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GUIDELINES

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

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Abstract

These updated guidelines are based on a first edition that was published in 2003, and have been edited and updated with the available scientific evidence until end of 2008. Their purpose is to supply a systematic overview of all scientific evidence pertaining to the treatment of acute mania in adults. The data used for these guidelines have been extracted from a MEDLINE and EMBASE search, from the clinical trial database *clinicaltrials.gov*, from recent proceedings of key conferences, and from various national and international treatment guidelines. Their scientific rigor was categorised into six levels of evidence (A–F). As these guidelines are intended for clinical use, the scientific evidence was finally asigned different grades of recommendation to ensure practicability.

Key words: *Bipolar disorder, mania, depression, acute treatment, evidence-based guidelines, pharmacotherapy, antipsychotics, mood stabiliser, electroconvulsive therapy*

Abbreviations

ADHD	Attention-deficit-hyperactivity disorder
CBT	Cognitive behavioral therapy
CE	Category of evidence
DSM	Diagnostic and Statistical Manual
ECT	Electroconvulsive therapy
HDL	High density lipoproteins
ICD	International Clssification of Diseases
LDL	Low density lipoproteins

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MAS	Bech-Rafaelsen Mania Scale
MRS	Mania Rating Scale (subset of items derived from the Schedule for Affective Disorders and Schizophrenia-Change Bipolar Scale (SADS-CB))
rTMS	Repetitive transcranial magnetic stimulation
RCT	Randomized controlled trial
RG	Recommendation grade
WFSBP	World Federation of Societies of Biological Psychiatry
YMRS	Young Mania Rating Scale

Preface and Disclosure Statement

As the other guidelines of this series, these practice guidelines for the biological, mainly pharmacological treatment of acute bipolar mania were developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). The preparation of these guidelines has not been financially supported by any commercial organization.

This practice guideline has mainly been developed mainly by psychiatrists and psychotherapists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. 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

Bipolar disorder is frequently misdiagnosed and under-diagnosed (Kasper et al. 2002; Angst 2006) although occasionally overdiagnosis may occur (Zimmerman et al. 2008). Particularly when unrecognised or misdiagnosed, and consequently ineffectively treated, bipolar disorder constitutes a devastating illness (Simpson and Jamison 1999; Morselli et al. 2004; Maina et al. 2007) with a significant socioeconomic burden (Woods 2000; Angst 2004; van Hakkaart et al. 2004; Runge and Grunze 2004). At first manifestation, the diagnosis of bipolar disorder may not be obvious; at least 20% and in some settings up to 50% of patients diagnosed with an index episode of depression may prove to be bipolar in the long run (Goldberg et al. 2001; Angst 2006). However, when the disorder presents as acute mania, which is the focus of the present guidelines, the diagnosis becomes easier, albeit it sometimes can be difficult to differentiate from schizophrenia and other conditions like severe ADHD.

In contrast to unipolar depression and to the more broadly defined bipolar spectrum, bipolar I disorder (characterized primarily by mania) as defined by the Diagnostic and Statistical Manual, 4th ed-TR (DSM-IV (American Psychiatric Association 1994) seems to have a worldwide lifetime incidence within a relatively narrow range between 0.5 and 1.6% for bipolar I disorder (Weissman et al. 1996). The reported lifetime prevalence for bipolar spectrum disorders (Bipolar I, II or NOS) is about 5.5% (Angst 1995; Regeer et al. 2004), although slight deviations of these numbers may occur depending on the sample (Merikangas et al. 2007). Together with increasing evidence of an underlying genetic aetiology (Hayden and Nurnberger 2006) the relatively uniform epidemiological figures support, without neglecting ethnic and cultural diversity, that an optimised biological, mostly psychopharmacological, treatment may bring comparable benefits across cultures.

Despite this assumption, there are multiple guidelines and strategies for the treatment of bipolar I disorder worldwide which place different emphases on different kinds of treatments (Fountoulakis et al. 2005). Although some may be due to biological diversities, much is due to different traditions in treatment and different attitudes towards particular agents and also the evidence upon which different approaches are based is limited or is subject to varying interpretation.

