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

Heinz Grunze[1,2*], Eduard Vieta[3], Guy M. Goodwin[4], Charles Bowden[5], Rasmus W.Licht[6], Hans-Jürgen Möller[2], Siegfried Kasper[7], WFSBP Task Force on Treatment Guidelines for Bipolar Disorders[8]

1 Newcastle University, Institute of Neuroscience, Newcastle upon Tyne, United Kingdom

2 Ludwig-Maximilians-University, Department of Psychiatry, Munich, Germany

3 Bipolar Disorders Programme, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

4 University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford, United Kingdom

5 University of Texas Health Science Center, Dept. of Psychiatry, San Antonio, USA

6 Mood Disorders Research Unit, Aarhus University Hospital, Risskov, Denmark

7 Medical University of Vienna, Department of Psychiatry and Psychotherapy, Vienna, Austria

8 WFSBP Task Force on Treatment Guidelines for Bipolar Disorders:

Siegfried Kasper (Chairman, Austria), Guy Goodwin (Co-Chairman, United Kingdom), Charles Bowden (Co-Chairman, USA), Heinz Grunze (Secretary, United Kingdom), Hans-Jürgen Möller (WFSBP Past-President, Germany), Rasmus W.Licht (Denmark), Eduard Vieta (Spain).

Hagop Akiskal (USA), José Luis Ayuso-Gutierrez (Spain), Michael Bauer (Germany), Per Bech (Denmark), Michael Berk (Australia), Istvan Bitter (Hungary), Graham Burrows (Australia), Joseph R. Calabrese (USA), Giovanni Cassano (Italy), Marcelo Cetkovich-Bakmas (Argentina), John C. Cookson (United Kingdom), Nicol I. Ferrier (United Kingdom), Maria Luisa Figueira (Portugal), Wagner F. Gattaz (Brazil), Frederik K. Goodwin (USA),

Gerhard Heinze (Mexico), Chantal Henry (France), Teruhiko Higuchi (Japan), Robert M. Hirschfeld (USA), Cyril Hoeschl (Czech Republik), Edith Holsboer-Trachsler (Switzerland), Kay Redfield Jamison (USA), Cornelius Katona (UK), Martin Keller (USA), Lars Vedel Kessing (Denmark), E. Kostukova (Russia), Hever Kruger (Peru), Parmanand Kulhara (India), Veronica Larach (Chile), Odd Lingjaerde (Norway), Henrik Lublin (Denmark), Mario Maj (Italy), Julien Mendlewicz (Belgium), Roberto Miranda Camacho (Mexico), Philip B. Mitchell (Australia), Sergey Mosolov (Russia), Stuart Montgomery (United Kingdom), Charles Nemeroff (USA), Willem Nolen (The Netherlands), Timucin Oral (Turkey), Eugene S. Paykel (United Kingdom), Robert M. Post (USA), Stanislaw Puzynski (Poland), Zoltan Rihmer (Hungary), Janusz K. Rybakowski (Poland), Simavi Vahip (Turkey), Per Vestergaard (Denmark), Peter C. Whybrow (USA), Kazuo Yamada (Japan)

Correspondence:
Prof. Dr. Heinz Grunze
Institute of Neuroscience
Department of Psychiatry, RVI
Newcastle University
Newcastle upon Tyne, NE1 4LP, United Kingdom
Tel: +44 191 282 5765 Fax: +44 191 222 6162
E-mail: Heinz.Grunze@ncl.ac.uk

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 until 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.

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
PNES	Prevention of TEE in Non-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 & Tolerability
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TAU	Treatment as usual
TEAS	Treatment emergent affective switch
OR	Odds ratio
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 2009b;Grunze et al 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 (Young et al 2011;Runge and Grunze 2004;Hakkaart-van Roijen et al 2004).

Starting with Kraepelin (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 (Altshuler et al 2006;Angst and Preisig 1995;Coryell et al 1993;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.

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., developed for major depression (Frank et al 1991b), 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.

Insert Figure 1 about here

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 (American Psychiatric Association 1994;World Health Organization 1992), separating 2 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) has been achieved. 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. (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 till one 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 drop-out 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 it is 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 vs. 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) vs. 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 (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 (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;Tohen et al 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 not acute response, but tolerability and mood stability, e.g. for a minimum of four weeks on lamotrigine including one 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.

Insert Figure 2 about here

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. (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. (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.

Insert Figure 3 about here

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 six days to six 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, Jr. 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 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(Calabrese et al 2003;Bowden 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 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;Licht et al 2010;Geddes 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 2009a;Grunze et al 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 (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 anti-depressants 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 1-5 medications, with over 55% of patients being on 2 or 3 medications, 31.8% requiring 4 or more drugs and 13.8% requiring 5 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 (Kessing 1998a;Roy-Byrne et al 1985;Angst 1981;Zis et al 1980), 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 (Baldessarini et al 1999c;Goodwin 1994) 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. five 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 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 one 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.

Insert Figure 4 about here

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 (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 (Murru et al 2011a) 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 x 100- and a post PA recurrence index – with PostPAri being defined as number of episodes / month duration of illness during PA x100- they propose to classify the percentage reduction from PrePAri to PostPAri ranging from excellent to lack of response (see Table1). 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.

Insert Table 1 about here

Less formalistic, but probably more informative is an approach introduced by Grof et al (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%–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;Kupka et al 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 & 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 (Miklowitz 2008;Beynon et al 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 2009b;Grunze et al 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 (Goodwin 2009;Vieta et al 2011;Vieta et al 2010a;Nolen et al 2008). A few additional trials were found by hand-searching 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 chapter 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 (Bandelow et al 2008;Anderson 2000;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 2). 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]

Insert Table 2 about here

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

[1] A point of discussion within the task force, raised by J.R.C., 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.

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 evidence to " - -" for strong negative or most concerning evidence (see Tables 3 and 4).

Insert Table 3 about here

Insert Table 4 about here

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 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 5), "Prevention in non-enriched samples" (Table 6) or "Prevention of TEE in Rapid-cycling patients" (Table 7) no matter prevention of any episode, mania or depression, were given an RG.

- 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

- 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 8).
- 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.

Insert Table 5 about here

Insert Table 6 about here

Insert Table 7 about here

Insert Table 8 about here

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;Lexchin and Light 2006;Heres et al 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 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 chapters, 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 chapter on "Methods of this review", and graded the other categories in a more simplified system (ranging from ++ to - -, see Table 3). 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, despite not assigning it a recommendation grade, 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 alphabetic 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 co-morbidities, 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 coworkers, 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 chapter 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 ($p < .05$) whereas there was no significant difference between the lithium and imipramine groups in the incidence of depressive episodes ($p > .05$). Compared to placebo, the article reports for imipramine only numbers and percentages, but no tests for significance. Of the 13 subjects randomized to placebo, 5 (38%) relapsed into depression, and 8 (62%) into mania. Of the 13 subjects randomized to imipramine, 7 (54%) had a manic and 4 (31%) a depressive relapse. Overall, 77% of patients in both groups had at least one recurrence of a mood episode over the two years of observation: 3 subjects in the placebo group and 1 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 vs. 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 vs. 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 one 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 = .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 vs. 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).

In a 1-year double blind follow up of a 10 week acute study comparing 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, 6 (27%) of the 22 acute partial responders had achieved positive treatment response at study endpoint ($p < .001$). Only 8 acute positive responders (13%) and 5 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 (Altshuler et al 2003;Altshuler et al 2009;Ghaemi et al 2008;Prien et al 1974).

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 five 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 (Grunze 2008;Ghaemi 2008). This may be also true for SSRI; 52 % of subjects in the study of Ghaemi et al (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. found no advantage of imipramine over placebo (Kane et al 1982). In combination with lithium, imipramine was also not more effective than lithium monotherapy (Quitkin et al 1978;Quitkin et al 1981).

Johnstone et al (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 (Amsterdam et al 1998) compared fluoxetine in unipolar depressed with fluoxetine in bipolar II depressed patients in acute and long-term treatment (up to one 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;Amsterdam and Shults 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 (Bond et al 2008;Parker et al 2006).

Rating of FE: 0

Safety & 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 (Stone et al 2009;Simon et al 2006) as well as pharmaco-epidemiological and large observational studies (Leon et al 2011;Gibbons et al 2007) 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, Jr. 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 paragraph 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 2 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 paragraph "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;Keck, Jr. et al 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 (Marcus et al 2011) included only 9.5% rapid cycler (defined as patient having 4-6 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 2009a), 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 (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 &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 3 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, 20489 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 (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 versus 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 coworkers (Greil et al 1997b;Greil and Kleindienst 1999a;Greil and Kleindienst 1999b) 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 = n.s.). These results hold true both in Bipolar I and II patients (Greil and Kleindienst 1999a;Greil and Kleindienst 1999b). 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 vs. manic or mixed symptomatology was numerically higher under carbamazepine (Kleindienst and Greil, personal communication 26.4.2012). 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 (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. (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 vs. 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;Hartong et al 2003;Denicoff et al 1997b), but all in sample sized insufficient for non-inferiority studies, as requested for CE "B" evidence.

Hartong et al (Hartong et al 2003) compared 94 patients in a randomized, two-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 three 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 vs. depressive recurrences with lithium and carbamazepine; in absolute numbers, 4 patients on lithium developed a new (hypo)manic episode vs. 10 on carbamazepine, and 8 on lithium a new depressed episode vs. 11 on carbamazepine.

Coxhead et al. carried out a one 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 2 groups (6 on carbamazepine, 8 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 (Coxhead et al 1992).

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 one 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 (Placidi et al 1986)and Watkins(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 (Watkins et al 1987) found lithium superior to carbamazepine, Placidi (Placidi et al 1986) did not report significant differences.

Denicoff et al.(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 & 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 P 450 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 (Calabrese et al 2003;Bowden 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 one week. Both studies were conducted in bipolar I patients only, with not more than 6 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 (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 =.002, lamotrigine vs. placebo; p = .010, lithium vs. placebo).

However, when applying a MOAT-BD analysis (see subchapter ”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 wit 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 per cent 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 = .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 (van der Loos et al 2009) conducted a RCT for the combination treatment of lithium + lamotrigine versus 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 one year, double blind follow up study. Fifty-five subjects (30 on lamotrigine + lithium, with 4 subjects on additional paroxetine, 25 on lithium + placebo, with 6 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)) versus 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 (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 six 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 five 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 during at least one week (in addition to study drugs and benzodiazepines) required after month 6 (after randomization) or hospitalization during at least one 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 five 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 (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 chapter 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 &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 (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 (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 (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 2-200 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 mikromol/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 200mg/d 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 2 RCT's, clearly more pronounced for prevention of depression (CE:A), with additional weaker evidence for mania (CE:D). However, the study by Kessing et al. (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 (Baastrup and Schou 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 (Goodwin and Jamison 2007) or Maj (Maj 2000), and more recently by Licht (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 (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 (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 five 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%), 7 of them into a manic, and 5 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 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 (Prien et al 1973a). 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 two 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 and coworkers (Prien et al 1974), already described in the section on "Antidepressants" lithium was significantly better than placebo and imipramine in preventing new affective episodes ($p < .01$, 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 ($p < .05$) whereas the incidence of depressive episodes was not statistically different ($p > .05$). 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 ($p < .05$). 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 have been conducted in the 1970 (Cundall et al 1972;Fieve et al 1976;Stallone et al 1973;Hullin et al 1972;Melia 1970) but each of them has methodological shortcomings, e.g. mixed patient populations, cross-over 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;Prien et al 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 4 large RCTs in which lithium was used as an internal comparator for assay sensitivity has been conducted since the 1990's. Different from the substances under investigation in 3 out of the 4 studies (2 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 (Calabrese et al 2003;Bowden 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 3 of 4 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 (Prien et al 1974), mentioned in the previous paragraph, the quetiapine study and the lamotrigine studies? Prien's study probably also separated because he limited enrollment 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, favoring 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 1998;Dunner and Fieve 1974). 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 six 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 vs. 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 metaanalyses 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 (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 chapter 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 (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/liter) in a double-blind, one 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. 330 patients with bipolar I 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 chapter on "Valproate").

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

Kessing et al (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 increased 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 $\geq$ 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 six 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 six months 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 (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 1/3 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 &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 (Zhang et al 2011;Young 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 hardly ever gives rise to not initiating lithium treatment, possible due to the fact that the risk is well characterized and relatively low in absolute terms (Nguyen et al 2009;Yonkers et al 2004). 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 (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. (Wasserman et al 2012;Gonzalez-Pinto et al 2006;Baldessarini et al 2006;Müller-Oerlinghausen et al 2006).

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 different from those for preventing depression. Lithium concentrations $\leq$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 (Severus et al 2009;Kleindienst et al 2007). 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 0.6-0.75 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 vs. 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 (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 > or =15, HAM-D score > or =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 vs. 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 (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 chapter 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 chapter 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 chapter 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). 99 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 per day) in combination with lithium or valproate (combination therapy), or placebo added to lithium or valproate (monotherapy). 41 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 (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 (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 chapter 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 (Tohen et al 2003a) report a 47-week comparison of olanzapine (5-20 mg/day) and valproate (500- 2500 mg/d). The study had two endpoints which have been reported separately, the first one after three 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 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 one 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 one week, and then they were offered the option of assignment to the combination treatment if wanted. Approximately 2/3 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. 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 & 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%–42%, a proportion much higher than the general population but similar to that observed in schizophrenia (30%–42%) (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).

