; KM, Kaplan–Meier; LAI, long acting injectable; LOCF, last observation carried forward; MADRS, Montgomery–Asberg Depression Rating Scale; MDE, major depressive episode; MOAT-BD, Multistate Outcome Analysis of Treatments in Bipolar Disorder; MRS, Mania Rating Scale; NNT, numbers needed to treat; OFC, olanzapine–fluoxetine combination; OR, odds ratio; PA, preventive agent; PES, prevention of TEE in enriched samples; PR, practicability; PRC, prevention of TEE in rapid cyclers; PSu, prevention of suicide; RC, rapid cycling; RCT, randomized controlled trial; RG, recommendation grade; RR, relative risk; rTMS, repetitive transcranial magnetic stimulation; SAS, Simpson–Angus Extrapyramidal Side Effect Scale; SD, standard deviation; SFBN, Stanley Foundation Bipolar Network; ST, safety and tolerability; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder; TAU, Treatment as usual; TEAS, treatment emergent affective switch; TEE, treatment emergent episode; VNS, vagus nerve stimulation; WFSBP, World Federation of Societies of Biological Psychiatry; YMRS, Young Mania Rating Scale.

Preface and disclosure statement

This practice guideline for the biological, mainly pharmacological maintenance treatment of bipolar disorder was developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP) and is part of a series covering the acute treatment of mania, bipolar depression and maintenance treatment of bipolar disorder. The preparation of these guidelines has not been financially supported by any commercial organization.

This guideline has mainly been developed by psychiatrists and psychotherapists who are in active clinical practice. Experts of the task force were selected according to their expertise and with the aim to cover a multitude of different cultures.

In addition, some contributors are primarily involved in research or other academic endeavours. It is possible that through such activities some contributors have received income related to medicines discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest.

Some drugs recommended in the present guideline may not be available in all countries, and approved doses may vary.

Introduction

Parts I and II of the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders (Grunze et al. 2009, 2010) concerned the acute treatment of mania and bipolar depression. The authors are aware that acute and long-term treatment are and must be closely linked together in terms of treatment planning and evaluation. However, in interest of reducing complexity, this guideline series deals with acute and long-term treatment separately.

Although it is of great importance to control the acute manifestations of the illness as rapidly and effectively as possible, the real key issue is successful maintenance treatment, i.e., the prevention of new episodes and all kinds of complications and disablement. In fact, bipolar disorder ranks worldwide among the top ten of the most disabling disorders in working age adults (The World Health Organisation 2002), and the socioeconomic impact is considerable (Hakkaart-van Roijen et al. 2004; Runge and Grunze 2004; Young et al. 2011).

Starting with Kraepelin (1921), several long-term observational studies have demonstrated that the duration of the symptom-free interval is inversely linked to the number of previous episodes (Zis et al. 1980; Angst 1981; Roy-Byrne et al. 1985; Kessing 1998a). Likewise, aspects of cognitive impairment are associated with increasing episode frequency (Kessing 1998b; Lebowitz et al. 2001; Lopez-Jaramillo et al. 2010a) leading to lasting psychosocial and work impairment (Dickerson et al. 2004; Wingo et al. 2009). Subsyndromal symptoms may also contribute significantly to long-term disability in individual patients (Coryell et al. 1993; Angst and Preisig 1995; Altshuler et al. 2006; Bonnin et al. 2010) and are a risk factor for the emergence of new mood episodes (Frye et al. 2006). Finally, bipolar disorder is associated with an excess mortality including an increased risk of suicide (Angst et al. 2002; Licht et al. 2008). Independent of the number of episodes, cognitive deficits and subsyndromal symptoms are causally related to a progressive course of this illness, goals of long-term treatment should be not only the prevention of new clinically significant episodes and suicide, but also minimization of subsyndromal symptoms and cognitive decline.

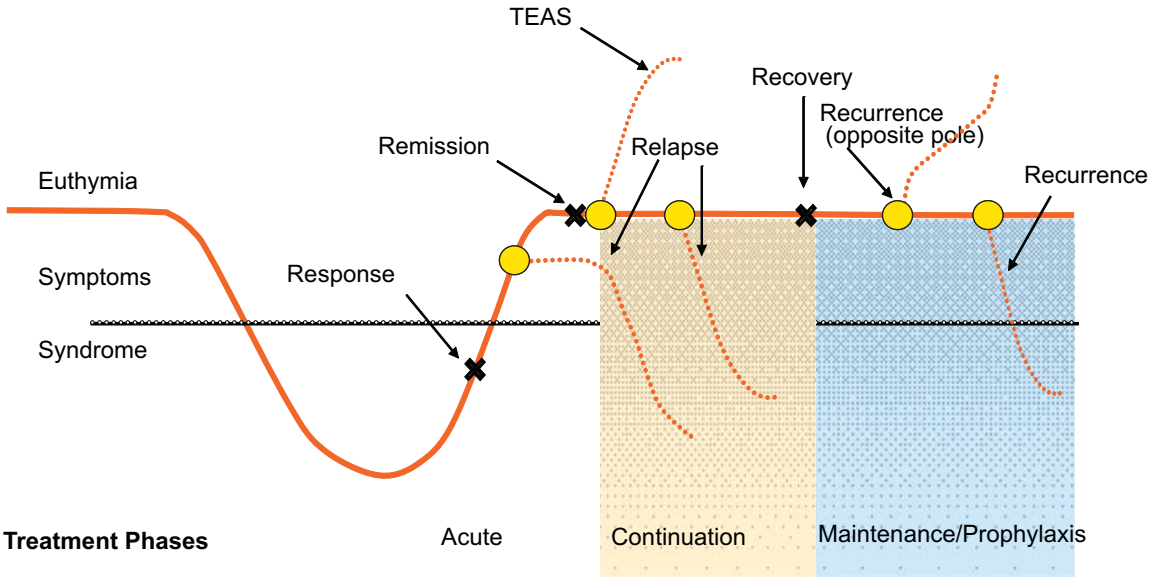

Figure 1. The different phases of treatment in bipolar disorder (modified from Frank et al. (1991)).

The different phases of long-term treatment

Long-term treatment in this article refers to the post-acute biological treatment of bipolar patients. Such treatment will in almost all cases be a psychopharmacological approach; in rare instances, physical treatments as maintenance electroconvulsive therapy (ECT) might be needed.

Long-term treatment in mood disorders has been traditionally divided into continuation and maintenance (or prophylactic) treatment, which are, in turn, associated with the starting points "remission" and "recovery", respectively (Figure 1). In the original proposal by Frank et al. (1991), developed for major depression, recovery was achieved when there was remission even in the absence of any treatment. Re-emergence of symptoms after that point was labelled "recurrence" in contrast to re-emerging symptoms as being part of the index-episode, labelled "relapse". Transferring this model to bipolar disorder, the primary goal of acute treatment is to improve symptoms to the point of remission. Once remission is achieved, the goals of the continuation treatment are to protect the patients from re-emergence of symptoms, i.e., relapses, and from treatment emergent affective switches (TEAS), defined as an episode of opposite polarity within the continuation phase. However, since we cannot identify the exact time point of recovery in treated patients, we do not know for sure when we move from relapse prevention to recurrence prevention, i.e., from continuation to maintenance treatment.

Even though these concepts of recurrence and relapse (and the corresponding treatment phases) are theoretically meaningful, they can only be identified under certain circumstances. Therefore, a wholly pragmatic set of definitions has been adopted by the DSM-IV and ICD-10 (World Health Organization 1992; American Psychiatric Association 1994), separating two episodes by an interval of at least 8 weeks of remission, regardless of treatment. This definition implies that the continuation phase ends after 8 weeks of continuous absence of symptoms (remission). The International Society of Bipolar Disorder (ISBD) suggested different time criteria for the continuation therapy phase, namely 4 weeks for recently manic and 8 weeks for recently depressed patients (Tohen et al. 2009a), taking into account the different time lines for recovery from mania and depression (Solomon et al. 2010). A more conservative estimate proposed by Calabrese et al. (2006) set a cut-off point of 90 and 180 days in patients with an index episode of mania/hypomania and bipolar depression, respectively.

Given the unclear boundary between continuation and prophylactic treatment due to the different approaches and definitions, there are also other pragmatic partitions in use. Instead of separating between continuation phase and maintenance phase, separating between "After-Care" (or "Medium-Term Treatment") lasting for up to 1 year after remission has been achieved for the first time, and long-term prophylaxis may make more sense clinically (R. Licht, personal communication). In line with this, the general term treatment emergent episodes (TEE) may be more useful than relapse and recurrence. Likewise, all post-acute treatment can be considered (and labelled) preventive treatment. However, when appropriate this review will stick to the concepts of relapse and recurrence and the corresponding treatment phases.

Methodological issues in long-term trials

What do we want to measure?

Primary outcome measures in randomized, controlled long-term trials (RCT) in bipolar disorder vary considerably, and this wide variation of outcome criteria makes it quite difficult to compare efficacy of medication across studies.

Most long-term studies use as primary outcome the result of Kaplan–Meier (KM) survival analyses based on time to intervention. However, some studies use as study endpoint "any reason of failure" (inefficacy as indicated by new mood episodes or need for additional treatments or hospitalization, adverse events, withdrawal of consent, lost to follow-up) as primary outcome, and some use dropout for emerging new mood episodes defined either by symptomatic DSM-IV criteria or/and by clinical rating scale thresholds. An intrinsic problem with KM survival analytic techniques is that they measure the occurrence of a predefined event, e.g., TEE, intervention, discontinuation, only at two time points, at baseline (absence of the event) and endpoint (occurrence of event). This might be suitable if in between these time points there is only one state possible, e.g., "absolutely healthy". Clearly, this is not the case in bipolar disorder, where subsyndromal fluctuations of mood, impairing functionality and quality of life, are rather the rule than exception. In addition, other clinical valuable information as tolerability and impact of medication on physical health will not be fully captured. Another issue in survival analysis is that the risk of censoring should be independent of the risk of the event in question, which most often is not the case. One reason why survival analyses have gained popularity in pivotal trials is that they are more sensitive for measuring differences than the more traditional counting of failures.

To address the limitations of KM techniques, a multi-state statistical technique has recently been developed and tested in data sets of published maintenance studies which allows clinical episodes to be entered multiple times and which can incorporate weightings for adverse effects and functional status. This procedure, Multistate Outcome Analysis of Treatments in Bipolar Disorder (MOAT-BD), provides statistical significance from bootstrapping estimates of the variance for the estimated times spent in each clinical states, including subsyndromal states of depression or mania (Singh et al. 2012). However, for the present, regulatory agencies are likely to require KM analytic techniques. The statistical procedures to conduct MOAT-BD analyses are now available from a URL site, with several studies in progress set to apply these approaches. Therefore, within the next several years prospects are promising that a priori application of this methodology will begin to provide analyses particularly pertinent to effectiveness considerations. Such novel analyses should strengthen the generalizability of maintenance study results for clinical practice and recommendations of guidelines such as this.

As an alternative to KM survival analyses mean change over time of symptomatic rating scales, e.g., the Young Mania Rating Scale (YMRS, Young et al. 1978) and the Montgomery–Asberg Depression Rating Scale (MADRS, Montgomery and Asberg 1979), has been used mainly in extension studies of acute efficacy studies, e.g., the olanzapine versus valproate study (Tohen et al. 2003a) or the asenapine 40-week extension study (McIntyre et al. 2010).

However, this appears unsatisfactory as it does not allow identification of the occurrence of clinically meaningful TEE in individual patients but only minor shifts of statistical means derived from all patients. The true value of rating scales in long-term studies lies in allowing an estimate of meaningful improvement (not just prevention of TEE) versus persistence of subsyndromal symptoms.

On the other hand, rating scales used in studies are not uniform which creates the "Tower of Babel" problem. The content overlap with the MADRS and the YMRS, for instance, might in themselves be a source of bias. To increase the content validity of different scales, e.g., MADRS and HAM-D some acute studies have focussed on the pure depression subscales in order to exclude secondary symptoms such as sleep and appetite. Furthermore, clinicians opinion may well differ from patients' experience. Zimmerman et al. (2012) have demonstrated that remission of depression as defined by a score HAM-D_{17} of <8 was discordant with the patient's own opinion in 25–50% of instances. Thus, in addition to clinician rating scales, brief patient-rated quality of life scales might be of special importance for an overall assessment of long-term treatment of bipolar disorder.

A general limitation in all current outcome evaluations is that the further outcome after a major TEE is not captured, making it impossible to assess relative response including gradual mood stabilization over time. Hopefully, future studies will give a priori more consideration to clinically more meaningful analyses of data.

Remission or recovery as study entrance criteria

Remission is, in most clinical studies, defined as achieving syndromal recovery to a degree that symptom severity scores are below a predefined threshold in established clinician rating scales, e.g., a MADRS score of ≤ 10 in patients with a recent depressive episode (Hawley et al. 2002), or a YMRS score

of ≤ 12 in recently manic patients (Tohen et al. 2009a).

Recently, the focus appears to be moving towards increasingly stringent definitions of remission (Chengappa et al. 2005; Martinez-Aran et al. 2008) with some incorporating criteria that require low scores on mood scales for both the total scores and scores for specific items (Ketter et al. 2007). A study with olanzapine operationally defined symptomatic remission in patients with bipolar I disorder using a combination of rating scales, including the YMRS (score ≤ 7), the Hamilton Depression Rating Scale (HAM-D) (score ≤ 7), and the Clinical Global Impression Bipolar Version (CGI-BP) (score ≤ 2) (Chengappa et al. 2005). Even these criteria might still be too broad for clinically meaningful remission, as a CGI-BP score of 1, not 2, corresponds to a symptom-free patient. Based on trials that used both CGI-BP and YMRS and MADRS, it appears that a cut-off score of < 5 on the MADRS and < 4 on the YMRS approximates a CGI-BP of 1 for a meaningful definition of remission (Berk et al. 2008b). Clinical meaningful remission is rarely achieved in published controlled trials; e.g., in the lamotrigine long-term studies, remission as entry criterion for the double-blind phase was defined as having a CGI-S score of ≤ 3 for four consecutive weeks (Goodwin et al. 2004)

A more general definition of remission has recently been proposed by the afore-mentioned ISBD task force. Specifically the group recommended that remission implies that the signs and symptoms of a specified clinical state (e.g., depression) be absent or nearly absent, and that no concomitant increase in symptoms of another bipolar clinical state (e.g., mania or hypomania) has occurred. Such a stringent definition could be operationalized in clinical studies by the absence of minimum DSM-IV criteria (excluding duration of symptoms) for depression or mania, respectively, and the CGI-BP score (Tohen et al. 2009a).

Recovery has been even less clearly defined and depends on the scales used to measure outcome, and the patient population studied (Martinez-Aran et al. 2007). In some instances, recovery is defined as a minimum number of weeks with sustained remission, e.g., 8 weeks (Sachs et al. 2007). In the mentioned open study by Chengappa et al. (2005) clinical recovery was defined as meeting the more operationalized remission criteria for ≥ 8 weeks as a proxy for a patient's ability to function (minimum symptomatology). In that open-label study, clinically meaningful symptomatic remission was achieved slowly and maintained for ≥ 8 weeks by only a few patients within an average of 7 months of continuous treatment.

In a broader, clinically relevant sense, recovery is a multidimensional concept in bipolar disorder which includes both symptomatic and functional recovery. Symptomatic recovery is the sustained resolution of the symptoms of the disorder. Functional recovery is the ability to return to an adequate level of functioning and includes an assessment of occupational status and living situation (Tohen et al. 2000, 2003c; Harvey 2006). Previous studies have indicated that the majority of patients achieve symptomatic recovery but less than half achieve functional recovery within 24 months of a first manic/mixed episode (Tohen et al. 2003c).

The study population and the research conditions

An important issue is patient selection. The vast majority of recent long-term studies have used enriched discontinuation designs wherein the patient's acute symptoms had to respond to the given medication during open label treatment to the point of syndromal remission before randomisation, which results in sample "enrichment" for acute responders (see Figure 2). In a few studies, e.g., in the pivotal lamotrigine studies, the criterion for selection was

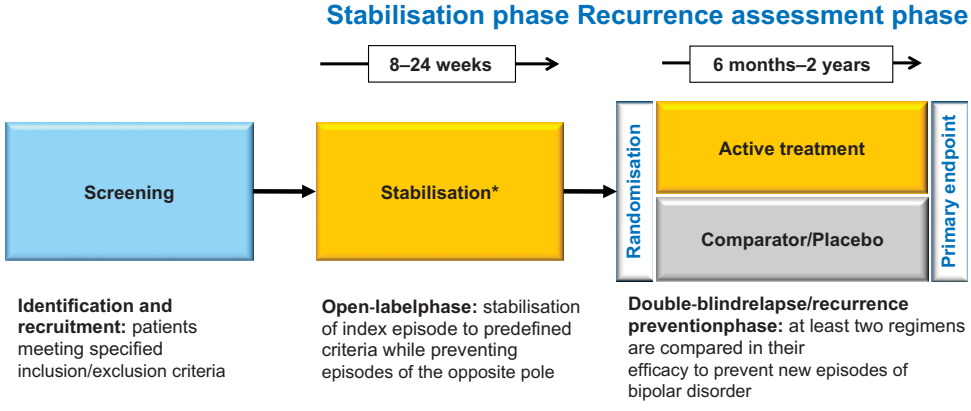

Figure 2. Design commonly used in bipolar long-term maintenance studies in enriched samples. *Period of 8–12 weeks recommended by the US Food and Drug Administration (FDA) for maintenance studies unless otherwise specified. Adapted from Gitlin et al. (2010).

not acute response, but tolerability and mood stability, e.g., for a minimum of 4 weeks on lamotrigine including 1 week of monotherapy, thus constituting a moderate degree of enrichment for lamotrigine tolerability and response, in contrast to no enrichment for lithium (Goodwin et al. 2004). An enriched design not only limits the generalizability of study results to patients treated under similar conditions, but also favours the test drug with respect to an active comparator if introduced at randomisation and not during the open phase. Also, a possible discontinuation effect of the drug under investigation might lead to a higher frequency of early relapses in the placebo and comparator arms of a study. On the positive side, though, discontinuation designs address the pragmatic clinical question of whether the drug that was used for an acute episode should be maintained beyond the achievement of remission.

Extrapolation of results from such a study to bipolar patients in general might also be limited for an additional reason. Predominance of polarity in bipolar disorder, defined as at least twice as many episodes of one pole of the disorder over the other, is a valid long-term prognostic parameter with important clinical and therapeutic implications (Vieta et al. 2009a). According to Colom et al. (2006), about one-half of bipolar disorder patients qualify for a specific predominant polarity. In a long-term study enriched for acute response to study drug, e.g., in mania, chances are increased that the study population has recurrent mania as the predominant polarity in the long-term course. Vieta et al. (2009b) showed that in a RCT in acute bipolar depression, predominant polarity of mood episodes could be demonstrated in 46.6% of patients by retrospective life-charting indicating a 2.7-fold excess of depressive over manic past episodes (34.1 vs. 12.4%). The implication of this finding for maintenance studies is that results will be biased toward the subgroup of patients who were enrolled with respective particular polarity, rather than be applicable to bipolar patients in general. Also if the duration of the maintenance phase of a study is short, it may not provide any indication of the efficacy of the drug for all kind of episodes. For example, a 6-month discontinuation study that includes manic patients with predominant manic polarity is unlikely to provide a sufficient number of depressive episodes to allow a meaningful analysis of the drug's utility for recently depressed patients. This has been clearly demonstrated by the two pivotal lamotrigine maintenance studies, which followed identical designs, except that one (Bowden et al. 2003) included subjects with a manic or hypomanic index episode, whereas the other (Calabrese et al. 2003) included acutely depressed bipolar patients. In both studies, interventions for an episode of identical polarity as the index episode outnumbered those for an episode of opposite polarity approximately by 3:1 in the lamotrigine arm. This effect is probably more prominent in studies with a relatively short stabilization phase and potential discontinuation effects, and thus an increased probability of early relapses.

Figure 3 illustrates a hypothetical long-term course for a bipolar patient with depressive polarity and an index episode of depression, and the treatment objectives during the different phases.

Time lines of studies

The duration of what is usually called the stabilisation phase of the study is a critical design issue for all long-term studies. By and large it corresponds to the post-acute continuation treatment phase (or part of it) in clinical practice. This becomes critical if we want to distinguish relapse-preventive from recurrence-preventive (prophylactic) properties of a drug. As detailed above, there is no consensus on the duration of continuation treatment before it should be considered maintenance (prophylactic) therapy. The FDA nowadays recommends 8–12 weeks in RCTs for the duration of the stabilization phase of (see Figure 2). However, in recent monotherapy studies with a stabilisation phase, the duration varied from only 6 days to 6 consecutive weeks. Looking into TEE rates with placebo in different RCTs, longer stabilization phases are clearly associated with longer time to TEE in the placebo-arm after discontinuation of medication (Gitlin et al. 2010). It was instructive to compare one study with a 2-week stabilization period (olanzapine) (Tohen et al. 2006), one with a 4-week stabilization period (lamotrigine) (Bowden et al. 2003) and one with a 6-week stabilization period (aripiprazole) (Keck et al. 2007). The 2-week stabilization period used in the olanzapine pivotal study resulted in a precipitous drop in probability of maintaining in remission; the median time to TEE on placebo was 22 days. In the lamotrigine study, in which the stabilization phase was 4 weeks the median time was 85 days. In the aripiprazole study which included a 6-week stabilization phase the median time to TEE on placebo was 203 days. Although some of these differences in time to relapse on placebo likely reflect other variables that differ across studies, e.g., a differential propensity of a medication to induce discontinuation syndromes when switched to placebo, thus resulting in early destabilization, the pattern is compelling. Unfortunately, we do not have a systematic examination of a single medicine with different stabilization times.

Thus, the length of the stabilization phase in modern long-term studies using a discontinuation design after enriching the study population for acute

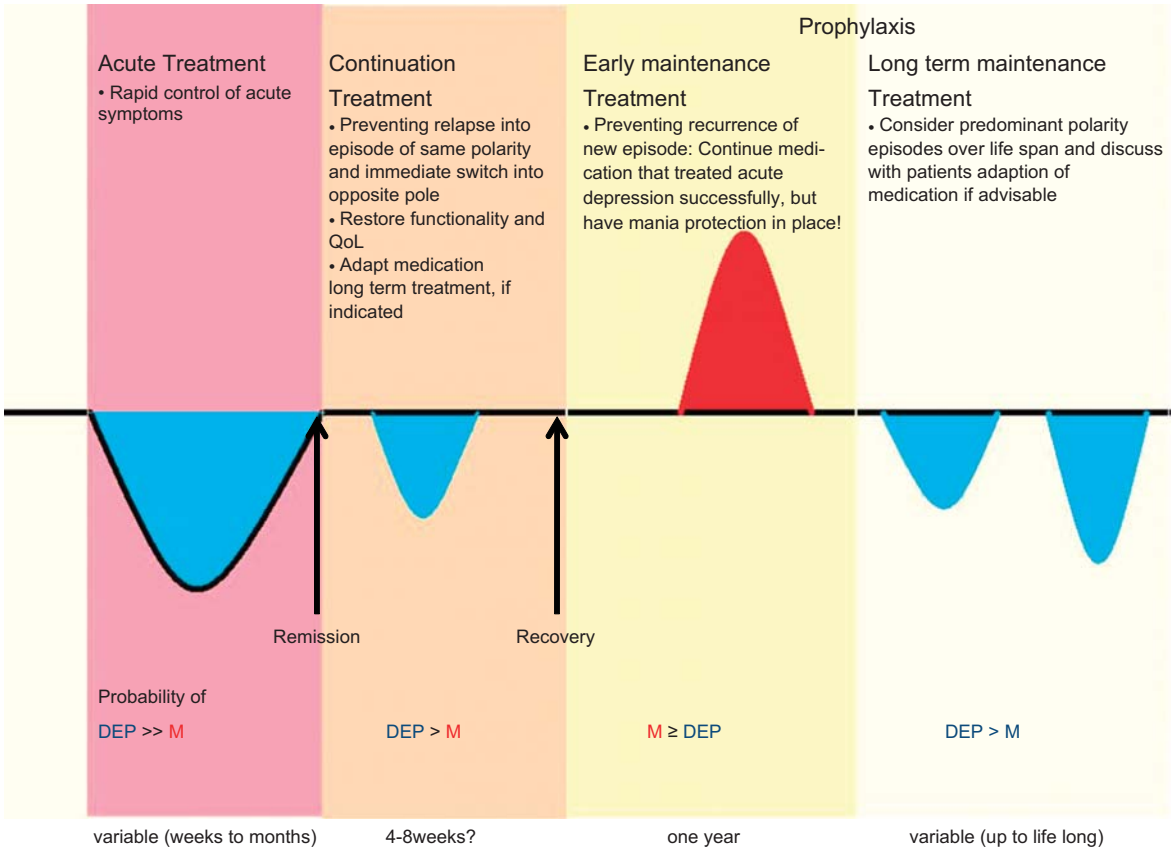

Figure 3. Hypothetical long-term course of a bipolar patient with depressive polarity and an index episode of depression, and treatment objectives during the different phases. DEP: Depressive episode, M: Manic (or mixed) episode.

response to the drug under investigation is critical for assessing whether a medication has only a relapse preventive effect or rather a recurrence preventive effect. Few studies have analysed potential recurrences separate from relapses and thus allowed separate analyses of their time of appearance after discontinuation, i.e., late versus early appearance, respectively. In the few studies where such additional information is available, we detail it in the section of the respective medication as it may allow clinicians a better estimate of the medications' various values in long-term treatment.

It can be argued that genuine prophylactic efficacy might exist independent of acute efficacy, but proof requires studies not to be enriched for responders to the drug being tested and that discontinuation effects also to be excluded, e.g., by a drug-free run in period. In practice, the closest we have come to such designs are studies in which a drug has been introduced as an internal active control under non-enriched conditions and with the discontinuation effect impacting this control and placebo equally (e.g., the lamotrigine maintenance studies, Bowden et al. 2003; Calabrese et al. 2003, or the paliperidone maintenance study, Berwaerts et al. 2012).

A final note of caution concerns the duration of clinical trials in regard to long-term safety. Whereas acceptable relapse/recurrence prevention studies can be as short as 26 weeks (Keck et al. 2006a), adequate pharmaco-vigilance of safety data requires longer term use (5 years or longer). Such evidence, admittedly expensive and impractical in blinded trials, can be derived from national registry studies (Kessing et al. 2011a), cohort and observational studies (Gitlin et al. 1995) or pragmatic trials (Licht et al. 2010).

Why elaborate so extensively on methodology?

In summary, study designs are heterogeneous as they have evolved over the past 20 years. Primary outcome criteria in long-term studies vary considerably, as do the samples enrolled and time lines. Each of these issues can critically impact the validity and informative value of long-term studies in bipolar disorder. In contrast to studies of acute mania (and acute depression), a core design for long-term therapy for bipolar disorder has not yet been agreed upon by researchers in the field. Therefore, disparate results observed may be the product of an

interaction between agents with different prophylactic potentials and different study designs (Gitlin et al. 2010).

Additionally, results from acute treatment studies are often relevant to maintenance issues of treatment choices, strategies of application and expectation of tolerability. This is particularly so in areas such as evidence regarding impact of a particular group of antidepressants on affective instability, including development of mania/hypomania and adverse effect profiles that are generally evident in acute treatment paradigms, e.g., weight gain.

Although it would be useful to see more non- or equally enriched, prospective head-to-head studies, to date these have been rare in this field. Although a few pragmatic head-to-head comparisons of lithium and different anticonvulsants have been conducted (Greil et al. 1997b; Hartong et al. 2003; Geddes et al. 2010; Licht et al. 2010), to date we have extremely limited reliable information comparing, e.g., different atypical antipsychotics in bipolar maintenance treatment. The reasons for this small number of comparative trials may be the fear of sponsors to fail in a superiority design, and the limitations of non-inferiority designs (Vieta and Cruz 2012).

As distinct from the guidelines on the treatment of acute episodes (Grunze et al. 2009, 2010), where we dealt with largely similar study designs, the heterogeneity of long-term study design leaves greater uncertainty when comparing different treatments.