For the bipolar spectrum, treatment guidelines, when published, differ even more, since the nosological issue, especially the delineation from unipolar depression, is not conclusively settled (Benazzi 2007; Goodwin et al. 2008). Given these diagnostic uncertainties and a lack of controlled evidence for treatment of the bipolar spectrum, all current guidelines, including this one, concentrate on Bipolar I disorder; if evidence is available, some more recent guidelines also include recommendations on the treatment of bipolar II disorder.

Despite all these limitations, guidelines appear quite welcome to clinicians. According to a recent census by Perlis (Perlis 2007), 64% of those who responded said that they make regular use of them when making treatment decisions.

Diagnostic issues in bipolar I disorder

In DSM-IV, bipolar I disorder is characterized by the occurrence of at least one manic or mixed episode. The International Classification of Diseases, 10th ed. (ICD-10, World Health Organization 1992) which is frequently used for clinical, but not

research purposes, however, does not separate between bipolar I and II disorder within the concept of bipolar disorder (F31), and requires at least two episodes (hypomania, mania, mixed state or depression) for the diagnosis. If only a single manic episode has occurred, it is defined as separate category (F30). Almost all controlled clinical studies conducted after 1994 use categorical DSM-IV criteria for inclusion/exclusion of manic subjects, and as a consequence, evidence-based guidelines, including this one, are based on DSM-IV diagnostic entities. However, since the definitions of mania within the DSM-IV and the ICD-10 are very similar (Licht et al. 2001) guidelines on mania can be implemented into clinical settings using the ICD-10, at least when treating pure or psychotic mania. Clinicians using the ICD-10 should be aware that the concept of mixed states in the ICD-10 is more loosely defined than in the DSM-IV. According to the DSM-IV, mixed states imply that diagnostic criteria for a manic episode and a depressive episode (except for the duration criterion) are fulfilled simultaneously. The concept of mixed mania (or dysphoric mania) is not well-defined, but sometimes used in the context of drug trials, referring to mania with some depressed features which are either not pronounced enough or insufficiently lasting enough to fulfil the criteria for a major depressive episode.

Tables I and II summarize DSM-IV diagnostic criteria for mania and mixed episodes. However, the complexity of mania is not adequately captured by the DSM-IV. Manic states are not uniform, nor do they always fit in clear clinical distinctions. Thus, a wide range of symptoms beyond the ones that defines the disorder may occur in an acute manic episode (see Table III). When additional psychotic symptoms are present, the manic episode or the mixed state are characterized as a psychotic mania or a psychotic mixed state, and this is considered a subtype, albeit on another level as the distinction between manic and mixed states. It is unclear whether secondary grandiose delusions – the commonest clinical manifestation of "psychosis" merits qualitative distinction since it looks much more like an expression of severity. Of importance, first rank symptoms also occur in mania and may confuse the distinction from schizophrenia. The separation between mood-congruent and mood-incongruent psychotic symptoms seems to be more relevant to prognosis than to treatment.

Finally, the task force is aware that there are even more manifestations of mania beyound DSM-IV and ICD-10 that are of clinical importance and should merit more attention in guidelines, e.g., mania with delirium, oligo-monosymptomatic forms of mania, chronic mania, and specific manifestations of mania in senium and childhood. However, controlled evidence for specific treatments is mostly lacking, and including all subtypes and manifestation of mania is virtually impossible for a comprehensive guideline.

Clinical experience with the various tentative antimanic agents over recent years has suggested that a drug that is efficacious in one subtype of mania is not necessarily the treatment of choice for the other subtypes. Secondary (and often post-hoc) analyses of large randomized trials usually dealt with pure (or classical) mania versus mixed states, and distinguished between the presence and absence of a rapid cycling course. In recognition of this available information, this guideline will, when data allow, also distinguish between pure mania, dysphoric mania and mixed states, psychotic mania, and, finally, hypomania. Rapid cycling as a course specifier, however, will no longer receive special attention in this updated guideline for two reasons: rapid cycling appears not to be a distinct class on its own (Kupka et al. 2005; Schneck et al. 2008) and to date no firm evidence has been found that manic patients with rapid cycling respond differently in the short term to acute antimanic treatment compared to those without rapid cycling in the short term (Vieta et al. 2004). Special treatment considerations depending on episode frequency are more important in treating bipolar depression (avoiding treatment emergent affective switches (TEAS)) and in the choice of maintenance treatment.