35 % 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. (Rummel-Kluge et al 2010;Kantrowitz and Citrome 2008).

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 (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 5-20 mg/d depending on monotherapy versus combination treatment and other modifying factors such as age and comorbidities. When re-analysing the lithium vs. olanzapine maintenance study (Tohen et al 2005), Severus et al (Severus et al 2010) found that patients with less than 10mg 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 (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/d) or olanzapine (5-20 mg/d). 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 chapter 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 & Tolerability (ST)

The study by Berwaerts et al (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 (versus 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% versus 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 (±SD) prolactin levels increased from acute treatment baseline to acute/continuation treatment endpoint in both sexes in the paliperidone ER group (men: + 22.37 ± 24.26; women: + 72.23 ± 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 1 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 3-12 mg/ d, depending on tolerability, as tested in the study by Berwaerts et al. (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 (Weisler et al 2011)- see also the chapter 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 4 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 2 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< .0001) and for lithium versus placebo (HR = 0.46; 95% CI, 0.36–0.59; p< .0001). Quetiapine and lithium significantly increased time to recurrence of both manic events (quetiapine: HR = 0.29; 95% CI, 0.21–0.40; P< .0001; lithium: HR = 0.37; 95% CI, 0.27–0.53; p< .0001) and depressive events (quetiapine: HR = 0.30; 95% CI, 0.20–0.44; p< .0001; lithium: HR = 0.59; 95% CI, 0.42–0.84; p< .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<.0001) for quetiapine versus placebo, 0.41 (p <.0001) for lithium versus placebo, and 0.70 (p =.041) for quetiapine versus 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 (Young et al 2012) all patients had a depressive index episode, and, before entering the one 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 chapter 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 (Suppes et al 2009;Vieta et al 2008c) add further to the evidence. Patients had manic/ mixed or depressive episodes, and were stabilized with open label quetiapine (400-800 mg/d) 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 (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% versus 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 (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% versus 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 and 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, 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. (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 (Suppes et al 2007;Duffy et al 2009;Suppes et al 2004;Altamura et al 2003) contributing to a

Rating for FE: +

Safety &Tolerability (ST)

The safety and tolerability data of the study of Weisler et al (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 (ie,≥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- 800 mg. In the monotherapy study by Weisler et al (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 RCT's (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. 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 of25 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 fullfilling DSM IV criteria and severity criteria. Time to recurrence was significantly longer in the risperidone LAI group than the placebo group (log-rank χ^2 = 23.5, df = 1, p< .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< .001; HR,95% CI: 0.25, 0.15 – 0.41) but not for depressive episodes (p = .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, and included besides risperidone LAI and placebo also an olanzapine arm for assay sensitivity (see chapter 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 chapter, 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 (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. 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 6 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. (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 (Benabarre et al 2009;Malempati et al 2008;Vieta et al 2008b;Han et al 2007). Some case

series also support the use of risperidone given as an oral tablet in preventing new mood episodes (Ghaemi and Sachs 1997;Yoshimura et al 2006;Ghaemi et al 2004;Fountoulakis et al 2004).

Rating of FE : +

Safety & Tolerability (ST)

The best evidence for the safety and tolerability of risperidone Lai can be derived from the study by Vieta et al (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 (≥ 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.

Mc Kenna et al reported in a prospective study eight cases of major congenital malformations associated with risperidone exposure including a case of corpus callosum agenesis (McKenna et al 2005), 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 chapter. 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 (Vernon et al 2012;Ho et al 2011;Lieberman et al 2005). 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% versus 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

per cent 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 (Esparon et al 1986) conducted a double-blind cross-over trial of depot flupenthixol in bipolar patients. All patients continued on lithium, and eleven patients completed the two-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 &Tolerability (ST)

Similar to antidepressants, anticonvulsants or atypical antipsychotics we are not likely to be dealing with an 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 two 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 1990's, 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, *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 8 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 favor of adjunctive aripiprazole therapy vs 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 one 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*, but a clinically very relevant additional analysis of the study was conducted by Keck et al. (Keck et al 2005). It showed that with valproate plasma levels between 75 and 99.9 mg/l valproate was 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, metaanalysis 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 also lithium 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 paragraph on olanzapine).

Previous to this more recent study, several open, but in part, randomised studies (Puzynski and Klosiewicz 1984a;Puzynski and Klosiewicz 1984b;Lambert 1984;Denicoff et al 1997a;Hirschfeld et al 1999;Emrich and Wolf 1992;Hayes 1989;Vencovsky et al 1984;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 chapter on lithium).

In line with the results from BALANCE are those of a large Danish registry review conducted by Kessing et al (Kessing et al 2011b). Kessing 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. 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 & 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 vs 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."(U.S.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 chapter 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 (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 (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 : 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 micromol/l) provided superior results than lower or higher concentrations in the one 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 8 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 8 episodes in the previous year into the trial, but a separate analysis of subjects with 4-7 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 &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 (Keck et al 2003)described a mean QTc prolongation of 11msec, but no prolongation of greater than 500 msec (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 msec (range 308- 73) with no subject exceeding 500 msec. 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 (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 5,123 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 i.m. injectable, 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 (Carta et al 2006). The study enrolled fourteen 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 RCT's in monotherapy (CE "A" for mania (Grunze et al 2009a)) and in one more recent combination therapy study (Szegedi et al 2012). The monotherapy studies included a one-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 one 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-epidemiologic database study using a two-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 (Hummel et al 2002;Zarate et al 1995;Puri et al 1995) ***(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 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 2009a). 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 (Rummel-Kluge et al 2010;Riedel 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 (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 one 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 weeks 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). 23 stable bipolar patients were studied who had at least one episode per year in the previous two years despite on-going prophylaxis. The majority of relapses during the last two 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 1-13 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 RCT's of acute mania, but both failed to separate from placebo (Grunze et al 2009a). 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 is 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 is no controlled data to support this practice (Carta et al 2003;Perugi et al 2002). 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 one 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 = .0046). No emerging manic or depressive symptoms were seen in either group as measured with standard scales, and gabapentin ws generally well tolerated.

The study falls short to our pre-set inclusion criteria of at least 25 bipolar I patient (as 6

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: +), it's 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, Vitamines, Amino acids and Fatty Acids

Berk et al (Berk et al 2008a) conducted a placebo-controlled add-on study of N-acetyl-cysteine (NAC, 1g 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 = .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 = .036 and p = .001, respectively. However, there was no effect of NAC on time to a TEE (log-rank test: p= .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 its active ingredient eicosapentanoic acid, in bipolar disorder is conflicting. For the acute treatment of bipolar depression, diverging results have been described (Keck et al 2006b;Frangou et al 2006). 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 (Stoll et al 1999) conducted a 4-month, double-blind, placebo controlled study, comparing Omega 3 fatty acids (9.6 g/d,

corresponding to 6.2 g/d eicosapentanoic acid) vs. 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 6/30 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= .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 d/yr (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 & 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 2009a;Grunze et al 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 (Nierenberg et al 2008;Rush et al 2005). 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 (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 3 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 3 patients (18%) and 7 (41%) after 24 weeks (n = 17), 5 (36%) and 5 (36%) after 1 year (n = 14), and 7 (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.(Beynon et al 2008;Scott et al 2007;Scott et al 2009).

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, patients 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. 1 or 2. 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.

Acknowledgements

We would like to specially thank Dr. Andrea King and Mrs. Reetta Karjalainen, WFSBP office Vienna, for general and editorial assistance.

Statement of interest of principal authors

Heinz Grunze received grants/ research support, consulting fees and honoraria within the last three years from Astra Zeneca, BMS, Desitin, Eli Lilly, Gedeon-Richter, Hoffmann-LaRoche, Janssen-Cilag, Lundbeck, Merck, Otsuka, Sanofi-Aventis, Servier, Sepracor, and UBC.

Eduard Vieta received grants/research support, consulting fees and honoraria within the last three years from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Jazz, Johnson & Johnson, Lundbeck, Merck-Sharp and Dohme, Novartis, Otsuka, Pfizer Inc, Roche Sanofi-Aventis, Servier, Shering-Plough, Solvay, Takeda, Teva and UBC.

Siegfried Kasper has received grant/research support from Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Sepracor and Servier; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pfizer, Schwabe, Sepracor, and Servier; and has served on speakers' bureaus for Angelini, AstraZeneca, Bristol Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Pfizer, Pierre Fabre, Schwabe, Sepracor, and Servier.

Guy Goodwin received grants/research support, consulting fees and honoraria within the last three years from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cephalon/Teva, Eisai, Eli Lilly, Lundbeck, Otsuka, P1Vital, Roche, Sanofi-Aventis, Servier, Takeda.

Charles Bowden received grants/research support, consulting fees and honoraria within the last three years from GSK, Sunovion, Teva and the National Institute of Mental Health.

Rasmus W. Licht received consulting fees and honoraria within the last three years from Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly and Lundbeck.

Hans-Jürgen Möller received grant/research support, consulting fees and honoraria within the last three years from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Eisai, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Organon, Pfizer, Sanofi, Schering-Plough, Schwabe,

Sepracor, Servier, Wyeth and the German Science Foundation, the German Ministry of Science and the German Ministry of Health.

References

Abou-Auda HS, Al-Yamani MJ, Abou-Shaaban RR, Khoshhal SI (2008) A new accurate method for predicting lithium clearance and daily dosage requirements in adult psychiatric patients. Bipolar Disord 10:369-376.

Adams J, Scott J (2000) Predicting medication adherence in severe mental disorders. Acta Psychiatr Scand 101:119-124.

Agarkar S, Mahgoub N, Young RC (2011) Use of transcranial magnetic stimulation in bipolar disorder. J Neuropsychiatry Clin Neurosci 23:E12-E13.

Ahlfors UG, Baastrup PC, Dencker SJ, Elgen K, Lingjaerde O, Pedersen V, Schou M, Aaskoven O (1981) Flupenthixol decanoate in recurrent manic-depressive illness. A comparison with lithium. Acta Psychiatr Scand 64:226-237.

Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL (2006) Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry 163:272-275.

Altamura AC, Salvadori D, Madaro D, Santini A, Mundo E (2003) Efficacy and tolerability of quetiapine in the treatment of bipolar disorder: preliminary evidence from a 12-month open-label study. J Affect Disord 76:267-271.

Altshuler L, Suppes T, Black D, Nolen WA, Keck PE, Jr., Frye MA, McElroy S, Kupka R, Grunze H, Walden J, Leverich G, Denicoff K, Luckenbaugh D, Post R (2003) Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am J Psychiatry 160:1252-1262.

Altshuler LL, Post RM, Black DO, Keck PE, Jr., Nolen WA, Frye MA, Suppes T, Grunze H, Kupka RW, Leverich GS, McElroy SL, Walden J, Mintz J (2006) Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: results of a large, multisite study. J Clin Psychiatry 67:1551-1560.

Altshuler LL, Post RM, Hellemann G, Leverich GS, Nolen WA, Frye MA, Keck PE, Jr., Kupka RW, Grunze H, McElroy SL, Sugar CA, Suppes T (2009) Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: a blinded, randomized study. J Clin Psychiatry 70:450-457.

American Psychiatric Association. 1994. Diagnostic and statistical manual of mental disorders. 4th revised ed.American Psychiatric Press, Washington DC.

Amsterdam JD, Garcia-Espana F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, Schweizer E, Beasley C (1998) Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. J Clin Psychopharmacol 18:435-440.

Amsterdam JD, Shults J (2005) Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study. Int Clin Psychopharmacol 20:257-264.

Amsterdam JD, Shults J (2010) Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. Am J Psychiatry 167:792-800.

Anderson J (2000) On variability of effects for a metaanalysis of rheumatoid arthritis radiographic progression. Journal of rheumatology 27:540-542.

Angst F, Stassen HH, Clayton PJ, Angst J (2002) Mortality of patients with mood disorders: follow-up over 34-38 years. J Affect Disord 68:167-181.

Angst J (1981) Course of affective disorders. In: van Praag HM, Lader HM, Rafaelson OJ, Sachar EJ (eds) Handbook of Biological Psychiatry.Marcel Dekker, New York: pp 225-242.

Angst J, Angst F, Gerber-Werder R, Gamma A (2005) Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res 9:279-300.

Angst J, Preisig M (1995) Outcome of a clinical cohort of unipolar, bipolar and schizoaffective patients. Results of a prospective study from 1959 to 1985. Schweiz Arch Neurol Psychiatr 146:17-23.

Baastrup PC, Poulsen JC, Schou M, Thomsen K, Amdisen A (1970) Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. Lancet 2:326-330.

Baastrup PC, Schou M (1967) Lithium as a prophylactic agents. Its effect against recurrent depressions and manic-depressive psychosis. Arch Gen Psychiatry 16:162-172.

Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J (2006) Decreased risk of suicides and atempts during long-term lithium treatment: A meta-analytic review. Bipolar Disord 8:625-639.

Baldessarini RJ, Tondo L, Hennen J (1999a) Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry 60:77-84.

Baldessarini RJ, Tondo L, Hennen J, Floris G (1999b) Latency and episodes before treatment: response to lithium maintenance in bipolar I and II disorders. Bipolar Disord 1:91-97.

Baldessarini RJ, Tondo L, Viguera AC (1999c) Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. Bipolar Disord 1:17-24.

Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, Zohar J, Hollander E, Kasper S, Moller HJ, Bandelow B, Allgulander C, yuso-Gutierrez J, Baldwin DS, Buenvicius R, Cassano G, Fineberg N, Gabriels L, Hindmarch I, Kaiya H, Klein DF, Lader M, Lecrubier Y,

Lepine JP, Liebowitz MR, Lopez-Ibor JJ, Marazziti D, Miguel EC, Oh KS, Preter M, Rupprecht R, Sato M, Starcevic V, Stein DJ, van AM, Vega J (2008) World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. World J Biol Psychiatry 9:248-312.

Bauer MS, Wisniewski SR, Marangell LB, Chessick CA, Allen MH, Dennehy EB, Miklowitz DJ, Thase ME, Sachs GS (2006) Are Antidepressants Associated With New-Onset Suicidality in Bipolar Disorder? A Prospective Study of Participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Clin Psychiatry 67:48-55.

Bech P, Vendsborg PB, Rafaelsen OJ (1976) Lithium maintenance treatment of manic-melancholic patients: its role in the daily routine. Acta Psychiatr Scand 53:70-81.

Becker D, Grinberg Y, Weizman A, Mester R (2002) Association between flupenthixol treatment and emergence of manic symptoms. Eur Psychiatry 17:349-352.

Belmaker RH, Bersudsky Y, Lichtenberg P (2010) Bayesian approach to bipolar guidelines. World J Biol Psychiatry 11:76-77.

Benabarre A, Castro P, Sanchez-Moreno J, Martinez-Aran A, Salamero M, Murru A, Franco C, Vieta E (2009) Efficacy and safety of long-acting injectable risperidone in maintenance phase of bipolar and schizoaffective disorder. Actas Esp Psiquiatr 37:143-147.

Bendz H, Schon S, Attman PO, Aurell M (2010) Renal failure occurs in chronic lithium treatment but is uncommon. Kidney Int 77:219-224.

Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, nderson-Hunt M, Bush AI (2008a) N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. Biol Psychiatry 64:468-475.

Berk M, Ng F, Wang WV, Calabrese JR, Mitchell PB, Malhi GS, Tohen M (2008b) The empirical redefinition of the psychometric criteria for remission in bipolar disorder. J Affect Disord 106:153-158.

Berwaerts J, Melkote R, Nuamah I, Lim P (2012) A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. J Affect Disord 138:247-258.

Beynon S, Soares-Weiser K, Woolacott N, Duffy S, Geddes JR (2008) Psychosocial interventions for the prevention of relapse in bipolar disorder: systematic review of controlled trials. Br J Psychiatry 192:5-11.

Beynon S, Soares-Weiser K, Woolacott N, Duffy S, Geddes JR (2009) Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. J Psychopharmacol 23:574-591.

Bond DJ, Noronha MM, Kauer-Sant'Anna M, Lam RW, Yatham LN (2008) Antidepressant-Associated Mood Elevations in Bipolar II Disorder Compared With Bipolar I Disorder and

Major Depressive Disorder: A Systematic Review and Meta-Analysis. J Clin Psychiatry 69:1589-1601.

Bonnin CM, Martinez-Aran A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, Murru A, Sanchez-Moreno J, Vieta E (2010) Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. J Affect Disord 121:156-160.

Born C, Dittmann S, Post RM, Grunze H (2005) Newer prophylactic agents for bipolar disorder and their influence on suicidality. Arch Suicide Res 9:301-306.

Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, Pope HG, Chou JC, Keck PE, Rhodes LJ, Swann AC, Hirschfeld RM, Wozniak PJ (2000) A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. Arch Gen Psychiatry 57:481-489.

Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, Montgomery P, Earl N, Smoot TM, DeVeaugh-Geiss J (2003) A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 60:392-400.

Bowden CL, Singh V, Weisler R, Thompson P, Chang X, Quinones M, Mintz J (2012) Lamotrigine vs. lamotrigine plus divalproex in randomized, placebo-controlled maintenance treatment for bipolar depression. Acta Psychiatr Scand.

Bowden CL, Swann AC, Calabrese JR, McElroy SL, Morris D, Petty F, Hirschfeld RM, Gyulai L (1997) Maintenance clinical trials in bipolar disorder: design implications of the divalproex-lithium-placebo study. Psychopharmacol Bull 33:693-699.

Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M (2010) Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. J Clin Psychiatry 71:130-137.

Calabrese J, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen O-P, Montgomery P, Ascher J, Paska W, Earl NL, DeVeaugh-Geiss J, for the Lamictal 605 Study group (2003) A Placebo-Controlled 18-Month Trial of Lamotrigine and Lithium Maintenance Treatment in Recently Depressed Patients with Bipolar I Disorder. J Clin Psychiatry 64:1024.

Calabrese JR, Goldberg JF, Ketter TA, Suppes T, Frye M, White R, Veaugh-Geiss A, Thompson TR (2006) Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies. Biol Psychiatry 59:1061-1064.

Calabrese JR, Meltzer HY, Markovitz PJ (1991) Clozapine prophylaxis in rapid cycling bipolar disorder. J Clin Psychopharmacol 11:396-397.

Calabrese JR, Shelton MD, Rapport DJ, Youngstrom EA, Jackson K, Bilali S, Ganocy SJ, Findling RL (2005) A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. Am J Psychiatry 162:2152-2161.

Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC, McElroy SL, Kusumakar V,

Ascher JA, Earl NL, Greene PL, Monaghan ET (2000) A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. J Clin Psychiatry 61:841-850.

Calabrese JR, Vieta E, El Mallakh R, Findling RL, Youngstrom EA, Elhaj O, Gajwani P, Pies R (2004) Mood state at study entry as predictor of the polarity of relapse in bipolar disorder. Biol Psychiatry 56:957-963.

Carlson BX, Ketter TA, Sun W, Timko K, McQuade RD, Sanchez R, Vester-Blokland E, Marcus R (2012) Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). Bipolar Disord 14:41-53.

Carta MG, Hardoy MC, Hardoy MJ, Grunze H, Carpiniello B (2003) The clinical use of gabapentin in bipolar spectrum disorders. J Affect Disord 75:83-91.

Carta MG, Zairo F, Mellino G, Hardoy MC, Vieta E (2006) An open label follow-up study on amisulpride in the add-on treatment of bipolar I patients. Clin Pract Epidemiol Ment Health 2:19.

Chengappa KN, Hennen J, Baldessarini RJ, Kupfer DJ, Yatham LN, Gershon S, Baker RW, Tohen M (2005) Recovery and functional outcomes following olanzapine treatment for bipolar I mania. Bipolar Disord 7:68-76.

Cipriani A, Pretty H, Hawton K, Geddes JR (2005) Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 162:1805-1819.

Colom F, Vieta E, Daban C, Pacchiarotti I, Sanchez-Moreno J (2006) Clinical and therapeutic implications of predominant polarity in bipolar disorder. J Affect Disord 93:13-17.

Colom F, Vieta E, Sanchez-Moreno J, Goikolea JM, Popova E, Bonnin CM, Scott J (2009) Psychoeducation for bipolar II disorder: an exploratory, 5-year outcome subanalysis. J Affect Disord 112:30-35.

Corya SA, Perlis RH, Keck PE, Jr., Lin DY, Case MG, Williamson DJ, Tohen MF (2006) A 24-week open-label extension study of olanzapine-fluoxetine combination and olanzapine monotherapy in the treatment of bipolar depression. J Clin Psychiatry 67:798-806.

Coryell W, Scheftner W, Keller M, Endicott J, Maser J, Klerman GL (1993) The enduring psychosocial consequences of mania and depression. Am J Psychiatry 150:720-727.

Coxhead N, Silverstone T, Cookson J (1992) Carbamazepine versus lithium in the prophylaxis of bipolar affective disorder. Acta Psychiatr Scand 85:114-118.

Cundall RL, Brooks PW, Murray LG (1972) A controlled evaluation of lithium prophylaxis in affective disorders. Psychol Med 2:308-311.

Denicoff KD, Ali SO, Sollinger AB, Smith-Jackson EE, Leverich GS, Post RM (2002) Utility

of the daily prospective National Institute of Mental Health Life-Chart Method (NIMH-LCM-p) ratings in clinical trials of bipolar disorder. Depress Anxiety 15:1-9.

Denicoff KD, Smith-Jackson EE, Bryan AL, Ali SO, Post RM (1997a) Valproate prophylaxis in a prospective clinical trial of refractory bipolar disorder. Am J Psychiatry 154:1456-1458.

Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM (1997b) Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry 58:470-478.

Diav-Citrin O, Shechtman S, Ornoy S, Arnon J, Schaefer C, Garbis H, Clementi M, Ornoy A (2005) Safety of haloperidol and penfluridol in pregnancy: a multicenter, prospective, controlled study. J Clin Psychiatry 66:317-322.

Dickerson FB, Boronow JJ, Stallings CR, Origoni AE, Cole S, Yolken RH (2004) Association between cognitive functioning and employment status of persons with bipolar disorder. Psychiatr Serv 55:54-58.

Dubovsky SL, Dubovsky AN (2011) Ziprasidone for maintenance treatment of bipolar I disorder in adults. Expert Opin Pharmacother 12:817-824.

Duffy A, Milin R, Grof P (2009) Maintenance treatment of adolescent bipolar disorder: open study of the effectiveness and tolerability of quetiapine. BMC Psychiatry 9:4.:4.

Dunner DL (1998) Lithium carbonate: maintenance studies and consequences of withdrawal. J Clin Psychiatry 59 Suppl 6:48-55; discussion 56.:48-55.

Dunner DL, Fieve RR (1974) Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 30:229-233.

El-Mallakh RS, Ghaemi SN, Sagduyu K, Thase ME, Wisniewski SR, Nierenberg AA, Zhang HW, Pardo TA, Sachs G (2008) Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. J Affect Disord ..

Elphick M (1985) An open clinical trial of carbamazepine in treatment-resistant bipolar and schizo-affective psychotics. Br J Psychiatry 147:198-200.

Emrich HM, Wolf R (1992) Valproate treatment of mania. Prog Neuropsychopharmacol Biol Psychiatry 16:691-701.

Ernst CL, Goldberg JF (2002) The reproductive safety profile of mood stabilizers, atypical antipsychotics, and broad-spectrum psychotropics. J Clin Psychiatry 63 Suppl 4:42-55.

Esparon J, Kolloori J, Naylor GJ, McHarg AM, Smith AH, Hopwood SE (1986) Comparison of the prophylactic action of flupenthixol with placebo in lithium treated manic-depressive patients. Br J Psychiatry 148:723-5.:723-725.

Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ (2005) Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord 7:424-430.

Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E (2003) Obesity as a correlate of outcome in patients with bipolar I disorder. Am J Psychiatry 160:112-117.

Fieve RR, Kumbaraci T, Dunner DL (1976) Lithium prophylaxis of depression in bipolar I, bipolar II, and unipolar patients. Am J Psychiatry 133:925-929.

Findling RL, Youngstrom EA, McNamara NK, Stansbrey RJ, Wynbrandt JL, Adegbite C, Rowles BM, Demeter CA, Frazier TW, Calabrese JR (2012) Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. J Clin Psychiatry 73:57-63.

Fitzgerald BJ, Okos AJ (2002) Elevation of carbamazepine-10,11-epoxide by quetiapine. Pharmacotherapy 22:1500-1503.

Fountoulakis KN, Gonda X, Samara M, Siapera M, Karavelas V, Ristic DI, Iacovides A (2012) Antiepileptic drugs and suicidality. J Psychopharmacol.

Fountoulakis KN, Nimatoudis I, Iacovides A, Kaprinis G (2004) Report of three cases that received maintenance treatment with risperidone as a mood stabilizer. Ann Gen Hosp Psychiatry 3:10.

Fountoulakis KN, Vieta E (2009) Efficacy and safety of aripiprazole in the treatment of bipolar disorder: a systematic review. Ann Gen Psychiatry 8:16.:16.

Franchini L, Zanardi R, Smeraldi E, Gasperini M (1999) Early onset of lithium prophylaxis as a predictor of good long-term outcome. Eur Arch Psychiatry Clin Neurosci 249:227-230.

Frangou S, Lewis M, McCrone P (2006) Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br J Psychiatry 188:46-50.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991b) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 48:851-855.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991a) Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 48:851-855.

Freeman MP, Freeman SA (2006) Lithium: clinical considerations in internal medicine. Am J Med 119:478-481.