- We therefore want to make the reader aware that both the recommendations and the assigned efficacy ratings may be to a greater degree subject to individual judgment in the absence of uniform measures.
- Therefore, it is crucial that the reader also inform his own perspective by referring to the original publications before implementing these recommendations into his clinical practice.

How to choose among the various episode preventive agents (PA)

The range of medication covered in this guideline needs some explanation. No single agent shows equally good efficacy for all mood deflections throughout the bipolar spectrum and would thus qualify as the "ideal" mood stabilizer (Grunze 2002). Following the suggestions of Ketter and Calabrese (2002), we have here included medicines that preferentially act on and prevent emergence of only one pole of the illness (mania or depression), without detrimental effect on the other. The modalities under consideration in this review include lithium, several anticonvulsants and antipsychotics, selected experimental treatments and physical therapies. We also briefly review the evidence for antidepressants as a group in long-term treatment of bipolar disorder since they are frequently used in clinical practice (Ghaemi et al. 2006), especially in complex treatment regimens (Goldberg et al. 2009a). An additional practical limitation of this international guideline is the fact that not all medicines are licensed and marketed in every country. The reader should consider such factors when applying them in clinical practice.

In accordance with the principle of evidence based medicine, when finally choosing among the graded mood stabilisers as outlined in this review, individual patient's characteristics such as the following should also be considered:

- Previous and current treatment history, in particular if the patients has responded acutely to a given drug (given the data supporting long-term efficacy from enriched discontinuation trials). On the other hand, in case of uncertainty about what made a patient respond acutely, data from non-enriched conditions should be consulted.
- Potential predictors of differential response, e.g., predominance of mania or hypomanic episodes versus depressive episodes over the course of illness, and/or selection for likelihood of medication response, e.g., lithium (Grof 2010).
- Severity of episodes including presence/absence of psychotic symptoms; this may argue in favour (or against) a combination treatment (including an antipsychotic) right from the beginning.
- Whether previous episodes were or were not related to concurrent treatment with antidepressants or use or misuse of psychostimulants.
- Special vulnerability to specific long-term adverse drug effects.
- History of suicide attempts or current suicidal ideation.
- Patient preferences as this will directly impact on adherence.

Monotherapy or combination treatment?

In routine practice, combination treatments in BBD are regularly employed to enhance efficacy of maintenance treatment and to address subsyndromal symptoms or functional impairment. For example, prospective data of the Stanley Foundation Bipolar

Network confirmed the complex medication regimens in 429 naturalistically treated bipolar disorder patients, with lithium (51%) and valproate (42%) being the most frequently prescribed medications at the time of clinical improvement: 96.5% of the patients who responded at 6 months were on one to five medications, with over 55% of patients being on two or three medications, 31.8% requiring four or more drugs and 13.8% requiring five or more medications, but still it took a mean time of 1.5 years to achieve such sustained remission (Post et al. 2010a). The treatment of bipolar disorder patients may also change frequently in response to side effects, emerging comorbities including physical health issues, and other needs to be specifically tailored for each patient. These needs in real world patients are virtually impossible to capture in a guideline whose focus is the efficacy of a given combination treatment over a limited time period and in a fair proportion of patients.

These limitations should be kept in mind when interpreting data of randomized controlled combination maintenance studies. For this reason, this guideline does not make a special note or recommendation for specific combination treatments as other guidelines, e.g., CANMAT (Yatham et al. 2009) did, unless there is clear evidence for a special synergistic action of medication – which, as far as we can tell, has not been proven for any of the most researched and prescribed combination regimens. Positive placebo-controlled RCTs exist for combination treatments of mood stabilizers, usually valproate or lithium, with all atypical antipsychotics that have a licence for bipolar maintenance treatment – aripiprazole (Marcus et al. 2011), quetiapine (Vieta et al. 2008c; Suppes et al. 2009), risperidone (Yatham et al. 2003) and ziprasidone (Bowden et al. 2010). The 18-month RCT of olanzapine + mood stabiliser vs. placebo + mood stabilizer is the exception as it was underpowered at end point due to a high attrition rate, contributing to olanzapine's separation from placebo only on secondary, post-hoc outcomes (Tohen et al. 2004). In this review, we will count evidence derived from combination treatments the same way as we do for monotherapy with the respective drug, and discuss the respective studies under the same header.

When should preventive treatment be initiated?

There is no doubt that all patients need some period of aftercare with continuation treatment after the acute symptoms have resolved. This period could last from a few months to a year. However, we have no controlled prospective study to indicate when long-term prophylaxis (beyond this after care) becomes compulsory. Retrospective chart analyses suggest that with every episode the length of the subsequent symptom-free interval decreases (Zis et al. 1980; Angst 1981; Roy-Byrne et al. 1985; Kessing 1998a), but the causality here is unknown. In addition, the duration of the untreated interval after a first episode seems to be predictive for poor long-term outcome (Post et al. 2010b). For lithium, there is also evidence that prophylactic efficacy may decrease with a longer delay between onset of illness and initiation of treatment (Franchini et al. 1999; Garcia-Lopez et al. 2001), but there are also contradictory data on this (Baldessarini et al. 1999b). These findings, together with all the literature on neurocognitive impairment associated with illness progression (Goodwin et al. 2008) might justify starting maintenance treatment as soon as possible after the diagnosis has been established. However, not all patients would suffer from an additional episode (Goodwin 2002), and the number needed to treat (NNT) will increase, the lower the risk is at the beginning of treatment. Also, the acceptance of long-term treatment by many patients is low at this early stage. Sudden discontinuation, especially of lithium, may harm patients more than having never been on prophylactic treatment (Goodwin 1994; Baldessarini et al. 1999c) and increase suicide risk (Baldessarini et al. 1999a).

Most recent guidelines, e.g., CANMAT (Yatham et al. 2009) or the British Association for Psychopharmcology Guidelines (Goodwin 2009) do not specify when long-term prophylactic treatment becomes necessary. Clinical practice in some countries seems to involve waiting for at least a second episode of illness, and only recommend maintenance treatment if these episodes occur within a rather short time interval (e.g., 5 years, Licht et al. 2003). More radically, US guidelines favour commencement of maintenance treatment with the first manic episode (Sachs et al. 2000). Compromising between these recommendations, the Dutch guideline considers the number of episodes and variables such as severity and positive family history of bipolar disorder suggestive of an increased genetic risk (Nolen et al. 2008). Thus, if the first episode is manic, of disruptive severity, and there is a family history, they recommend considering seriously the start of maintenance treatment. Otherwise, with two episodes (one of them manic), maintenance treatment should be initiated if at least one is of particular severity or the patient has a positive family history. With the third episode, prophylaxis should always be recommended to patients (Figure 4). But whatever the advice from doctors, the limiting consideration at this stage is often the attitude of patient and family, underlining the necessity of psychoeducation (Colom et al. 2009; Reinares

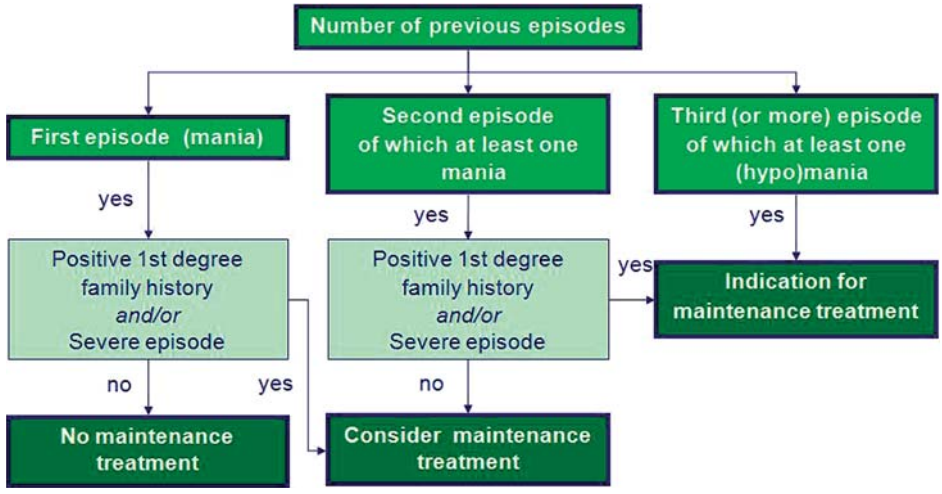

Figure 4. Algorithm for indication for maintenance treatment (Dutch guidelines (Nolen et al. 2008)).

et al. 2009). As to the attitude of the patients, the concept of "aftercare" may be useful: when conferring to the patient that he or she in any case needs pharmacological aftercare up to 1 year after remission has been achieved, this will give time for the clinician to discuss the future perspective and also to assess the tolerability of the current treatment.

When to amend preventive treatments and how long should preventive treatment last?

The proportion of bipolar treated with monotherapy is generally very small, as no drug seems to address all aspects of the disease. The consistently low completion rates in published maintenance trials, most around 10%, make a strong case for evidence informed combination regimens. Combination of mood stabilizers, such as lithium and valproate, are supported by a strong rationale from preclinical science (Kramer et al. 2001; Ryves and Harwood 2001; Perova et al. 2010). However, a superiority of combination treatments versus monotherapy has not consistently be established in pragmatic studies such as the BALANCE study (Geddes et al. 2010).

Therefore, it is usual practice to try patients on monotherapy with a preventive agent (PA) and only amend or switch treatments when ineffective. However, the important question little supported by data from research is the question, when and based on what criteria a PA should be considered as only partially beneficial or ineffective and treatment needs to be changed, either by adding or switching medication.

Current RCTs do not answer the problem, since patients are usually withdrawn from a trial at the first worsening, no matter potential benefits of the drug in question beyond this point. Only few studies, e.g., the valproate maintenance study (Bowden et al. 2000) allowed addition of medication in case of a manic or depressive break-through episode. A PA or combination of PAs may need time beyond a first treatment emergent episode to develop full prophylactic efficacy. In some patients this might not mean a total absence of recurrences, but a marked reduction in number and intensity of new episodes (Vieta and Cruz 2012). A longitudinal evaluation of the patient's history of illness before and after the onset of treatment seems crucial to understand whether a medication is properly acting as a PA.

For lithium, Serretti and Artioli (2003) proposed that recurrence rates should be evaluated by considering the number of recurrences prior to the introduction of lithium (pre-lithium treatment recurrence index = number of episodes/month duration of illness before lithium treatment × 100) and during actual lithium treatment (on-lithium treatment recurrence index = number of recurrences/ month duration of lithium treatment × 100). Starting from this proposal, Murru et al. (2011) generalised it from lithium to the wider concept of PA. They suggested a scheme which may help clinicians evaluating whether a PA is being useful or not in improving a patient's course of illness. Namely, after having obtained a pre PA recurrence index (PrePAri) – with PrePAri being defined as number of episodes/month duration of illness before PA × 100 – and a post PA recurrence index – with PostPAri being defined as number of episodes/month duration of illness during PA × 100 – they propose to classify the percentage reduction from PrePAri to PostPAri ranging from excellent to lack of response (see Table I). However, this is a very formal equation and does not take into account other important variables such as the PA's impact on physical health issues and suicidality.

Table I. Classifying maintenance treatment success and therapeutic consequences derived from it (modified from Murru et al. 2011).

Reduction pre/post number of episodes	Response	Category description	Subsequent therapeutic step
100%	Excellent	No relapse/ recurrences, no residual symptoms	Continue therapy with PA
>50%	Good	Objective improvement in terms of number of new episodes/ severity of symptoms. Excellent improvement in a cluster of symptoms (i.e., sleep, anxiety, impulsivity)	Continue therapy. Consider combination therapy
<50%	Partial	Less clear improvement in the patient's course, partial or no improvement in a cluster of symptoms	Consider combination therapy Consider switch to new PA
<10%	Lack	No appreciable changes in the course of illness with respect to previous history	Switch to new PA

Less formalistic, but probably more informative is an approach introduced by Grof et al. (2002), the so called Alda scale. It is used to retrospectively identify quantity and quality of lithium response, but theoretically can also be applied to other PA.

Given the high disposition for recurrences in bipolar disorder, it appears to be common clinical sense that maintenance treatment should be continued lifelong whenever possible. Discontinuation studies, e.g., after 2 years of successful prophylaxis, targeting this question are non-existing and may raise ethical concerns. Limiting factors of prophylactic treatment, besides lack of efficacy, could be side effects, safety issues, newly emerging medical comorbidities or special circumstances, e.g., pregnancy. In clinical practice, however, the limiting factor is quite often the wish of the patient to try a life without medication, and if this request is not addressed in a satisfactory way, he or she may discontinue medication without medical supervision. Reported non-adherence rates for long-term prophylaxis in BD range from 20 to 66% (Bech et al. 1976; Adams and Scott 2000). This implies that clinicians often have to compromise between what they consider in the patients best interest and self-determination of the patient.

Scope of this review

Due to the quality and quantity of evidence, this guideline has its primary focus on bipolar I disorder. However, despite belonging to the same spectrum, the longitudinal course of bipolar I and II disorder is distinct enough to allow separation as separate subcategories (Judd et al. 2003; Vieta and Suppes 2008) and while it is becoming apparent that to define rapid cycling in a separate category is to some degree artificial (Kupka et al. 2003, 2005) it is still consistently applied in prophylactic treatment trials. Therefore, when evidence is available, we will also refer to bipolar II disorder and rapid cycling patients. As the evidence has been derived by and large from studies in adults aged 18–65, this guideline is primarily only applicable to this patient group. In the few cases where additional information for efficacy or safety in children or old age was retrieved, we also cited it in the body of text but did not include it for primary efficacy ratings, but as additional supportive/non-supportive evidence (category "Further evidence (FE)").

Different from the previous edition of this guideline (Grunze et al. 2004) we did not include schizoaffective disorders despite their wide similarities with bipolar disorder (Marneros 2001) as it was felt that such a broad spectrum view would go beyond the scope of this paper. In addition, the positioning of schizoaffective disorder as a separate disorder between affective disorders and schizophrenia remains debatable, and future classification systems (like Diagnostic and Statistical Manual 5th edition, DSM-5) might substantially change this diagnosis (Lake and Hurwitz 2007).

When considering efficacy in preventive treatment, we will focus on the prevention of manic and depressive episodes. There is a virtual absence on separately extractable information regarding the prevention of hypomania or mixed states as separate entities; when fulfilling threshold criteria – which can differ from trial to trial – they were usually counted as "manic" relapse. In addition, there is the expectation that future classification systems as DSM-5 will no longer consider mixed states as an episode subtype but rather as a specifier.

When information is available, we will distinguish between a medication's efficacy in preventing manic and depressive relapses. "Prevention of any episode" refers to the aggregated outcome measure in studies and does not imply, e.g., that a drug literally has an effect in prevention of any distinct type of episode, i.e., for the prevention of mania as well as the prevention of depression. The reader should be aware that a category of evidence (CE) for "any relapse" could mean three different scenarios: Either (especially in older studies) manic and depressive relapses have not been reported

separately, or a drug is effective in preventing both mania and depression (e.g., quetiapine), or the effect size in preventing one pole is so strong that it drives the overall signal to be positive. For example, aripiprazole has a CE "A" for manic relapses and a CE"E" for depressive relapse. However, the CE for "any relapse", the reported primary study outcome, is still "A" as the strong antimanic efficacy compensates for the lack of prevention of depressive TEE. In this case, "any relapse" has to be understood as a technical term (primary efficacy measure) rather than indication that a medication prevents both poles in clinical practice. These apparent short-comings when reporting on CE for "any relapse" also underlines the importance of studying the same compound in populations of patients who present both recently depressed and/or recently manic/hypomanic/or mixed to improve the generalizability of the data. Unfortunately, for most more modern compounds we lack this data.

Besides efficacy, we will also give close consideration to safety and tolerability issues, although all practical details regarding the management of these issues will not be covered. Physical health issues in bipolar patients, related and unrelated to medication, have also increasingly become a major focus. Finally, given the high rate of death by suicide in bipolar patients, considering suicide-preventive properties of individual medications should be self-evident when making the best informed treatment decision. Unfortunately, these important issues are not uniformly captured across studies and seldom measured as rigorously as efficacy; thus, any in-depth grading of these important aspects is difficult and subject to bias.

Biological treatments, i.e., pharmacological or physical treatments of bipolar disorder, are generally tailored towards the needs of the current stage of the disorder, and may change from acute phase treatment to long-term prophylactic treatment (see also Figure 3). Ideally, combinations of different medication needed for control of a range of acute symptoms will be slimmed down over time to a lean and simple (mono-) therapy regimen. Clinical reality, however, shows that there is not much of a difference in the use of combinations between acute treatment and long-term treatment (Goldberg et al. 2009b), especially in patients with a high burden of depressive illness in the past. Unfortunately, controlled data on different combination strategies are still limited. Combination treatments in clinical practice therefore often rest on choices of medicines, which properties have being established, in many cases, only as monotherapies. The rational for combinations are often to combine medicines with differential preventive efficacy on mania and depression. In the review presented here we will focus both on the published evidence for individual medicines, as confirmed by controlled trials or large-scale naturalistic studies, as well as on evidence from combination treatment strategies when making an efficacy rating and recommendation for a specific drug. This is done with the – potentially wrong and unproven – assumption that medication effects in these studies are additive, and, unless proven otherwise, that there is no unique, efficacy multiplying effect of a specific combination.

At the end, this guideline aims to supply the reader with the following information on a specific medication:

- Evidence for efficacy in preventing treatment emergent episodes of any polarity, and separately manic/mixed and depressive episodes in study samples enriched for acute response and/or acute tolerability of this medication ***("Prevention of TEE in enriched samples (PES)")***
- Evidence for efficacy in preventing treatment emergent episodes of any polarity, and separately manic/mixed and depressive episodes in non-enriched study samples ***("Prevention of TEE in non-enriched samples (PNES)")***
- Evidence for efficacy in frequently relapsing patients (rapid cycling) ***("Prevention of TEE in rapid cyclers (PRC)")***
- Further important supportive/unsupportive evidence, e.g., from large scale naturalistic studies, extension studies, post-hoc analyses of small numbers from RCTs, or in specific subgroups, e.g., children, adolescents, old age ***("Further evidence (FE)")***
- Long-term safety and tolerability of the medication ***("Safety and tolerability (ST)")***
- Antisuicidal properties if documented ***("Prevention of suicide (PSu)")***
- Practicability of the use of this medication, including variety of application forms, dosing strategies, need of routine monitoring examinations, potential discontinuation symptoms***("Practicability (PR)")***
- Overall grade of recommendation, taking all the information above into account ***(" Recommendation grade (RG)")***

Although this guideline is focussing on biological treatment modalities, the authors clearly recognize the importance of and evidence for psychotherapies and psychoeducation as additional therapies (Beynon et al. 2008; Miklowitz 2008; Vieta et al. 2009c). Various psychological approaches are not only tools for optimizing the outcome in individual patients

and for the substantial proportion of patients not benefiting from any biological treatment, but may be of benefit to all patients, at least to increase to understand the importance of and the adherence to biological treatments.

Methods of this review

The methods of retrieving and reviewing the evidence base, and deriving a recommendation are by large identical to those described in the WFSBP guideline for acute mania and bipolar depression (Grunze et al. 2009, 2010). For those readers who are not familiar with these guidelines, we will summarize the methods in brief.

The data used for these guidelines have been extracted from a MEDLINE and EMBASE search, the Science Citation Index at Web of Science (ISI) and a check of the Cochrane library for recent meta analyses (all until February 2012), and from recent proceedings of key conferences. To ensure comprehensiveness of data, we also consulted various national and international treatment guidelines, review papers and consensus statements (Nolen et al. 2008; Goodwin 2009; Vieta et al. 2010a, 2011). A few additional trials were found by handsearching in text books. In addition, www.clinicaltrials.gov was accessed to check for unpublished studies. All searches cover the time span from 1967 to April 2012.

Given the large heterogeneity of study designs, we did not use the results of meta-analyses as evidence of the same level as results from single RCTs fulfilling inclusion criteria. In addition to the methodological problems inherent to bipolar disorder maintenance studies (see section on Methodology), meta-analyses may have a number of methodological shortcomings of their own, which can make their conclusions less reliable than those of the original studies (Anderson 2000; Bandelow et al. 2008; Möller and Maier 2010; Maier and Möller 2010).

In order to achieve uniform and, in the opinion of this taskforce, appropriate ranking of evidence we adopted the same hierarchy of evidence based rigor and level of recommendation as was published in the WFSBP Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders (Bandelow et al. 2008) (see Table II). In brief, a drug must have shown its efficacy in double-blind placebo-controlled studies in order to be recommended with substantial confidence (Categories of evidence (CE) A or B, corresponding to RGs 1–3). Lower level evidence from open studies (CE "C") or conflicting results (CE "D") were accepted for a low RG 4 or 5, respectively. Substantial concerns about long-term safety and tolerability of a drug could also result in a downgrading of the RG, especially when making a distinction between RG 1 and 2.[1]

Different from other disease areas, studies in bipolar disorder are frequently subject to post-hoc analyses. Many of these analyses were done on data sets that have been not informative in their primary outcome, were not hypothesis generated, and therefore have been counted as CE "C" (similar to open studies). However, when a post-hoc analysis has been included a priori in the analyses plan and is sufficiently powered, a CE "B" could be considered.

Depending on the number of positive trials and the absence or presence of negative evidence, different CEs for efficacy were assigned. A distinction was also made between "lack of evidence" (i.e., studies proving efficacy or non-efficacy do not exist, CE "F") and "negative evidence" (i.e., the majority of controlled studies shows non-superiority to placebo or inferiority to a comparator drug (CE "E"). When there is lack of evidence, a drug could still reasonably be tried in a patient unresponsive to standard treatment, while such an attempt should not be undertaken with a drug that showed negative evidence.

We set a minimum of 25 participants for a placebo-controlled study to be considered as evidence for the categories of evidence A or B, as we found a multitude of small studies with low methodological standard and thus a high probability of error. However, those studies could still be considered for the category "Further evidence (FE)". Further evidence (FE), safety and tolerability (ST), practicability (PR) and evidence for suicide preventive effects (PSu) were graded with a simplified system ranging from "++" for most supportive

[1]A point of discussion within the task force, raised by JRC, was applying more restrictive criteria for a drug to meet the highest category of evidence (CE) criteria "A". It was proposed that the optimal bipolar drug development maintenance therapy design should be one in which data are obtained on both recently manic patients and recently depressed patients. This should be considered as the "gold standard" and all of the maintenance studies that limited study entry to just mania or just depression be defined as being at its best Category B – as being less methodologically rigorous and less valid. However, it would have meant creating a CE category content different from the one used in the other WFSBP guidelines. In addition, it was felt that this categorization might give too much weight to discontinuation (enriched) studies and undervalues pure prophylactic studies randomizing euthymic patients, but neither patients in mania nor in depression. Nevertheless, although not applied in this update, the feasibility of this proposal should be tested in parallel in future updates of this guideline.

Table II. Categories of evidence (CE) and recommendation grades (RG).

Category of Evidence		Description
A		**Full evidence from controlled studies is based on:** Two or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding) *and* One or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.
B		**Limited positive evidence from controlled studies is based on:** one or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") *or* a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial *and* In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least one more positive study or a meta-analysis of all available studies showing superiority to placebo or at least one more randomized controlled comparison showing non-inferiority to an established comparator treatment.
C		**Evidence from uncontrolled studies or case reports/expert opinion**
	C1	**Uncontrolled studies is based on:** One or more positive naturalistic open studies (with a minimum of five evaluable patients) *or* a comparison with a reference drug with a sample size insufficient for a non-inferiority trial *and* no negative controlled studies exist
	C2	**Case reports** is based on: one or more positive case reports *and* no negative controlled studies exist
	C3	Based on the opinion of experts in the field or clinical experience
D		**Inconsistent results** Positive RCTs are outweighed by an approximately equal number of negative studies
E		**Negative evidence** The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") or inferiority to comparator treatment
? F		**Lack of evidence** Adequate studies proving efficacy or non-efficacy are lacking.
Recommendation grade (RG)		**Based on:**
1		Category A evidence *and* good risk–benefit ratio
2		Category A evidence *and* moderate risk–benefit ratio
3		Category B evidence
4		Category C evidence
5		Category D evidence

evidence to "–" for strong negative or most concerning evidence (see Tables III and IV).

A profound difference from the acute treatment guidelines is how the final recommendation grades (RG) were derived. In the mania and bipolar depression guidelines the recommendation is based on acute efficacy against the specific pole of the disorder, safety and tolerability, and practicability. This long-term treatment guideline, however, has to consider multiple areas of efficacy (in enriched samples, in non-enriched samples, prevention of mania, prevention of depression, prevention of rapid cycling) and the vast majority of medications have data only in some, but not all areas of efficacy. Simply using a mean value of all categories would not be useful given the rapidly changing landscape of regulatory advice. Older medications, e.g., lithium or carbamazepine, were subject to study designs

Table III. Grading of categories FE, ST, PSu and PR.

	Further evidence (FE)	Safety and tolerability (ST)	Prevention of suicide (PSu)	Practicability (PR)
++	Several supportive FE, e.g., metaanalysis or positive studies which, however, fall short of criteria to be considered as evidence for CE "A" or "B" for enriched or non-enriched samples	Very good	Good evidence	Easy to use, several formulations, likely to support adherence
+	Some (or more) supportive FE, e.g., limited evidence from open studies in samples where enrichment is unclear	Good	Some supportive evidence	Choice between different formulations, simple titration, no discontinuation effects
0	Conflicting data or unknown	Equally advantages and disadvantages, or Unknown	Conflicting data or unknown	Equally advantages and disadvantages
−	Some (or more) non-supportive FE, e.g., limited negative evidence from open studies in samples where enrichment is unclear	Some concerns	May enhance suicidal ideation	Aspects that make the use difficult in clinical practice
−	Several non-supportive FE, e.g., negative metaanalysis or negative studies which, however, fall short of criteria to be considered as evidence for CE "A" or "B" for enriched or non-enriched sample.	Major concerns	May enhance suicide attempts and/or suicides	Virtually impossible to use in clinical practice

considered as truly prophylactic, and they were only seldom tested in a design enriched for acute response; whereas the opposite is true for medications developed more recently.

- Thus, the RG given to medication by the taskforce values not necessarily its efficacy and usefulness in all areas, but gives special consideration and weight to its strength in only one (or more) efficacy area.
- Only medications with any positive CE rating (A–D) in the areas of "Prevention in enriched samples" (see Table V), "Prevention in non-enriched samples" (Table VI) or "Prevention of TEE in rapid-cycling patients" (Table VII) no matter prevention of any episode, mania or depression, were given an RG.

Table IV. Ratings for Further evidence (FE), Safety and tolerability (ST) and Practicability (PR).

Agent	FE	ST	PR
Amisulpride	−	−	+
Antidepressants	0	0	+
Aripiprazole	+	+	+
Asenapine	0	+	−
Carbamazepine	++	−	−
Clozapine	+	−	−
Gabapentin	+	+	−
Lamotrigine	+	+	0
Lithium	++	−	−
Olanzapine	++	−	+
Oxcarbazepine	0	0	0
Paliperidone	0	0	0
Phenytoin	0	−	0
Quetiapine	+	−	0
Risperidone	+	−	+
Topiramate	+	+	+
Typical AP (all)	0	−	+
Valproate	+	0	+
Ziprasidone	0	0	+
Omega 3 fatty acids	−	+	−
ECT	+	−	−

Table V. CE in enriched samples.

Agent	Prevention of mania	Prevention of depression	Prevention of any mood episode*
Amisulpride	F	F	F
Antidepressants	D	C	D
Aripiprazole	A	E	A
Asenapine	C	F	F
Carbamazepine	F	F	F
Clozapine	F	F	F
Gabapentin	F	F	F
Lamotrigine	D	A	A
Lithium	B	B	B
Olanzapine	A	B	A
Oxcarbazepine	F	F	F
Paliperidone	B	E	B
Phenytoin	F	F	F
Quetiapine	A	A	A
Risperidone	A	E	D
Topiramate	F	F	F
Typical AP (perphenazine)	E	E	E
Valproate	F	F	C
Ziprasidone	B	E	B
Omega 3 fatty acids	F	F	F
ECT	F	F	C

*In this and the following tables, "Prevention of any episode" refers to the aggregated outcome measure in studies and does not imply, e.g., that a drug literally has an effect in prevention of any distinct type of episode, i.e., for the prevention of mania as well as the prevention of depression.