Methods

These guidelines address the treatment of acute mania mainly in adults, although, when evidence was available, they also mention treatment options in adolescents and the elderly. They are primarily based on evidence from randomised clinical studies, thereby adhering to the principles of evidence-based medicine. The data used for these guidelines have been extracted from a MEDLINE and EMBASE search, the Science Citation Index at Web of Science (ISI) (all until end of 2008), from recent proceedings of key conferences, and from various national and international treatment guidelines. A few additional trials were found by hand-searching in text books. In addition, www.clinicaltrials.gov was accessed to check for unpublished studies.

Categorization of efficacy and recommendations derived from the evidence are, whenever available, based on studies that fulfilled certain methodological requirements, including standard diagnostic criteria, adequate sample size, use of a control group, randomization to treatment, double-blind conditions, valid and sensitive psychometric rating scales

Table I. Diagnostic criteria for acute mania according to DSM-IV.

Criteria for Manic Episode (DSM-IV, p. 332)

- A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary).
- B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
  - Inflated self-esteem or grandiosity
  - Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
  - more talkative than usual or pressure to keep talking
  - flight of ideas or subjective experience that thoughts are racing
  - distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
  - increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  - excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
- C. The symptoms do not meet criteria for a Mixed Episode.
- D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
- E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatments) or a general medical condition (e.g., hyperthyroidism).

and appropriate statistical tests, fulfilment of good clinical practice (GCP) criteria, and approval by properly-constituted ethics committee. Unfortunately, abstracts of some recent key studies which have been presented as posters so far do not supply all these information. In these instances, additional information was requested from the sponsoring companies of these studies. When randomised, double-blind trials were not available, other sources of information such as open studies and case reports have also been collected.

The results of metanalyses had been used only to a minor extent. Generally, meta-analyses mostly exist for groups of drugs, but not for every single drug and intervention. Moreover, meta-analyses have a number of methodological shortcomings, which can make their conclusions less reliable than those of the original studies (Anderson 2000; Bandelow et al. 2008). For acute mania, some methodologically sound metaanalyses are available (e.g., Scherk et al. 2007; Smith et al. 2007b), limiting individual study inclusion to trials meeting rigorous criteria. With that level of individual study input, some useful comparative efficacy and tolerability analyses and effect size comparisons are feasible both for drug vs. placebo and for individual drugs vs. lithium, the most frequently used main active comparator, become possible and effect size comparisons are feasible. Even metanalyses carry the risk of overpowering, i.e. finding a difference to placebo that may be statistically, but not clinically significant, the increase of power may be useful in answering important secondary clinical questions about subgroups.

As an additional source of information, other guideline activities published after the first edition of this guideline (Grunze et al. 2003a) were also considered (Zarin et al. 2002; Licht et al. 2003; Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar Disorder 2004; National Collaborating Centre for Mental Health 2006; Yatham et al. 2006; Jon et al. 2008; Nolen et al. 2008).

In contrast with the preceding WFSBP Bipolar Mania guidelines (Grunze et al. 2003a), but in line with the bipolar depression (Grunze et al. 2002) and maintenance treatment guideline (Grunze et al. 2004), this update is structured in terms of groups of medication rather than by subtypes of mania, although summaries on treatment of subtypes are provided in the end of the paper.

In order to achieve uniform and, in the opinion of this taskforce, appropiate ranking of evidence we adopted the same hierarchy of evidence based rigor and level of recommendation as was published recently in the WFSBP Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders (Bandelow

Table II. Diagnostic criteria for a mixed episode according to DSM-IV.

A. The criteria are met both for a Manic Episode and for a Major Depressive Episode (except for duration) nearly every day during at least a 1-week period.

B. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Table III. Frequency of symptoms observed clinically during acute manic episodes (adapted from Goodwin and Jamison (2007).

Symptom	Weighted mean (%)
Mood symptoms	
Irritability	71
Euphoria	63
Depression	46
Lability	49
Expansiveness	60
Cognitive symptoms	
Grandiosity	73
Flight of ideas, racing thoughts	76
Distractibility, poor concentration	75
Confusion	29
Psychotic symptoms	
Any delusions	53
Grandiose delusions	31
Persecutory/paranoid delusions	29
Passivity delusions	12
Any hallucinations	23
Auditory hallucinations	18
Visual hallucinations	12
Olfactory hallucinations	15
Presence or history of psychotic symptoms	61
Thought disorder	19
First rank Schneiderian symptoms	18
Activity and behaviour during mania	
Hyperactivity	90
Decreased sleep	83
Violent, assaultive behavior	47
Rapid, pressured speech	88
Hyperverbosity	89
Nudity, sexual exposure	29
Hypersexuality	51
Extravagance	32
Religiosity	39
Head decoration	34
Regression (pronounced)	28
Catatonia	24
Fecal incontinence (smearing)	13

et al. 2008) (See Table IV). The WFSBP Anxiety guideline supplies a detailed rational for choosing the different levels of evidence and derived recommendations. 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, recommendation grades 1–3). Depending on the number of positive trials and the absence or presence of negative evidence, different categories of evidence for efficacy are assigned. A distinction was also made between "lack of evidence" (i.e. studies proving efficacy or non-efficacy do not exist) and "negative evidence" (i.e. the majority of controlled studies shows non-superiority to placebo or inferiority to a comparator drug). 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. Recommendations were then derived from the category of evidence for efficacy (CE) and from additional aspects as safety, tolerability and interaction potential (in the body of text summarized under the heading "effectiveness"). The recommendation grades (RG) can be viewed as steps: Step 1 would be a prescription of a medication with RG 1. When this treatment fails, all other Grade 1 options should generally be tried first before switching to treatments with RG 2, then 3, 4 and 5. In some cases, e.g., the combination of an RG 1 and an RG 2 option can preferentially be tried instead of combining two RG 1 options. We have not considered the direct or indirect costs of treatments as these vary substantially across different health care systems. Additionally, some of the drugs recommended in this guideline may not (or not yet) have received approval for the treatment of mania in every country. As the approval by national regulatory authorities is dependent on a variety of factors, including the sponsor's commercial interest (or lack thereof) this guideline is exclusively based on the available evidence.

Large placebo-controlled studies include subjects with a variety of severity grades of mania above a predefined threshold (usually a YMRS (Young et al. 1978) score of $\geq$20 or a SADS-C–derived Mania Rating Scale (MRS) (Endicott and Spitzer 1978) of $\geq$14 in monotherapy studies; in adjunctive, placebo-controlled trials also lower inclusion scores have been used, e.g., YMRS score $\geq$16). Mean baseline scores for YMRS ratings are mostly between 28 and 32 (corresponding to moderate to severe mania), but with a large standard deviation. Unless specific subanalyses have been made, the results do not allow conclusions about efficacy in very severe mania or, conversely, mild mania. Thus, when grading evidence for efficacy, any grading refers somewhat artificially to "moderate" mania, which represents a mean of all single scores, but is not a homogeneous group. If specific positive or negative evidence exists for severe mania or psychotic mania, either by subanalyses of patient groups or specific trials, this information is also provided. Furthermore, most RCTs in acute mania have a duration of 3 weeks, and only more recently double-blind extension periods up to 12 weeks had been added to the protocols. Thus, the clinically important question of maintenance of effect could not be considered as a core criterion for efficacy.

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

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

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

sponsors to supply this information. Thus, this information may not always be complete and may bias evidence of efficacy in favour of a drug where access to such information is limited. However, this potential bias has been minimized as much as possible by checking the www.clinicaltrials.gov database.

Another methodological limitation is sponsor bias (Lexchin et al. 2003; Perlis et al. 2005; Heres et al.