Frye MA (2011) Clinical practice. Bipolar disorder--a focus on depression. N Engl J Med 364:51-59.

Frye MA, Altshuler LL, Bitran JA (1996) Clozapine in rapid cycling bipolar disorder. J Clin Psychopharmacol 16:87-90.

Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck PE, Jr., Nolen WA,

Kupka R, Leverich GS, Grunze H, Mintz J, Post RM, Suppes T (2009) Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry 166:164-172.

Frye MA, Yatham LN, Calabrese JR, Bowden CL, Ketter TA, Suppes T, Adams BE, Thompson TR (2006) Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. J Clin Psychiatry 67:1721-1728.

Garcia-Lopez A, Ezquiaga E, Nieves P, Rodriguez-Salvanes F (2001) Factores predictores de respuesta al litio en pacientes bipolares en seguimiento a largo plazo. Actas Esp Psiquiatr 29:327-332.

Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM (2004) Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 161:217-222.

Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, Ostacher MJ, Morriss R, Alder N, Juszczak E (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 375:385-395.

Ghaemi SN (2008) Treatment of rapid-cycling bipolar disorder: are antidepressants mood destabilizers? Am J Psychiatry 165:300-302.

Ghaemi SN, Hsu DJ, Rosenquist KJ, Katzow JJ, Goodwin FK (2004) Long-term observational comparison of risperidone and olanzapine in bipolar disorder. Ann Clin Psychiatry 16:69-73.

Ghaemi SN, Hsu DJ, Thase ME, Wisniewski SR, Nierenberg AA, Miyahara S, Sachs G (2006) Pharmacological Treatment Patterns at Study Entry for the First 500 STEP-BD Participants. Psychiatr Serv 57:660-665.

Ghaemi SN, Ostacher MM, El-Mallakh RS, Borrelli D, Baldassano CF, Kelley ME, Filkowski MM, Hennen J, Sachs GS, Goodwin FK, Baldessarini RJ (2010) Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. J Clin Psychiatry 71:372-380.

Ghaemi SN, Sachs GS (1997) Long-term risperidone treatment in bipolar disorder: 6-month follow up. Int Clin Psychopharmacol 12:333-338.

Ghaemi SN, Wingo AP, Filkowski MA, Baldessarini RJ (2008) Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand 118:347-356.

Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, Herings RM, Mann JJ (2007) Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 164:1356-1363.

Gibbons RD, Hur K, Brown CH, Mann JJ (2009) Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. Arch Gen Psychiatry 66:1354-1360.

Gitlin M (1999) Lithium and the kidney: an updated review. Drug Saf 20:231-243.

Gitlin MJ, Abulseoud O, Frye MA (2010) Improving the design of maintenance studies for bipolar disorder. Curr Med Res Opin 26:1835-1842.

Gitlin MJ, Swendsen J, Heller TL, Hammen C (1995) Relapse and impairment in bipolar disorder. Am J Psychiatry 152:1635-1640.

Goetz I, Tohen M, Reed C, Lorenzo M, Vieta E (2007) Functional impairment in patients with mania: baseline results of the EMBLEM study. Bipolar Disord 9:45-52.

Goldberg JF, Bowden CL, Calabrese JR, Ketter TA, Dann RS, Frye MA, Suppes T, Post RM (2008) Six-month prospective life charting of mood symptoms with lamotrigine monotherapy versus placebo in rapid cycling bipolar disorder. Biol Psychiatry 63:125-130.

Goldberg JF, Brooks JO, III, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, Miklowitz DJ, Ketter TA, Sachs GS, Thase ME (2009a) Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. J Clin Psychiatry 70:155-162.

Goldberg JF, Brooks JO, III, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, Miklowitz DJ, Ketter TA, Sachs GS, Thase ME (2009b) Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. J Clin Psychiatry 70:155-162.

Goldsmith DR, Wagstaff AJ, Ibbotson T, Perry CM (2003) Lamotrigine: a review of its use in bipolar disorder. Drugs 63:2029-2050.

Goncalves N, Stoll K-D (1985) Carbamazepin bei manischen Syndromen. Eine kontrollierte Doppelblind-Studie. Nervenarzt 56:43-47.

Gonzalez-Pinto A, Mosquera F, Alonso M, Lopez P, Ramirez F, Vieta E, Baldessarini RJ (2006) Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. Bipolar Disord 8:618-624.

Gonzalez-Pinto A, Vieta E, Reed C, Novick D, Barraco A, Aguado J, Haro JM (2011) Effectiveness of olanzapine monotherapy and olanzapine combination treatment in the long term following acute mania--results of a two year observational study in bipolar disorder (EMBLEM). J Affect Disord 131:320-329.

Goodwin FK (2002) Rationale for long-term treatment of bipolar disorder and evidence for long-term lithium treatment. J Clin Psychiatry 63 Suppl 10:5-12.

Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D (2003) Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 290:1467-1473.

Goodwin FK, Jamison KR. 2007. Manic -depressive illness. 2 ed.Oxford University Press,

New York.

Goodwin GM (1994) Recurrence of mania after lithium withdrawal. Implications for the use of lithium in the treatment of bipolar affective disorder. Br J Psychiatry 164:149-152.

Goodwin GM (2009) Evidence-based guidelines for treating bipolar disorder: revised second edition--recommendations from the British Association for Psychopharmacology. J Psychopharmacol 23:346-388.

Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Greene P, Leadbetter R (2004) A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 65:432-441.

Goodwin GM, Martinez-Aran A, Glahn DC, Vieta E (2008) Cognitive impairment in bipolar disorder: neurodevelopment or neurodegeneration? An ECNP expert meeting report. Eur Neuropsychopharmacol 18:787-793.

Grande I, Balanza-Martinez V, Jimenez-Arriero M, Iglesias Lorenzo FG, Franch Valverde JI, de AR, Zaragoza S, Cobaleda S, Vieta E (2012a) Clinical factors leading to lamotrigine prescription in bipolar outpatients: Subanalysis of the SIN-DEPRES study. J Affect Disord.

Grande I, de AR, Jimenez-Arriero MA, Lorenzo FG, Valverde JI, Balanza-Martinez V, Zaragoza S, Cobaleda S, Vieta E (2012b) Patterns of pharmacological maintenance treatment in a community mental health services bipolar disorder cohort study (SIN-DEPRES). Int J Neuropsychopharmacol1-11.

Greil W, Kleindienst N (1999a) Lithium versus carbamazepine in the maintenance treatment of bipolar II disorder and bipolar disorder not otherwise specified. Int Clin Psychopharmacol 14:283-285.

Greil W, Kleindienst N (1999b) The comparative prophylactic efficacy of lithium and carbamazepine in patients with bipolar I disorder. Int Clin Psychopharmacol 14:277-281.

Greil W, Ludwig-Mayerhofer W., Erazo N, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T (1997a) Lithium vs carbamazepine in the maintenance treatment of schizoaffective disorder: a randomised study. Eur Arch Psychiatry Clin Neurosci 247:42-50.

Greil W, Ludwig-Mayerhofer W, Erazo N, Schöchlin C, Schmidt S, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T (1997b) Lithium versus carbamazepine in the maintenance treatment of bipolar disorders--a randomised study. J Affect Disord 43:151-161.

Grof P (1979) Some practical aspects of lithium treatment: blood levels, dosage prediction, and slow-release preparations. Arch Gen Psychiatry 36:891-893.

Grof P (2010) Sixty years of lithium responders. Neuropsychobiology 62:8-16.

Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, O'Donovan C, Alda M (2002) Is response to prophylactic lithium a familial trait? J Clin Psychiatry 63:942-947.

Grunze H (2002) The search for the Holy Grail- the ideal mood stabilizer: fiction or future ? In: Maj M, Akiskal H, Lopez-Ibor JJ, Sartorius N (eds) WPA Series "Evidence Experience in Psychiatry"- Bipolar disorder.Wiley & Sons, Chichester: pp 229-232.

Grunze H, Kasper S, Goodwin G, Bowden CL, Möller H-J, WFSBP Task Force on Treatment Guidelines for Bipolar Disorders (2004) The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders. Part III: Maintenance treatment. World J Biol Psychiatry 5:120-135.

Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, Kasper S (2009a) The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2009 on the Treatment of Acute Mania. World J Biol Psychiatry 10:85-116.

Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, Kasper S (2010) The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry 11:81-109.

Grunze H, Vieta E, Goodwin GM, Bowden CL, Licht RW, Moeller HJ, Kasper S (2009b) The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2009 on the Treatment of Acute Mania. World J Biol Psychiatry, in press

Grunze H, Walden J. 2004. Valproat bei manisch-depressiven (bipolaren) Erkrankungen. 2 ed.Thieme Verlag, Stuttgart.

Grunze HC (2008) Switching, induction of rapid cycling, and increased suicidality with antidepressants in bipolar patients: fact or overinterpretation? CNS Spectr 13:790-795.

Grunze HC (2010) Anticonvulsants in bipolar disorder. J Ment Health 19:127-141.

Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, Chou JC, Wassef A, Risch CS, Hirschfeld RM, Nemeroff CB, Keck PE, Jr., Evans DL, Wozniak PJ (2003) Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 28:1374-1382.

Hakkaart-van Roijen L, Hoeijenbos MB, Regeer EJ, ten Have M, Nolen WA, Veraart CP, Rutten FF (2004) The societal costs and quality of life of patients suffering from bipolar disorder in the Netherlands. Acta Psychiatr Scand 110:383-392.

Han C, Lee MS, Pae CU, Ko YH, Patkar AA, Jung IK (2007) Usefulness of long-acting injectable risperidone during 12-month maintenance therapy of bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 31:1219-1223.

Hartong EG, Moleman P, Hoogduin CA, Broekman TG, Nolen WA (2003) Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. J Clin Psychiatry 64:144-151.

Harvey PD (2006) Defining and achieving recovery from bipolar disorder. J Clin Psychiatry

67 Suppl 9:14-8; discussion 36-42.:14-18.

Harvey PW, Everett DJ, Springall CJ (2008) Adverse effects of prolactin in rodents and humans: breast and prostate cancer. J Psychopharmacol 22 Suppl 2:20-27.

Hawley CJ, Gale TM, Sivakumaran T (2002) Defining remission by cut off score on the MADRS: selecting the optimal value. J Affect Disord 72:177-184.

Hayes SG (1989) Long-term use of valproate in primary psychiatric disorders. J Clin Psychiatry 50 Suppl:35-39.

Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S (2006) Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 163:185-194.

Hirschfeld R, Weisler RH, Keck PE (1999) Cost-effectiveness evaluation of divalproex versus lithium in the treatment of bipolar disorder. 152nd APA Annual meeting abstractsNR 686.

Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V (2011) Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Arch Gen Psychiatry 68:128-137.

Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, Wint D, Craighead MC, Kozarsky J, Chismar R, Moreines JL, Mewes K, Posse PR, Gutman DA, Mayberg HS (2012) Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry 69:150-158.

Hullin RP, McDonald R, Allsopp MN (1972) Prophylactic lithium in recurrent affective disorders. Lancet 1:1044-1046.

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

Jefferson JW (2010) A clinician's guide to monitoring kidney function in lithium-treated patients. J Clin Psychiatry 71:1153-1157.

Johannessen SI, Landmark CJ (2010) Antiepileptic drug interactions - principles and clinical implications. Curr Neuropharmacol 8:254-267.

Johnston AM, Eagles JM (1999) Lithium-associated clinical hypothyroidism. Prevalence and risk factors. Br J Psychiatry 175:336-339.

Johnstone EC, Owens DG, Lambert MT, Crow TJ, Frith CD, Done DJ (1990) Combination tricyclic antidepressant and lithium maintenance medication in unipolar and bipolar depressed patients. J Affect Disord 20:225-233.

Jones MW (1998) Topiramate--safety and tolerability. Can J Neurol Sci 25:S13-S15.

Joyce PR (1988) Carbamazepine in rapid cycling bipolar affective disorder. Int Clin Psychopharmacol 3:123-129.

Judd LL, Akiskal HS, Schettler PJ, Coryell W, Maser J, Rice JA, Solomon DA, Keller MB (2003) The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? J Affect Disord 73:19-32.

Kane JM, Quitkin FM, Rifkin A, Ramos-Lorenzi JR, Nayak DD, Howard A (1982) Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. Arch Gen Psychiatry 39:1065-1069.

Kantrowitz JT, Citrome L (2008) Olanzapine: review of safety 2008. Expert Opin Drug Saf 7:761-769.

Karayal ON, Anway SD, Batzar E, Vanderburg DG (2011) Assessments of suicidality in double-blind, placebo-controlled trials of ziprasidone. J Clin Psychiatry 72:367-375.

Keck PE, Bowden CL, Meinhold JM, Gyulai L, Prihoda TJ, Baker JD, Wozniak PJ (2005) Relationship between serum valproate and lithium levels and efficacy and tolerability in bipolar maintenance therapy. Int J Psychiaty Clin Practice 9:271-277.

Keck PE, Jr., Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JM, Carlson BX, Marcus RN, Sanchez R (2007) Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 68:1480-1491.