Table VI. CE in non-enriched samples.

Agent	Prevention of mania	Prevention of depression	Prevention of any mood episodes
Amisulpride	C	F	C
Antidepressants	E	B	E
Aripiprazole	F	F	F
Asenapine	F	F	F
Carbamazepine	F	F	C
Clozapine	F	F	C
Gabapentin	F	F	C
Lamotrigine	F	F	F
Lithium	A	D	A
Olanzapine	B	B	B
Oxcarbazepine	F	C	C
Paliperidone	F	F	F
Phenytoin	F	F	C
Quetiapine	F	F	F
Risperidone	F	F	F
Topiramate	F	F	F
Typical AP (all)	F	F	F
Valproate	F	B	F
Ziprasidone	F	F	F
Omega 3 fatty acids	F	F	C
ECT	F	F	F

- However, we detailed in the text and tables if we found other studies suitable for the category "Further evidence" or supporting effects on suicidality as we feel that these information are valuable for treatment decisions.

This use of RGs which differs from the previous mania and bipolar depression guideline implies that

Table VII. Ratings for PRC and effects on suicide prevention (PSu).

Agent	Rapid cyclers/frequently relapsing patients	Prevention of suicide
Amisulpride	F	0
Antidepressants	E	+
Aripiprazole	C	0
Asenapine	F	0
Carbamazepine	F	0
Clozapine	C	+†
Gabapentin	F	0
Lamotrigine	E	0
Lithium	F	++
Olanzapine	C	0
Oxcarbazepine	F	0
Paliperidone	F	0
Phenytoin	F	0
Quetiapine	C	0
Risperidone	B	0
Topiramate	C	–
Typical AP (all)	F	0
Valproate	F	0
Ziprasidone	F	0
Omega 3 fatty acids	F	0
ECT	C	0

†so far only demonstrated in patients with schizophrenia

- the RG in this guideline is clearly more subject to arbitrary judgement then in the depression and mania guideline. It is largely derived from the highest score in those areas where CE ratings are given (see Table VIII).
- Thus, use of any given medication should never be uncritically based on the RG without an understanding on which strengths or weaknesses the recommendation is based upon.

We have not considered the direct or indirect costs of treatments as these vary substantially across different health care systems. It may be worth noting that medication costs are usually a minor (if measurable) component of direct costs, especially in the long term. Some of the drugs recommended in this guideline may not (or not yet) have received approval for the long-term treatment of bipolar disorder in every country. As the approval by national regulatory authorities is also dependent on a variety of factors, including the sponsor's commercial interest (or lack thereof) this guideline is exclusively based on the available evidence.

The task force is aware of several inherent limitations of these guidelines. When taking negative evidence into consideration, we rely on their publication or their presentation or the willingness of study sponsors to supply this information. This information may not always be complete and may inflate evidence of efficacy in favour of a drug where access to such complete information is limited. This potential bias has been minimized as much as possible by checking the www.clinicaltrials.gov database. Another methodological limitation is sponsor bias (Lexchin et al. 2003; Perlis et al. 2005; Heres et al. 2006; Lexchin and Light 2006) inherent in most single studies on which the guidelines are based. Although all recommendations are formulated by experts trying their best to be objective, they are still subject to their individual pre-determined attitudes and views for or against particular choices. Therefore, no review of evidence and guideline can in itself be an absolutely balanced and conclusive piece of evidence, but should direct readers to the original publications and, by this, enhance their own knowledge base.

Finally, the major limitation of any guideline is defined by the limitations of the evidence. One of the most important clinical questions that cannot be sufficiently answered in an evidence based way is what to do when any first step treatment fails, which happens in a significant number of cases. Therefore, with the current level of knowledge we cannot provide rigorous algorithms for long-term treatment.

Once a draft of this guideline had been prepared by the Secretary and co-authors it was sent out to the 53 members of the WFSBP Task Force on Treatment

Table VIII. Overall Recommendation Grades for long-term treatment.

Agent	RG	Mainly based on:
Amisulpride	**4**	CE "C" in PNES for "mania" and "any episode"
Antidepressants	**3**	CE "B" in PNES for "depression"
Aripiprazole	**1**	CE "A" in PES for "mania" and "any episode"
Asenapine	**4**	CE "C" in PES for"mania"
Carbamazepine	**4**	CE "C" in PNES for "any episode"
Clozapine	**4**	CE "C" in PRC for "any episode" CE "C" in PNES for "any episode"
Gabapentin	**4**	CE "C" in PNES for"any episode"
Lamotrigine	**1**	CE "A" in PES for "depression" and "any episode"
Lithium	**1**	CE "A" in PNES for "mania" and "any episode" CE "B" in PES for "any episode, "mania" and "depression"
Olanzapine	**2**	CE "A" in PES for "mania" and "any episode" CE "B" in PES for "depression" and in PNES for "depression" , "mania" and "any episode" Downgraded because of safety issues (weight gain and metabolic issues)
Oxcarbazepine	**4**	CE "C" in PNES for "any episode" and "depression"
Paliperidone	**3**	CE "B" in PES for "mania" and "any episode"
Phenytoin	**4**	CE "C" in PNES for "any episode"
Quetiapine	**1**	CE "A" in PES for "mania" , "depression" and "any episode" CE "C" in PRC
Risperidone	**2**	CE "A" in PES for "mania" CE "B" in PRC for "any episode" Downgraded because of safety issues (weight gain and prolactin related AE)
Topiramate	**4**	CE "C" in PRC for "any episode"
Typical AP	**Ø**	Insufficient (negative) evidence, Issues with long-term safety
Valproate	**3**	CE "B" in PNES for "depression"
Ziprasidone	**3**	CE "B" for combination treatment in PES for "mania" and any episode"
Omega 3 fatty acids	**4**	CE of "C" for PNES
ECT	**4**	CE "C" in PES and PRC for "any episode"

Guidelines for Bipolar Disorders for critical review and addition of remarks about specific treatment peculiarities in their respective countries. A second draft, revised according to the respective recommendations, was then distributed for final approval.

These guidelines were established without any financial support from pharmaceutical companies. Experts of the task force were selected according to their expertise and with the aim to cover a multitude of different cultures.

Medications commonly used as preventive agents and their ranking by evidence

In the following sections, we will highlight pivotal studies supporting (or speaking against) efficacy of a PA, amended by other supportive evidence if clinically relevant, key findings referring safety, tolerability and antisuicidal effects, and an estimate of its practicability to use. We assigned ratings for efficacy as detailed in the section on "Methods of this review", and graded the other categories in a more simplified system (ranging from ++ to −/−, see Table III). As this guideline should useful for the practicing clinician, PA under consideration are not exclusively those where data of randomized controlled long-term studies are available, but those which are either used with some trust and frequency by clinicians in bipolar patients, e.g., antidepressants as a group, or in specific subgroups, e.g., clozapine in otherwise treatment refractory patients. This explains, for example, why we consider and list from the frequently used antiepileptic drugs gabapentin, but, e.g., not ethosuximide. Given the large heterogeneity of what has been grouped as "atypical antipsychotics" and "mood stabilizer", we will consider the evidence for each of these substances individually, mentioning them in alphabetical order. "Antidepressants" and "typical antipsychotics", however, will be dealt with as a group of medication, given the relative lack of evidence for single drugs of these groups.

Amisulpride: see "Other atypical antipsychotics used in bipolar disorder"

Antidepressants

With the exception of imipramine, antidepressants have hardly been studied as maintenance treatment of bipolar disorder, and their use is highly controversial, not only in short-term treatment, but even more so in the long term (Frye 2011; Vieta and Grunze 2011). Given that rigorous evidence is limited, we

have considered antidepressants as a group. We are aware that this is a simplification as we see differences at least in the side effect profile and in the potential risk of inducing Treatment emergent switches (TEAS) and RC; given the multitude of licensed antidepressants, looking into each individually would be unprofitable. However, the reader should be aware that there are subtle differences in the rate of TEAS, and SSRI, bupropion and MAO inhibitors may have a lower intrinsic risk to induce TEAS than other antidepressants (Leverich et al. 2006; Nolen et al. 2007).

When discussing antidepressants, we also have to be aware of the caveat that the vast majority of studies look into combination treatment of an antidepressant and a mood stabilizer; thus, drawing conclusions about antidepressant monotherapy is misleading as the mood stabilizer will impact on side effects and TEAS in these studies.

Despite the lack of evidence from RCTs, antidepressants play an important role in daily clinical practice. A recent large study looking into prescribing habit in both academic and non-academic centres in Spain (SIN-DEPRES) found that almost 40% of patients were on a long-term combination treatment including at least one antidepressant. Factors associated with the use of an antidepressant were bipolar disorder II diagnosis (Odds ratio (OR) = 2.278, $P = 0.008$) and depressive polarity of the most recent episode (OR = 2.567, $P = 0.003$) (Grande et al. 2012b). It can be assumed that in most cases the use of antidepressants in long-term treatment of bipolar disorder is not de novo as a pure prophylactic treatment, but a continuation in acute antidepressant responders.

Univariate factor analysis in large cohorts revealed that antidepressant use in bipolar patients is associated with lifetime depressive morbidity (including first-episode depression, more depressive episodes, and melancholic features at index episode), more years ill, and less affective illness in first-degree relatives (Undurraga et al. 2012). Especially the presence of anxiety symptoms are a strong indicator for antidepressant use, but the causality remains unclear (Pacchiarotti et al. 2011). It has been suggested that antidepressants may provoke increased irritability and dysphoria (El-Mallakh et al. 2008) and also mixed states, which might be more common with SNRIs (Valenti et al. 2011). The risk of TEAS and consequently of cycle acceleration with antidepressant use may be especially prominent in patients having distinct manic symptoms while depressed, namely increased motor activity, speech, and language-thought disorder (Frye et al. 2009).

The British Association for Psychopharmacology suggests that there is not sufficient evidence to recommend the discontinuation of antidepressant as a general principle (Goodwin 2009), but an individual decision rests with the clinician considering factors such as previous or current mood instability with manic features, tolerability and safety, special comorbidities, e.g., panic disorder, and the existence/non-existence of more promising treatment options for the individual patient. A Bayesian approach to the use of antidepressants in long-term treatment might be currently the most practical and patient-centred way of treatment (Belmaker et al. 2010).

Prevention of TEE in Enriched samples (PES)

We identified one randomized and blinded study testing the efficacy of imipramine as bipolar disorder maintenance treatment against placebo and lithium. In this study by Prien and co workers, labeled as "study 2" in the accompanying paper (Prien et al. 1974), hospitalized patients with an index episode of depression were treated openly with imipramine and lithium, and at the time of discharge randomized to continuing on lithium, imipramine or placebo. Similar to the study of Prien et al. in patients with a manic index episode (Prien et al. 1973a), see section on "Lithium", patients and raters, but not treating clinicians were blinded to medication. Of the 122 patients, 44 were bipolar. Of the 44 bipolar patients, 18 were randomized to lithium, and 13 each to imipramine or placebo. Imipramine was statistically significant less effective than lithium in preventing any relapse. The difference between the lithium and imipramine groups was due almost entirely to the higher incidence of manic episodes in the group receiving imipramine ($P < 0.05$), whereas there was no significant difference between the lithium and imipramine groups in the incidence of depressive episodes ($P > 0.05$). Compared to placebo, the article reports for imipramine only numbers and percentages, but no tests for significance. Of the 13 subjects randomized to placebo, five (38%) relapsed into depression, and eight (62%) into mania. Of the 13 subjects randomized to imipramine, seven (54%) had a manic and four (31%) a depressive relapse. Overall, 77% of patients in both groups had at least one recurrence of a mood episode over the 2 years of observation: three subjects in the placebo group and one subject on imipramine had more than one recurrence. Thus, in this study imipramine was not better than placebo; a slight advantage in protecting against depression was gained on the expenses of more new manic episodes.

Two large open studies have addressed antidepressant continuation versus discontinuation after acute response to treatment. Antidepressants were not

restricted to specific drug, and subjects also received mood stabilizer treatment in addition. One study (Ghaemi et al. 2010) which was part of the STEP-BD program used a randomized discontinuation design; the other (Altshuler et al. 2003), part of the Stanley Foundation Bipolar Network (SFBN) portfolio, used a naturalistic design leaving the decision to continue versus discontinue antidepressants to patients and clinicians. In the STEP-BD study, the primary outcome was change of depression scores in the STEP-BD Clinical Monitoring Form (CMF). The CMF grades DSM IV manic and depressive symptoms on a severity scale ranging from −2 (severe depressive symptom) to +2 (severe manic symptom) with 0 meaning absence of the specific symptom. Antidepressant continuation had a marginal effect trending toward less severe depressive symptoms after 1 year (mean difference in CMF depression score = −1.32 [95% CI, −0.30 to 3.16] and, as a secondary outcome, mildly delayed depressive episode relapse (HR = 2.13 [1.00–4.56]), without increased manic symptoms. The subgroup of patients with RC, however, had three times more depressive episodes with antidepressant continuation (RC = 1.29 vs. non-RC = 0.42 episodes/year, $P = 0.04$) which was not observed in the antidepressant discontinuation group and clearly questions the utility of antidepressants in this subgroup (Ghaemi et al. 2010).

The Stanley Foundation study examined the effect of antidepressant discontinuation versus continuation in 84 subjects with bipolar disorder who achieved remission from a depressive episode with the addition of an antidepressant to an on-going mood stabilizer regimen, prospectively followed for 1 year. One year after successful antidepressant response, 70% of the antidepressant discontinuation group experienced a depressive relapse compared with 36% of the continuation group. By the 1-year follow-up evaluation, 15 (18%) of the 84 subjects had experienced a manic relapse; only six of these subjects were taking an antidepressant at the time of manic relapse (Altshuler et al. 2003).

A 1-year double-blind follow-up of a 10-week acute study compared sertraline, bupropione and venlafaxine in addition to on-going mood stabilizers in acute bipolar depression (Leverich et al. 2006), among patients acutely responsive to antidepressant treatment. At the study endpoint 69% of the 61 acute positive responders maintained positive response and 53% achieved remission. Compared to the acute positive responders, six (27%) of the 22 acute partial responders had achieved positive treatment response at study endpoint ($P < 0.001$). Only eight acute positive responders (13%) and five acute partial responders (22%) developed mania (Altshuler et al. 2009).

Overall, the few studies conducted are neither persuasive in supporting nor refuting mania protective effects of antidepressants; results remain ambiguous whether antidepressants are protective or neutral as far as TEAS are concerned.

In summary, we conclude that the effect of antidepressants for PES has not been sufficiently studied in placebo-controlled designs; however, evidence from open studies indicate that antidepressants may be beneficial in non-rapid cycling patients who showed acute response to this treatment. This holds true for the prevention of new depression, whereas for any episode and mania results are equivocal (Prien et al. 1974; Altshuler et al. 2003, 2009; Ghaemi et al. 2008). ***CE for PES for depression: "C"; for any mood episode and for mania: "D".***

Prevention of TEE in non-enriched samples (PNES)

We identified only one study in bipolar I patients where a antidepressant was used a priori as preventive treatment in euthymic patients (Prien et al. 1973b). Subjects received lithium ($n = 18$), imipramine ($n = 13$) or placebo ($n = 13$) for time periods between 5 and 24 months. Thus, with 26 patients either on imipramine or placebo, the study just meets our inclusion criteria for potential CoE "A" or "B". No difference in overall recurrence rates between imipramine and placebo has been reported. However, imipramine had a significant advantage over placebo in preventing new depression (RR, 95% CI : 0.40 [0.17–0.95], whereas there were not statistically significantly more manic episodes with imipramine compared to placebo (RR,95% CI1.60 [0.71–3.60] (Ghaemi et al. 2008). However, because of the small samples there is a risk of a type 2 error occurring; another flaw of the study is that the incidence of hypomania was not stated. ***CE for PNES for depression "B", for mania and any mood episode: "E".***

Prevention of TEE in rapid cyclers (PRC)

Although there are no blinded RCTs of antidepressants in RC patients, all available evidence from uncontrolled studies and charts reviews suggest that at least older TCAs and SNRI are more likely to induce RC than to prevent new episodes in RC patients (Ghaemi 2008; Grunze 2008). This may be also true for SSRI; 52% of subjects in the study of Ghaemi et al. (2010) had an SSRI. However, the paper does not supply a breakdown of new episodes

in RC patients by medication. Clinical wisdom would suggest avoiding antidepressants in RC patients. We therefore consider the CE for antidepressants as preventive agent in RC patients as "E". ***CE for PRC: "E"***

Further evidence (FE)

We found a few older studies with tricyclic antidepressants or fluoxetine in usually small numbers of patients and mixed unipolar/ bipolar study populations.

When investigating bipolar II patients, Kane at al. (1982) found no advantage of imipramine over placebo. In combination with lithium, imipramine was also not more effective than lithium monotherapy (Quitkin et al. 1978, 1981).

Johnstone et al. (1990) reported that in a randomized study, lithium alone versus amitriptyline + lithium showed no advantage in 13 bipolar patients for the combination treatments in reducing depressive relapses.

Amsterdam et al. (1998) compared fluoxetine in unipolar depressed with fluoxetine in bipolar II depressed patients in acute and long-term treatment (up to 1 year). During long-term relapse-prevention therapy, relapse rates were similar in bipolar II and unipolar patients. One bipolar II and two unmatched unipolar patients taking fluoxetine had a TEAS. Two more studies by the same group (Amsterdam and Shults 2005, 2010) also support the efficacy and low switch risk of fluoxetine in bipolar II patients. It appears that fluoxetine monotherapy is relatively safe in bipolar II patients which is in line with other analyses of rates of short-term TEAS (Parker et al. 2006; Bond et al. 2008). ***Rating of FE: "0"***

Safety and tolerability (ST)

Given the very heterogeneous group of antidepressants, ranging from usually well tolerated and safe SSRI to older tricyclics and MAO-I associated both with safety and tolerability problems we cannot make a uniform statement applicable to all antidepressants. A comprehensive review of the safety and tolerability of antidepressants has been recently published by the Collegium Internationale Neuro-Psychopharmacologicum (CINP) (Sartorius et al. 2007). ***Rating of ST: "0"***

Prevention of suicide (PSu)

There had been much discussion of the possibility that antidepressants, mainly SSRI and the SNRI venlafaxine, induce suicidal behaviours in depressed patients. This is sometimes further linked to undiagnosed bipolar spectrum disorder in depressed populations. Careful reanalysis of the randomized controlled data (Simon et al. 2006; Stone et al. 2009) as well as pharmaco-epidemiological and large observational studies (Gibbons et al. 2007; Leon et al. 2011) refute the hypothesis that antidepressants induce suicidality. Specifically for bipolar patients, the STEP-BD study did not observe an increase of new onset suicidality in response to initiation, dosage increase or decrease of antidepressants (Bauer et al. 2006).

On the other hand, there is compelling evidence for a reduction of suicides in bipolar patients treated with antidepressants (Angst et al. 2005). Data derived from the large Zurich cohort study showed a significant long-term protective effect of treatment with antidepressants (and also with lithium and antipsychotics) against completed suicide. ***Rating of PSu: "+"***

Practicability (PR)

Most antidepressants are available in a variety of formulations allowing also once daily administration and graded dosage steps to enable easy tapering. ***Rating of PR: "+"***

Recommendation grade (RG)

Based on CE "B" evidence for PNES, we assigned antidepressants a ***RG "3".*** Otherwise, evidence for PES is "C" to prevent new depression which may be considered as too weak to make a general recommendation for the long-term use of antidepressants in bipolar disorder. Readers should be aware that more than in the case of any other medication, this CE and subsequent RG ratings are based on data derived from combination treatments. It cannot be excluded with certainty that synergistic effects between the antidepressants and antimanic agents or mood stabilizers occur, which might influence efficacy, tolerability or suicidality. Clearly, further conclusive research is needed.

Aripiprazole

Prevention of TEE in Enriched samples (PES)

One monotherapy study (with a first endpoint after 26 weeks, Keck et al. 2006a, and a second endpoint after 100 weeks, Keck et al. 2007) and one combination treatment study (aripiprazole add on to lithium or valproate, Marcus et al. 2011) support the efficacy of aripiprazole in preventing new manic and mixed

episodes in samples enriched for acute response to aripiprazole in acute mania. These studies appear adequately powered, and given the extended and rigorously controlled stabilization phase of 6 and 12 weeks, respectively, they measure rather recurrence of mood episodes but relapse (see section on "Time lines in studies", Gitlin et al. 2010). However, when the stabilization criteria become too strict, a study might end up with a population of "super-stable" patients, independent from treatment intervention. A further combination treatment study comparing lamotrigine + aripiprazole versus lamotrigine + placebo in patients recently manic or mixed and being stabilized for 9–24 weeks showed a numerical, but not statistical significant advantage of the combination treatment (Carlson et al. 2012). Given the implications and uncertainties associated with such an extended stabilization phase and selection of patients, the task force decided to consider this study as "failed" study rather than "negative". Thus, the ***CE for the prevention of any episode and mania in ES would remain "A"*** with two positive and one failed (not "negative") study.

All these studies did not find a positive signal for the prevention of depressive episodes. It remains unclear whether this is a signal that also holds true in a population not selected for mania as index episode, or resembles a design artefact. In addition, as there is a greater likelihood that a subsequent episode is of the same polarity as the index episode, depressive relapses are much less likely during short observation periods and "time to episode" being the study endpoint (see section "What is the population under examination?" Calabrese et al. 2004). Larger study populations and longer observation periods might clarify this issue, but as it stands now the ***CE to prevent new depressive episodes in ES is "E".*** However, as the overall outcome of the pivotal studies was still significantly in favour of aripiprazole, the ***CE to prevent any episode and mania in ES is "A".***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any long–term aripiprazole study in non-enriched samples satisfying inclusion criteria for this review. ***CE for PNES: "F"***

Prevention of TEE in rapid cyclers (PRC)

A post-hoc analysis of the 26- and 100-week monotherapy studies (Keck et al. 2006a, 2007) showed that time to any mood relapse in RC was significantly longer with aripiprazole monotherapy compared with placebo at week 26 ($P = 0.033$) and at week 100 ($P = 0.017$), despite the small sample size of 28 patients (Muzina et al. 2008). The combination treatment study of Marcus et al. (2011) included only 9.5% rapid cycler (defined as patient having four to six episodes in the past 12 months), a number too small allowing a meaningful separate analysis. ***CE for PRC: "C"***

Further evidence (FE)

The efficacy of aripiprazole as maintenance treatment to prevent new manic episodes has also been supported by a recent metaanalysis (Vieta et al. 2011). Also quite recently, a double blind add-on study from Korea has been published comparing valproate + aripiprazole vs. valproate + placebo for 6 months in patients acutely responsive to open combination treatment in mania (Woo et al. 2011). During the 6-month double-blind treatment, the time to relapse of any mood episode in the aripiprazole group was longer than the placebo group, but the difference did not reach statistical significance ($P = 0.098$). Numerically fewer patients in the aripiprazole group experienced TEEs (15.0%) than in the placebo group (32.6%) ($P = 0.076$). Aripiprazole combination treatment was also associated with a lower severity of inter-episode mania and depression symptoms during the period of remission than placebo combination treatment, as measured by YMRS, MADRS, and CGI-BP-S. The proportion of patients relapsing into mania was minimal and only around 10% under both treatments. After controlling for mean valproate level, the time to depressive episode relapse in the aripiprazole group was longer than those in the placebo group ($P = 0.029$).

This study raised some discussion within the task force whether it should be counted as negative evidence thus leading to a downgrading of aripiprazole. However, it was decided to rather consider it as failed, but with some supportive evidence in secondary outcomes. The main reasons are insufficient power and design issues. With only 83 patients included (43 on valproate + placebo and 40 on valproate + aripiprazole, with 25 and 23 patients, respectively, staying in the study for 6 months) it is unlikely to see separation in combination studies comparing one versus two active and effective treatments. Both treatments have also demonstrated reliable antimanic properties (Grunze et al. 2009), and are tested in a population with a manic index episode where depressive recurrence is less likely than manic relapse (Calabrese et al. 2004). The generally low relapse rate into mania is suggestive of a lack of assay sensitivity. Given the small number of patients included and low likelihood of a depressive recurrence, separation for depressive

relapses, although significant, is unlikely to drive the overall result.

A 46-week, open-label extension of an acute mania combination treatment study (Vieta et al. 2008d) also supports continuous antimanic efficacy of aripiprazole. In total, 283 (aripiprazole + lithium, $n = 108$; aripiprazole + valproate, $n = 175$) completers of the acute study entered and 146 (aripiprazole + lithium, $n = 55$; aripiprazole + valproate, $n = 91$) completed the 46-week, open-label extension. Over the 46-week extension, aripiprazole provided continued YMRS improvement showing an YMRS reduction of 2.9 with aripiprazole + lithium, and 3.3 with aripiprazole + valproate (Vieta et al. 2010b).

Findling et al. (2012) conducted a 6-month, placebo-controlled study in children where, after acute response in mania, 30 patients (mean age = 7.1 years) were randomly assigned to continue aripiprazole and 30 patients (mean age = 6.7 years) were randomly assigned to placebo. The study was inconclusive as both aripiprazole and placebo groups showed substantial rates of withdrawal from maintenance treatment over the initial 4 weeks (15/30 [50%] for aripiprazole; 27/30 [90%] for placebo), suggesting a possible nocebo effect (i.e., knowledge of possibly switching from active medication to placebo increasing concern about relapse). ***Rating of FE: "+"***

Safety and tolerability (ST)

Common side effects during aripiprazole treatment are akathisia, tremor, headache, dizziness, somnolence, sedation fatigue, nausea, vomiting, dyspepsia, constipation, light-headedness, insomnia, restlessness, sleepiness, anxiety, hypersalivation and blurred vision. Rarely described side effects, whose frequency is not precisely known, include uncontrollable twitching or jerking movements, seizures, weight gain, orthostatic hypotension or tachycardia, allergic reactions, speech disorder, agitation, fainting, transaminasaemia, pancreatitis, muscle pain, stiffness, or cramps and very rarely neuroleptic malignant syndrome and tardive dyskinaesia (Fountoulakis and Vieta 2009). However, side effects are still relatively rare and do not necessarily lead to treatment discontinuation in RCTs. This is different in clinical settings where the principal causes of discontinuation for any drug should be vigilantly addressed by the psychiatrist, and, given the array of alternative drugs, discontinued unless the adverse reaction ceases. The principle should be *primum nos nocere*, especially for what would interfere with adherence or social comfort.

Safety analyses were performed on LOCF data from the combined 26- and 100-week double-blind studies. Rates of discontinuation due to treatment emergent adverse events (TEAEs) were 16% in the aripiprazole group and 28% in the placebo group. The most common adverse event (AE) leading to discontinuation was labelled as manic reaction (7% for aripiprazole and 11% for placebo). During the 100-week study, 60 patients (78%) in the aripiprazole group and 60 patients (72%) in the placebo group reported ≥ 1 TEAE. Extrapyramidal motor symptoms (EPS) associated TEAEs were more frequently reported with aripiprazole than with placebo (22 vs. 15%); the most common of these were tremor (9 vs. 1%), akathisia (8 vs. 1%), and hypertonia (4 vs. 2%). The applied scales measuring EPS – the Simpson–Angus extrapyramidal side effect scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) – showed no significant differences between aripiprazole and placebo. Only two patients discontinued the study due to akathisia.

The metabolic profile of aripiprazole appears rather benign. At week 100, no significant differences between groups in terms of combined fasting and non-fasting glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides were observed. There was no increase of prolactin associated with aripiprazole treatment. The mean (± standard deviation, SD) weight change was + 0.4 (0.8) kg in the aripiprazole group and –1.9 (0.8) kg in the placebo group, a non-significant finding. However, a clinically significant (≥ 7%) weight increase occurred in 12 patients (20%) in the aripiprazole group but only in three patients (5%) in the placebo group ($P = 0.01$) (McIntyre 2010), indicating, against some common belief, that aripiprazole is not free of significant weight gain.