2006; Lexchin and Light 2006) inherent in most single studies on which the guidelines are based. Also, all recommendations are formulated by experts who may try their best to be objective but 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 evidence. One of the most important clinical questions that can not be sufficiently answered in an evidence based way is what to do when any first step treatment fails, which happens in up to 50% of cases. Therefore, with the current level of knowledge we can only provide suggestive guidelines and not rigorous algorithms.

Once a draft of this guideline had been prepared by the Secretary and Chairmen of the Task Force, 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.

Lithium and anticonvulsants

Traditionally, lithium and some anticonvulsants, mainly valproate and carbamazepine, have been grouped together as so called "mood stabilizers" in order to differentiate their broader, both acute and prophylactic action from the notionally limited acute antimanic effect of some typical neuroleptics, e.g., chlorpromazine and haloperidol. Also, the term has implied that both mania and depression potentially were ameliorated. However, with the emergence of atypical antipsychotics, some of them showing both acute and long-term efficacy, and others also having antidepressant efficacy, these agents could also be characterized as "mood stabilizers". As a consequence, we will avoid using the term "mood stabilizer" for lithium and anticonvulsants, since it may imply an artificial distinction between these substances and the atypical antipsychotics. However, it remains appropriate to summarize the evidence on lithium and anticonvulsants under a single heading in the light both of clinical tradition and of other aspects such as their potentially shared intracellular mechanisms of action and their continuous high ranking as a primary choice for maintenance treatment.

Lithium

Efficacy. To date a total of 29 published or presented studies have evaluated the acute antimanic efficacy of lithium. Lithium therefore has clearly the largest pool of studies. Four early studies, starting with Schou's evaluation from 1954 (Schou et al. 1954), tested lithium against placebo. However, only more recent studies, starting with a three-arm study comparing valproate and lithium against placebo (Bowden et al. 1994) can be considered to fulfil current methodological standards for a drug approval study. In the latter study, both lithium and valproate were significantly more effective than placebo. Subsquently, lithium has also been employed as an internal comparator in other phase III approval studies, thus allowing a judgement of its efficacy. Lithium was superior to placebo in a study with quetiapine as investigational drug (Bowden et al. 2005), in two studies with topiramate as investigational drug (Kushner et al. 2006), and in one study with aripiprazole as investigational drug (Keck et al. 2007). In two studies with lamotrigine as investigational drug (GlaxoSmithKline study SCA 2008 and SCA 2009, unpublished) lithium did separate numerically, but not significantly from placebo. However, one of the studies (SCA 2008) was not powered to show such a difference; in the other, lithium just missed significance at $P=0.05$ in the LOCF analysis of the primary outcome, the MRS-11 (Endicott and Spitzer 1978).

In other methodologically less sophisticated comparator studies without a placebo arm, the antimanic efficacy of lithium was tested versus various antipsychotics (a total of 11 studies versus chlorpromazine and/or haloperidol (Grunze 2003), one versus zuclopenthixol (Gouliaev et al. 1996), two versus olanzapine (Berk et al. 1999; Niufan et al. 2008), one against risperidone (Segal et al. 1998), one against verapamil (Walton et al. 1996) one against clonazepam (Clark et al. 1997), one against lamotrigine (Ichim et al. 2000) and five versus carbamazepine (Placidi et al. 1986; Lerer et al. 1987; Lusznat et al. 1988; Okuma et al. 1990; Small et al. 1991). The response rates given for lithium in randomised studies (whereby different treatment duration and responder criteria were applied from study to study) range from 32% (Small et al. 1991) to 94% (Freeman et al. 1992) which may also reflect the different severities of mania in these studies. For example, in the study of Prien et al. (1972) lithium

did not perform as well as chlorpromazine in the subgroup of highly agitated patients. A recent metaanalysis of six randomized, controlled trials with lithium in acute mania (four of them published: Bowden et al. 1994, 2005; Kushner et al. 2006), and two as part of a registration dossier (SCA 2008 and SCA 2009) revealed an overall standardized effect size of 0.40 [95% confidence interval (CI): 0.28, 0.53] and an overall NNT ("numbers-needed-to treat") for response of 6 (95% CI: 4, 13) (Storosum et al. 2007).