Keck PE, Calabrese JR, McQuade RD, Carson WH, Carlson BX, Rollin LM, Marcus RN, Sanchez R (2006a) A Randomized, Double-Blind, Placebo-Controlled 26-Week Trial of Aripiprazole in Recently Manic Patients With Bipolar I Disorder. J Clin Psychiatry 67:626-637.

Keck PE, Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, Altshuler LL, Kupka R, Nolen WA, Leverich GS, Denicoff KD, Grunze H, Duan N, Post RM (2006b) Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. Biol Psychiatry 60:1020-1022.

Keck PE, Versiani M, Potkin S, West SA, Giller E, Ice K (2003) Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. Am J Psychiatry 160:741-748.

Kemp DE, Gao K, Ganocy SJ, Elhaj O, Bilali SR, Conroy C, Findling RL, Calabrese JR (2009) A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and Co-occurring substance abuse or dependence. J Clin Psychiatry 70:113-121.

Kemp DE, Karayal ON, Calabrese JR, Sachs GS, Pappadopulos E, Ice KS, Siu CO, Vieta E (2012) Ziprasidone with adjunctive mood stabilizer in the maintenance treatment of bipolar I disorder: long-term changes in weight and metabolic profiles. Eur Neuropsychopharmacol 22:123-131.

Kessing (1998a) Recurrence in affective disorders. British J Psychiatry 172:23-28.

Kessing LV (1998b) Cognitive impairment in the euthymic phase of affective disorder. Psychol Med 28:1027-1038.

Kessing LV, Hellmund G, Andersen PK (2011a) An observational nationwide register based cohort study on lamotrigine versus lithium in bipolar disorder. J Psychopharmacol.

Kessing LV, Hellmund G, Geddes JR, Goodwin GM, Andersen PK (2011b) Valproate v. lithium in the treatment of bipolar disorder in clinical practice: observational nationwide register-based cohort study. Br J Psychiatry 199:57-63.

Ketter TA, Calabrese JR (2002) Stabilization of mood from below versus above baseline in bipolar disorder: a new nomenclature. J Clin Psychiatry 63:146-151.

Ketter TA, Jones M, Paulsson B (2007) Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania. J Affect Disord 100 Suppl 1:S45-53. Epub@2007 Mar 26.:S45-S53.

Kleindienst N, Severus WE, Greil W (2007) Are serum lithium levels related to the polarity of recurrence in bipolar disorders? Evidence from a multicenter trial. Int Clin Psychopharmacol 22:125-131.

Kovacsics CE, Gottesman II, Gould TD (2009) Lithium's antisuicidal efficacy: elucidation of neurobiological targets using endophenotype strategies. Annu Rev Pharmacol Toxicol 49:175-198.

Kraepelin E. 1921. Manisch-depressives Irresein und Paranoia.

Kramer OH, Gottlicher M, Heinzel T (2001) Histone deacetylase as a therapeutic target. Trends Endocrinol Metab 12:294-300.

Kupka RW, Luckenbaugh DA, Post RM, Leverich GS, Nolen WA (2003) Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies. J Clin Psychiatry 64:1483-1494.

Kupka RW, Luckenbaugh DA, Post RM, Suppes T, Altshuler LL, Keck PE, Jr., Frye MA, Denicoff KD, Grunze H, Leverich GS, McElroy SL, Walden J, Nolen WA (2005) Comparison of rapid-cycling and non-rapid-cycling bipolar disorder based on prospective mood ratings in 539 outpatients. Am J Psychiatry 162:1273-1280.

Lake CR, Hurwitz N (2007) Schizoaffective disorder merges schizophrenia and bipolar disorders as one disease--there is no schizoaffective disorder. Curr Opin Psychiatry 20:365-379.

Lambert PA (1984) Acute and prophylactic therapies of patients with affective disorders using valpromide (dipropylacetamide). In: Emrich HM, Okuma T, Müller AA (eds) Anticonvulsants in affective disorders.Elsevier Science Publishers, Amsterdam, Oxford, Princeton: pp 33-44.

Lancon C, Llorca PM (1996) Clozapine et traitement des troubles bipolaires a cycles rapides. Encephale 22:468-469.

Lebowitz BK, Shear PK, Steed MA, Strakowski SM (2001) Verbal fluency in mania: relationship to number of manic episodes. Neuropsychiatry Neuropsychol Behav Neurol 14:177-182.

Leon AC, Solomon DA, Li C, Fiedorowicz JG, Coryell WH, Endicott J, Keller MB (2011) Antidepressants and risks of suicide and suicide attempts: a 27-year observational study. J Clin Psychiatry 72:580-586.

Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE, Jr., Kupka RW, Denicoff KD, Nolen WA, Grunze H, Martinez MI, Post RM (2006) Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 163:232-239.

Lexchin J, Bero LA, Djulbegovic B, Clark O (2003) Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ 326:1167-1170.

Lexchin J, Light DW (2006) Commercial influence and the content of medical journals. BMJ 332:1444-1447.

Licht RW (2012) Lithium: still a major option in the management of bipolar disorder. CNS Neurosci Ther 18:219-226.

Licht RW, Nielsen JN, Gram LF, Vestergaard P, Bendz H (2010) Lamotrigine versus lithium as maintenance treatment in bipolar I disorder: an open, randomized effectiveness study mimicking clinical practice. The 6th trial of the Danish University Antidepressant Group (DUAG-6). Bipolar Disord 12:483-493.

Licht RW, Vestergaard P, Brodersen A (2008) Long-term outcome of patients with bipolar disorder commenced on lithium prophylaxis during hospitalization: a complete 15-year register-based follow-up. Bipolar Disord 10:79-86.

Licht RW, Vestergaard P, Kessing LV, Larsen JK, Thomsen PH (2003) Psychopharmacological treatment with lithium and antiepileptic drugs: suggested guidelines from the Danish Psychiatric Association and the Child and Adolescent Psychiatric Association in Denmark. Acta Psychiatr Scand Suppl1-22.

Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, Keefe RS, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, Tohen M (2005) Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62:361-370.

Loo C, Katalinic N, Mitchell PB, Greenberg B (2011) Physical treatments for bipolar disorder: a review of electroconvulsive therapy, stereotactic surgery and other brain stimulation techniques. J Affect Disord 132:1-13.

Lopez-Jaramillo C, Lopera-Vasquez J, Gallo A, Ospina-Duque J, Bell V, Torrent C, Martinez-Aran A, Vieta E (2010a) Effects of recurrence on the cognitive performance of

patients with bipolar I disorder: implications for relapse prevention and treatment adherence. Bipolar Disord 12:557-567.

Lopez-Jaramillo C, Lopera-Vasquez J, Ospina-Duque J, Garcia J, Gallo A, Cortez V, Palacio C, Torrent C, Martinez-Aran A, Vieta E (2010b) Lithium treatment effects on the neuropsychological functioning of patients with bipolar I disorder. J Clin Psychiatry 71:1055-1060.

Lusznat RM, Murphy DP, Nunn CM (1988) Carbamazepine vs lithium in the treatment and prophylaxis of mania. Br J Psychiatry 153:198-204.

Macfadden W, Alphs L, Haskins JT, Turner N, Turkoz I, Bossie C, Kujawa M, Mahmoud R (2009) A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. Bipolar Disord 11:827-839.

Magalhaes PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M (2011) N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. J Affect Disord 129:317-320.

Maier W, Möller HJ (2010) Meta-analyses: a method to maximise the evidence from clinical studies? Eur Arch Psychiatry Clin Neurosci 260:17-23.

Maj M (2000) The impact of lithium prophylaxis on the course of bipolar disorder: a review of the research evidence. Bipolar Disord 2:93-101.

Maj M, Pirozzi R, Magliano L, Bartoli L (1998) Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 155:30-35.

Malempati RN, Bond DJ, Yatham LN (2008) Depot risperidone in the outpatient management of bipolar disorder: a 2-year study of 10 patients. Int Clin Psychopharmacol 23:88-94.

Mander AJ, Loudon JB (1988) Rapid recurrence of mania following abrupt discontinuation of lithium. Lancet 2:15-17.

Marcotte D (1998) Use of topiramate, a new anti-epileptic as a mood stabilizer. J Affect Disord 50:245-251.

Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W, Sanchez R (2011) Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. Bipolar Disord 13:133-144.

Marneros A (2001) Expanding the group of bipolar disorders. J Affect Disord 62:39-44.

Martinez-Aran A, Vieta E, Chengappa KN, Gershon S, Mullen J, Paulsson B (2008) Reporting outcomes in clinical trials for bipolar disorder: a commentary and suggestions for

change. Bipolar Disord 10:566-579.

Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, Malhi GS, Gonzalez-Pinto A, Daban C, varez-Grandi S, Fountoulakis K, Kaprinis G, Tabares-Seisdedos R, yuso-Mateos JL (2007) Functional outcome in bipolar disorder: the role of clinical and cognitive factors. Bipolar Disord 9:103-113.

McElroy SL, Bowden CL, Collins MA, Wozniak PJ, Keck PE, Jr., Calabrese JR (2008) Relationship of open acute mania treatment to blinded maintenance outcome in bipolar I disorder. J Affect Disord 107:127-133.

McElroy SL, Weisler RH, Chang W, Olausson B, Paulsson B, Brecher M, Agambaram V, Merideth C, Nordenhem A, Young AH (2010) A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry 71:163-174.

McIntyre RS (2010) Aripiprazole for the maintenance treatment of bipolar I disorder: A review. Clin Ther 32 Suppl 1:S32-8.:S32-S38.

McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J (2009) Asenapine versus olanzapine in acute mania: a double-blind extension study. Bipolar Disord 11:815-826.

McIntyre RS, Cohen M, Zhao J, Alphs L, Macek TA, Panagides J (2010) Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. J Affect Disord 126:358-365.

McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O, Levinson A, Zipursky RB, Einarson A (2005) Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. J Clin Psychiatry 66:444-449.

McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR (2012) Lithium toxicity profile: a systematic review and meta-analysis. Lancet 379:721-728.

Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW (2009) Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 360:1597-1605.

Melia PI (1970) Prophylactic lithium: a double-blind trial in recurrent affective disorders. Br J Psychiatry 116:621-624.

Meltzer HY, Baldessarini RJ (2003) Reducing the risk for suicide in schizophrenia and affective disorders. J Clin Psychiatry 64:1122-1129.

Miklowitz DJ (2008) Adjunctive psychotherapy for bipolar disorder: state of the evidence. Am J Psychiatry 165:1408-1419.

Minnai GP, Salis PG, Oppo R, Loche AP, Scano F, Tondo L (2011) Effectiveness of maintenance electroconvulsive therapy in rapid-cycling bipolar disorder. J ECT 27:123-126.

Mishory A, Winokur M, Bersudsky Y (2003) Prophylactic effect of phenytoin in bipolar disorder: a controlled study. Bipolar Disord 5:464-467.

Möller HJ, Maier W (2010) Evidence-based medicine in psychopharmacotherapy: possibilities, problems and limitations. Eur Arch Psychiatry Clin Neurosci 260:25-39.

Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382-389.

Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, Irwin B, McGivern RC, Morrison PJ, Craig J (2006) Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry 77:193-198.

Moskowitz AS, Altshuler L (1991) Increased sensitivity to lithium-induced neurotoxicity after stroke: a case report. J Clin Psychopharmacol 11:272-273.

Müller-Oerlinghausen B, Ahrens B, Felber W (2006) The suicide-preventive and mortality reducing effect of lithium. In: Bauer M, Grof P, Müller-Oerlinghausen B (eds) Lithium in Neuropsychiatry: The Comprehensive Guide.Informa Healthcare, Oxfordshire, UK: pp 179-192.

Murru A, Colom F, Nivoli A, Pacchiarotti I, Valenti M, Vieta E (2011a) When should mood stabilizers be withdrawn due to lack of efficacy? Some methodological considerations. Eur Psychiatry.

Murru A, Colom F, Nivoli A, Pacchiarotti I, Valenti M, Vieta E (2011b) When should mood stabilizers be withdrawn due to lack of efficacy? Some methodological considerations. Eur Psychiatry.

Muzina DJ, Momah C, Eudicone JM, Pikalov A, McQuade RD, Marcus RN, Sanchez R, Carlson BX (2008) Aripiprazole monotherapy in patients with rapid-cycling bipolar I disorder: an analysis from a long-term, double-blind, placebo-controlled study. Int J Clin Pract 62:679-687.

Neels HM, Sierens AC, Naelaerts K, Scharpe SL, Hatfield GM, Lambert WE (2004) Therapeutic drug monitoring of old and newer anti-epileptic drugs. Clin Chem Lab Med 42:1228-1255.

Newcomer JW (2007) Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry 68 Suppl 4:8-13.:8-13.

Nguyen HT, Sharma V, McIntyre RS (2009) Teratogenesis associated with antibipolar agents. Adv Ther 26:281-294.

Nielsen J, Kane JM, Correll CU (2012) Real-world effectiveness of clozapine in patients with bipolar disorder: results from a 2-year mirror-image study. Bipolar Disord 14:863-869.