Aripiprazole is in the US Food and Drug administration (FDA) "C" pregnancy category, meaning that risk cannot be ruled out as human studies are lacking, and animal studies are either positive for foetal risk or lacking as well (Nguyen et al. 2009). ***Rating of ST: "+"***

Prevention of suicide (PSu)

Fortunately, suicide is still a too rare event to be sufficiently captured and analysed from controlled studies with a limited number of participants. As aripiprazole is rather activating than sedative, there has been some worries that it may increase suicide risk. An epidemiological study, using administrative data from three US sources, assessed study endpoints of suicide attempts and death by suicide in patients aged ≥ 18 and being enrolled

continuously for ≥3 months in their health plans before receiving their first ever antipsychotic (November 2002–December 2005, 20,489 antipsychotic users, 8985 patient-years). It found that compared with other SGA combined, aripiprazole is not associated with an increased risk of suicide events in this naturalistic cohort of patients with schizophrenia or bipolar disorder (Ulcickas et al. 2010). On the other hand, we do not know whether aripiprazole has a specific preventive effect against suicide. ***Rating of PSu: "0"***

Practicability (PR)

Aripiprazole is in most countries available as tablets of different strength, orodispersable tablets, oral solution and as intramuscular injectable solution. Thus, there is a very reasonable choice of applications. The recommended treatment dose for recurrence prevention of mania is 15 mg once daily, if necessary; maximal 30 mg once daily. This is the dose that had been used in the pivotal monotherapy studies; lower doses may work but have not been tested in controlled studies. In the combination treatment study, dosages from 10–30 mg have been employed (Marcus et al. 2011).

An injectable depot formulation has already been tested in schizophrenia (ClinicalTrials.gov Identifier: NCT00705783) but results have not been published yet. It has been communicated that the study was positive for relapse prevention (Park et al. 2011). Aripiprazole injectable depot is currently under investigation as Bipolar I maintenance treatment (ClinicalTrials.gov Identifier: NCT01567527). ***Rating of PR: "+"***

Recommendation grade (RG)

Aripiprazole has well proven efficacy in the recurrence prevention of mania in enriched samples (CE: "A") with additional evidence for rapid cycling patients (CE: "C"). The CE to prevent new depressive episodes is "E". In non-enriched samples, the CE is "F" as no informative studies have been conducted. Further evidence, the safety and tolerability profile and practicability of use (all rated "+") also support the use of aripiprazole. ***Thus, for patients with a index episode of mania and acute response to aripiprazole, the RG is "1".*** For all other groups of patients, the long-term use of aripiprazole is not supported by solid evidence, but should not be excluded in specific clinical scenarios as non-response, tolerability or safety problems with other long-term treatments.

Asenapine: see "Other atypical antipsychotics used in bipolar disorder"

Carbamazepine

Prevention of TEE in enriched samples (PES)

We could not identify any randomized, controlled, long-term study of carbamazepine in enriched samples which satisfied our inclusion criteria. The study by Lusznat et al. (1988) (see section on "Further evidence") was insufficiently powered to allow reliable statistics for non-inferiority. Additionally, we found a 26-week study comparing carbamazepine + placebo vs. carbamazepine + the herbal remedy "Free and easy Wanderer (FEW)" which was conducted in bipolar patients acutely responsive either to carbamazepine or the combination with FEW. However, as this study lacks a placebo control for carbamazepine or an established comparator, it can only supply safety and tolerability data for carbamazepine. Thus, the ***CE for the prevention of manic episodes in ES is "F". CE for the prevention of new depressive episodes in ES is "F". CE to prevent any episode in ES is "F".***

Prevention of TEE in non-enriched samples (PNES)

Greil and co-orkers (Greil et al. 1997b; Greil and Kleindienst 1999a,b) compared carbamazepine and lithium in an open-label, but randomized parallel group study, lasting for 2.5 years and involving 144 patients with bipolar I, bipolar II and not otherwise specified bipolar disorders. No significant difference was observed between both treatments based on survival analysis with time to hospitalization or episode recurrence (hospitalization: 22% for lithium and 35% for carbamazepine, recurrence: 28% for lithium and 47% for carbamazepine, both *P* values. These results hold true both in bipolar I and II patients (Greil and Kleindienst 1999a,b). However, when combining different outcome-measures giving a more complete picture of clinical usefulness (recurrence and need for additional medication and/or adverse events) lithium was significantly better than carbamazepine.

The relative frequency of recurrences with a depressive versus manic or mixed symptomatology was numerically higher under carbamazepine (Kleindienst and Greil, personal communication). Although not statistically significant ($P = 0.1002$), these data provide a first indication, that under carbamazepine bipolar disorder patients might be more prone towards relapse to the depressive pole than under lithium.

Despite being the probably most informative study on carbamazepine, it falls short of satisfying criteria for

a CE "B" evidence. In the absence of a placebo arm, the sample size is insufficient for a non- inferiority trial, and although randomized, it was not blinded (see "Table III. Check list for Quality of Controlled Studies" in Bandelow et al. (2008) which outlines the CE criteria of WFSBP guidelines)

Based on this study, the ***CE for the prevention of manic episodes in NES "F"; CE to prevent new depressive episodes in NES is "F";*** and the ***CE to prevent any episode in NES is "C".***

Prevention of TEE in rapid cyclers (PRC)

The study of Denicoff et al. (1997b) comparing lithium, carbamazepine and the combination of both showed a poor response to both lithium and carbamazepine in RC patients compared to non-RC patients (for carbamazepine: 19 vs. 31.4% for CGI improvement). An open study (Joyce 1988) and a case report (Riemann et al. 1993) are suggestive of some positive effects of carbamazepine in RC patients, but controlled evidence is missing. ***CE for RC: "C"***

Further evidence (FE)

The only placebo-controlled published study for carbamazepine (Okuma et al. 1981) felt short of satisfying criteria to be counted for CE "A" or "B" evidence, as it included only 22 subjects (12 randomized to carbamazepine, 10 to placebo). It was a true prophylactic study investigating bipolar I patients who were euthymic at study entry, however previous exposure or response to carbamazepine was not an exclusion criterion; thus, the degree of potential enrichment is unknown. Primary efficacy variable was the proportion of patients with no recurrence or less frequent recurrences over one year when compared to the year prior to study. Carbamazepine was found to be effective in 60% of the cases and placebo in 22.2% (U-test, $P < 0.10$). Approximately the same percentages were reported for manic versus depressive relapses; however, numbers were too small and thus power too low to reach significance.

Six studies compared carbamazepine with lithium (Placidi et al. 1986; Watkins et al. 1987; Lusznat et al. 1988; Coxhead et al. 1992; Denicoff et al. 1997b; Hartong et al. 2003), but all in sample sized insufficient for non-inferiority studies, as requested for CE "B" evidence.

Hartong et al. (2003) compared 94 patients in a randomized, 2-year double-blind design. Only patients who had not been previously been treated with lithium or carbamazepine, or had less than 6 months lifetime exposure, were included. The study was designed and powered as a superiority trial for carbamazepine over lithium. Out of 44 patients on lithium, 12 patients developed a new episode compared with 21/50 on carbamazepine treatment (P = n.s.). Interestingly, relapse with lithium occurred almost exclusively within the first 3 months of the trial, while carbamazepine patients carried a constant risk of a new episode of about 40% per study year. Unfortunately, the publication does not supply statistics of (hypo)manic versus depressive recurrences with lithium and carbamazepine; in absolute numbers, four patients on lithium developed a new (hypo)manic episode vs. 10 on carbamazepine, and eight on lithium a new depressed episode vs. 11 on carbamazepine.

Coxhead et al. (1992) carried out a 1-year prophylaxis study in 31 patients enriched for lithium, not carbamazepine. All were previously stable on lithium; 15 were switched over to carbamazepine and 16 remained on lithium. The overall relapse rate was similar in the two groups (six on carbamazepine, eight on lithium). The authors concluded that carbamazepine is as effective as lithium in the prophylaxis of bipolar affective disorder, but change over from lithium to carbamazepine should be done slowly to avoid relapse due to lithium discontinuation.

The study by Lusznat et al. (1988) was enriched both for acute lithium and carbamazepine response. Of the 54 subjects entering the acute study while manic or hypomanic, 40 (20 in each arm) continued for 1 year in a rater-blind design. No statistically significant differences were found, but carbamazepine appeared slightly less effective as a treatment for acute mania and more effective as a prophylactic treatment in this group of patients.

The studies by Placidi et al. (1986) and Watkins et al. (1987) included mixed populations with bipolar, schizoaffective und schizophreniform disorder (Placidi et al. 1986) or unipolar and bipolar patients (Watkins et al. 1987), respectively, not allowing a differentiation of response depending on diagnosis. Whereas Watkins et al. (1987) found lithium superior to carbamazepine, Placidi et al. (1986) did not report significant differences.

Denicoff et al. (1997b) compared carbamazepine, lithium and the combination of both in 52 bipolar I patients in an open, randomized study. Patients were randomized either to carbamazepine or lithium treatment for the first year, then switched over to the alternative treatment for the second year and finally to combination treatment for the third year. Whereas the prophylactic efficacy of both monotherapies was statistically not different and overall disappointing, combination treatment with both lithium and carbamazepine was clearly superior to each monotherapy.

Looking across studies into specific sub-groups of patients where carbamazepine may be especially helpful, it seems to have clinical value in patients with incomplete response to lithium or rapid cycling (Denicoff et al. 1997b), patients with co-morbid organic (neurological) disorders (Schneck 2002) and schizoaffective patients (Elphick 1985; Goncalves and Stoll 1985; Greil et al. 1997a). ***Rating of FE: "++"***

Safety and tolerability (ST)

Tolerability problems with carbamazepine are not infrequent, and the therapeutic index is relatively low. Most frequent side effects include ataxia, nausea, dizziness, drowsiness, vomiting, blurred vision and diplopia. Less frequent are hair loss, light sensitivity, polyuria, erectile dysfunction, headaches, tinnitus, dry mouth and constipation. Severe and potentially life threatening adverse events include allergic reactions (Steven–Johnson Syndrome), hyponatraemia, liver failure, agranulocytosis and other blood dyscrasias with increased risk of bleeding.

Carbamazepine is teratogenic with an estimated risk of neural tube defects of 0.5–1%, and should be avoided during pregnancy (FDA pregnancy category "D") (Ernst and Goldberg 2002). ***Rating of ST: "–"***

Prevention of suicide (PSu)

There are only sparse data about effects of carbamazepine on suicide prevention. Data from the MAP study (Thies-Flechtner et al. 1996; Greil et al. 1997b) and from the SFBN (Born et al. 2005) suggest that it is less effective than lithium in preventing suicide and suicidal ideation; on the other hand, there is no evidence that carbamazepine may enhance suicide risk. ***Rating of PSu: "0"***

Practicability (PR)

Carbamazepine is in most countries available as tablets and oral solutions. Thus, there is a choice of applications. The recommended plasma concentrations for recurrence prevention are 4–12 mg/l (with slight variations depending on laboratories), though this recommendation is extrapolated from data in epileptic patients. When used purely for prophylactic reasons in euthymic patients it should be tapered in slowly; when initiated in acute mania, faster loading strategies can be applied (Weisler et al. 2006).

When used in combination treatment, a major disadvantage of carbamazepine is the induction of different members of the cytochrome P450 family (Spina et al. 1996). This may cause an increased metabolism of different antidepressants and antipsychotics, including olanzapine (Tohen et al. 2008), quetiapine (Fitzgerald and Okos 2002) and risperidone (Yatham et al. 2003) leading to reduced effectiveness. In addition, carbamazepine shows significant interactions both with valproate and lamotrigine. Carbamazepine also interacts with contraceptives potentially causing unwanted pregnancy. ***Rating of PR: "–"***

Recommendation grade (RG)

Carbamazepine has CE "B" evidence for preventing any mood episode in non-enriched samples, preventing mania in one study more effective than lithium, resulting in a ***Recommendation grade for PNES: RG "3".*** Otherwise, evidence for long-term efficacy in other patient populations only comes from either underpowered or open studies which would result in a lower recommendation grade. The clinical usefulness is also clearly limited given problems with tolerability and a high interaction potential.

Cariprazine: see "Other atypical antipsychotics used in bipolar disorder"
Clozapine: see "Other atypical antipsychotics used in bipolar disorder"
Gabapentin: see "Other anticonvulsants used in bipolar disorder"

Lamotrigine

Prevention of TEE in enriched samples (PES)

Two RCTs provided proof of lamotrigine' s efficacy in preventing TEE in patients who had been treated openly with lamotrigine for a minimum of 8 weeks before randomization to double-blind continuation on lamotrigine, or switch to lithium or placebo (Bowden et al. 2003; Calabrese et al. 2003). Enrichment for lamotrigine in these studies was primarily for tolerability; patients could be stabilized during open treatment with any other treatment in parallel with titrating lamotrigine. However, they needed to maintain stability for at least 4 weeks before randomization, being on lamotrigine monotherapy for at least 1 week. Both studies were conducted in bipolar I patients only, with not more than six episodes in the year prior to study, and having an index episode of either mania or hypomania (Bowden et al. 2003) or depression (Calabrese et al. 2003). Both studies showed significant separation in time to intervention for a mood episode, the primary outcome, for lamotrigine and lithium from placebo. Lamotrigine was also superior to placebo in both studies for time to

intervention for depression, but not for mania or hypomania, whereas lithium outperformed placebo for hypomania/mania prevention, but not for depression. However, the studies were not primarily powered to show such a difference for lithium. In a pooled analysis of the two studies (Goodwin et al. 2004), lamotrigine was superior to placebo in all three outcomes, time for intervention for any mood episode, (hypo)mania and depression. The hazard ratio for a manic/hypomanic recurrence in the pooled data analysis was 0.642 (95% CI 0.427–0.966, $P = 0.033$). Of special interest is also a secondary analysis of these studies by Calabrese et al. (2006) trying to separate relapses from recurrences. The studies had a reasonable requirement for stabilization (at least 4 weeks with multiple checks), and both lamotrigine and lithium were more effective than placebo in delaying the time to intervention for any mood episode (depression, mania, hypomania, or mixed) when relapses that occurred in the first 90 days were excluded from the analyses ($P = 0.002$, lamotrigine vs. placebo; $P = 0.010$, lithium vs. placebo).

However, when applying a MOAT-BD analysis (see subsection "What do we want to measure?") to the two lamotrigine maintenance studies, the clinical utility of lamotrigine appears less favourable. The MOAT-BD analyses indicate no benefits from lamotrigine for mania, no differences in groups for time in remission in the recently depressed study, and partial benefit for lamotrigine solely for subsyndromal depression in the recently depressed study (C. Bowden, personal communication, 30.5.2012).

In clinical practice, lamotrigine appears to be prescribed mostly in patients with predominant depressive polarity and in bipolar II patients (Grande et al. 2012a). For clinicians, a crucial question is whether they can predict response to guide their treatment choice. A Canadian research group looked into 164 patients with either good lamotrigine or lithium response (Passmore et al. 2003). The course of illness in lamotrigine responders was rapid cycling or chronic, while episodic in responders to lithium, and lamotrigine-responders had a higher comorbidity with panic disorder and substance abuse compared to lithium responders. The relatives of lithium responders had a significantly higher risk of bipolar disorder, while relatives of lamotrigine responders had a higher prevalence of schizoaffective disorder, major disorder and panic attacks.

Thus, we would consider a ***CE for the prevention of manic episodes in ES "D"*** with single studies (and MOAT-BD analyses) failing, but combined analysis supporting it. The ***CE to prevent any episode and depressive episodes in ES is "A".***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any RCT with a blinded and/or placebo-controlled design testing lamotrigine in non-enriched samples. ***CE: "F"***

Prevention of TEE in rapid cyclers (PRC)

Two studies have focused on lamotrigine's efficacy in rapid cycling bipolar disorder, of which one has been published. In this double-blind study (SCAA2012) lamotrigine was added to current therapy of rapid cycling bipolar I and II disorder patients. Lamotrigine was slowly titrated and psychotropic drugs other than lithium or valproate were tapered over a 6–8-week open period. Patients with HAM-D scores ≤ 14 and MRS ≤ 12 entered a 26-week blinded phase with immediate discontinuation of lamotrigine if randomized to placebo. Fifty-six percent of placebo-treated and 50% of lamotrigine-treated patients continued to receive additional lithium or divalproex during the blinded, randomized phase (Calabrese et al. 2000).

Time to additional pharmacotherapy for emerging symptoms was the primary outcome measure. Interestingly, 80% of additional pharmacotherapy was commenced for depressive symptom, but the specific drugs added were not reported. Overall and in bipolar I subjects, lamotrigine was not more effective than placebo over 6 months. On a secondary measure, stability without relapse on monotherapy for 6 months, bipolar II patients, but not bipolar I patients, had significantly better outcomes on lamotrigine than placebo. However, the positive effect of lamotrigine in bipolar II disorder was a post-hoc finding and related to reduction of depression only. Further post-hoc analyses revealed that subjects taking lamotrigine were also 1.8 times more likely than those taking placebo to achieve euthymia, as measured by the Life chart method (Denicoff et al. 2002), for at least once per week over 6 months (95% CI = 1.03–3.13). Subjects taking lamotrigine also had an increase of 0.69 more days per week being euthymic as compared with those taking placebo ($P = 0.014$) (Goldberg et al. 2008).

A second, negative study in rapid cycling bipolar II patients (SCAB2005) was not published separately but is reported on the GSK web site (www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId = SCAB2005&studyId = 8462FC12-9812-4B49-8DF4-B095BAAC08BA&compound=lamotrigine) and mentioned in a review (Goldsmith et al. 2003). With two negative studies in rapid cycling patients – despite a few positive secondary outcomes, mainly in Bipolar II patients – the ***CE for PRC would be "E".***

Further evidence (FE)

van der Loos et al. (2009) conducted a RCT for the combination treatment of lithium + lamotrigine vs. lithium + placebo in patients with acute bipolar depression and insufficient response to lithium monotherapy (see also Grunze et al. 2010). Patients stabilized after 8 weeks or after 16 weeks following addition of paroxetine were then included in a 1-year, double-blind follow-up study. Fifty-five subjects (30 on lamotrigine + lithium, with four subjects on additional paroxetine, 25 on lithium + placebo, with six subjects on additional paroxetine) were included. During follow-up the efficacy of lamotrigine was maintained: time to relapse or recurrence was longer for the lamotrigine group (median time 10.0 months (CI: 1.1–18.8)) vs. the placebo group (3.5 months (CI: 0.7–7.0)), but no formal statistical test was performed as numbers of subjects were low and thus the probability of statistical error high (van der Loos et al. 2011). The unequally distributed use of paroxetine between groups to achieve remission in the first place also makes an interpretation of results difficult. However, the study adds to evidence for the usefulness of lamotrigine combination treatment in enriched samples (in this case for tolerability and response in acute depression).

Licht et al. (2010) compared lamotrigine to lithium under conditions more similar to clinical routine conditions than in ordinary RCTs. Adult bipolar I disorder patients with an index episode requiring treatment were openly randomized to lithium ($n = 78$) or to lamotrigine ($n = 77$; up-titrated to 400 mg/day. Patients could continue up to 6 months after randomization with additional psychotropics and monotherapy failures (primary end-point) were not recorded until after that point in time. Thus, this study deals with a reasonably mood- stable population. The non-restrictive design also allowed that a subgroup of patients could be followed for more than 5 years. The primary outcome measure was time to any of the predefined endpoints indicating insufficient maintenance treatment. This included psychotropic treatment in addition to study drugs and benzodiazepines still required at month 6 (after randomization), hospitalization still required at month 6 (after randomization), psychotropic treatment for at least 1 week (in addition to study drugs and benzodiazepines) required after month 6 (after randomization) or hospitalization lasting at least 1 week required after month 6 (after randomization). For the primary outcome measure, any recurrence independent of polarity, the relative risk (RR) for lamotrigine relative to lithium was 0.92 (95% CI: 0.60–1.40). When the primary endpoints were broken down by polarity, the RR (lamotrigine relative to lithium) for mania and depression were, respectively, 1.91 (95% CI: 0.73–5.04) and 0.69 (95% CI: 0.41–1.22). There was no between-group difference in terms of staying in study (RR: 0.85 (95% CI: 0.61–1.19)). Most treatment failures occurred within the first 1.5 years of treatment, and, among patients followed for at least 5 years, practically no patients were maintained successfully on monotherapy with either of the drugs. In summary, no differences in maintenance effectiveness between lithium and lamotrigine were demonstrated, but numbers might still have been too low to find such a difference. Overall, the study can be seen as supportive of the use of lamotrigine.

In potential contrast to this finding, the Danish registry study by Kessing et al. (2011a) noted that lithium might still be more effective than lamotrigine over long observation periods, although this finding may be influenced by selection bias (see section on "Lithium – Further evidence") .

Finally, three recent meta-analyses of the placebo-controlled studies support the findings for lamotrigine in enriched samples (Smith et al. 2007; Beynon et al. 2009; Vieta et al. 2011). ***Rating of FE: "+"***

Safety and tolerability (ST)

Lamotrigine is usually very well tolerated which additionally makes it an attractive choice for long-term treatment. The combined analysis of the two RCT's by Goodwin et al. (2004) showed that during the open label run-in phase a skin rash occurred in 11% of patients. During double-blind treatment, side effects with lamotrigine were not more frequent than with placebo: headache (19% lamotrigine and placebo, 15% lithium), nausea (11% placebo, 14% lamotrigine, 20% lithium) and diarrhoea (8% placebo, 7% lamotrigine, 19% lithium).

During double-blind treatment the incidence of benign rash was similar in all treatment groups. There were two cases of a more severe skin reaction. A case of a maculopapular facial rash required hospitalization, and one case of a mild Stevens–Johnson syndrome occurred 31 days after initiating lamotrigine, but hospitalization was not required. Overall, the incidence of a serious rash appears low with the recommended slow titration scheme. An analysis of placebo-controlled studies with lamotrigine in different indications demonstrated that the incidence of serious rashes, including Stevens–Johnson syndrome, in clinical trials of bipolar and other mood disorders is approximately 0.08% (0.8/1000) in adult patients on lamotrigine monotherapy and 0.13% (1.3/1000) in adult patients receiving lamotrigine as adjunctive therapy (Seo et al. 2011).

A major advantage of lamotrigine for long-term treatment is the benign metabolic profile and the lack of weight gain.

Major congenital defects have been described with lamotrigine in 1.0–5.6% of pregnancies. Despite an FDA pregnancy category "C" rating, a teratogenic risk with lamotrigine treatment is suggested at doses exceeding 200 mg/day (Morrow et al. 2006). Case registers also indicate that lamotrigine is associated with a 10–24 times increased risk of oral cleft versus the general population (Viguera et al. 2007), and folic acid supplementation is recommended as with other antiepileptic drugs.

In summary, the tolerability and long-term impact on weight and metabolic parameters of lamotrigine is good, but there are concerns with birth defects and allergic reactions. ***Rating of ST: "+"***

Prevention of suicide (PSu)

The FDA report on the relationship between antiepileptics and suicidal behaviour (US Food & Drug Administration 2008) included 199 RCTs concerning 11 drugs: carbamazepine; divalproex; felbamate; gabapentin; lamotrigine; levetiracetam; oxcarbazepine; pregabalin; tiagabine; topiramate; zonisamide. For all agents, the 95% CI includes an odds ratio of 1, except that for topiramate (95% CI 1.21– 5.85) and lamotrigine (95% CI 1.03– 4.40), suggesting that, beyond reasonable doubt, only these two might put patients at a higher risk to experience a suicide-related event, a composite outcome for what was considered as suicidal ideation or behaviour.

The FDA analysis does not account for a number of methodological problems that limit its suitability for bipolar disorder patients (Fountoulakis et al. 2012). Adverse event outcome data from RCTs were used, instead of systematically collected data, the sample sizes were small and the number of events was limited. In most of the epilepsy trials (92%) included in the final analysis, the study drug was add-on therapy and although 11 antiepileptics were included in the conclusion, only two of the drugs showed a statistically significant increase in risk of suicidal ideation. Most important, the potentially modifying effect of comorbid mental disorders was not taken into account, and, e.g., the comorbid presence of a depressive syndrome with suicidality might have aided the use of lamotrigine.

As a matter of fact, Gibbons et al. (2009) could not corroborate the FDA warning when examining data on patients with bipolar disorder receiving antiepileptic drugs (AED). They looked for suicide attempts in a cohort of 47,918 patients with bipolar disorder with a minimum 1-year window of information before and after the index date of their illness. There was no significant difference in suicide attempt rates for patients treated with an AED (13 per 1000 person-years, PY) vs. patients not treated with an AED or lithium (13 per 1000 PY). Treatment with AED appeared suicide protective as in AED-treated subjects, the rate of suicide attempts was significantly higher before treatment (72 per 1000 PY) than after (13 per 1000 PY). For lamotrigine, the figures were 39 suicide attempts per 1000 PY before and 13 per 1000 PY after treatment initiation. The authors concluded that, as a class, AEDs do not increase risk of suicide attempts in patients with bipolar disorder relative to patients not treated with an AED or lithium.

Also in contrast to the FDA findings in predominantly epileptic patients, Born et al. (2005) found that compared to lithium, the relative risk of suicidal ideation in a cohort of 128 bipolar patients was numerically slightly higher for valproate and carbamazepine, but lower in patients treated with lamotrigine, without reaching statistical significance. ***Rating of PSu: "0"***

Practicability (PR)

Lamotrigine is in most countries available as tablets (ranging from 2 to 200 mg) and as water-soluble tablets. The recommended plasma levels for safety (not efficacy) in epilepsy are 3–14 mg/l (11.7–56.4 μmol/l), with slight variations depending on laboratories (Neels et al. 2004), and there is a linear relationship between dose and plasma concentration. Titration to the recommended dosage in bipolar maintenance of 200 mg/day takes 6 weeks. Lamotrigine has significant plasma level interactions with carbamazepine, valproate and with the ethinyl estradiol contained in oral contraceptives, which means that the lamotrigine dosage should be doubled (in the presence of carbamazepine), increased (with oral contraceptives) and halved (with valproate) (Johannessen and Landmark 2010). On the other hand, lamotrigine might increase the levonorgestrel clearance and, by this, change FSH and LH serum levels which might make contraception unreliable. ***Rating of PR: "0"***

Recommendation grade (RG)

Lamotrigine has efficacy in the recurrence prevention of any episode in enriched samples (CE:A) as proven by two RCTs, clearly more pronounced for prevention of depression (CE:A), with additional weaker evidence for mania (CE:D). However, the study by Kessing et al. (2011a), the MOAT analyses and the lamotrigine–valproate combination study (Bowden et al. 2012) all soften the evidence even for depressive prevention. Lamotrigine provides partial,

i.e., subsyndromal depression benefit in both MOAT analyses of the RCTs. There is CE "C" evidence for rapid cycling patients. In non-enriched samples, the CE is "F" as no informative studies have been conducted. Further evidence rated "+", and good tolerability also support the use of lamotrigine. However, there are minor concerns with safety in pregnancy and practicability (slow titration scheme).

Thus, for patients tolerating lamotrigine where the predominant treatment goal is to prevent depressive recurrences or any episode, the task force decided to assign a RG of "1". However, some doubts about lamotrigine's clinical utility remain as explained above. For all other groups of patients, the long-term use of lamotrigine is not supported by solid evidence, but should not be excluded in specific clinical scenarios such as non-response, or tolerability or safety problems with other long-term treatments.