As to the efficacy of lithium in psychotic mania, earlier comparative studies indicated that it was more the degree of severity than the presence of psychotic symptoms that was associated with a poorer response to lithium (compared to a typical neuroleptic) (Licht 2006). In the study comparing quetiapine with placebo, using lithium as internal comparator (Bowden et al. 2005), it was reported that quetiapine and lithium did equally well (and superior to placebo) in terms of reduction in the PANSS positive subscale scores. Also a post-hoc analysis analysis of data from the valproate–lithium–placebo trial by Bowden et al. (Bowden et al. 1994) found similar responses to lithium and valproate in a subgroup of psychotic patients (Swann et al. 2002).

Protocol-defined target plasma levels for lithium in recent controlled studies were usually in the range between 0.6 and 1.3 mmol/l. In clinical practice, adolescents and young adults may require and tolerate at the higher end of this range, whereas elderly patients may tolerate only dosages at the lower end of this range.

Lithium is available in different salt preparations, e.g., lithium carbonate, lithium citrate and lithium sulfate. There is no evidence for different efficacy between these salts. However, lithium carbonate and lithium citrate are also available as extended release preparation, which may have advantages for tolerability.

Effectiveness. The usefulness of lithium in acute mania may be limited by the need for regular plasma level checks to avoid toxicity, as well as by its side effect profile and contraindications. These limitations have been dealt with extensively in textbooks (Goodwin and Jamison 2007) and reviews (McIntyre et al. 2001). A slower onset of action of lithium, relative to the investigational drug, has been observed in some controlled studies (e.g., Keck et al. 2007), but not in others (e.g., Bowden et al. 1994, 2005).

Recommendation. Based on the available studies, lithium falls into CE for antimanic efficacy "A".[1] Efficacy may be more pronounced in pure (euphoric) mania than in mania with concomitant dysphoric or depressive features (Swann et al. 1997). However, its potentially slower onset of action together with the low level of sedative properties often makes it necessary to combine it with a tranquilizing agent at treatment initiation. In addition, regular plasma level monitoring is essential due to its relative small safety margin. Although not absolutely contraindicted, lithium is rarely suitable in certain medical conditions, which therefore should be excluded before treatment initiation, e.g., renal problems or thyroid dysfunction. In these instances, regular medical checkups are mandatory. With this reduced practicability, the RG would be "2"[2] for the solely acute use of lithium. If considerations of maintenance treatment play an additional role at the time of acute treatment initiation, lithium alone or in combination may become the primary choice (RG"1") already at this early stage.

Carbamazepine

Efficacy. Starting with the first studies of Okuma et al. (1973), the efficacy of carbamazepine for the acute treatment of mania has been demonstrated in several small studies, both by Okuma's group and by other investigators (e.g., Ballenger and Post 1980; Müller and Stoll 1984; Emrich et al. 1985; Post et al. 1987). Comparative studies have been conducted with both typical neuroleptics, lithium and with valproate (Okuma et al. 1979; Klein et al. 1984; Placidi et al. 1986; Stoll et al. 1986; Lerer et al. 1987; Lusznat et al. 1988; Brown et al. 1989; Okuma et al. 1990; Small et al. 1991; Vasudev et al. 2000). The impression of these studies was that carbamazepine was overall equally effective as comparators, with a probably slightly slower onset of response compared to neuroleptics (Brown et al.

[1] A: Full evidence from controlled studies is based on: two or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding) and one or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists). In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfill established methodological standards.The decision is based on the primary efficacy measure.

[2] Recommendation Grade 2 corresponds to "Category A evidence and moderate risk-benefit ratio".

1989) and valproate (Vasudev et al. 2000), but slightly faster acting than lithium (Small et al. 1996).