Nierenberg AA, Alpert JE, Gardner-Schuster EE, Seay S, Mischoulon D (2008) Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. Biol

Psychiatry 64:455-460.

Nierenberg AA, Sylvia LG, Leon AC, Reilly-Harrington NA, Ketter TA, Calabrese JR, Thase ME, Bowden CL, Friedman ES, Ostacher MJ, Novak L, Iosifescu DV (2009) Lithium treatment -- moderate dose use study (LiTMUS) for bipolar disorder: rationale and design. Clin Trials 6:637-648.

Nolen WA, Kupka RW, Hellemann G, Frye MA, Altshuler LL, Leverich GS, Suppes T, Keck PE, Jr., McElroy S, Grunze H, Mintz J, Post RM (2007) Tranylcypromine vs. lamotrigine in the treatment of refractory bipolar depression: a failed but clinically useful study. Acta Psychiatr Scand 115:360-365.

Nolen WA, Kupka RW, Schulte PFJ, Knoppert-van der Klein EAM, Honig A, Reichart CG, Goossens PJJ, Daemen P, Ravelli DP. 2008. Richtlijn bipolaire stoornissen. 2 ed.De Tijdstrom uitgerverij BV, Utrecht.

Okuma T, Inanaga K, Otsuki S, Sarai K, Takahashi R, Hazama H, Mori A, Watanabe S (1981) A preliminary double-blind study on the efficacy of carbamazepine in prophylaxis of manic-depressive illness. Psychopharmacology (Berl) 73:95-96.

Oquendo MA, Galfalvy HC, Currier D, Grunebaum MF, Sher L, Sullivan GM, Burke AK, Harkavy-Friedman J, Sublette ME, Parsey RV, Mann JJ (2011) Treatment of suicide attempters with bipolar disorder: a randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior. Am J Psychiatry 168:1050-1056.

Pacchiarotti I, Mazzarini L, Kotzalidis GD, Valenti M, Nivoli AM, Sani G, Torrent C, Murru A, Sanchez-Moreno J, Patrizi B, Girardi P, Vieta E, Colom F (2011) Mania and depression. Mixed, not stirred. J Affect Disord 133:105-113.

Park MH, Han C, Pae CU, Lee SJ, Patkar AA, Masand PS, Fleischhacker WW (2011) Aripiprazole treatment for patients with schizophrenia: from acute treatment to maintenance treatment. Expert Rev Neurother 11:1541-1552.

Parker G, Tully L, Olley A, Hadzi-Pavlovic D (2006) SSRIs as mood stabilizers for Bipolar II Disorder? A proof of concept study. J Affect Disord 92:205-214.

Passmore MJ, Garnham J, Duffy A, MacDougall M, Munro A, Slaney C, Teehan A, Alda M (2003) Phenotypic spectra of bipolar disorder in responders to lithium versus lamotrigine. Bipolar Disord 5:110-114.

Perlis RH, Perlis CS, Wu Y, Hwang C, Joseph M, Nierenberg AA (2005) Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. Am J Psychiatry 162:1957-1960.

Perova T, Kwan M, Li PP, Warsh JJ (2010) Differential modulation of intracellular Ca2+ responses in B lymphoblasts by mood stabilizers. Int J Neuropsychopharmacol 13:693-702.

Perugi G, Toni C, Frare F, Ruffolo G, Moretti L, Torti C, Akiskal HS (2002) Effectiveness of adjunctive gabapentin in resistant bipolar disorder: is it due to anxious-alcohol abuse comorbidity? J Clin Psychopharmacol 22:584-591.

Petrides G, Tobias KG, Kellner CH, Rudorfer MV (2011) Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. Neuropsychobiology 64:129-140.

Placidi GF, Lenzi A, Lazzerini F, Cassano GB, Akiskal HS (1986) The comparative efficacy and safety of carbamazepine versus lithium: a randomized, double-blind 3-year trial in 83 patients. J Clin Psychiatry 47:490-494.

Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E (2011) Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. Eur Neuropsychopharmacol.

Post RM, Altshuler LL, Frye MA, Suppes T, Keck PE, Jr., McElroy SL, Leverich GS, Luckenbaugh DA, Rowe M, Pizzarello S, Kupka RW, Grunze H, Nolen WA (2010a) Complexity of pharmacologic treatment required for sustained improvement in outpatients with bipolar disorder. J Clin Psychiatry 71:1176-1186.

Post RM, Leverich GS, Altshuler L, Mikalauskas K (1992) Lithium-discontinuation-induced refractoriness: preliminary observations. Am J Psychiatry 149:1727-1729.

Post RM, Leverich GS, Kupka RW, Keck PE, Jr., McElroy SL, Altshuler LL, Frye MA, Luckenbaugh DA, Rowe M, Grunze H, Suppes T, Nolen WA (2010b) Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. J Clin Psychiatry 71:864-872.

Potkin SG, Keck PE, Jr., Segal S, Ice K, English P (2005) Ziprasidone in Acute Bipolar Mania: A 21-Day Randomized, Double-Blind, Placebo-Controlled Replication Trial. J Clin Psychopharmacol 25:301-310.

Prien RF, Caffey EM, Jr., Klett CJ (1973a) Prophylactic efficacy of lithium carbonate in manic-depressive illness. Report of the Veterans Administration and National Institute of Mental Health collaborative study group. Arch Gen Psychiatry 28:337-341.

Prien RF, Klett CJ, Caffey EM, Jr. (1973b) Lithium carbonate and imipramine in prevention of affective episodes. A comparison in recurrent affective illness. Arch Gen Psychiatry 29:420-425.

Prien RF, Klett CJ, Caffey EM, Jr. (1974) Lithium prophylaxis in recurrent affective illness. Am J Psychiatry 131:198-203.

Puri BK, Taylor DG, Alcock ME (1995) Low-dose maintenance clozapine treatment in the prophylaxis of bipolar affective disorder. Br J Clin Pract 49:333-334.

Puzynski S, Klosiewicz L (1984a) Valproic acid amide as a prophylactic agent in affective and schizoaffective disorders. Psychopharmacol Bull 20:151-159.

Puzynski S, Klosiewicz L (1984b) Valproic acid amide in the treatment of affective and schizoaffective disorders. J Affect Disord 6:115-121.

Quiroz JA, Yatham LN, Palumbo JM, Karcher K, Kushner S, Kusumakar V (2010)

Risperidone Long-Acting Injectable Monotherapy in the Maintenance Treatment of Bipolar I Disorder. Biol Psychiatry.

Quitkin F, Rifkin A, Kane J, Ramos-Lorenzi JR, Klein DF (1978) Prophylactic effect of lithium and imipramine in unipolar and bipolar II patients: a preliminary report. Am J Psychiatry 135:570-572.

Quitkin FM, Kane JM, Rifkin A, Ramos-Lorenzi JR, Saraf K, Howard A, Klein DF (1981) Lithium and imipramine in the prophylaxis of unipolar and bipolar II depression: a prospective, placebo-controlled comparison. Psychopharmacol Bull 17:142-144.

Rabheru K, Persad E (1997) A review of continuation and maintenance electroconvulsive therapy. Can J Psychiatry 42:476-484.

Raucher-Chene D, Charrel CL, de Maindreville AD, Limosin F (2008) Manic episode with psychotic symptoms in a patient with Parkinson's disease treated by subthalamic nucleus stimulation: improvement on switching the target. J Neurol Sci 273:116-117.

Reinares M, Colom F, Rosa AR, Bonnin CM, Franco C, Sole B, Kapczinski F, Vieta E (2009) The impact of staging bipolar disorder on treatment outcome of family psychoeducation. J Affect Disord.

Riedel M, Musil R, Seemuller F, Spellmann I, Moller HJ, Schennach-Wolff R (2010) Safety evaluation of zotepine for the treatment of schizophrenia. Expert Opin Drug Saf 9:659-666.

Riemann D, Gann H, Hohagen F, Bahro M, Muller WE, Berger M (1993) The effect of carbamazepine on endocrine and sleep EEG variables in a patient with 48-hour rapid cycling, and healthy controls. Neuropsychobiology 27:163-170.

Roy-Byrne PP, Post RM, Uhde TW, Porcu T, Davis D (1985) The longitudinal course of recurrent affective illness: life chart data from research patients at the NIMH. Acta Psychiatr Scand Suppl 317:1-34.

Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, Kissling W, Davis JM, Leucht S (2010) Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 123:225-233.

Runge C, Grunze H (2004) Jährliche Krankheitskosten bipolarer Störungen in Deutschland. Nervenarzt 75:896-903.

Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, Lavori P, Howland R, Kling MA, Rittberg B, Carpenter L, Ninan P, Moreno F, Schwartz T, Conway C, Burke M, Barry JJ (2005) Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry 58:355-363.

Rybakowski JK, Chlopocka-Wozniak M, Suwalska A (2001) The prophylactic effect of long-term lithium administration in bipolar patients entering treatment in the 1970s and 1980s. Bipolar Disord 3:63-67.

Rybakowski JK, Suwalska A (2010) Excellent lithium responders have normal cognitive functions and plasma BDNF levels. Int J Neuropsychopharmacol 13:617-622.

Ryves WJ, Harwood AJ (2001) Lithium inhibits glycogen synthase kinase-3 by competition for magnesium. Biochem Biophys Res Commun 280:720-725.

Sachdev PS (1986) Lithium potentiation of neuroleptic-related extrapyramidal side effects. Am J Psychiatry 143:942.

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 356:1711-1722.

Sachs GS, Printz DJ, Kahn DA, Carpenter D, Docherty JP (2000) The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. Postgrad Med Spec Report1-104.

Sartorius N, Baghai TC, Baldwin DS, Barrett B, Brand U, Fleischhacker W, Goodwin G, Grunze H, Knapp M, Leonard BE, Lieberman J, Nakane Y, Pinder RM, Schatzberg AF, Svestka J, Baumann P, Ghalib K, Markowitz JC, Padberg F, Fink M, Furukawa T, Fountoulakis KN, Jensen P, Kanba S, Riecher-Rossler A (2007) Antidepressant medications and other treatments of depressive disorders: a CINP Task Force report based on a review of evidence. Int J Neuropsychopharmacol 10 Suppl 1:1-207.

Schneck CD (2002) Bipolar Disorder in Neurologic Illness. Curr Treat Options Neurol 4:477-486.

Scott J, Colom F, Popova E, Benabarre A, Cruz N, Valenti M, Goikolea JM, Sanchez-Moreno J, Asenjo MA, Vieta E (2009) Long-term mental health resource utilization and cost of care following group psychoeducation or unstructured group support for bipolar disorders: a cost-benefit analysis. J Clin Psychiatry 70:378-386.

Scott J, Colom F, Vieta E (2007) A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders. Int J Neuropsychopharmacol 10:123-129.

Seemuller F, Forsthoff A, Dittmann S, Born C, Bernhard B, Severus WE, Grunze H (2005) The safety and tolerability of atypical antipsychotics in bipolar disorder. Expert Opin Drug Saf 4:849-868.

Seo HJ, Chiesa A, Lee SJ, Patkar AA, Han C, Masand PS, Serretti A, Pae CU (2011) Safety and tolerability of lamotrigine: results from 12 placebo-controlled clinical trials and clinical implications. Clin Neuropharmacol 34:39-47.

Serretti A, Artioli P (2003) Predicting response to lithium in mood disorders: role of genetic polymorphisms. Am J Pharmacogenomics 3:17-30.

Severus WE, Kleindienst N, Evoniuk G, Bowden C, Moller HJ, Bohus M, Frangou S, Greil

W, Calabrese JR (2009) Is the polarity of relapse/recurrence in bipolar-I disorder patients related to serum lithium levels? Results from an empirical study. J Affect Disord 115:466-470.

Severus WE, Lipkovich IA, Licht RW, Young AH, Greil W, Ketter T, Deberdt W, Tohen M (2010) In search of optimal lithium levels and olanzapine doses in the long-term treatment of bipolar I disorder. A post-hoc analysis of the maintenance study by Tohen et al. 2005. Eur Psychiatry 25:443-449.

Severus WE, Littman AB, Stoll AL (2001) Omega-3 fatty acids, homocysteine, and the increased risk of cardiovascular mortality in major depressive disorder. Harv Rev Psychiatry 9:280-293.

Shelton RC (2006) Olanzapine/fluoxetine combination for bipolar depression. Expert Rev Neurother 6:33-39.

Shukla S, Godwin CD, Long LE, Miller MG (1984) Lithium-carbamazepine neurotoxicity and risk factors. Am J Psychiatry 141:1604-1606.

Simon GE, Savarino J, Operskalski B, Wang PS (2006) Suicide risk during antidepressant treatment. Am J Psychiatry 163:41-47.

Singh V, Mintz J, Tohen M (2012) Novel strategies to improve generalizability of maintenance trial results in Bipolar Disorder (BD). Bipolar Disord 14 Suppl 1:13-14.

Smith LA, Cornelius V, Warnock A, Bell A, Young AH (2007) Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. Bipolar Disord 9:394-412.