Lithium

Following Baastrup and Schou's (1967) observation in 1967 of lithium decreasing the frequency of episodes in bipolar disorder (and in recurrent unipolar depression), a number of early placebo-controlled RCTs (1970–1978) preliminary established the long-term efficacy of lithium in bipolar disorder. These studies have been extensively reviewed, e.g., by Goodwin and Jamison (2007) or Maj (2000), and more recently by Licht (2012). These studies built the foundation of the widespread clinical use of lithium in bipolar disorder for decades, despite some evidence that they may have overestimated the clinical utility of the drug (Maj et al. 1998) and its restrictions by long-term physical health issues (Gitlin 1999). However, the vast majority of these early prophylaxis studies would nowadays not fulfil methodological criteria to be considered as sufficient scientific proof of evidence. Thus, we will not give them extensive consideration. The only exception is the study by Prien et al. (1973a); the majority of good evidence now stems from studies published from 2000 onwards, which used lithium as an established standard comparator in placebo-controlled RCTs of other drugs of interest. This should not derogate the merits of the early pioneers in lithium research as, in the end, modern studies confirmed what had been suggested before.

However, the treasure trove of experience to which also older studies contribute is of great clinical value as it allows predicting potential response to lithium. Putative predictors of favourable response to lithium (family history of bipolar disorder, Mania-Depression-Free interval course, no rapid cycling, no alcohol or drug abuse and, especially, good adherence) should also be considered when recommending treatment with lithium (Grof 1979).

Prevention of TEE in enriched samples (PES)

In 1970, Baastrup et al. (1970) conducted a placebo-controlled maintenance discontinuation study with lithium in stable female outpatients who had suffered in the past from recurrent unipolar depression or bipolar disorder. In that way the sample was enriched on stabilization, albeit not necessarily on acute response to lithium. Questionable applying today's ethical standards, patients were not made aware that they participated in a study and that their lithium might be substituted with placebo. For this reason, investigators decided to keep observation time to an absolute minimum and stopped the study after 5 months when the predetermined significance level ($P < 0.001$) conducting sequential analysis of pairs matched for number of previous episodes was achieved. The mean duration on trial medication for patients without relapse was 19.7 weeks for placebo and 20.3 weeks on lithium. None of the 45 lithium continuation patients relapsed, but 21 out of 39 who were switched to placebo. Secondary subanalysis of the bipolar patients revealed that 12 of the 22 patients on placebo relapsed (35%), seven of them into a manic, and five into a depressive episode, whereas all 28 lithium continuation patients remained well. As by trial design, the overall relapse rate was significantly lower with lithium ($P > 0.001$); the authors did not supply statistical analyses of manic and depressive relapses separately. The clear limitations of the study are the short observation period under double blind conditions, and inclusion of females only.

Soon afterwards, Prien et al. (1973a) conducted a maintenance study in 205 patients (101 on lithium, 104 on placebo) who had been post-acutely stabilized on lithium (serum levels 0.5–1.5 mmol/l) after a manic episode treated with lithium and/or other drugs. Thus, the study sample was enriched at least for post-acute stabilization. Prien used a composite outcome distinguishing between "severe relapse" (requiring hospitalization) and "moderate relapse" (requiring additional medication). For clarification, a distinction between relapse and recurrence was not made in this paper; any new mood episode was termed "relapse". Over 2 years, 67% of patients on placebo had at least one relapse compared to 31% on lithium ($P < 0.001$), 29% in the placebo group and 12% in the lithium group had two or more severe recurrences of mood episodes, which was non-significant. When combining severe and moderate relapses the proportion of patients remaining relapse-free was significantly

higher in the lithium group (57 vs. 19%, $P<0.001$). Given a high pre-existing manic polarity in the study subjects (Prien et al. 1974) and that the index episode was mania, it is not surprising that 64% of relapses with lithium were manic and 24% depressive, the rest was clustered as mixed or schizo-affective. Distribution between polarity of relapse was similar for placebo; however, statistical significance for a superiority of lithium was only achieved for manic, not depressive relapses (Prien et al. 1974). A problem with the study is that it is, strictly speaking, not entirely double-blind, although rater and patients were blinded to medication. However, the treating physicians, responsible for managing any relapse, were aware of the identity of subjects' medication. They were also instructed to increase the dose of lithium when a patient on lithium started to show symptoms. The importance of this issue is that it means that the treatment conditions of the two groups were not entirely comparable, and lithium was dosed not only in response to plasma levels, but also treatment success.

In a second study by Prien et al. (1974), already described in the section on "Antidepressants", lithium was significantly better than placebo and imipramine in preventing new affective episodes ($P<0.01$, using Fisher's exact probability test). The difference between the lithium and imipramine groups was due almost entirely to the higher incidence of manic episodes in the group receiving imipramine ($P<0.05$) whereas the incidence of depressive episodes was not statistically different ($P>0.05$). The difference between the lithium and placebo groups was due to both manic and depressive episodes: both, types of episodes were about three times as prevalent in the placebo group. However, the difference between the lithium and placebo groups reached statistical significance only for depressive episodes ($P<0.05$). The lack of statistical significant separation for new manic episodes can be explained by the lack of power and the characteristics of patients included. New depressive episodes clearly prevailed in the lithium and placebo group (but not in the imipramine group), reflecting a pre-existing depressive polarity in the participants.

Further lithium discontinuation studies were conducted in the 1970s (Melia 1970; Cundall et al. 1972; Hullin et al. 1972; Stallone et al. 1973; Fieve et al. 1976), but each of them has methodological shortcomings, e.g., mixed patient populations, crossover designs, small numbers and observation period, unclear enrichment, or incomplete or mixed outcome reporting which disqualifies them from being utilized as higher ranked evidence. Nevertheless, they can be seen as supportive further evidence (FE) for the use of lithium.

In summary, we identified several placebo-controlled studies supporting the efficacy of lithium for PES. Three of them (Baastrup et al. 1970; Prien et al. 1973a, 1974) appear reasonably informative, but still have not the same rigor in methods and reporting as other more recent studies to which we assigned top CE ratings. Thus, the task force felt that a CE rating of "A" would be not adequate, but, considering the combined bulk of evidence, the ***CE to prevent manic, depressive and any episode in PES should be "B".***

Prevention of TEE in non-enriched samples (PNES)

A total of four large RCTs in which lithium was used as an internal comparator for assay sensitivity has been conducted since the 1990s. Different from the substances under investigation in three out of the four studies (two with lamotrigine, one with quetiapine) the lithium arm was incorporated in a non-enriched way, meaning that lithium (in contrast to the others) was tested independently of showing any mood-stabilizing effect and tolerability during the index episode prior to randomization. Also, lithium was not favoured by any discontinuation effect since this influenced the lithium and placebo group equally. The first study comparing valproate, lithium and placebo failed for both valproate and lithium (Bowden et al. 2000), most likely due to methodological shortcomings (Bowden et al. 1997). However, all subsequent studies confirmed lithium's efficacy. On a significant level, lithium separated from placebo in time to intervention for any recurrence, manic and depressive recurrences in the quetiapine study (Weisler et al. 2011), and for any recurrence and for manic recurrence in the two lamotrigine studies (Bowden et al. 2003; Calabrese et al. 2003), as well as in a combined analysis of these studies (Goodwin et al. 2004). Lithium did not separate from placebo for prolonging time to a depressive episode in neither lamotrigine study, nor in the combined analysis ($P=0.325$). Whereas lithium's efficacy in preventing new manic episodes in non-enriched samples is confirmed in three of four studies, the evidence for preventing new depressive episodes is, at the moment, at odds.

What are, besides enrichment, likely reasons for the diverging results for lithium preventing new depressive symptoms between the study of Prien et al. (1974), mentioned in the previous paragraph, the quetiapine study and the lamotrigine studies? Prien et al.'s study probably also separated because they limited enrolment to severely ill hospitalized patients with bipolar I depression. In the lamotrigine study, lithium might have not separated because patients entering the study were less seriously ill outpatients.

The patients in the quetiapine study, which included a mixture of in- and outpatients, might have been less severely ill, too. However, this study recruited more than twice as many patients on lithium and placebo than the two lamotrigine studies together, favouring the detection of a significant difference.

Thus, given this evidence from three positive studies, the ***CE to prevent any episode and manic episodes in PNES is "A".*** With conflicting results, the ***CE to prevent depressive episodes in PNES is "D".***

Prevention of TEE in rapid cyclers (PRC)

The prophylactic use of lithium in rapid cycling patients has been discouraged for a long time based on the observation of insufficient acute and prophylactic efficacy in these patients (Dunner and Fieve 1974; Dunner 1998). Based on case series in rapid cyclers, valproate has been preferred over lithium for a long time. However, the direct head-to-head comparison of lithium and valproate in a double-blind, randomized design did not reveal a statistical significant advantage of valproate over lithium (Calabrese et al. 2005). Unfortunately, attrition in this trial was high (76% premature discontinuations) as even with open combined lithium + valproate treatment the fast majority of patients did not meet stability criteria sufficient for randomization. So, in the end, this study is inconclusive.

Other than this study, we found only one further double-blind RCT for lithium in rapid cycling patients, comparing over 6 months lithium monotherapy with combined lithium/valproate treatment in bipolar patients with comorbid substance abuse or dependence (Kemp et al. 2009). Patients had been stabilized on the combination treatment, and then valproate was withdrawn and replaced by placebo in half of the subjects. Again, attrition during open-label stabilization was high with 79% drop outs, so that only 31 patients could be randomized. In all outcome parameters (any relapse, manic or depressive relapse), the authors found no advantage of the combination versus lithium monotherapy.

A positive interpretation of these two studies would be that lithium is at least as good as the "standard" valproate; a more realistic interpretation would be that neither treatment is particularly efficacious in preventing new mood episodes in rapid cycling patients. However, as these studies lack a placebo arm and there is no clear proof for efficacy of the comparator valproate in RC patients, a CE of "E", meaning negative evidence, would not be justified, also keeping in mind that there have been no RCTs demonstrating a drug–placebo difference for any compound in rapid-cycling patients. Therefore, the appropriate ranking would be a ***CE: "F" for PRC.***

Further evidence (FE)

Several meta-analyses confirm the prophylactic efficacy for lithium in preventing any relapse and manic relapses (Geddes et al. 2004; Smith et al. 2007; Beynon et al. 2009; Vieta et al. 2011). However, as all were published too early to include the latest study of Weisler et al. (2011), and since they primarily were based on the other studies reviewed here above, they do not yet support the efficacy of lithium in preventing bipolar depression. It can be assumed that this will change in future metaanalysis using today's base of knowledge.

In the MAP study (Greil et al. 1997b) (see section on "Carbamazepine") differences in TEE in non-enriched samples were not different between lithium and carbamazepine on a statistically significant level (Kleindienst and Greil, personal communication 26.4.2012), but composite outcomes were in favour of lithium. Similarly, in the study by Hartong et al. (2003) lithium was numerically more effective than carbamazepine but just missing significance.

In a head-to-head comparison, olanzapine ($n = 217$) was compared to lithium ($n = 214$, target blood level: 0.6–1.2 mmol/l) in a double-blind, 1-year study in patients that were stabilized for 6–12 weeks on the combination of both agents given while manic, and then randomized to continuation on either substance (Tohen et al. 2005). The primary outcome was testing non-inferiority of olanzapine against lithium for the occurrence of a TEE. Symptomatic relapse/recurrence (score $>$ or $= 15$ on either the YMRS or HAM-D scale) occurred in 30.0% of olanzapine-treated and 38.8% of lithium-treated patients, and non-inferiority of olanzapine relative to lithium was established. Secondary results showed that compared with lithium, olanzapine had significantly lower risks of manic episode and mixed episode relapse/recurrence, but no difference was observed for depressive recurrences. Both agents were comparable in preventing recurrence of depression. As the primary hypothesis of this study was non-inferiority of olanzapine versus lithium (and not vice versa), and statistical assumptions were made accordingly, we cannot use it as level "B" evidence for lithium (but for olanzapine). Nevertheless, this company sponsored study also supports the usefulness of lithium in long-term treatment relative to olanzapine.

In the multinational BALANCE study (Geddes et al. 2010) lithium was tested against valproate and the combination of both for 2 years. A total of 330 bipolar I patients were randomly allocated to

open-label lithium monotherapy (plasma concentration 0.4–1.0 mmol/l, $n = 110$), valproate monotherapy (750–1250 mg, $n = 110$), or both agents in combination ($n = 110$), after an active run-in of 4–8 weeks on the combination. Thus, the study was enriched for tolerability of both lithium and valproate. The primary outcome was initiation of new intervention for a TEE. Fifty-nine (54%) of 110 subjects in the combination therapy group, 65 (59%) of 110 in the lithium group, and 76 (69%) of 110 in the valproate group needed intervention for a new mood episode during follow-up. Lithium was significantly more effective than valproate, whereas there was no significant difference between lithium monotherapy and the combination treatment. Hazard ratios (HR) for the primary outcome were 0.59 (95% CI 0.42–0.83, $P = 0.0023$) for combination therapy versus valproate, 0.82 (0.58–1.17, $P = 0.27$) for combination therapy versus lithium, and 0.71 (0.51–1.00, $P = 0.0472$) for lithium versus valproate. This study clearly supports the use of lithium, however, it felt short of being counted towards higher evidence (large non-inferiority study against an established comparator) as, strictly speaking, valproate cannot be considered as established comparator for maintenance treatment based on its lack of positive controlled evidence from single RCTs (see section on "Valproate").

Two studies compared lamotrigine with lithium. The already cited study by Licht et al. (2010) found no difference in effectiveness for observation periods up to 5 years (see section on "Lamotrigine").

Kessing et al. (2011a) compared rates of switch to, or add on of, another psychotropic, and rates of psychiatric hospitalization for patients treated with lamotrigine or lithium in clinical practice. From the Danish registers they identified 730 patients who received lamotrigine and 3518 patients received lithium between 1995 and 2006. The overall rate of switch to or add on of another psychotropic was higher for lamotrigine compared with lithium (HR = 2.60, 95% CI: 2.23–3.04), regardless of whether the index episode was depressive, manic, mixed or remission. In addition, the overall rate of psychiatric hospitalization was increased for lamotrigine compared with lithium (HR = 1.45, 95% CI: 1.28–1.65), as were the rates for patients with a depressive (HR = 1.31, 95% CI: 1.01–1.70) and patients with a manic (HR = 1.65, 95% CI: 1.31–2.09) index episode. Rates did not differ significantly between the drugs for patients with a mixed index episode and for patients in remission. Kessing et al. concluded that, in daily practice, lithium is still superior to lamotrigine in long-term treatment. However, when interpreting these data, the risk of selection bias should be taken into account.

A recent NIMH funded multisite comparative effectiveness study was conducted to address whether tolerable doses of lithium either alone or added to other medications improved 6-month outcomes of clinically symptomatic (CGI-S ≥ 3) bipolar I and II patients (Nierenberg et al. 2009). The LiTMUS project compared lithium plus optimized treatment (OPT) with OPT without lithium. The study retained over 80% of subjects for the full 6-month trial. All planned outcomes found no significant differences between the two regimens despite assessing outcomes in the patients on a broad range of measure. The study, not yet published, may have enrolled patients with more depression weighted illnesses, which, given the mixed evidence of lithium prophylaxis for depression could have contributed to the negative result for low dose lithium. Another issue might be that a 6-month study duration is too brief for lithium to establish its full effectiveness.

To some degree unique, lithium seems to enable a fair proportion of bipolar patients to achieve and maintain full (also functional) remission. Paul Grof proposed the term "excellent lithium responders" for patients in whom lithium monotherapy has dramatically changed their lives by the total prevention of further episodes. He found that the best response to lithium is associated with clinical features of an episodic clinical course, complete remission, bipolar family history and low psychiatric comorbidity similar to those described by Kraepelin as *manisch-depressives Irresein* (Grof 2010). Rybakowski et al. (2001) demonstrated that patients on lithium monotherapy who do not experience affective episodes for 10 or more years (excellent lithium responders) make up one-third of lithium-treated patients. Important for full functional recovery, excellent lithium responders seem to preserve their cognitive function similar to control subjects (Rybakowski and Suwalska 2010). ***Rating for FE: "++"***

Safety and tolerability (ST)

Lithium has a low therapeutic index, with serum levels not more than double the therapeutic levels occasionally leading to serious CNS toxicity, potentially lethal. Dehydration may put patients under such risk. Benign side effects of lithium are also well known and in their majority dependent on plasma level. Up to 75% of patients on lithium experience some side effects, but most are minor (transient metallic taste in mouth, polyuria, polydipsia, weight gain, mild oedema, concentration difficulties, sedation) and can be reduced or eliminated by dose adjustment or dosage schedule. Mild CNS symptoms with higher plasma levels of lithium are frequent. Tremor affects up to 65% of patients treated

with lithium and a severe tremor may be a sign of toxicity. Nausea, diarrhoea or blurred vision may also be signs of toxicity (Freeman and Freeman 2006). These side effects might be more exaggerated in combination treatments with increased risk of neurotoxicity, e.g., typical antipsychotics (Sachdev 1986) or carbamazepine (Shukla et al. 1984), or in patients with pre-existing neurological conditions (Moskowitz and Altshuler 1991).

From the patient perspective, in addition to the just mentioned adverse effects, the risk of weight gain and the risk of mental side effects (cognitive impairment and/or reduced intensity of perceptions and emotions) may be most crucial (Licht 2012). The discussion whether lithium (in non-toxic plasma levels) can cause cognitive impairment is controversial; patients report feeling less creative and emotionally blunted; however, psychological testing in lithium patients is not conclusive (Lopez-Jaramillo et al. 2010b). On the other hand, there is some evidence from animal research that lithium might delay Alzheimer's disease (Young 2011; Zhang et al. 2011).

Long-term lithium treatment affects kidney function (Tredget et al. 2010), and after many years of treatment, renal impairment may occur (Bendz et al. 2010). Close monitoring of the eGRF is essential part of lithium safety measures (Jefferson 2010). Hypothyroidism is frequent with lithium treatment, and substitution treatment is often indicated. Especially women seem to be on increased risk (women 14% vs. men 4.5%) (Johnston and Eagles 1999).

Lithium's teratogenic effect rarely gives rise to not initiating lithium treatment, possibly due to the fact that the risk is well characterized and relatively low in absolute terms (Yonkers et al. 2004; Nguyen et al. 2009). Potential heart dysplasias can nowadays be detected early by routine sonography and be corrected in utero. Discontinuing lithium during pregnancy might not be justified balancing risks and benefits (Baldessarini et al. 1999c).

Lithium also has a significant, albeit infrequent, impact on parathyroid function (leading to hyperparathyroidism) and calcium levels, which is widely unappreciated (McKnight et al. 2012). ***Rating for ST: "–"***

Prevention of suicide (PSu)

Much evidence has been accumulated for a specific, suicide preventive effect of lithium, which might be independent from improvement of an affective disorder. Lithium has anti-agressive and anti-impulsive properties which might link it to anti-suicidal effects (Kovacsics et al. 2009) as shown in a metaanalysis of RCTs conducted by Cipriani et al. (2005). They found that patients who received lithium compared to other treatments were less likely to die by suicide (odds ratio (OR) = 0.26; 95% CI = 0.09–0.77). The composite measure of suicide plus deliberate self-harm was also lower in patients who received lithium (OR = 0.21; 95% CI = 0.08–0.50). There were fewer deaths overall in patients who received lithium (OR = 0.42, 95% CI = 0.21–0.87) which is in line with large observational studies as the Zurich cohort study, finding a decreased mortality from all causes with lithium (Angst et al. 2002). For more in depth information on this clinically highly relevant topic we refer the reader to the pertinent literature (e.g., Baldessarini et al. 2006; Gonzalez-Pinto et al. 2006; Müller-Oerlinghausen et al. 2006; Wasserman et al. 2012). ***Rating for Psu: "++"***

Practicability (PR)

For use in bipolar disorder, lithium is available in different salt preparations, as lithium carbonate, lithium citrate, lithium hydrogenaspartate and lithium sulfate. It is available as tablets, including extended release formulations, or droplets and syrup (lithium citrate only). There is no evidence for differences in efficacy between lithium salts; the choice of preparation is based on slight differences in tolerability and ease of administration.

In most cases, lithium is up titrated in small steps guided by individual experience and plasma level monitoring; however, it is also possible to predict the target dose by calculating the lithium clearance (Abou-Auda et al. 2008).

Due to its relatively small safety margin, plasma concentrations need to be checked on a frequent and regular basis until equilibrium in the therapeutic range has been achieved and thereafter. It is recommended to check every 3–6 months in patients with stable lithium levels and whenever the clinical status changes, physical health issues appear or co-medication that might affect lithium levels (e.g., furosemide) is introduced (Zarin et al. 2002). Renal and thyroid function should also be checked regularly, every 6–12 months depending on risks.

Plasma levels for successful prevention of mania are likely to be different from those for preventing depression. Lithium concentrations ≤ 0.6 mmol/l seemed to be ineffective preventing new manic episodes in RCTs , but may be still sufficient to prevent depression (Severus et al. 2010). Higher lithium concentrations may not necessarily protect better against depression; a post-hoc analysis of the MAP study found that lithium concentrations preceding

reappearance of depressive symptoms were significantly higher than those preceding new manic episodes (Kleindienst et al. 2007; Severus et al. 2009). A meta-review by Severus et al. concluded that "the minimum efficacious serum lithium concentration in the long-term treatment of bipolar disorder was 0.4 mmol/l with optimal response achieved at serum concentrations between 0.6 and 0.75 mmol/l. Lithium concentrations >0.75 mmol/l may not confer additional protection against overall morbidity but may further improve control of inter-episode manic symptoms. Abrupt reduction of serum concentrations of more than 0.2 mmol/l was associated with increased risk of relapse" (Severus et al. 2010). Despite the recommendations outlined here above, it should be born in mind that the optimal concentration is highly individual.

Any need to discontinue lithium often poses a problem. Especially for lithium, an increased relapse risk after its sudden discontinuation has been described (Mander and Loudon 1988) and reinstituting lithium may not always be effective (Post et al. 1992; Goodwin 1994). If necessary, it is strongly recommended that lithium maintenance is always tailed off slowly over some weeks or even months (Suppes et al. 1993).

Before lithium is initiated the patient should always be instructed carefully regarding signs of toxicity and risk situations (Licht 2012). ***Rating for PR: "–"***

Recommendation grade (RG)

Unique in comparison to the other PAs, lithium does not only score with the highest CE in the category PNES for "any relapse" and "mania", but also receives a good score (CE: "B") for PNES "depression", PES "any episode" and substantial support from ratings for FE and PSu. Undoubtedly, lithium is more difficult to use than other PAs and has safety and tolerability issues; however, these are outweighed by its overall effectiveness, so clearly the ***RG is "1"***.

Olanzapine

Prevention of TEE in enriched samples (PES)

All pivotal maintenance studies with olanzapine have been conducted in samples enriched for acute response in mania, except of one follow-up study with olanzapine, olanzapine/fluoxetine combination or placebo where the index episode was bipolar depression (Shelton 2006).

Focussing on studies which recruited patients with a manic index episode, there are four randomized, double-blind trials investigating the efficacy of olanzapine compared to placebo or lithium monotherapy as well as augmentation in maintenance therapy for prevention of relapse of affective episodes in bipolar I disorder. Enrichment for olanzapine response in these studies varied; in the olanzapine versus placebo study, all patients were previously stabilized on olanzapine monotherapy. In the olanzapine versus lithium study, enrichment was for response to combined olanzapine and lithium. Finally, in the combination treatment studies, manic patients had previously participated in an acute trial (Tohen et al. 2002b) and had responded to the combination of olanzapine and either lithium or valproate acutely.

One study compared olanzapine with placebo in bipolar I patients with a manic or mixed index episode who have responded to open olanzapine treatment (Tohen et al. 2006). The criteria for stabilization prior to randomization were quite liberal and required only two consecutive weekly visits fulfilling criteria for symptomatic remission. As pointed out by Gitlin et al. (2010) this will favour early relapse in the placebo arm due to a still on-going underlying acute episode and withdrawal of effective medication. Two hundred and twenty-five patients were randomly assigned to double-blind maintenance treatment with olanzapine or placebo ($N=136$) for up to 48 weeks. The primary measure of efficacy was time to symptomatic relapse into any mood episode. Time to symptomatic relapse into any mood episode, defined as YMRS score ≥ 15, HAM-D score ≥ 15, or hospitalization, was significantly longer among patients receiving olanzapine (a median of 174 days, compared with a median of 22 days in patients receiving placebo). Times to symptomatic relapse into manic, depressive, and mixed episodes were also all significantly longer among patients receiving olanzapine than among patients receiving placebo. The overall relapse rate was significantly lower in the olanzapine group (46.7%) than in the placebo group (80.1%); however, the RR of relapse compared to placebo was only significant for any relapse and manic or mixed relapses, but not for depression (Vieta et al. 2011). This may be due to the relatively higher risk of manic relapses in patients with a manic index episode, but could also suggest a weaker prophylactic effect of olanzapine against depressive recurrences.

A post-hoc analysis of this study also revealed similar efficacy of olanzapine in mixed patients versus placebo as with pure manic patients (Tohen et al. 2009b).

More recently, olanzapine was also used as a comparator in two placebo-controlled long-term studies involving paliperidone extended release (ER; Berwaerts et al. 2012) and risperidone long-term injectable (LAI; Vieta et al. 2012a). These studies are

especially remarkable as they support olanzapine's efficacy in RCTs which were not sponsored by the producer of olanzapine. The study of Vieta et al. was conducted in a sample of patients with a manic index episode without enrichment for olanzapine response and will therefore be considered in the next paragraph on PNES.

The study by Berwaerts et al. (2012) compared paliperidone ER, placebo and olanzapine as internal comparator for assay sensitivity for up to 24 months (for more details see section on "Paliperidone"). Post-hoc pairwise comparisons of olanzapine with placebo, and olanzapine with paliperidone ER showed that time to recurrence of any mood symptoms (the primary outcome) was significantly longer with olanzapine ($P \leq 0.001$ vs. either treatment group). The NNT for olanzapine at 12 and 24 months of treatment in the maintenance phase was 3 (95% CI: 2–5), which is one of the lowest ever reported for a maintenance study. Post-hoc pairwise comparisons of olanzapine with placebo, and olanzapine with paliperidone ER also showed that time to recurrence of manic symptoms was significantly longer in the olanzapine group compared with the placebo ($P \leq 0.001$), or paliperidone ER groups ($P = 0.014$). Recurrence of depression occurred in 18% ($n = 26$) of those on placebo and 24% ($n = 35$) on paliperidone ER, and 12% ($n = 10$) on olanzapine; testing for significance has not been reported, but due to the small number of depressive recurrences such testing is unlikely to demonstrate a significant difference.

Two studies compared olanzapine head-to-head to other PAs without a placebo control. The study comparing olanzapine with lithium has been described in the section on lithium. It supports the long-term use of olanzapine to prevent any episode, mania and depression in patients with a manic or mixed index episode. The sample used in this study is as much enriched for tolerability to olanzapine as it is for lithium, and partly for acute efficacy as we cannot make a distinction who responded to olanzapine, lithium or both during acute treatment.

The other study (Tohen et al. 2003a) is an extension study of an acute double-blind head-to-head comparison of olanzapine and valproate (Tohen et al. 2002a). Patients remitting during the acute 3-week study were followed up for another 44 weeks without re-randomization. As valproate cannot be considered as a well-established comparator for prophylactic treatment (see section on "Valproate") this study is listed in the category "Further evidence".

The combination of olanzapine + lithium or valproate versus lithium or valproate + placebo was tested in an 18-month RCT (Tohen et al. 2004). Ninety-nine patients who received combination treatment during a preceding acute phase trial (Tohen et al. 2002b) and had achieved syndromic remission of both mania and depression were randomly re-assigned at visit 8 (week 6 of the acute phase) in a 1:1 ratio to receive an additional 18 months of double-blind therapy, consisting of either olanzapine (flexible dosage range of 5–20 mg/day) in combination with lithium or valproate (combination therapy), or placebo added to lithium or valproate (monotherapy). Forty-one of the 99 subjects had a rapid cycling course and 26 exhibited psychotic features in their index episode of mania which may have contributed to a high rate of premature discontinuation. Due to the high attrition rate with 78 of 99 subjects discontinuing before study end, the results are inconclusive. The treatment difference in time to relapse into either mania or depression was not significant for syndromic relapse (median time to relapse: combination therapy 94 days, monotherapy 40.5 days; $P = 0.742$), but was significant for symptomatic relapse (combination therapy 163 days, monotherapy 42 days; $P = 0.023$).