The first large randomized, placebo controlled mania study with carbamazepine as investigational drug was not published until 2004 (Weisler et al. 2004b). Both this study and a replication study (Weisler et al. 2005) showed significant superiority of carbamazepine over placebo in the treatment of acute mania. Looking into specific sub-groups of patients, carbamazepine may be helpful in patients with incomplete response to lithium (or presumably other agents as well) in acute mania (Lerer et al. 1987; Post et al. 1987; Okuma et al. 1990), in patients with co- morbid organic (neurological) disorders (Schneck 2002) and schizoaffective patients (Goncalves and Stoll 1985; Elphick 1985).

Effectiveness. Common side effects of carbamazepine include oversedation and blurred vision, especially with high dosages and rapid titration. Rare, but potentially severe side effects include allergic reactions, lupus erythematosus, agranulocytosis and hyponatremia. Tolerability isssues may be less problematioc with extended release formulations. Detailed information on the tolerability and safety profile of carbamazepine is available in recent reviews and text books (Grunze and Walden 2002; Gajwani et al. 2005; Grunze 2006). In addition, carbamazepine is associated with an increased risk of birth defects (Morrow et al. 2006). Carbamazepine's main shortcoming in routine use, however, is its capacity for interaction with other psychotropic medication, including several antipsychotics, antidepressants and anticonvulsants (Spina et al. 1996). Since a majority of patients with acute mania may be on treatment with several medications (Wolfsperger et al. 2007), this complicates and limits the utility of carbamazepine.

Recommendation. Based on two double-blind, placebo-controlled studies and several comparator studies, with at least one of them (Okuma et al. 1979) adequately powered to show non-inferiority, the **CE** for antimanic efficacy for carbamazepine is "**A**". The main short-comings of carbamazepine are some tolerability issues with rapid titration and its interaction potential with a variety of other psychiatric and non-psychiatric medication, including contraceptives, through enzymatic induction making it a **RG** "**2**" recommendation.

Valproate

This guideline uses "valproate" as common generic name for the different preparations tested in acute mania, e.g., valproic acid, sodium valproate, divalproate, divalproex sodium, and valpromide. As far as pharmacokinetics and pharmacodynamics are concerned, only valproic acid finally reaches and penetrates the blood-brain barrier. Although tolerability is enhanced with extended release preparations, the difference does not warrant grouping valproic acid derivatives as different medications.

Efficacy. The antimanic activity of valproate was first reported by Lambert et al. (1966). Subsequently, the efficacy of valproate in the treatment of acute mania has been evaluated in short-term randomised controlled trials, both as monotherapy (Emrich et al. 1980; Pope et al. 1991; Bowden et al. 1994, 2006) and in combination with a neuroleptic (Müller-Oerlinghausen et al. 2000). These studies have provided consistent evidence that valproate is an efficacious treatment for acute mania (Macritchie et al. 2003). Similar antimanic efficacy was observed for valproate in comparator trials with lithium (Freeman et al. 1992; Bowden et al. 1994, 2008) haloperidol (McElroy et al. 1996a) and in one study against olanzapine (Zajecka et al. 2002) but not in two others (Zajecka et al. 2002; Tohen et al. 2009b). Compared to carbamazepine (Vasudev et al. 2000), valproate appeared superior in terms of overall outcome.

Based on secondary analyses from the comparative trials with olanzapine and the comparative trial with lithium and placebo by Bowden and co-workers (Bowden et al. 1994; Swann et al. 2002) and the study by McElroy et al. (1996a) comparing valproate with haloperidol, albeit small in sample size, there are indications that valproate also works in psychotic mania.

Effectiveness. In acute manic patients, dose-loading with 20–30 mg/kg body weight seems to be more effective than slower titration schemes (Keck et al. 1993; Grunze et al. 1999; Hirschfeld et al. 2003). Plasma levels of 75–99 mg/l (520–690 mmol/l) seem to be associated with the best efficacy/tolerability ratio (Keck et al. 2005; Allen et al. 2006). The tolerability of valproate appears fair across trials. Gastointestinal discomfort, sedation and tremor are in most trials more frequently observed with valproate than with placebo, but usully do not result in higher discontinuation rates. For rare, but severe complications as thrombocytopenia, hepatic failure, pancreatitis or hyperammonaemic coma and precaution measures we refer to the pertinent reviews (e.g., Bowden and Singh 2005).