Solomon DA, Keitner GI, Ryan CE, Miller IW (1998) Lithium plus valproate as maintenance polypharmacy for patients with bipolar I disorder: a review. J Clin Psychopharmacol 18:38-49.

Solomon DA, Leon AC, Coryell WH, Endicott J, Li C, Fiedorowicz JG, Boyken L, Keller MB (2010) Longitudinal course of bipolar I disorder: duration of mood episodes. Arch Gen Psychiatry 67:339-347.

Spina E, Pisani F, Perucca E (1996) Clinically significant pharmacokinetic drug interactions with carbamazepine. An update. Clin Pharmacokinet 31:198-214.

Staiano AE, Reeder BA, Elliott S, Joffres MR, Pahwa P, Kirkland SA, Paradis G, Katzmarzyk PT (2012) Body mass index versus waist circumference as predictors of mortality in Canadian adults. Int J Obes (Lond).

Stallone F, Shelley E, Mendlewicz J, Fieve RR (1973) The use of lithium in affective disorders. 3. A double-blind study of prophylaxis in bipolar illness. Am J Psychiatry 130:1006-1010.

Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB (1999) Omega 3 fatty acids in bipolar disorder: a preliminary double-blind,

placebo-controlled trial. Arch Gen Psychiatry 56:407-412.

Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, Temple R, Rochester G (2009) Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 339:b2880. doi: 10.1136/bmj.b2880.:b2880.

Suppes T, Baldessarini RJ, Faedda GL, Tondo L, Tohen M (1993) Discontinuation of maintenance treatment in bipolar disorder: risks and implications. Harv Rev Psychiatry 1:131-144.

Suppes T, Brown E, Schuh LM, Baker RW, Tohen M (2005) Rapid versus non-rapid cycling as a predictor of response to olanzapine and divalproex sodium for bipolar mania and maintenance of remission: post hoc analyses of 47-week data. J Affect Disord 89:69-77.

Suppes T, Kelly DI, Keck PE, Jr., McElroy SL, Altshuler LL, Mintz J, Frye MA, Nolen WA, Luckenbaugh DA, Post RM, Leverich GS, Kupka RW, Grunze H (2007) Quetiapine for the continuation treatment of bipolar depression: naturalistic prospective case series from the Stanley Bipolar Treatment Network. Int Clin Psychopharmacol 22:376-381.

Suppes T, McElroy SL, Keck PE, Altshuler L, Frye MA, Grunze H, Leverich GS, Nolen WA, Chisholm K, Dennehy EB, Post RM (2004) Use of quetiapine in bipolar disorder: a case series with prospective evaluation. Int Clin Psychopharmacol 19:173-174.

Suppes T, Phillips KA, Judd CR (1994) Clozapine treatment of nonpsychotic rapid cycling bipolar disorder: a report of three cases. Biol Psychiatry 36:338-340.

Suppes T, Vieta E, Liu S, Brecher M, Paulsson B (2009) Maintenance treatment for patients with bipolar I disorder: results from a north american study of quetiapine in combination with lithium or divalproex (trial 127). Am J Psychiatry 166:476-488.

Szabo CP (1993) Depot flupenthixol-induced mania. S Afr Med J 83:442.

Szegedi A, Calabrese JR, Stet L, Mackle M, Zhao J, Panagides J (2012) Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week core study and 40-week extension. J Clin Psychopharmacol 32:46-55.

The World Health Organisation(2002) The World Health Report 2001, Mental Health: New understanding, new hope. Chapter 2: Burden of mental and behavioural disorder. Electronic Citation http://www.who.int/whr/2001/main/en/pdf/GGTSPU-1368-326547-DAT/chapter2.en.pdf

Thies-Flechtner K, Müller-Oerlinghausen B, Seibert W, Walther A, Greil W (1996) Effect of prophylactic treatment on suicide risk in patients with major affective disorders. Data from a randomized prospective trial. Pharmacopsychiatry 29:103-107.

Tohen M, Baker RW, Altshuler LL, Zarate CA, Suppes T, Ketter TA, Milton DR, Risser R, Gilmore JA, Breier A, Tollefson GA (2002a) Olanzapine versus divalproex in the treatment of acute mania. Am J Psychiatry 159:1011-1017.

Tohen M, Bowden CL, Smulevich AB, Bergstrom R, Quinlan T, Osuntokun O, Wang WV, Oliff HS, Martenyi F, Kryzhanovskaya LA, Greil W (2008) Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. Br J Psychiatry 192:135-143.

Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, Baker RW, Chou JC, Bowden CL (2006) Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 163:247-256.

Tohen M, Chengappa KN, Suppes T, Baker RW, Zarate CA, Bowden CL, Sachs GS, Kupfer DJ, Ghaemi SN, Feldman PD, Risser RC, Evans AR, Calabrese JR (2004) Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. Br J Psychiatry 184:337-345.

Tohen M, Chengappa KN, Suppes T, Zarate CA, Calabrese JR, Bowden CL, Sachs GS, Kupfer DJ, Baker RW, Risser RC, Keeter EL, Feldman PD, Tollefson GD, Breier A (2002b) Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 59:62-69.

Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, Malhi GS, Calabrese JR, Nolen WA, Vieta E, Kapczinski F, Goodwin GM, Suppes T, Sachs GS, Chengappa KR, Grunze H, Mitchell PB, Kanba S, Berk M (2009a) The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord 11:453-473.

Tohen M, Greil W, Calabrese JR, Sachs GS, Yatham LN, Oerlinghausen BM, Koukopoulos A, Cassano GB, Grunze H, Licht RW, Dell'Osso L, Evans AR, Risser R, Baker RW, Crane H, Dossenbach MR, Bowden CL (2005) Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 162:1281-1290.

Tohen M, Hennen J, Zarate C.M., Baldessarini RJ, Strakowski SM, Stoll AL, Faedda GL, Suppes T, Gebre MP, Cohen BM (2000) Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. Am J Psychiatry 157:220-228.

Tohen M, Ketter TA, Zarate CA, Suppes T, Frye M, Altshuler L, Zajecka J, Schuh LM, Risser RC, Brown E, Baker RW (2003a) Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry 160:1263-1271.

Tohen M, Sutton VK, Calabrese JR, Sachs GS, Bowden CL (2009b) Maintenance of response following stabilization of mixed index episodes with olanzapine monotherapy in a randomized, double-blind, placebo-controlled study of bipolar 1 disorder. J Affect Disord 116:43-50.

Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW, Evans AR, Beymer K, Dube S, Tollefson GD, Breier A (2003b)

Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 60:1079-1088.

Tohen M, Zarate CA, Hennen J, Khalsa HM, Strakowski SM, Gebre-Medhin P, Salvatore P, Baldessarini RJ (2003c) The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 160:2099-2107.

Tredget J, Kirov A, Kirov G (2010) Effects of chronic lithium treatment on renal function. J Affect Disord 126:436-440.

Tural U, Onder E (2010) Clinical and pharmacologic risk factors for neuroleptic malignant syndrome and their association with death. Psychiatry Clin Neurosci 64:79-87.

U.S.Food & Drug Administration(1975) FDA pregnancy categories. Electronic Citation http://depts.washington.edu/druginfo/Formulary/Pregnancy.pdf

Ulcickas YM, Delorenze G, Quesenberry CP, Jr., Tsai AL, Phillips S, Willey VJ, Niemcryk SJ, Wells K, Skovron ML, Cziraky MJ, Carson W, Oliveria SA (2010) Epidemiologic study of aripiprazole use and the incidence of suicide events. Pharmacoepidemiol Drug Saf 19:1124-1130.

Undurraga J, Baldessarini RJ, Valenti M, Pacchiarotti I, Tondo L, Vazquez G, Vieta E (2012) Bipolar depression: clinical correlates of receiving antidepressants. J Affect Disord 139:89-93.

US Food & Drug Administration. Statistical review and evaluation: antiepileptic drugs and suicidality. 2008. 12-4-2012.
Ref Type: Report

Valenti M, Pacchiarotti I, Rosa AR, Bonnin CM, Popovic D, Nivoli AM, Murru A, Grande I, Colom F, Vieta E (2011) Bipolar mixed episodes and antidepressants: a cohort study of bipolar I disorder patients. Bipolar Disord 13:145-154.

Van Amelsvoort T, Bakshi R, Devaux CB, Schwabe S (1994) Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. Epilepsia 35:181-188.

van der Loos ML, Mulder P, Hartong EG, Blom MB, Vergouwen AC, van Noorden MS, Timmermans MA, Vieta E, Nolen WA (2011) Long-term outcome of bipolar depressed patients receiving lamotrigine as add-on to lithium with the possibility of the addition of paroxetine in nonresponders: a randomized, placebo-controlled trial with a novel design. Bipolar Disord 13:111-117.

van der Loos ML, Mulder PG, Hartong EG, Blom MB, Vergouwen AC, de Keyzer HJ, Notten PJ, Luteijn ML, Timmermans MA, Vieta E, Nolen WA (2009) Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J Clin Psychiatry 70:223-231.

Vencovsky E, Soucek K, Kabes J (1984) Prophylactic effect of dipropylacetamide in patients with bipolar affective disorder. In: Emrich HM, Okuma T, Müller AA (eds) Anticonvulsants in affective disorders.Excerpta Medica, Amsterdam: pp 66-67.

Vernon AC, Natesan S, Crum WR, Cooper JD, Modo M, Williams SC, Kapur S (2012) Contrasting effects of haloperidol and lithium on rodent brain structure: a magnetic resonance imaging study with postmortem confirmation. Biol Psychiatry 71:855-863.

Vieta E, Berk M, Wang W, Colom F, Tohen M, Baldessarini RJ (2009a) Predominant previous polarity as an outcome predictor in a controlled treatment trial for depression in bipolar I disorder patients. J Affect Disord 119:22-27.

Vieta E, Berk M, Wang W, Colom F, Tohen M, Baldessarini RJ (2009b) Predominant previous polarity as an outcome predictor in a controlled treatment trial for depression in bipolar I disorder patients. J Affect Disord 119:22-27.

Vieta E, Cruz N (2012) Head to head comparisons as an alternative to placebo-controlled trials. Eur Neuropsychopharmacol 22:800-803.

Vieta E, Cruz N, Garcia-Campayo J, de AR, Manuel CJ, Valles V, Perez-Blanco J, Roca E, Manuel OJ, Morinigo A, Fernandez-Villamor R, Comes M (2008a) A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. Int J Neuropsychopharmacol 11:445-452.

Vieta E, Grunze H (2011) Bipolar disorder--a focus on depression. N Engl J Med 364:1581.

Vieta E, Gunther O, Locklear J, Ekman M, Miltenburger C, Chatterton ML, Astrom M, Paulsson B (2011) Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. Int J Neuropsychopharmacol 14:1029-1049.

Vieta E, Manuel GJ, Martinez-Aran A, Comes M, Verger K, Masramon X, Sanchez-Moreno J, Colom F (2006) A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. J Clin Psychiatry 67:473-477.

Vieta E, Montgomery S, Sulaiman AH, Cordoba R, Huberlant B, Martinez L, Schreiner A (2012a) A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder . Eur Neuropsychopharmacol, in press

Vieta E, Murru A, Pueyo MJ(2010a) Guia sobre el maneig del trastorn bipolar a Catalunya (Guidelines on the management of bipolar disorder in Catalunya). Electronic Citation http://www.gencat.cat/salut/depsan/units/aatrm/pdf/guia_trastorn_bipolar_aiaqs_2010ca.pdf

Vieta E, Nieto E, Autet A, Rosa AR, Goikolea JM, Cruz N, Bonet P (2008b) A long-term prospective study on the outcome of bipolar patients treated with long-acting injectable risperidone. World J Biol Psychiatry 9:219-224.

Vieta E, Owen R, Baudelet C, McQuade RD, Sanchez R, Marcus RN (2010b) Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. Curr Med Res Opin 26:1485-1496.

Vieta E, Pacchiarotti I, Valenti M, Berk M, Scott J, Colom F (2009c) A critical update on psychological interventions for bipolar disorders. Curr Psychiatry Rep 11:494-502.

Vieta E, Parramon G, Padrell E, Nieto E, Martinez-Aran A, Corbella B, Colom F, Reinares M, Goikolea JM, Torrent C (2002) Quetiapine in the treatment of rapid cycling bipolar disorder. Bipolar Disord 4:335-340.

Vieta E, Sanchez-Moreno J, Goikolea JM, Colom F, Martinez-Aran A, Benabarre A, Corbella B, Torrent C, Comes M, Reinares M, Brugue E (2004) Effects on weight and outcome of long-term olanzapine-topiramate combination treatment in bipolar disorder. J Clin Psychopharmacol 24:374-378.

Vieta E, Suppes T (2008) Bipolar II disorder: arguments for and against a distinct diagnostic entity. Bipolar Disord 10:163-178.

Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M (2008c) Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). J Affect Disord 109:251-263.

Vieta E, Suppes T, Ekholm B, Udd M, Gustafsson U (2012b) Long-term efficacy of quetiapine in combination with lithium or divalproex on mixed symptoms in bipolar I disorder. J Affect Disord 142:36-44.