This, we would consider a ***CE for the prevention of manic episodes in ES of "A"***, and also the ***CE to prevent any episode in ES is "A".***

The CE to prevent new depressive episodes in ES is "B" based on the placebo-controlled study by Tohen et al. (2006). We felt that the lack of a statistical significant signal in the other RCTs is rather a methodological artefact than contradicting efficacy of olanzapine in preventing depression. These studies were not designed to show such a separation, neither from the patients included, nor from the numbers assigned to the respective olanzapine arms.

Prevention of TEE in non-enriched samples (PNES)

A RCT by Vieta et al. (2012a) compared risperidone long acting injectable (LAI), placebo and olanzapine as internal comparator for assay sensitivity. After a 12-week open-label period with risperidone LAI ($n = 560$), patients who did not experience a recurrence entered an 18-month randomized, double-blind period with risperidone LAI ($n = 132$) or placebo ($n = 135$); a third treatment arm ($n = 131$) was randomized to oral olanzapine (10 mg/day + placebo injections) for reference and exploratory comparisons. Thus, different from the other studies, this study did not enrich for acute olanzapine response as patients were stabilized on risperidone. The primary efficacy endpoint was time to recurrence of any mood episode. For a detailed description of the outcome for risperidone LAI the reader should refer to the section on risperidone. Time to recurrence of any

mood episode was significantly longer with oral olanzapine than with placebo in both the prespecified analysis and analysis stratified for region ($P < 0.0001$ and $P < 0.001$, respectively). An additional exploratory post-hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone LAI ($P = 0.001$, stratified by region). Times to recurrence of an elevated mood episode ($P < 0.0001$) or depressive episode ($P = 0.011$) were also significantly longer with olanzapine compared with placebo. Importantly, this study also adds to the body of evidence of olanzapine's ability to prevent depressive recurrences in patients with a manic index episode. Based on this study, the ***CE for PNES is "B" for any TEE, manic and depressive recurrences***

Prevention of TEE in rapid cyclers (PRC)

Post-hoc analysis of the 47-week olanzapine versus valproate study revealed that rapid cycling patients did less well over long-term treatment than non-rapid cycling patients. Among rapid cycling patients, olanzapine and valproate appear similarly effective against manic symptoms; however, among non-rapid cycling patients, olanzapine-treated patients experienced superior mania improvement. Olanzapine-treated, non-rapid cyclers experienced greater mania improvement than rapid cyclers (Suppes et al. 2005).

Although the observation is interesting, the equal efficacy on manic symptoms of olanzapine and valproate cannot count as solid CE "B" evidence, as the evidence of efficacy of valproate in rapid cycling patients is weak. We therefore decided on a ***CE for PRC "C".***

Further evidence (FE)

Tohen et al. (2003a) report a 47-week comparison of olanzapine (5–20 mg/day) and valproate (500–2500 mg/day). The study had two endpoints which have been reported separately, the first one after 3 weeks (Tohen et al. 2002a) and the second one at week 47. Two hundred and fifty-one manic or mixed patients were included. The primary efficacy instrument was the YMRS. Over 47 weeks, the mean improvement in the YMRS score was significantly greater for the olanzapine group, but there was only a numerical, but not significant advantage for olanzapine in the rates of subsequent relapse into mania or depression (42.3 and 56.5%).

Olanzapine was also used as internal comparator in a double-blind 12-week (McIntyre et al. 2009) and an additional 40-week extension study (McIntyre et al. 2010) of two acute studies testing asenapine against olanzapine and placebo (which was discontinued after 3 weeks). Changes in the YMRS ratings were numerically not different between asenapine and olanzapine in observed cases; however, attrition over 1 year was high.

Whereas the previous studies used subjects with a manic or mixed episode at entry, one study included patients who recovered from bipolar depression while taking olanzapine. Responders and remitters of the acute bipolar depression study comparing olanzapine, olanzapine–fluoxetine combination and placebo (Tohen et al. 2003b) had the option to continue treatment for another 24 weeks. The study was not randomized, but patients could choose between olanzapine monotherapy and the combination treatment. Patients were started on open-label olanzapine alone for 1 week, and then they were offered the option of assignment to the combination treatment if wanted. Approximately two-thirds of patients who had responder status at study entry achieved remission over 24 weeks. The rates of relapse, however, even in patients who achieved remission, were high (more than 37% of remitters within 24 weeks), suggesting that continuation of olanzapine alone was not very efficacious. However, rates of TEAS to mania were low and did not differ between patients treated with olanzapine or the combination (both $< 7\%$) (Corya et al. 2006; Shelton 2006).

The positive results of RCTs for long-term olanzapine treatment are reflected in the outcome of the large naturalistic study EMBLEM (Goetz et al. 2007). This open-label, non-randomized study compared the 2-year outcomes of patients with a manic/mixed episode of bipolar disorder taking olanzapine monotherapy or olanzapine in combination with other agents. The study consisted of two phases: acute (12 weeks) and maintenance (follow-up over 2 years). The longitudinal outcome measure was the CGI-BP scale. Cox regression models compared outcomes of both therapy groups using intention-to-treat and switching medication analysis. 1076 patients were included in this analysis. A total of 29% took olanzapine as monotherapy ($n = 313$) and 71% as combination ($n = 763$) at 12 weeks post-baseline (end of study acute phase). After adjusting for patient characteristics using switching medication analysis, relapse rates differed ($P = 0.01$) in favour of monotherapy-treated patients (Gonzalez-Pinto et al. 2011). This might indicate that olanzapine alone is already an effective treatment in patients improving on olanzapine, and additional medication does not necessarily add additional benefits. However, there is a caveat: due to the non-randomized design of the study, the findings could also be interpreted as indicating that the patients

who were treated with the combination had more severe illness that was not able to be controlled with olanzapine monotherapy. ***Rating of FE: "++"***

Safety and tolerability (ST)

The olanzapine monotherapy study versus placebo (Tohen et al. 2006) is probably most informative for assessing tolerability and safety aspects.

The most common adverse events reported during the open-label phase were weight gain, dry mouth, increased appetite, and somnolence. During the double-blind phase, adverse events reported by patients who received olanzapine were weight gain and fatigue.

The prevalence rate of a metabolic syndrome in bipolar disorder ranges from 30 to 42%, a proportion much higher than the general population but similar to that observed in schizophrenia (Fagiolini et al. 2005). Metabolic changes and weight gain are those side effects which may limit the usefulness of olanzapine in many patients. The most common emergent event in this study was weight gain. During the open-label phase which lasted 8–14 weeks, patients who received olanzapine gained a mean of 3.1 kg (SD = 3.4). During double-blind treatment, placebo patients lost a mean of 2.0 kg (SD = 4.4) and patients who continued to take olanzapine gained an additional 1.0 kg (SD = 5.2).

Thirty-five percent of patients experienced an increase in baseline weight of ≥ 7% during the open-label phase while treated with olanzapine. Among these 125 patients, 14 (17.7%) of 79 patients who received olanzapine and one (2.2%) of 46 patients who received placebo experienced an additional increase in weight of ≥7% from the point of randomization in the double-blind phase.

Weight gain is closely linked to metabolic abnormalities. Increases in non-fasting glucose (mean = 5.3 mg/dl, SD = 34.4) and cholesterol (mean = 10.7 mg/dl, SD = 29.6) levels were reported during the open-label phase. Three patients in the olanzapine group and two in the placebo group had treatment-emergent elevations in glucose level during the double-blind phase. Two patients in the olanzapine group had treatment-emergent elevations in cholesterol level; maximum cholesterol values for those patients were 283.2 and 248.2 mg/dl, respectively. No patient in the placebo group had an elevation in cholesterol level.

Considering all olanzapine exposures, regardless of study phase, treatment-emergent elevation in prolactin level occurred in 134 (27.0%) of 496 patients.

Incidence rates of extrapyramidal symptoms were low in both the open-label and double-blind phases. No differences were found between the olanzapine and placebo groups in rates of treatment-emergent parkinsonism, akathisia and dyskinesia.

QTc prolongations were found in eight (4.5%) of 179 patients who received olanzapine and one (0.9%) of 117 patients who received placebo.

For a more extensive review of olanzapine-associated metabolic risks we refer the reader to the pertinent literature (e.g., Kantrowitz and Citrome 2008; Rummel-Kluge et al. 2010).

Olanzapine has a FDA pregnancy "C" category rating. Cases of cleft lip, encephalocele, and aqueductal stenosis associated with the use of olanzapine have been reported, and the incidence of major congenital malformations associated with olanzapine has been estimated as 1% (Nguyen et al. 2009) which largely corresponds to the expected population figure.

Given the issues with weight gain and metabolic changes which might result in increased susceptibility to relapse (Fagiolini et al. 2003) and increased morbidity and mortality from physical illness (Staiano et al. 2012; Newcomer 2007), the ***Rating of ST is "–".***

Prevention of suicide (PSu)

It has been suggested by Angst et al. (2005) that antipsychotics in general have an ameliorating effect upon suicide rates in affective disorders, similar to antidepressants and lithium. However, we could not retrieve any information more specific to olanzapine. In schizophrenic patients it appears that olanzapine has no comparable benefits as does clozapine on suicidality and suicidal behaviour (Meltzer and Baldessarini 2003). ***Rating of PSu: "0"***

Practicability (PR)

Olanzapine is available as tablets, oral soluble tablets and a soluble powder for short-acting injection as well as long-action injection. Thus a fair selection of application forms is available. The recommended doses for olanzapine for long-term treatment range from 5 to 20 mg/day depending on monotherapy versus combination treatment and other modifying factors such as age and comorbidities. When re-analysing the lithium versus olanzapine maintenance study Tohen et al. (2005) and Severus et al. (2010) found that patients with less than 10 mg olanzapine/day had a significantly increased risk of depressive (HR = 2.24, $P = 0.025$) TEE compared to patients with higher olanzapine dosages (10–20 mg/day). However, there was no statistically significant difference in risk for

manic/mixed episodes between the two groups (HR = 0.94, $P = 0.895$). This appears in contrast to lithium dosing where higher lithium levels were associated with a greater risk of depressive recurrences. ***Rating of PR: "+"***

Recommendation grade (RG)

Olanzapine has a solid body of evidence for the prevention of TEE with a CE "A" in PES for "mania" and "any episode" and a CE "B" in PES for "depression" and in PNES for "depression", "mania" and "any episode". However, weight gain accompanied by metabolic changes puts a significant burden on patients and their physical health, and may lead to non-adherence or increased morbidity and mortality from cardiovascular disease. Balancing risks and benefits, the task force decided to downgrade the ***RG to "2".***

Oxcarbazepine: see "Other anticonvulsants used in bipolar disorder"

Paliperidone

Paliperidone is the major active metabolite of risperidone. There is no a priori reason to expect very different properties from the parent compound.

Prevention of TEE in enriched samples (PES)

In the study by Berwaerts et al. (2012), manic patients were randomized to a 15-week, double-blind acute treatment phase with either paliperidone extended release (ER; 3–12 mg/day) or olanzapine (5–20 mg/day). Olanzapine patients who fulfilled remission criteria at the end of week 15 were continued on olanzapine ($n = 83$) whereas the group of paliperidone remitters was split into those continuing on paliperidone ($n = 152$) or being switched to placebo ($n = 148$). The primary efficacy endpoint was time to first recurrence of any mood symptoms (i.e., manic or depressive) during the maintenance phase. The key secondary efficacy endpoint was the time to the first recurrence of manic symptoms. Time to recurrence of mood symptoms was significantly longer with paliperidone ER versus placebo ($P = 0.017$). The median time to recurrence was 558 days on paliperidone ER and 283 days on placebo; but could not be calculated with olanzapine, as less than 50% of patients (23%) reported recurrence of any mood symptoms. During the first year of treatment in the maintenance phase, the NNT was 8 (95% CI: 4; 885); however, this advantage was not seen at the end of the second-year of treatment.

The time to recurrence of manic symptoms was significantly longer in the paliperidone ER group versus placebo ($P < 0.001$). The HR (placebo: paliperidone ER) was 2.06 (95% CI: 1.32; 3.22) indicating that patients on placebo were twice as likely as patients on paliperidone ER to report recurrence of manic symptoms. A depressive recurrence occurred in 18% ($n = 26$) on placebo and 24% ($n = 35$) on paliperidone ER, but testing for statistical significance has not been performed.

In summary, we identified one study that supplied evidence for efficacy of paliperidone in preventing TEE in a sample enriched for a manic index episode and acute response to paliperdone. Thus, we would consider a ***CE for the prevention of any episode and of manic episodes in ES "B"***. The ***CE to prevent new depressive episodes in ES is "E"*** for similar reasons as seen with the ziprasidone maintenance study (see section on "Ziprasidone").

Prevention of TEE in non-enriched samples (PNES)

We could not identify any relevant trials of paliperidone for the category PNES. ***CE for PNES: "F"***

Prevention of TEE in rapid cyclers (PRC)

We could not identify any relevant information on effects of paliperidone on PRC. ***CE for PRC: "F"***

Further evidence (FE)

We could not identify any other relevant evidence for the use of paliperidone for recurrence prevention in bipolar patients. ***Rating of FE: "0"***

Safety and tolerability (ST)

The study by Berwaerts et al. (2012) is probably most informative as it contains not only information on TEAS compared to placebo, but also in relation to olanzapine as a standard treatment. In summary, slightly more EPS-related AEs and a moderate, but transient prolactin increase was observed. The proportion of patients reporting EPS-related AEs during the 15 weeks of acute and continuation treatment was higher in the paliperidone ER ($n = 207$, 34%) than olanzapine ($n = 23$, 16%) group, but during the maintenance phase this changed and reported EPS-related AEs were higher in the olanzapine group ($n = 8$, 10%) than paliperidone ER ($n = 6$, 4%) or placebo ($n = 4$, 3%) groups. EPS-related AEs in the paliperidone ER group during the maintenance phase were dyskinesia,

akathisia, hypokinesia, tremor ($n = 1$, 1% each) and extrapyramidal disorder ($n = 2$, 1%); the event of dyskinesia resulted in study discontinuation. Median change from baseline to endpoint in the SAS and AIMS scores during the maintenance phase was 0 in all treatment groups. Based on BARS scores, the proportion of patients with mild or moderate akathisia was similar at baseline and endpoint for all groups during the maintenance phase. Parkinsonism (defined as SAS total score > 0.3) and akathisia (defined as BARS global clinical rating ≥ 2) occurred in a similar proportion of patients on paliperidone ER ($n = 9$ (6%) and $n = 1$ (1%), respectively) and olanzapine ($n = 5$ (6%) and $n = 1$ (1%), respectively) during the maintenance phase (vs. placebo: $n = 4$ (3%) and $n = 2$ (1%), respectively). However, the use of anti-EPS medications was higher in the paliperidone ER group than other groups during the 15-week acute and continuation phases ($n = 151$, 25% vs. olanzapine: $n = 13$, 9%) and maintenance phase ($n = 29$, 19% vs. placebo: $n = 24$, 16% and olanzapine: $n = 7$, 8%) which might have obscured true EPS rates. Glucose-related AEs were generally low, also with olanzapine. The mean ($\pm$ SD) prolactin levels increased from acute treatment baseline to acute/continuation treatment endpoint in both sexes in the paliperidone ER group (men: $+22.37 \pm 24.26$; women: $+72.23 \pm 93.19$ ng/mL) but decreased from maintenance phase baseline to endpoint in both sexes with paliperidone ER (men: -7.19 ± 20.83; women: -5.55 ± 52.88 ng/ml). Potentially prolactin-related AEs occurred in 32 (5%) patients on paliperidone ER and 5 (3%) on olanzapine during the 15 week acute and continuation phases. During the maintenance phase, potentially prolactin-related AEs occurred in 8 patients on paliperidone ER (galactorrhea ($n = 3$), decreased libido and amenorrhea ($n = 2$, each), irregular menstruation and erectile dysfunction ($n = 1$, each)) and one patient on placebo (breast pain).

So far, there is little known about risks of paliperidone in pregnancy. It can be assumed that they may be similar to the parent substance, risperidone. ***Rating of ST: "0"***

Prevention of suicide (PSu)

We could not identify any relevant information on effects of paliperidone on suicide or suicide related behaviours. ***Rating of PSu: "0"***

Practicability (PR)

Paliperidone is not available in all countries. Formulations include oral extended release tablets and a long-acting injectable suspension. Thus, the choice of available formulations is limited, but may be sufficient for the purpose of long-term treatment. The recommended treatment dose ranges from 3 to 12 mg/day, depending on tolerability, as tested in the study by Berwaerts et al. (2012). ***Rating of PR: "0"***

Recommendation grade (RG)

Paliperidone has ***CE "B" evidence for the prevention of treatment emergent mania and any episode in PES*** which relates to a ***RG of "3"***. However, it is of note that it has no evidence in any other category, not even for "Further evidence". And it is one of the few compounds in which a maintenance placebo-controlled RCT showed numerically better results for placebo in preventing depression. In addition, it seems to be clearly less effective than olanzapine in all outcome parameters tested. On the other hand, there is little reason to treat it separately from risperidone and clinicians are referred to the data also extant for risperidone.

Phenytoin: see "Other anticonvulsants used in bipolar disorder"
Pregabaline: see "Other anticonvulsants used in bipolar disorder"

Quetiapine

Prevention of TEE in enriched samples (PES)

The evidence for quetiapine to prevent TEE in patient populations enriched for acute response to the drug (both with an index episode of mania and depression) is quite convincing. Two monotherapy RCT's and two add-on studies support the efficacy of quetiapine in this population.

The study by Weisler et al. (2011) (see also the section on "Lithium") investigated the efficacy and safety of quetiapine monotherapy (330–800 mg) as maintenance treatment in bipolar I disorder compared with switching to placebo or lithium in patients with a manic/mixed or depressive index episode stabilized on quetiapine for 4–25 weeks. To be eligible for the double-blind randomized phase, patients had to achieve stabilization at the latest by week 20 and to maintain stability for at least four subsequent weeks. Patients achieving stabilization were randomized to continue quetiapine or to switch to placebo or lithium (0.6–1.2 mmol/l) for up to 2 years in a double-blind trial. The primary outcome measure was time to recurrence of any mood event; secondary measures were times to manic or depressive events. Recurrence was defined as at least one of the following: initiation of an antipsychotic, antidepressant, anxiolytic (other than lorazepam), or other

medication to treat a mood event; hospitalization for a mood event; YMRS score ≥ 20 or MADRS score ≥ 20 at two consecutive assessments or final assessment if the patient discontinued or discontinuation from the study if, according to the investigator, discontinuation was due to a mood event. Approximately 50% of those receiving open label quetiapine were successfully stabilized and randomized ($n = 1226$). Time to recurrence of any mood event was significantly longer for both quetiapine versus placebo (HR = 0.29; 95% CI, 0.23–0.38; $P < 0.0001$) and for lithium vs. placebo (HR = 0.46; 95% CI, 0.36–0.59; $P < 0.0001$). Quetiapine and lithium significantly increased time to recurrence of both manic events (quetiapine: HR = 0.29; 95% CI, 0.21–0.40; $P < 0.0001$; lithium: HR = 0.37; 95% CI, 0.27–0.53; $P < 0.0001$) and depressive events (quetiapine: HR = 0.30; 95% CI, 0.20–0.44; $P < 0.0001$; lithium: HR = 0.59; 95% CI, 0.42–0.84; $P < 0.004$) compared with placebo. When data were censored to exclude events in the first 4 weeks after randomization, the HR for the time to recurrence of any mood event was 0.27 ($P < 0.0001$) for quetiapine versus placebo, 0.41 ($P < 0.0001$) for lithium versus placebo, and 0.70 ($P = 0.041$) for quetiapine vs. lithium in the intend-to treat (ITT) population pointing towards a true effect of quetiapine in preventing recurrences rather than just relapses.

Different from the first study, in the study by Young et al. (2012), all patients had a depressive index episode, and, before entering the 1-year, double-blind maintenance phase, they participated in two acute bipolar depression RCTs (McElroy et al. 2010; Young et al. 2010) comparing quetiapine, placebo and an internal comparator (lithium in one, paroxetine in the other trial). Patients ($N = 584$) with bipolar I or II disorder who achieved remission after 8 weeks of treatment with quetiapine (300 or 600 mg/day) in these RCTs were randomised to the same quetiapine dose or placebo for up to 52 weeks or until mood event recurrence. As a result, the risk for a TEE was significantly lower with quetiapine than placebo (HR 0.51 (95% CI: 0.38–0.69); $P < 0.001$). Quetiapine was associated with a lower risk for recurrence of depressive events (HR 0.43 (95% CI: 0.30–0.62); $P < 0.001$) but recurrence of manic/hypomanic events was not significantly reduced (HR 0.75 (95% CI: 0.45–1.24; $P = 0.263$). This might be related to the selection of patients with an index episode of depression (see section on "Population under examination"). There was a lower risk of recurrence of mood events both in bipolar I (HR 0.58 (95% CI: 0.41–0.82), $P = 0.002$) and bipolar II patients (HR 0.33 (95% CI: 0.18–0.60), $P < 0.001$).

Finally, two identically designed combination treatment studies comparing lithium or valproate + quetiapine versus lithium or valproate + placebo (Vieta et al. 2008c; Suppes et al. 2009) add further to the evidence. Patients had manic/mixed or depressive episodes, and were stabilized with open label quetiapine (400–800 mg/day) for up to 36 weeks until they fulfilled stability criteria for at least 12 weeks. After randomization to either treatment arm they were followed-up double-blind for up to 2 years. Results in both studies are virtually identical: the combination treatment of quetiapine + lithium or valproate was significantly superior to lithium or valproate + placebo for all primary and secondary outcome parameters: In the study by Vieta et al. (2008c), a multinational study, the proportion of patients having a mood event was markedly lower in the quetiapine than in the placebo group (18.5 vs. 49.0%). The HR for time to recurrence of any mood event was 0.28 ($P < 0.001$), a mania event 0.30 ($P < 0.001$), and a depression event 0.26 ($P < 0.001$) corresponding to risk reductions of 72, 70 and 74%, respectively. In the study by Suppes et al. (2009), conducted in North America, also significantly fewer patients in the quetiapine group experienced a TEE compared with the placebo group (20.3 vs. 52.1%). The HR for time to recurrence of a mood event was 0.32. HRs were similar for mania and depression events (0.30 and 0.33, respectively, all significant at $P < 0.001$). A pooled analysis of both studies (Vieta et al. 2008c; Suppes et al. 2009) showed that quetiapine was effective in preventing TEE in patients with mixed index episodes (Vieta et al. 2012b).

In summary, based on two monotherapy and two combination treatment studies, quetiapine has solid evidence for the prevention of TEE in enriched samples. The ***CE for PES is "A" for any mood episode, mania and depression.***

Prevention of TEE in non-enriched samples (PNES)

Our literature search could not identify any studies of quetiapine in NES that would satisfy CE criteria "A–D". Thus, the ***CE for PNES is "F" for any mood episode, mania and depression.***

Prevention of TEE in rapid cyclers (PRC)

About 15% of patients in the monotherapy study by Weisler et al. (2011), and up to 30% in the combination treatment studies had a rapid cycling course, but a separate subanalysis of this group has not been published yet. An open explorative study by Vieta et al. (2002) in 14 patients, treated with quetiapine add on to on-going medication for a mean of 112 ± 3 days, suggested benefits for acute manic, but not

depressive symptom remission and relapse prevention. Accordingly, the ***CE for PRC is "C" for any mood episode and mania.***

Further evidence (FE)

Prior to the pivotal RCTs, several open studies on quetiapine as bipolar maintenance treatment have been published (Altamura et al. 2003; Suppes et al. 2004, 2007; Duffy et al. 2009) contributing to a ***Rating for FE: "+"***

Safety and tolerability (ST)

The safety and tolerability data of the study of Weisler et al. (2011) are probably most informative as they are generated in monotherapy and also allow comparison to lithium. During the open-label quetiapine stabilization phase of 4–25 weeks, 170 patients (7.0%) experienced adverse events leading to discontinuation, most commonly sedation ($n = 40$, 1.6%) and somnolence ($n = 26$, 1.1%).

16.8% of patients had an increase of body weight $>7\%$ during open quetiapine treatment. After randomization, 10.6% of those randomized to quetiapine, 5.4% of those on lithium and 2.6% of those receiving placebo had a $>7\%$ increase of body weight. Clinically important elevations in blood glucose (i.e., ≥ 7.0 mmol/l) at any time after randomization in subgroups with documented fasting glucose concentrations were recorded in 30 patients (8.5%) in the quetiapine, 17 (4.4%) in the lithium, and 13 (3.5%) in the placebo group. Quetiapine treatment during the randomized phase was also associated with a greater increase of triglycerides, total cholesterol and LDL cholesterol than treatment with lithium or placebo.

Adverse events potentially associated with EPS during randomized treatment were reported by 16 (4.0%), 38 (9.1%), and 18 (4.5%) patients receiving quetiapine, lithium, and placebo, respectively, with no apparent differences in mean SAS, BARS, or AIMS scores.

Data on safety in pregnancy with quetiapine are sparse. Animal studies suggested that quetiapine may delay skeletal ossification as well as reduce birth weight (Nguyen et al. 2009) and as a consequence it is listed by the FDA as a category "C" medication for safety in pregnancy.

In summary, and in line with other observations, safety and tolerability problems associated with quetiapine are sedation after treatment initiation, and later weight gain and metabolic changes. Weight gain and metabolic changes appear not of the magnitude as observed with, e.g., clozapine or olanzapine, but nonetheless might constitute a physical health problem in the long run. ***Rating of ST: " −"***

Prevention of suicide (PSu)

There are no reliable data available specific to an antisuicidal effect of quetiapine. On the other hand, there is no evidence that quetiapine might enhance suicide risks. ***Rating of PSu: "0"***

Practicability (PR)

Quetiapine is only available in tablets, both for immediate and extended release. Thus, the portfolio of available formulations is rather restricted. Dosages of quetiapine used in maintenance studies range from 300 to 800 mg. In the monotherapy study by Weisler et al. (2011) the mean (SD) median quetiapine dose was 546 (± 173) mg in stable patients during the randomized phase. ***Rating of PR: "0"***

Recommendation grade (RG)

The evidence for quetiapine, both in monotherapy and combination treatment, to prevent TEE in enriched samples is quite outstanding and merits a ***RG "1".*** There are issues with weight gain and metabolic changes that need to be carefully monitored; however, the task force felt that balancing risks and benefits, these issues are still outweighed by the bulk of evidence for efficacy.

Risperidone

Prevention of TEE in enriched samples (PES)

There are no published RCTs on bipolar maintenance treatment with oral risperidone. Two RCTs (Quiroz et al. 2010; Vieta et al. 2012a) investigated the efficacy of risperidone LAI monotherapy for the prevention of TEE in patients with a manic/mixed index episode after successful stabilization on oral risperidone and switch to LAI.

The study by Quiroz et al. (2010) compared risperidone LAI monotherapy against placebo injections in 303 patients, stabilized for 6 months on risperidone LAI after a manic/mixed index episode, for 2 years. Most (77%) of the patients in the risperidone LAI group remained on the minimum dose of 25 mg every 2 weeks. The primary efficacy variable was the time to recurrence of a mood episode during double-blind treatment, with "recurrence" being defined as a composite outcome of fulfilling DSM-IV criteria and severity criteria. Time to recurrence was significantly longer in the risperidone LAI

group than the placebo group (log-rank $\chi^2 = 23.5$, df = 1, $P < 0.001$). In the risperidone LAI group, 42 (30%) of 140 patients experienced recurrence during double-blind treatment versus 76 (56%) of 135 in the placebo group. Patients in the risperidone LAI group were less than half as likely to experience a recurrence than patients in the placebo group (estimated HR, 95% CI): 0.40, 0.27–0.59). Time to recurrence was significantly longer in the risperidone LAI group than the placebo group for time to recurrence of elevated mood episodes ($P < 0.001$; HR,95% CI: 0.25, 0.15–0.41) but not for depressive episodes ($P = 0.805$; HR, 95% CI: 1.09, 0.55– 2.17). However, the overall number of depressive recurrences was small ($n = 20$ for risperidone LAI and $n = 14$ for placebo) as this population with a manic index episode was possibly not at high risk for depression anyway.