Vieta E, T'joen C, McQuade RD, Carson WH, Jr., Marcus RN, Sanchez R, Owen R, Nameche L (2008d) Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. Am J Psychiatry 165:1316-1325.

Viguera AC, Koukopoulos A, Muzina DJ, Baldessarini RJ (2007) Teratogenicity and anticonvulsants: lessons from neurology to psychiatry. J Clin Psychiatry 68 Suppl 9:29-33.

Wasserman D, Rihmer Z, Rujescu D, Sarchiapone M, Sokolowski M, Titelman D, Zalsman G, Zemishlany Z, Carli V (2012) The European Psychiatric Association (EPA) guidance on suicide treatment and prevention. Eur Psychiatry 27:129-141.

Watkins SE, Callender K, Thomas DR, Tidmarsh SF, Shaw DM (1987) The effect of carbamazepine and lithium on remission from affective illness. Br J Psychiatry 150:180-182.

Weisler RH, Hirschfeld R, Cutler AJ, Gazda T, Ketter TA, Keck PE, Swann A, Kalali A (2006) Extended-release carbamazepine capsules as monotherapy in bipolar disorder : pooled results from two randomised, double-blind, placebo-controlled trials. CNS Drugs 20:219-231.

Weisler RH, Nolen WA, Neijber A, Hellqvist A, Paulsson B (2011) Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (trial 144: a randomized controlled study). J Clin Psychiatry.

Wingo AP, Harvey PD, Baldessarini RJ (2009) Neurocognitive impairment in bipolar disorder patients: functional implications. Bipolar Disord 11:113-125.

Woo YS, Bahk WM, Chung MY, Kim DH, Yoon BH, Lee JH, Ahn YM, Chung SK, Kim JG,

Lee KH, Paik KC (2011) Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial. HUM PSYCHOPHARMACOL 26:543-553.

World Health Organization. 1992. The ICD-10 Classification of Mental and behavioural Disorders. Clinical Descriptions and Diagnostic Guidelines.WHO, Geneva.

Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran A (2003) Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial. Br J Psychiatry 182:141-147.

Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, MacQueen GM, McIntyre RS, Sharma V, Ravindran A, Young T, Young AH, Alda M, Milev R, Vieta E, Calabrese JR, Berk M, Kyooseob H, Kapczinski F (2009) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord 11:225-255.

Yildiz A, Vieta E, Leucht S, Baldessarini RJ (2011) Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. Neuropsychopharmacology 36:375-389.

Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L, Manber R, Viguera A, Suppes T, Altshuler L (2004) Management of bipolar disorder during pregnancy and the postpartum period. Am J Psychiatry 161:608-620.

Yoshimura R, Ueda N, Shinkai K, Nakamura J (2006) Two cases of bipolar disorder successfully stabilized for five years with a low dose of risperidone and lithium. Pharmacopsychiatry 39:233-234.

Young AH (2011) More good news about the magic ion: lithium may prevent dementia. Br J Psychiatry 198:336-337.

Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, Paulsson B, Brecher M (2010) A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J Clin Psychiatry 71:150-162.

Young AH, McElroy SL, Olausson B, Paulsson B (2012) A randomised, placebo-controlled 52-week trial of continued quetiapine treatment in recently depressed patients with bipolar I and bipolar II disorder. World J Biol Psychiatry.

Young AH, Rigney U, Shaw S, Emmas C, Thompson JM (2011) Annual cost of managing bipolar disorder to the UK healthcare system. J Affect Disord 133:450-456.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133:429-435.

Zarate CA, Tohen M (2004) Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients. Am J Psychiatry 161:169-171.

Zarate CA, Tohen M, Banov MD, Weiss MK, Cole JO (1995) Is clozapine a mood stabilizer? J Clin Psychiatry 56:108-112.

Zarin D, Pincus HA, McIntyre JS(2002) APA Practice Guideline For The Treatment Of Patients With Bipolar Disorder. Electronic Citation http://www.psych.org/clin_res/pg_bipolar.cfm

Zhang X, Heng X, Li T, Li L, Yang D, Zhang X, Du Y, Doody RS, Le W (2011) Long-term treatment with lithium alleviates memory deficits and reduces amyloid-beta production in an aged Alzheimer's disease transgenic mouse model. J Alzheimers Dis 24:739-749.

Zimmerman M, Martinez JA, Attiullah N, Friedman M, Toba C, Boerescu DA, Rahgeb M (2012) Why do some depressed outpatients who are in remission according to the Hamilton Depression Rating Scale not consider themselves to be in remission? J Clin Psychiatry 73:790-795.

Zis AP, Grof P, Webster M, Goodwin FK (1980) Prediction of relapse in recurrent affective disorder. Psychopharmacol Bull 16:47-49.

Table 1. Classifying maintenance treatment success and therapeutic consequences derived from it (modified from Murru et al. (Murru et al

2011b).

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

Table 2. Categories of Evidence (CE) and recommendation grades (RG).

Category of Evidence	Description
A	**Full Evidence From Controlled Studies**
	is based on: 2 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 1 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 2 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: 1 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 1 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: 1 or more positive naturalistic open studies (with a minimum of 5 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: 1 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

Table 3. Grading of categories FE, ST, PSu and PR.

	Further evidence (FE)	Safety & 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	Some concerns	May enhance suicidal ideation	Aspects that make the use

	FE, e.g limited negative evidence from open studies in samples where enrichment is unclear			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

Table 4. Ratings for "Further evidence (FE)", "Safety & 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 5. 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 6. 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

Table 7. 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

Table 8. 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”

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

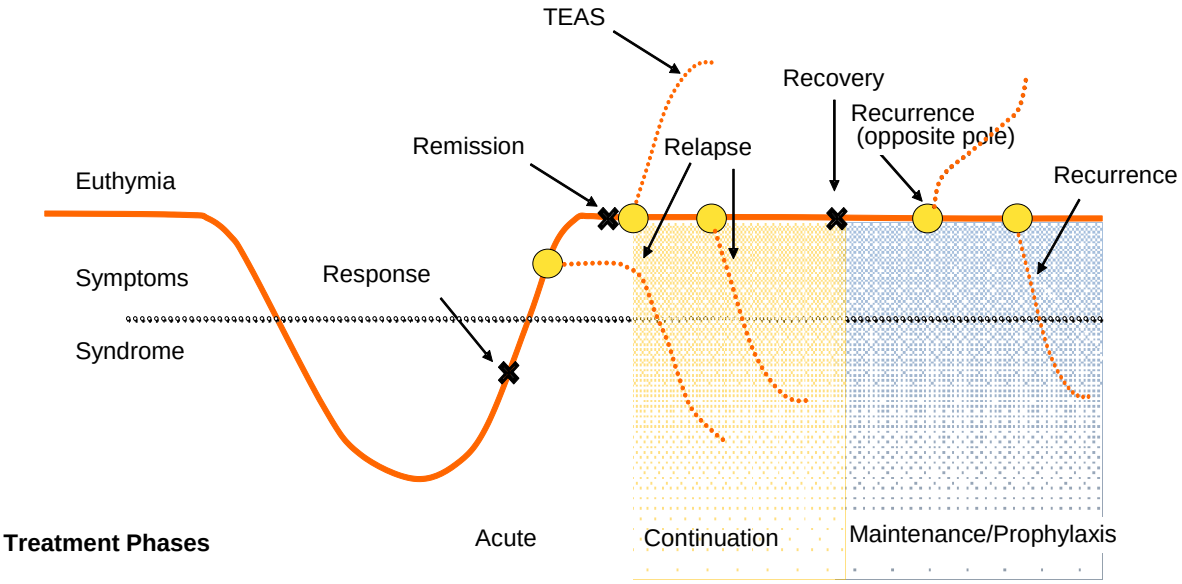
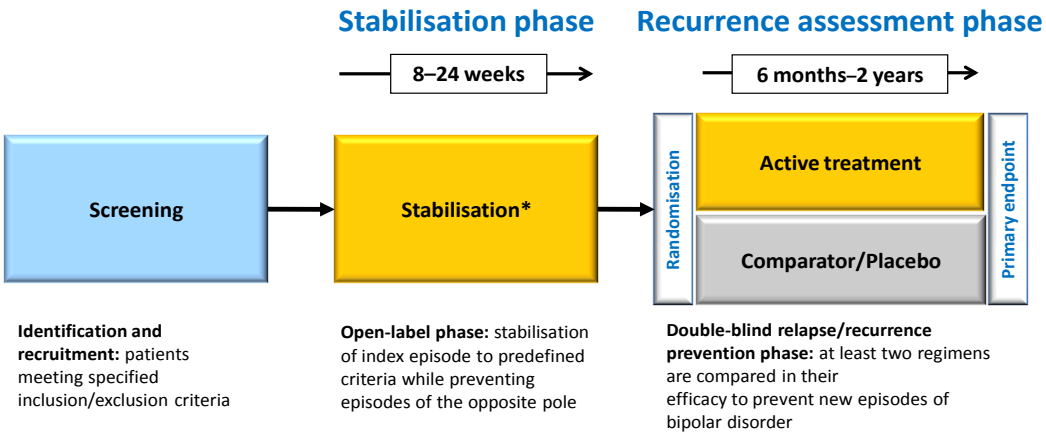
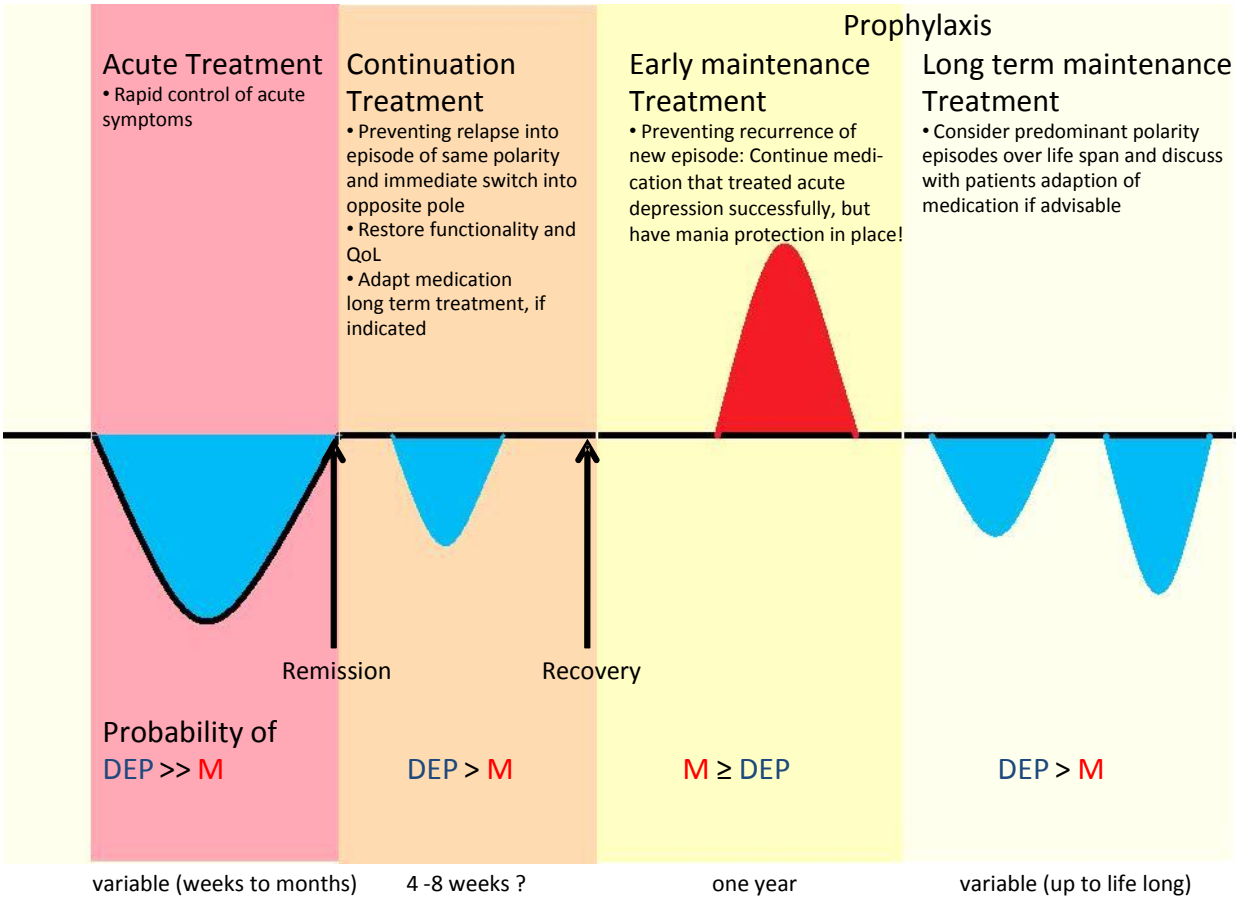


Figure 2. Design commonly used in Bipolar long-term maintenance studies in enriched samples. Adapted from Gitlin et al. (2010).



*) Period of 8–12 weeks recommended by the US Food and Drug Administration (FDA) for maintenance studies unless otherwise specified.

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.

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