The second study in an enriched population was conducted by Vieta et al. (2012a), and included besides risperidone LAI and placebo also an olanzapine arm for assay sensitivity (see section on "Olanzapine"). Patients first entered a 2-week screening period (Period I) in which non-acute patients continued to receive their current medication, while acute patients were treated at the investigator's discretion. At the end of the screening period, eligible patients entered a 12-week open-label period (Period II) in which all patients received risperidone LAI (25, 37.5 or 50 mg every 2 weeks; initiated at 25 mg or, if deemed by the investigator to be clinically appropriate, 37.5 mg). During Period II, patients were assessed for recurrence events, defined as the occurrence of a new episode or need for change of treatment. At the end of Period II, patients ($n = 398$) who had responded to treatment (i.e., had not experienced a recurrence event) were randomized to double-blind treatment (Period III) with risperidone LAI (25, 37.5 or 50 mg) + oral placebo or oral and injectable placebo or oral olanzapine 10 mg/day + placebo injection. In Period III, patients randomized to risperidone LAI received a fixed dose throughout, according to their final dose in Period II (25 mg, 64%; 37.5 mg, 32%; 50 mg, 4%). So, at the beginning of Period III, we deal with a patient population that is enriched both for tolerability and continuation treatment efficacy of risperidone LAI. The primary efficacy evaluation was the time to recurrence of any TEE (as defined above) in Period III.

In the pre-specified analysis (log-rank test stratified by patient type and region), time to recurrence of any mood episode in Period III did not differ significantly between the risperidone LAI and placebo arms ($P = 0.057$). Time to recurrence of an elevated (hypomanic, manic or mixed) mood episode was significantly longer with risperidone LAI compared with placebo ($P = 0.005$). There was no significant difference in time to recurrence of a depressive episode between risperidone LAI and placebo ($P = 0.655$). As detailed in the olanzapine section, olanzapine was not only significantly superior to placebo in all primary outcome variables, but also to risperidone LAI.

In summary, we have to consider the following data basis: One positive and one negative study for ***PES any episode, which relates to a CE of "D".*** Two positive subanalyses support the prevention of manic TEE which relates to a ***CE for PES manic episode of "A".*** And, finally, two subanalyses showing no benefit of risperidone LAI compared to placebo in preventing new depressive episodes, with the additional information that olanzapine did so (in other words, it would have been possible to show depression preventive effects in the Vieta et al. (2012a) study if a medication is efficacious.) Thus the ***CE for PES depressive episode is "E".***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any studies satisfying CE "A–D" criteria testing risperidone long-term treatment in samples not previously enriched for acute response or tolerability. ***CE for PNES for any TEE, mania or depression: "F"***

Prevention of TEE in rapid cyclers (PRC)

One RCT (Macfadden et al. 2009) investigated risperidone LAI in combination with on-going medication (treatment as usual = TAU) in bipolar patients with frequent relapses. Eligible patients were between 18 and 70 years of age and had experienced four or more mood episodes (defined as an event requiring psychiatric intervention) in the past 12 months. Different from the monotherapy studies in non-RC patients, there was no requirement for a manic or mixed index episode. Patients in any phase of bipolar illness (manic, hypomanic, depressed, mixed or euthymic) at study entry were included. TAU consisted of any number or combinations of antidepressants, mood stabilizers or anxiolytics, determined for each patient by his or her investigator. Risperidone LAI and TAU could be changed or adjusted at any time during the first 12 weeks of the stabilization phase but to be eligible for the double-blind phase, risperidone LAI and TAU medications and dosages had to be stable for at least 4 weeks prior to randomization. This design implies that patients have been selected for tolerability of risperidone LAI, but not

necessarily for efficacy in an acute episode. In the stabilization phase, the risperidone LAI modal dose was 25 mg in 79.2% of patients, 37.5 mg in 19.6% of patients, and 50 mg in 1.3% of patients. A total of 183 of 240 subjects completed the stabilization phase (76.3%), and 124/240 (51.7%) fulfilled stabilization criteria and were randomised to either continue double-blind risperidone LAI or switch to placebo injections. The primary endpoint was time to relapse from randomization in the double-blind relapse-prevention phase that lasted 12 months. "Relapse" was a composite outcome defined as fulfilling DSM-IV criteria of an acute episode and, additionally, showed a marked worsening according to predefined YMRS, MADRS and CGI-BP criteria, or being either hospitalized for worsening of symptoms according to predefined criteria and suicidal ideation.

Adjunctive risperidone LAI treatment was associated with a significant delay in the time to relapse of any mood episode compared with adjunctive placebo treatment ($P = 0.010$). Relapse rates were 23.1% ($n = 15$) with adjunctive risperidone LAI treatment and 45.8% ($n = 27$) with adjunctive placebo. The relative risk of relapse was 2.3-fold higher with adjunctive placebo compared with adjunctive risperidone LAI ($P = 0.011$, chi-square (Cox regression). The study was not powered to conclusively demonstrate prevention of particular types of mood episodes (mania, depression, mixed states). Numerically, 19 patients in the total double-blind study population relapsed to a depressive episode (adjunctive risperidone LAI, $n = 8$ (12.3%); adjunctive placebo, $n = 11$ (18.6%)), 17 patients relapsed to a manic episode (adjunctive risperidone LAI, $n = 5$ (7.7%); adjunctive placebo, $n = 12$ (20.3%)), and six relapsed to a mixed episode (adjunctive risperidone LAI, $n = 2$ (3.1%); adjunctive placebo, $n = 4$ (6.8%)). A post-hoc calculation of the RR for relapse by Vieta et al. (2011) showed a RR of 0.40 (0.18–0.90, $P = 0.026$) for manic relapses, whereas there was no significance for depressive relapses which might be attributable to the lack of power.

Based on this double-blind RCT, the ***CE for PRC is "B" for any episode, and "C" for manic/mixed and "F" for depressive TEE.***

Further evidence (FE)

Earlier case series also support the use of risperidone LAI to prevent new mood episodes (Han et al. 2007; Malempati et al. 2008; Vieta et al. 2008b; Benabarre et al. 2009). Some case series also support the use of risperidone given as an oral tablet in preventing new mood episodes (Ghaemi and Sachs 1997; Fountoulakis et al. 2004; Ghaemi et al. 2004; Yoshimura et al. 2006). ***Rating of FE: "+"***

Safety and tolerability (ST)

The best evidence for the safety and tolerability of risperidone LAI can be derived from the study by Vieta et al. (2012a) as it is monotherapy and allows not only comparison against placebo, but also olanzapine. The most common AEs in Period II during open-label risperidone LAI treatment were insomnia (16%), akathisia (7%) and headache (6%). Adverse events considered to be potentially prolactin related (such as galactorrhoea or libido decreased), as reported by the investigator, occurred in 33 patients (6%). Clinically significant increase in body weight ($\geq 7\%$) was reported in 14% of patients.

During Period III (double-blind maintenance phase), the most common AES occurring in patients receiving risperidone LAI were weight increase (24%), insomnia (17%) and amenorrhoea (8%). Placebo rates were for weight increase 9%, insomnia 18%, amenorrhoea 2%. The most common adverse events in the olanzapine arm were weight increase (27%), somnolence (12%) and insomnia (10%). Discontinuations because of adverse events occurred in five patients (4%) receiving risperidone LAI, five patients (4%) receiving olanzapine and two patients (2%) receiving placebo. Extrapyramidal Symptoms Rating Scale (ESRS) score from Period III baseline to endpoint were low and remained low in all three arms.

Hyperprolactinaemia was reported during Period III in two patients (1%) receiving risperidone LAI, with potentially prolactin-related adverse events reported in 14% of patients receiving risperidone LAI and 3% receiving placebo. Two patients receiving risperidone LAI (1%) reported diabetes mellitus as an adverse event. Clinically significant weight increase (defined as $>7\%$ increase) was seen at the end of Period III in 18% of patients receiving risperidone LAI, 28% of patients receiving olanzapine and 5% of patients receiving placebo.

McKenna et al. (2005) in a prospective study reported eight cases of major congenital malformations associated with risperidone exposure including a case of corpus callosum agenesis, the FDA safety-in-pregnancy category rating for risperidone is "C".

In summary, risperidone LAI was well tolerated, and the rate of extrapyramidal side effects and prolactin elevation is clearly less from that has been reported in acute studies with oral risperidone. Still, issues with prolactin are not trivial given the increased risk of breast cancer (Harvey et al. 2008).

Weight gain, however, is also of some concern, both with risperidone LAI and olanzapine. ***Rating of ST: "–"***

Prevention of suicide (PSu)

We could not identify any relevant literature that gives evidence for effects of risperidone on suicidality, other than the general observation that antipsychotics as a group might prevent suicide (Angst et al. 2005). ***Rating of PSu: "0"***

Practicability (PR)

Risperidone is available as tablets, oral soluble tablets, solutions and as long acting injectable. Risperidone LAI was also used in the pivotal studies cited in this section. Both in monotherapy and combination treatment with TAU, the majority of patients were on 25 mg risperidone LAI every second week which would be the recommended dose. A dosage increase to 37.5 or 50 mg biweekly can be considered in partial responders, but it may increase the rate of adverse events. ***Rating of PR: "+"***

Recommendation grade (RG)

A uniform finding of all studies is that risperidone LAI delays manic relapses in enriched samples (CE "A"). It is also effective in preventing any relapse in RC patients (CE "B"). However, its overall efficacy in non-rapid cycling patients to prevent any relapse remains controversial (CE "D"). This makes it different from other medications that do prevent mania, e.g., aripiprazole, but also still differ from placebo for any relapse due to their very powerful mania-protective effect as expressed in their polarity index (Popovic et al. 2011). In addition, weight gain and prolactin-associated side effects are of some concern. Therefore, the task force feels that it would appropriate to assign risperidone an ***RG "2".***

Typical antipsychotics (first-generation antipsychotics)

The long-term use of typical antipsychotics has always been complicated by the high risk of extrapyramidal side effects and, as a consequence, non-adherence. More recently, there is also increasing evidence that their long-term use can be neurotoxic in schizophrenia and lead to loss of grey matter volume (Lieberman et al. 2005; Ho et al. 2011; Vernon et al. 2012). Thus, not only peripheral motor side effects can complicate treatment, but much more cognitive decline in addition to the one caused by the disorder itself.

Prevention of TEE in enriched samples (PES)

We could only identify one study (Zarate and Tohen 2004) with a sufficient number of patients investigating the continuous use of a typical antipsychotic (perphenazine) in addition to lithium, carbamazepine or valproate versus lithium, carbamazepine or valproate + placebo. Following remission of a manic episode treated with the combination of perphenazine and either lithium, carbamazepine, or valproate, 37 patients were randomly assigned to 6 months of double-blind treatment with continuation of this treatment regimen or exchange of perphenazine against placebo. Patients receiving placebo were more likely than those who continued receiving perphenazine to complete the study (83.3 vs. 47.4%, respectively), have a longer time to depressive relapse ($P < 0.03$), remain in the study for a longer duration of time ($P < 0.03$), and experience less frequently akinesia, dysphoria (both $P < 0.05$), and parkinsonism ($P < 0.01$). There were no differences in manic relapses between the groups. YMRS total scores at endpoint did not differ between the groups. ***CE for PES for any episode, mania and depression: "E"***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any long-term treatment trials with typical antipsychotics in non-enriched samples of bipolar disorder patients. ***CE for PNES for any episode, mania and depression: "F"***

Prevention of TEE in rapid cyclers (PRC)

We could not identify any long-term treatment trials with typical antipsychotics in RC samples of bipolar disorder patients. ***CE for PRC for any episode, mania and depression: "F"***

Further evidence (FE)

A small randomized, open comparison of flupenthixol and lithium (Ahlfors et al. 1981) showed no advantage of either substance compared to the previous course of illness. A second study in a larger group of 93 patients showed that flupenthixol decanoate was associated with significant decrease of the frequency of manic episodes and percentage of time ill in mania, but also with a significant rise of the frequency of depressive episodes and percent time ill in depression. Increase of depressive morbidity was

seen only in patients who had been given lithium during the pre-trial period and could presumably be a result of the discontinuation of lithium. However, the exact modalities of pre-treatment in this group are not described in the paper, so it is unclear whether and to which degree the group was enriched to acute flupenthixol response. In summary, it appears that flupenthixol may have some mania-protective properties. On the other hand, Esparon et al. (1986) conducted a double-blind cross-over trial of depot flupenthixol in bipolar patients. All patients continued on lithium, and 11 patients completed the 2-year trial. The authors report that flupenthixol appeared to have no prophylactic effect. In addition, some case reports have been published suggestive of flupenthixol-induced mania (Szabo 1993; Becker et al. 2002). ***Rating for FE: "0"***

Safety and tolerability (ST)

Similar to antidepressants, anticonvulsants or atypical antipsychotics we are not likely to be dealing with a homogenous group of medications for the typical antipsychotics. The safety and tolerability profile varies, but any member of the group has at least one safety and tolerability issue which might compromise its use. Frequency and severity of side effects with typical antipsychotics is dose and time dependent, and clearly in the past there has been a tendency of overdosing them, at least in acute mania treatment. The use of all typical antipsychotics is associated with extrapyramidal motor symptoms both in the short and long term, with tardive dyskinesias and probably CNS neurotoxic effects in the long run, as well as with differing degrees of prolactin elevation and weight gain. As far as weight gain is concerned, some typical AP are by large weight neutral, such as molindone, fluphenanzine, perphenazine, pimozide or haloperidol, others may cause significant weight gain, e.g., chlorpromazine. Finally, typical antipsychotics put patients at greater risk of a malignant neuroleptic syndrome than atypical antipsychotics (Tural and Onder 2010).

The risk of major congenital malformations in pregnancy might differ between agents. Haloperidol is generally considered as a relatively safe option (FDA safety in pregnancy rating "C") (Diav-Citrin et al. 2005); perphenazine has not been formally assigned to a FDA pregnancy category as animal studies have not been reported and there are no controlled data in human pregnancy. ***Rating for ST: "–"***

Prevention of suicide (PSu)

We could not identify any relevant literature that gives evidence for effects of typical antipsychotics on suicidality in bipolar patients, other than the general observation that antipsychotics as a group might prevent suicide (Angst et al. 2005). ***Rating of PSu: "0"***

Practicability (PR)

Typical antipsychotics are offered in a wide range of preparations, including tablets, solution, and short- and long-acting injectables. This is true for the most frequently used typical neuroleptic, haloperidol, but not for every single substance all options are necessarily available. Titration of most typical antipsychotics is usually straight forward, and plasma concentration checks or extensive pathology tests are not necessary. More recent, some concerns have been voiced over QTc prolongation with pimozide and haloperidol, especially when given intravenously (FDA alert 9/2007); routine ECG has been recommended. However, this might not affect the routine use of oral haloperidol preparations. ***Rating of PR: "+"***

Recommendation grade (RG)

Given the absence of reliable evidence and the more unfavourable side effects profile, the long-term use of typical antipsychotics in bipolar patients cannot be recommended. ***RG: "Ø"***

Valproate (incl. divalproate, divalproex, valpromide)

The different formulations of sodium 2-propylpentanoate, or sodium valproate, are summarized here as "valproate". The reason for this is that the active compound that penetrates the brain–blood barrier is always valproic acid; the different preparations may show differences in gastric tolerability, but not CNS activity (Grunze and Walden 2004). Valproate has a widespread use as a prophylactic medication in bipolar disorder which developed at a time where alternatives to lithium were scarce but urgently needed. The unequivocal scientific evidence for long-term beneficial effects, however, is rather poor, and licensing in some countries, e.g., Germany, for prevention of new mood episodes has been based on its established clinical use rather than evidence. However, it has to be said in favour of valproate that it has not received the benefit of having been prospectively examined in modern discontinuation design following prior enrichment for response, as most atypical antipsychotics have been. There is only one RCT versus placebo (and lithium as internal comparator) published which, however, failed in its

primary outcome measure. Thus, the data for the primary outcome (time to recurrence of any mood episode) for valproate in maintenance treatment are rather inconclusive than negative, but it is unlikely that valproate will be subject to further pivotal studies given the lack of incentives for a potential sponsor. However, there were several secondary outcome measures that were established a priori, including time to a manic episode, time to a depressive episode, average change from baseline in scores on the Mania Rating Scale (MRS), Depressive Syndrome Scale (DSS) score (derived from SADS-C) and GAS during maintenance treatment, rate of early discontinuation for depression, proportion of patients with depressive relapses, mean change in DSS from baseline, proportion of patients receiving adjunctive antidepressants, and time in the study (Bowden et al. 2000; Gyulai et al. 2003). The analyses of these outcome measures appear of good scientific reliability as they were not decided post hoc, but as part of the protocol. Thus, the task force decided to consider them for CE "B" evidence if adequately powered and reported.

This sole placebo-controlled RCT for valproate is actually also difficult to classify as to its degree of enrichment. During the up to 3-month run-in phase the index manic episode was treated at the discretion of the investigator, and 117 patients had been treated with valproate only (31.5%), 124 with lithium only (33.3%), 50 with both drugs (usually sequentially) (13.4%), and 81 with neither drug (21.8%). Considering that 187 subjects were subsequently randomised to valproate, 91 to lithium, and 94 to placebo (a 2:1:1 randomisation scheme) and that patients taking valproate or lithium on the day of randomisation had the drug gradually withdrawn over 2 weeks, this design might slightly have favoured valproate over placebo and lithium. On the other hand, the frequency of use of valproate and lithium as antimanic treatment largely reflects clinical practice in the 1990s, at least in those patients who were not too ill to be considered as eligible for an RCT. Excluding or limiting the number of patients on valproate would rather have created a bias against valproate and not reflect actual treatment habits. Thus, the task force feels that the enrichment was not artificial per study protocol, but resembled clinical practice, and thus the study should be considered in this section on non-enriched study populations. However, post-hoc analysis of the subjects in this study who were treated with valproate during the open phase supplies some information which we value with a lower CE in the PES section. The same applies for the adjunctive maintenance studies with aripiprazole (Marcus et al. 2011) and ziprasidone (Bowden et al. 2010) where subsets of data for patients receiving valproate as mood stabilizer were available.

Prevention of TEE in enriched samples (PES)

We identified one long-term study with valproate following a systematic prior enrichment for acute efficacy and/or tolerability (Bowden et al. 2012). In this underpowered study, recently depressed Bipolar I and II patients were stabilized with lamotrigine + valproate combination treatment, and then randomized to 8 months of maintenance treatment with either lamotrigine + placebo or lamotrigine + valproate. While the primary outcome (time to a new depressive episode) was not significantly different, several secondary outcomes were supportive of additional benefits by adding valproate to lamotrigine. Furthermore, a post-hoc analysis of the randomized, double-blind, placebo- and lithium-controlled valproate maintenance study (Bowden et al. 2000) showed that the 148 patients treated with open phase valproate and then randomized to valproate achieved longer times to any mood episode than did patients randomized to placebo ($P = 0.05$) (McElroy et al. 2008).

Valproate or lithium was used as primary mood stabilisers in two maintenance studies with aripiprazole or ziprasidone. In the aripiprazole study, patients who achieved predefined stability criteria for 12 consecutive weeks were randomized to double-blind aripiprazole (ARI, 10–30 mg/day) or PLC + LiI/VPA. Relapse was monitored for 52 weeks (see also section on "Aripiprazole"). In the ziprasidone study, patients achieving at least eight consecutive weeks of stability with open-label ziprasidone and lithium or valproate were randomly assigned in the 6-month, double-blind maintenance period to ziprasidone plus mood stabilizer or placebo plus mood stabilizer (see also section on "Ziprasidone"). In the adjunctive aripiprazole maintenance study the time to a relapse to any episode was in favour of adjunctive aripiprazole therapy versus lithium alone (16% ARI + LI vs. 45% PLC + LI; $P = 0.002$). Among the subgroup of patients treated with valproate, the time to a relapse to any episode was not significantly different between the ARI + VAL and PLC + VAL groups (18 vs. 19%, respectively; $P = 0.824$) (Marcus et al. 2011). Numerically similar findings were published for the ziprasidone maintenance study, although not statistical tests were made (Bowden et al. 2010). These results indicate equivalence of valproate to aripiprazole plus valproate, or ziprasidone plus valproate on time to any episode, despite the studies being enriched for ziprasidone and aripiprazole response. No study analysed mania or depression separately, and both studies enrolled only manic and mixed patients.

CE for PES any episode: "C", for mania and depression "F".

Prevention of TEE in non-enriched samples (PNES)

Almost all of the controlled evidence about valproate's ability to prevent TEE stems from one pivotal study, comparing valproate, lithium and placebo in a 1-year, double-blind RCT (Bowden et al. 2000). Patients had recovered from a manic index episode, which could be treated with any suitable medication, including valproate or lithium.

The primary outcome measure was time to recurrence of any mood episode. As mentioned, the study failed in this primary outcome. The valproate group did not differ significantly from the placebo group in time to any mood episode. However, valproate was statistical significantly superior in a number of a priory determined secondary analyses:

Valproate was superior to placebo in terms of lower rates of discontinuation for any reason ($P = 0.05$) and depression ($P = 0.02$); in addition, it outperformed lithium on several other outcomes: discontinuation for any reason ($P = 0.03$), time to intervention for emerging depressive symptoms with an SSRI ($P = 0.03$), and worsening of depression (Change of Depressive Symptom Scale from baseline, $P = 0.04$).

Although not defined a priori, a clinically very relevant additional analysis of the study was conducted by Keck et al. (2005). It showed that with valproate plasma levels between 75 and 99.9 mg/l valproate were significantly better than placebo for discontinuation for any reason ($P < 0.05$), mania and depression (both $P = 0.03$).

In summary, the evidence for valproate maintenance in PNES is difficult to grade and was subject to diverging opinions in the task force. Valid secondary, but a priori defined analysis supports a ***CE of "B" for the prevention of depression***. The fact that valproate was also better than lithium in depression related outcomes appears to some degree at odds with the data from the BALANCE study which are in line with mania-protective, but not depression-protective effects. In this study, the advantage of lithium compared to valproate was most apparent for depressive relapses ($P = 0.0331$). On the other hand, meta-analysis of acute studies is suggestive of acute antidepressant effects of valproate (Grunze et al. 2010), which makes a prophylactic efficacy to some degree likely. Neither primary nor secondary analysis of the Bowden et al. (2000) study, however, supply clear evidence for prevention of mania or any episode; such a prophylactic effect may hold true with optimal plasma levels as demonstrated post hoc by Keck et al. (2005), but they have not been demonstrated in the whole study sample. As lithium also failed in this study, probably for reasons as outlined by Bowden et al. (2000), we consider this study rather a failed but negative one. Therefore, the ***CE for any relapse and mania would be "F".***

Prevention of TEE in rapid cyclers (PRC)

Only one substantial RCT has been conducted comparing valproate to lithium. The outcome was that neither both substances by themselves nor their combination during the open run-in phase were very effective in preventing new episodes (see paragraph on lithium). However, this study had no placebo control, so the ***CE for PRC is "F"***

Further evidence (FE)

In a 47-week, double-blind extension phase of a RCT comparing olanzapine and valproate in patients with a manic index episode (Tohen et al. 2003a), the mean improvement in the YMRS score was significantly greater for the olanzapine group. However, as far as TEE are concerned there was no significant difference between valproate and olanzapine in the rates of subsequent relapse into mania or depression (see also section on "Olanzapine").

Previous to this more recent study, several open, but in part, randomised studies (Lambert 1984; Puzynski and Klosiewicz 1984a,b; Vencovsky et al. 1984; Hayes 1989; Emrich and Wolf 1992; Denicoff et al. 1997a; Hirschfeld et al. 1999; Solomon et al. 1998) have been conducted, and their overall outcome supports some prophylactic efficacy of valproate against TEE.

However, this seems to be not fully reflected in daily clinical practice, at least not when it comes to comparison with lithium. A large open-label, randomized study (BALANCE) (Geddes et al. 2010) demonstrated that valproate monotherapy is significantly less effective than lithium in preventing TEE over 2 years: 69% of patients on valproate needed an intervention compared to 59% on lithium (for more details of this study, see section on "Lithium").

In line with the results from BALANCE are those of a large Danish registry review conducted by Kessing et al. (2011b). These authors reviewed data on all people with a diagnosis of bipolar disorder in psychiatric hospital settings who were prescribed valproate or lithium in Denmark during a period from 1995 to 2006. A total of 719 subjects received valproate and 3549 received lithium subsequent to the diagnosis of bipolar disorder. Lithium significantly outperformed valproate in all outcomes: rate of switch/add on to the opposite drug (lithium or

valproate), antidepressants, antipsychotics or anticonvulsants (other than valproate), rate of psychiatric hospital admissions regardless of the type of episode leading to a hospital admission (depressive or manic/mixed). Similarly, for participants with a depressive index episode, a manic index episode or a mixed index episode the overall rate of hospital admissions was significantly increased for valproate compared with lithium.

Although less effective than lithium, the other cited studies are suggestive of some evidence that valproate has a recurrence preventive effect. ***Rating of FE: "+"***

Safety and tolerability (ST)

Usually valproate is well tolerated. More frequent dose-dependent side effects include gastrointestinal side effects, neurological symptoms such as tremor and mild sedation, thrombopenia or leukopenia and asymptomatic increase of liver transaminases which attenuates with dose reduction. Thrombocytopenia and leucopenia is usually benign and fully reversible after discontinuation of valproate. Hair loss or change of hair texture may occur. Of the severe and potentially life threatening adverse events, idiosyncratic hepatic failure occurs in approximately 1 in 50,000 patients with valproate and is not dose dependent. Retrospective analysis of patient charts identified potential risk factors as age under 2 years, combination treatment with several anti-epileptics, family history of severe liver disease, genetically determined carnitine deficiency or disturbances of the urea metabolism. Acute haemorrhagic pancreatitis with valproate has been observed in a few cases and occurs most likely in the first 3 months of treatment. Identified risk factors are a young age and polypharmacy. Valproate- induced encephalopathies caused by hyperammonemia are described in epilepsy treatment. A genetically determined deficiency of carnitine or ornithine transaminase as well as a combination with several antiepileptic medications, especially phenobarbital is a risk factor. Symptoms usually develop within 3–4 days and reverse with instant discontinuation of valproate (Grunze and Walden 2004).

Weight gain is probably the most prominent side effect in long-term treatment and may impact medication adherence. At endpoint (LOCF) of the olanzapine versus valproate study (Tohen et al. 2003a), 23.6% ($N = 29$) of 123 olanzapine patients and 17.9% ($N = 22$) of 123 valproate patients had gained at least 7% of their baseline weight (Fisher's exact test, $P = 0.35$). Polycystic ovary syndrome (PCOS) in valproate treated female patients is also an important issue, and together with valproate's terotogenicity (FDA pregnancy category "D") makes it use not suitable in young women of child-bearing age. Valproate is associated with the highest rate of major congenital malformations (6.2–16%) (Nguyen et al. 2009). In addition, lasting developmental delays of children of mothers who had taken valproate during pregnancy has been described (Meador et al. 2009). As a consequence, the FDA assigned valproate a safety in pregnancy "D" rating which means that "there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks" (US Food & Drug Administration 1975)

The interaction potential of valproate with other medications frequently used in bipolar disorder is low. When combined with barbiturates, neuroleptics, benzodiazapines and MAO inhibitors or other antidepressants valproate may increase their sedative effects. Valproate inhibits the metabolism of lamotrigine, meaning that doses have to be adapted in combination treatment. As carbamazapine and valproate show interaction, this combination needs special monitoring when clinically used (see section on "Carbamazepine"). ***Rating of ST: "0"***

Prevention of suicide (PSu)

In contrast to the FDA warning about increased suicide risk with antiepileptic drugs (US Food & Drug Administration 2008), Gibbons et al. (2009) demonstrated that most antiepileptic drugs, including valproate, are not associated with increased suicide risk. On the other hand, valproate did not show similar protective effects as lithium as demonstrated by Goodwin et al. (2003). However, more recent randomized controlled data suggest that, if at all, the risk of suicidal behaviours including suicide attempts, and suicide seems to be not substantially different between lithium and valproate, although subtle differences cannot be excluded (Oquendo et al. 2011). Thus, we would consider the ***Rating of PSu as "0"***

Practicability (PR)

There is a wide range of preparations for valproate available, including immediate and slow release tablets, mini tablets, oral solutions and solutions for intravenous injections. Whereas plasma levels for acute mania treatment have been quite firmly established (Allen et al. 2006), the optimal serum levels for maintenance are less clear. A plasma concentration range of 45–100 mg/l (315–700 µmol/l) provided superior results than lower or higher concentrations in the 1-year maintenance trial by Bowden et al. (Keck et al. 2005). ***Rating of PR: "+"***

Recommendation grade (RG)

In summary, valproate has CE evidence "B" for depression in PNES, and further supportive evidence from a CE "C" for PES any relapse. Thus, ***the RG is "3".*** However, the safety and tolerability profile is not without issues, and therefore ***it should not be routinely used as long-term treatment in women of child-bearing age.*** However, if a woman of child-bearing age unambiguously achieves better mood stabilization with a regimen including valproate, understands the risks and their cause, and reliably practices birth control, risks should be balanced against benefits in the individual case.

Ziprasidone

Prevention of TEE in enriched samples (PES)

We identified one placebo-controlled add-on study to lithium or valproate (Bowden et al. 2010). Patients were included with a manic or mixed index episode, stabilized on ziprasidone and either lithium or valproate, and after fulfilling stabilization criteria for eight consecutive weeks, randomized to continuation on combination treatment ($n = 127$) or lithium/valproate + placebo ($n = 113$) for 6 months. Combined ziprasidone + lithium/valproate was significantly superior to lithium/valproate + placebo for PES for any TEE ($P = 0.027$) (CE "B") and manic/mixed TEE ($P = 0.014$) (CE "B"), but not for depressive TEE ($P = 0.682$) (CE "E"). The lack of preventive effects against depressive recurrences is likely due to similar reasons as assumed in the aripiprazole add-on study (Marcus et al. 2011), and different study designs might be needed to detect depression protective effects of ziprasidone if existing. ***CE for the prevention of manic episodes in ES "B"; CE to prevent new depressive episodes in ES is "E";*** and the ***CE to prevent any episode in ES is "B".***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any long-term study with ziprasidone for PNES which would satisfy CE "A", "B" or "C" criteria. ***CE to prevent a manic, depressed or any episode in NES is "F".***

Prevention of TEE in rapid cyclers (PRC)

The only bipolar disorder maintenance RCT (Bowden et al. 2010) allowed patients with less than eight episodes in the previous year into the trial, but a separate analysis of subjects with four to seven episodes in the year preceding the study has not been published. We also could not identify any other evidence such as case series supporting the use of ziprasidone in preventing new episodes in RC patients. ***CE for RC: "F"***

Further evidence (FE)

One-year open-label extension of the first two pivotal 3-week acute mania studies (Keck et al. 2003; Potkin et al. 2005) gave evidence for a maintenance of antimanic effectiveness, together with a good safety and tolerability profile (Dubovsky and Dubovsky 2011). ***Rating for FE: "+"***

Safety and tolerability (ST)

The safety and tolerability profile of ziprasidone is generally good; of note is the negligible impact on metabolic parameters, prolactin and the fact that ziprasidone is relatively weight neutral (Kemp et al. 2012). Some sedation, although less than with several other APs, and EPS, especially tremor and akathisia, are more frequent side effects (Seemuller et al. 2005). The most frequent side effects (≥5% incidence) in the long-term add-on study were sedation (22.9%), somnolence (17%), tremor (12.5%), insomnia (10.1%), dizziness (8.4%), akathisia (8%), fatigue (7.5%), nausea (7.2%) and headache (5.5%).

QTc prolongation has been a major concern with the use of ziprasidone in the past. An analysis of the acute mania study by Keck et al. (2003) described a mean QTc prolongation of 11 ms, but no prolongation of greater than 500 ms (Seemuller et al. 2005). In the add-on maintenance study no critical QTc prolongation was observed. At the end of the 16-week stabilization phase the mean QTc time was 390.3 ms (range 308–73 ms) with no subject exceeding 500 ms. ECG monitoring is recommended with the use of ziprasidone; however, the risk of QTc prolongations resulting in torsades de pointe appear minimal in otherwise healthy subjects.

Ziprasidone is in the FDA "C" pregnancy category meaning that risk cannot be ruled out as there are no controlled data in human pregnancy, but animal studies have revealed evidence of developmental toxicity including possible teratogenic effects, an increase in the number of offspring born dead, and a decrease in postnatal survival. However, a developmental delay after in utero exposure has been observed for ziprasidone in a preliminary report so, for now, ziprasidone should be used even more cautiously in pregnancy than other antipsychotics (Nguyen et al. 2009).

In summary, the favourable metabolic profile on the one hand, and possible minor QTc prolongation and some concerns in pregnancy on the

other hand balance each other, so the ***Rating of ST: "0"***

Prevention of suicide (PSu)

Karayal et al. (2011)conducted a pooled analysis to identify possibly suicide-related adverse events in sponsored placebo-controlled, double-blind, adult and paediatric randomized controlled trials of ziprasidone. No cases of completed suicide occurred in this analysis. Suicidality events (suicidality and suicidal behaviour) were identified in 52 among 5123 subjects treated with either ziprasidone or placebo in 22 trials. There were no statistically significant differences between ziprasidone and placebo in any of the individual classification categories derived from the Columbia Classification Algorithm of Suicide Assessment. ***Rating of PSu: "0"***

Practicability (PR)

Ziprasidone is available as an i.m. injectable or oral solution and as tablets in different strengths. Thus, there is a reasonable choice of forms of applications. The recommended dose for maintenance treatment in combination with lithium or valproate is 80–160 mg which is identical to the recommended monotherapy dosage in acute mania. If there is a need, e.g., in break-through mania, ziprasidone can be titrated quickly to achieve a rapid response. ***Rating of PR: "+"***

Recommendation grade (RG)

Based on a CE "B" for combination treatment in PES for "mania" and any episode", the ***RG is "3".***

Zotepine: see "Other atypical antipsychotics used in bipolar disorder"

Other atypical antipsychotics used in bipolar disorder

Amisulpride is a frequently used medication in bipolar disorder in some countries, also beyond acute treatment. The only published evidence we found was an open-label amisulpride add-on study by Carta et al. (2006). The study enrolled 14 bipolar I outpatients not responding to on-going standard therapy: 11 were followed-up for 11.7 ± 8.2 months before and 5.2 ± 2.7 months after the introduction of amisulpride. Relapse rates before and during treatment with amisulpride were calculated in accordance to an increase of 1 or more in the CGI-BP score that was at the same time accompanied by a change in therapy or to an exacerbation of the symptoms that required hospitalization. The authors found a statistically significant decrease in overall relapse rate during the period of added amisulpride. The relative risk of relapse in the absence of amisulpride therapy was 3.1 ($P < 0.05$). Similarly, the rates of manic/mixed and depressive relapse were decreased but only manic episodes reached statistical significance (RR = 5.3, $P < 0.02$). These data give amisulpride a CE of "C" for any relapse and manic relapses in PNES. If used in long term, the metabolic profile appears quite acceptable, but prolactin elevation and extrapyramidal motor symptoms might limit its usefulness (Rummel-Kluge et al. 2010). Similar to risperidone, the rating for ST would be "–".

Asenapine has proven antimanic efficacy in two RCTs in monotherapy (CE "A" for mania (Grunze et al. 2009)) and in one more recent combination therapy study (Szegedi et al. 2012). The monotherapy studies included a 1-year double-blind extension comparing asenapine against olanzapine. Maintenance of efficacy as measured with regular YMRS assessments appeared similar between medications; however, it was only a secondary outcome with predefined wide non-inferiority criteria. Also the combination treatment study included a 1-year extension; however, due to a very high attrition rate results are not conclusive. Thus, asenapine can be assigned a ***CE of "C" for prevention of mania in ES,*** whereas the other efficacy categories are CE "F". There is also no published further supportive evidence (FE "0"). The available long-term data raise only minor concerns when it comes to weight gain and mild sedation (ST "+"), but practicability (only as sublingual formulation available) may be a problem in some patients (PR "–").

Cariprazine has recently demonstrated antimanic efficacy in a RCT (Yildiz et al. 2011); however, long-term data still need to be generated.

Albeit there are no placebo-controlled RCTs with **clozapine** in bipolar disorder, it is frequently used in otherwise treatment-refractory bipolar patients.

A pharmaco-epidemiological database study using a 2-year mirror-image design was carried out in Denmark, investigating the effectiveness of clozapine in 326 BD patients (Nielsen et al. 2012). The mean follow-up time was 544 ± 280 days. During clozapine treatment, the mean number of bed-days decreased from 177.8 to 34.6 ($P < 0.001$), the mean number of admissions from 3.2 to 2.0 ($P < 0.001$), and the number of psychotropic co-medications from 4.5 defined daily doses (DDD) to 3.9 DDD ($P = 0.045$). There is also more evidence based on

case reports (Puri et al. 1995; Zarate et al. 1995; Hummel et al. 2002) ***(CE "C" for any episode in PNES)*** but issues exist with safety (especially agranulocytosis) and, consequently, practicability making frequent blood check mandatory (ST and PR "–").

Case series support the use of clozapine in rapid cycling patients not responsive to standard treatments (Calabrese et al. 1991; Suppes et al. 1994; Frye et al. 1996; Lancon and Llorca 1996) that merit a ***CE of "C" for PRC and a RG "3" for prevention of TEE in RC (PRC).***

Also of note are the suicide preventive effects of clozapine in schizophrenic patients, which, however, still need replication in bipolar subjects (PSu "+"). However, the mentioned study by Nielsen et al. (2012) also found that somatic hospital visits for intentional self-harm/overdose were significantly reduced during clozapine treatment from 8.3 to 3.1% ($P = 0.004$).

We could not identify any published studies for **zotepine** supporting its long-term use in bipolar disorder. CE "C" evidence in bipolar disorder is, so far, restricted to acute mania (Grunze et al. 2009). When used as maintenance treatment, zotepine might be associated with modest weight gain, hyperlipidaemia and sedation, but to a lesser degree than pharmacologically similar agents such as olanzapine. However, there are surprisingly little data available for the side effect profile of zotepine, especially in direct comparison to other atypical antipsychotics (Riedel et al. 2010; Rummel-Kluge et al. 2010).

Other anticonvulsants used in bipolar disorder

Oxcarbazepine has been infrequently used in bipolar patients as alternative to carbamazepine in patients not tolerating carbamazepine well or in need of co-medication that strongly interferes with carbamazepine. However, also oxcarbazepine has a interaction potential with other medication, and the risk of hyponatraemia might be higher than with carbamazepine (Van Amelsvoort et al. 1994). There is some evidence from acute mania studies supporting oxcarbazepine's use in this indication (Grunze 2010): however, we could identify only one RCT testing the prophylactic efficacy of oxcarbazepine. Vieta et al. (2008a) evaluated the prophylactic efficacy and the long-term tolerability of oxcarbazepine in bipolar I and II disorder as an adjunctive therapy to lithium in a 1-year, double-blind RCT. Bipolar I and II patients currently in remission were randomly assigned to oxcarbazepine ($n = 26$) or placebo ($n = 29$) as adjuncts to on-going treatment with lithium. The primary efficacy variable was the length of the remission period assessed by means of the YMRS and MADRS. The mean time to first recurrence of any type was 19.2 ± 13.9 and 18.6 ± 17.0 weeks for oxcarbazepine and placebo, respectively ($P = 0.32$). Ten (38.5%) patients had a recurrence of any kind in the oxcarbazepine group vs. 17 (58.6%) in the placebo group ($P = 0.14$). There was a trend for depressive episodes being less likely in the oxcarbazepine group compared to the placebo group (11.5 and 31%, respectively, $P = 0.085$). The small number of patients included in this study could be a likely reason for results not reaching significance. Strictly speaking, this trial has failed; however, with the clear numerical superiority of oxcarbazepine addition, we would consider it as a ***CE "C" evidence for PNES any episode and depression and a RG "4".***

Phenytoin has demonstrated relapse preventive effects in small sample of patients (Mishory et al. 2003). Twenty-three stable bipolar patients were studied who had at least one episode per year in the previous 2 years despite on-going prophylaxis. The majority of relapses during the last 2 years were manic/mixed indicating that this population might consist of a larger number of patients with a manic polarity. The period of stability, however, was less well controlled and ranged from 1 to 13 months. Phenytoin or placebo was added to their current therapy in a double-blind cross-over design for 6 months in each phase. The mean dose of phenytoin at month 6 was 380 ± 80 mg. Three patients relapsed on phenytoin and nine on placebo which was a significant difference (Cox's F-test for comparing survival in two groups: $F = 3.44$, $P = 0.02$). Twice as many relapses were into mania compared to depression for both phenytoin and placebo.

Although this is an interesting note for potential prophylactic efficacy of phenytoin, the study does not fulfil the methodological criteria to be counted as evidence sufficient for a CE "B". Thus, similar to oxcarbazepine, phenytoin should be considered as a medication with a ***CE of "C" evidence for PNES any episode, and a RG "4"***.

Gabapentin and topiramate have been tested in RCTs of acute mania, but both failed to separate from placebo (Grunze et al. 2009). As a result, the respective sponsors were not pursuing a bipolar disorder indication, and no conclusive maintenance studies have been conducted. A retrospective chart review of **topiramate** as bipolar maintenance treatment is suggestive of some efficacy, especially in RC patients (Marcotte 1998), and in combination with olanzapine, primarily initiated with the intention to limit weight gain (Vieta et al. 2004). These studies merit a "+" for further evidence (FE) and a CE of "C" for RC patients, in the absence of prospective

studies in enriched/non-enriched samples (CE "F"). Practicability of its use has no major issues (rating "+"), and the safety/tolerability profile of topiramate appears reasonable in low doses commonly used in bipolar disorder (rating "+"); however, neurological side effects are not entirely dose dependent, including cognitive impairment and rare cases of transient hemiparesis (Jones 1998). There is still some concern about increased suicidality as suggested by the FDA (US Food & Drug Administration 2008); different from lamotrigine, there are no data for topiramate and suicide risk in bipolar patients which may put this into the right perspective. Thus, the rating for PSu would be "–". In summary, and based on the CE "C" for PRC, topiramate would be assigned a **RG "4".**

As with topiramate for weight gain, **gabapentin** is nowadays primarily used in bipolar disorder patients to treat comorbidities as anxiety disorder or substance abuse though there are no controlled data to support this practice (Perugi et al. 2002; Carta et al. 2003). Studies supporting such a use are either retrospective or in small numbers of subjects (FE: "+"). The best evidence, however, for the long-term use of gabapentin in bipolar disorder is a small, but placebo-controlled trial of adjunctive gabapentin for 1 year (Vieta et al. 2006). It included euthymic bipolar I and II patients who were randomly assigned to gabapentin ($N = 13$) or placebo ($N = 12$) added to the current treatment. The primary efficacy parameter was the modified CGI-BP, which was assessed at all visits. After 12 months, mean CGI-BP score change from baseline to endpoint in the gabapentin group was −2.1, and the mean score change in the placebo group was −0.6 ($P = 0.0046$). No emerging manic or depressive symptoms were seen in either group as measured with standard scales, and gabapentin was generally well tolerated.

The study falls short to our pre-set inclusion criteria of at least 25 bipolar I patient (as six patients had a bipolar II diagnosis). However, based on this study, gabapentin can be classified as **CE "C" for any mood episode in PNES.** Gabapentin is mostly well tolerated (ST: "+"), its short half life necessitating three daily dosages, however, limits practicability (PR: "–"). Positive or negative effects on suicidality are unknown by large (PSu: "0").

We could not identify evidence of some impact for the long-term use of the following anticonvulsants in bipolar disorder: eslicarbazepine, pregabalin, levetiracetam, vigabatrine, barbiturates or bromides. However, our search may have missed evidence, especially for the first generation antiepileptics, as it may have been published prior to the inclusion period of our literature search.

Hormones, vitamins, amino acids and fatty acids

Berk et al. (2008a) conducted a placebo-controlled add-on study of *N*-acetylcysteine (NAC, 1 g twice daily) to ongoing treatment in bipolar patients ($n = 75$) with treatment-resistant sub-threshold depression. Study duration was 24 weeks, with a 4-week washout. The two primary outcomes were the MADRS and time to a mood episode. NAC treatment was associated with a significant reduction in symptoms at treatment completion (week 24) on the MADRS primary score (least squares (LS) mean difference (95% CI): −8.05 (−13.16, −2.95), $P = 0.002$). Response, defined as a 50% reduction in total MADRS score, at weeks 20 and 24 compared with baseline was observed in 46 and 51% of participants in the NAC group compared with 21 and 18% in the placebo group, respectively ($P = 0.036$ and $P = 0.001$, respectively. However, there was no effect of NAC on time to a TEE (log-rank test: $P = 0.968$). Similar benefits of NAC were seen in a subgroup analysis of bipolar II patients (Magalhaes et al. 2011). Thus, NAC might be beneficial in treating persistent, sub-threshold depressive symptoms, but does not seem to have protective effects against recurrence of episodes.

The evidence for the use of omega-3 fatty acids, or their active ingredient eicosapentanoic acid, in bipolar disorder is conflicting. For the acute treatment of bipolar depression, diverging results have been described (Frangou et al. 2006; Keck et al. 2006b). In a mixed population of euthymic, depressed and (hypo) manic patients, however, omega-3 fatty acids seemed to ameliorate symptoms and prevent recurrences. Stoll et al. (1999) conducted a 4-month, double-blind, placebo-controlled study, comparing omega-3 fatty acids (9.6 g/day, corresponding to 6.2 g/day eicosapentanoic acid) versus placebo (olive oil), in addition to usual treatment, in 30 patients with bipolar disorder. Patients needed to have had at least one (hypo) manic episode during the year preceding the study. At study entry the majority of subjects still had at least residual symptoms, only six of the 30 were classified as euthymic. The study population was not enriched for previous exposure to omega-3 fatty acids. The primary finding was that the omega-3 fatty acid patient group had a significantly longer period of remission than the placebo group ($P = 0.002$; Mantel–Cox). Omega-3 fatty acids were generally well tolerated, and may have additional benefits in reducing the risk of cardiac mortality in affectively ill patients (Severus et al. 2001).

The random mixture of syndromal and euthymic patients with only a small number of patients entering controlled trial condition in euthymia, however,

disqualifies this study from CE "A" or "B" evidence, but is considered as sufficient for a CE of "C" for PNES, and by this for an **RG"4".**

Maintenance electroconvulsive therapy (ECT)

Prevention of TEE in enriched samples (PES)

In the literature, the terms "continuation ECT" and "maintenance ECT" are used randomly and interchangeably. Even more than in the case of pharmacotherapy, the distinction between continuation ECT (c-ECT) and maintenance ECT (m-ECT) is purely hypothetical, as m-ECT develops gradually out of c-ECT without fixed boundaries. In addition there is nothing like "prophylactic" ECT which would imply an irrational use of ECT by starting stable and euthymic patients on ECT.

Due to the nature of ECT which makes it unethical to conduct "placebo" studies, e.g., with sham ECT, we have no data available allowing classification as CE "A" and "B". However, there is nowadays a reasonable literature on open and comparator studies (albeit in numbers too small to test for non-inferiority) supporting the use of maintenance ECT (m-ECT) in bipolar depressed patients responding to an acute course of ECT (Loo et al. 2011). A recent review looking into articles published in the English language between 1998 and 2009 identified 32 reports on continuation and/or maintenance ECT. These articles included 24 case reports and retrospective reviews on 284 patients. Two of these reports included comparison groups, and one had a prospective follow-up in a subset of subjects. The authors also identified six prospective naturalistic studies and two randomized controlled trials (Petrides et al. 2011). The overall outcome of all these studies was clearly positive showing a marked reduction of future mood episodes, and supports the use of m-ECT in patients non-responsive or non-tolerant to long-term medication treatment. However, m-ECT protocols (stimulus paradigms, frequency) were not uniform, and direct comparisons between protocols were not made. This leaves some degree of uncertainty for clinicians, and the need to develop individualized treatment protocols based on the patient's history of relapses and recurrences. ***CE in PNES: "C"***

Prevention of TEE in non-enriched samples (PNES)

We could not identify studies where maintenance ECT was conducted without a previous course of acute ECT. Clearly, it would also be paradoxical to use ECT a priori in stable, euthymic patients. ***CE in PNES: "F"***

Prevention of TEE in rapid cyclers (PRC)

In a recent open study, 14 patients with BPD (type I or II), unresponsive to previous medication treatment, and an RC course were treated with monthly m-ECT. Response was assessed as days ill 2 years before and after sessions of m-ECT. The mean treatment duration was 21 months, and all patients improved during treatment. Illness duration decreased 13-fold from 304 to 24 days of illness per year, and illness-free intervals increased from 52 to 334 days per year (all $P < 0.0001$) (Minnai et al. 2011). ***CE in RC: "C"***

Further evidence (FE)

There is also older literature (pre-1998 which was the lower inclusion limit of the review by Petrides et al. 2011), mainly case reports, supporting the use of continuation and maintenance ECT, as reviewed by Rabheru and Persad (1997). ***Rating of FE: "+"***

Safety and tolerability (ST)

Progressive cognitive impairment, especially of memory, is a main worry associated with repetitive ECT sessions. In addition, every session has the inherited risks associated with short-term anaesthesia. The case reports of m-ECT do not explicitly support these concerns; however, in most instances memory impairment was not specifically measured. In addition, evidence based on single cases or series is also more subject to publication bias than controlled studies; unfavourable outcomes are seldom reported. Thus, clinicians should take these concerns serious unless proven otherwise. ***Rating of ST: "–"***

Prevention of suicide (PSu)

There are no data reported on suicide prevention for m-ECT. It is reasonable to assume that successful prevention of new mood episodes in severely ill bipolar patients reflects positively on suicide rates, but, different to, e.g., lithium, we have no data supporting antisuicidal effects independent from treatment success. ***Rating of ST: "0"***

Practicability (PR)

Compared to medication treatment, ECT is clearly associated with more efforts and man power. However, we should keep in mind that m-ECT can usually be administered on a outpatient basis not

requiring hospitalization, it is mostly a low frequency, biweekly or monthly event with a high adherence (different from medication that has to be taken daily with unclear compliance). ***Rating of PR: "–"***

Recommendation grade (RG)

Given the overall evidence, we would assign m-ECT a **RG "4".** However, in severely ill bipolar patients who have failed on multiple prophylactic medication trials, we would recommend to consider ECT not only for the acute phase (Grunze et al. 2009, 2010) but also as a serious option for long-term treatment.

Other physical treatments

Sleep deprivation, coupled with sleep phase advance, and bright light therapy are regularly applied for the treatment of acute depression, including bipolar depression; however, we did not find published evidence on their long-term use to prevent new episodes in bipolar patients. Some pioneering work has been carried out in the acute treatment of bipolar patients with repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Whereas the efficacy of rTMS as bipolar maintenance treatment is largely unknown (Agarkar et al. 2011), some open evidence exists for the usefulness of VNS in treatment refractory bipolar depression; however, the reported long-term data do not include separate analysis for bipolar disorder patients (Rush et al. 2005; Nierenberg et al. 2008). The use of DBS to treat bipolar disorder patients has evolved quite recently; in the past, case reports, e.g., from Parkinson patients, were more suggestive of risks to induce mania by DBS (e.g., Raucher-Chene et al. 2008). This might deter research from using DBS in bipolar I disorder patients; the so far largest case series was done in unipolar and bipolar II disorder patients with treatment refractory depression. In an open-label trial with a sham lead-in phase, Holtzheimer et al. (2012) assessed the efficacy and safety of subcallosal cingulate DBS in ten patients with MDD and seven with BP who were enrolled from a total of 323 patients screened. Patients received single-blind sham stimulation for 4 weeks followed by active stimulation for 24 weeks. Patients then entered a single-blind discontinuation phase; this phase was stopped after the first three patients because of ethical concerns. Patients were evaluated for up to 2 years after the onset of active stimulation. A significant decrease in depression and increase in function were associated with chronic stimulation. Remission and response were seen in three patients (18%) and seven (41%) after 24 weeks ($n = 17$), five (36%) and five (36%) after 1 year ($n = 14$), and seven (58%) and 11 (92%) after 2 years ($n = 12$) of active stimulation. No patient achieving remission experienced a spontaneous relapse. Efficacy was similar for patients with unipolar and those with bipolar depression. Chronic DBS was considered as safe and well tolerated, and no hypomanic or manic episodes occurred.

In conclusion, the evidence for physical treatments other than m-ECT is still too weak to give a recommendation for bipolar I disorder patients. For Bipolar II disorder patients, there is some preliminary evidence for DBS to prevent TEE.

The role of psychotherapy and psychoeducation

As we clarified at the beginning, this guideline is not focussing on the evidence of psychotherapies and psychoeducation in the long-term treatment of bipolar disorder. The important role of these techniques for improving compliance and resilience against mood instability are well documented and they are an integrative and established component of treatment, accompanying medication. For an up-to date reviews of their differential efficacy and cost-effectiveness, we refer the reader to recent publications (e.g., Scott et al. 2007, 2009; Beynon et al. 2008).

Conclusion

Using the established approach of the WFSBP guideline series, and making minor modifications to suit the topic of bipolar maintenance, we identified six medications with the two highest recommendation grades, based on their evidence for different aspects of bipolar disorder maintenance treatment in diverse patient population. None of these medications can fully cover all areas and patient groups equally well; so we are pleased to see that the number of alternatives has grown since the first edition of this guideline in 2004 (Grunze et al. 2004). We also notice that despite the development of promising alternatives, lithium is still a top standard for the long-term treatment of bipolar disorder.

By far, the body of evidence originates from RCTs conducted with PAs which have been launched in the last two decades. However, this should not imply that we ignore real world practice and longstanding clinical experience with "old" PAs just because of a lack of RCTs. Even more important, we should be aware of the hazards switching stable bipolar patients

from their established treatment as it may cause a worsening of disease course, increase of suicidal risk and new side effects. A low recommendation grade (RG) for "old" PA (like carbamazepine or clozapine) could, but does not necessarily mean a lower effectiveness and safety in comparison with other drugs. The reason may also be a historical lack of RCTs fulfilling today's criteria for evidence based medicine.

But not only has the choice of candidate medication increased since the first edition of the WFSBP bipolar maintenance guideline, the field has also advanced otherwise. We had to spend much more thought on trial designs, and how they allow us to extract clinical valuable information. Clinicians want to know the real recurrence preventive properties of a drug, not so much the disastrous effects of drug discontinuation in insufficiently stabilized patients. This is why we spend much thought on trial design when writing the guideline, to help clinicians to develop a more critical reading and appraisal of studies. Given the heterogeneous trial designs, the different strengths and weaknesses of available medication, and finally the subjectivity of experts when making a recommendation – even when based on evidence – we can only encourage the reader to draw his/her own conclusions from the evidence using this guideline as a – hopefully useful – reference.

For the reason of diversity of trials designs, patient populations examined, and pursued outcome, e.g., having strong antimanic or antidepressive prophylaxis in place, we cannot give a general recommendation up to which RG a medication should be used, as we did with the mania and bipolar depression guideline. Clearly, the choice of RG "1" or "2" recommendations is wider in the prophylaxis of mania in patients responsive to acute antimanic treatment than, e.g., specifically in the prevention of rapid cycling, and thus the numerical value of the maximum RG can be lower, e.g., "3" or "4". On the other hand, in clinical manifestations with lack of evidence for treatment, the clinician may consider a top to bottom approach when choosing medication, tailored to the specific need of the patient, down to RG 5 which is based on equivocal evidence. However, additional information on safety, tolerability and suicide prevention should always be considered for the final treatment decision.

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