Recommendation. The **CE** for efficacy can be classified as "**A**" with comparable effect sizes for pure

mania (with or without psychotic symptoms) and mania with dysphoric/depressive features. The safety margin of valproate is relatively large allowing rapid titration ("dose loading") and a subsequent earlier onset of action. Valproate is not appropriate in some medical conditions, e.g., liver disease, and in combination with some medication, e.g., warfarin. As these conditions can usually be ruled out clinically with a good degree of certainty, the **RG** would be "**1**" for the acute treatment of mania. However, caution should be used in women of child-bearing age, not only because of teratogenicity and high risk of developmental delay (Viguera et al. 2007), but also because of the supposed increased risk of a polycystic ovary syndrome (PCOS) (Soares 2000; Rasgon et al. 2005). Thus, the RG for younger women is no more than"2".

Other anticonvulsants with potential antimanic properties

Several other anticonvulsants have been poposed as having antimanic properties, but none of them has been studied enough to allow the conclusion that efficacy and tolerability were within the same range as the drugs previously reviewed in detail. Additionally, for some, substantial evidence of marginal or unsatisfactory tolerability exists, and/or evidence of lack of difference from placebo is conclusive. Thus, their RG is usually low and furthermore, they should not be considered as equal alternatives when other antimanic drugs fail to yield optimal outcomes.

Phenytoin has demonstrated antimanic properties in a small, double blind, placebo-controlled add-on study to haloperidol (Mishory et al. 2000) (**CE** of efficacy "**B**[3]"). The side effect profile of phenytoin, especially cognitive side effects and cerebellar atrophy (De Marcos et al. 2003), however, makes it a medication of subordinate choice for acute mania (**RG** "**3**").

Evidence for the antimanic properties of **oxcarbazepine** is not convincing (Hirschfeld and Kasper 2004); a recent review of several small, underpowered or placebo-uncontrolled studies came to the conclusion that it may be useful in treating manic symptoms (Popova et al. 2007), but conclusive evidence is lacking (**CE** for efficacy "**C1**", **RG** "**4**"). Due to the chemical resemblance with carbamazepine it is often assumed that it may be beneficial in patients who previously responded well to carbamazepine but had to discontinue it for reasons of tolerability or interaction with other medication. Oxcarbazepine may also exhibit both interactions with other medications and tolerability issues, but to a lesser degree than carbamazepine; however, the risk of hyponatremia appears to be greater with oxcarbazepine.

Other anticonvulsants with **CE** of efficacy "**C1**"[4] include *levetiracetam* (Goldberg and Burdick 2002; Grunze et al. 2003b; Kyomen 2006; Desarkar et al. 2007) and *zonisamide* (Kanba et al. 1994; McElroy et al. 2005; Anand et al. 2005). One small case series (Amann et al. 2006) gives **retigabine** "**C1**" evidence. The **RG** derived from these studies is "**4**". The **CE** for *topiramate, gabapentin,* and *lamotrigine* is "**E**"[5] (Ichim et al. 2000; Pande et al. 2000; Goldsmith et al. 2003; Kushner et al. 2006) and for *pregabaline* and *tiagabine* "**F**".[6] In the case of tiagabine, open studies were suggestive of no efficacy together with an increased risk of epileptiform seizures (Grunze et al. 1998; Suppes et al. 2002).

Atypical antipsychotics

During recent years, the treatment portfolio of acute mania has significantly increased with the emergence of atypical antipsychotics. For this article we list the different antipsychotics in alphabetical order within the group of atypical antipsychotics approved for mania, and within the group of atypical antipsychotics not yet approved or marketed.

Aripiprazole

Efficacy. Four placebo-controlled acute mania studies have been published or presented in scientific meetings as posters so far (Keck et al. 2003a; Sachs et al. 2006; Keck et al. 2007; Young et al. 2009) one of them including a lithium arm (Keck et al. 2007) and

[3] B: Limited positive evidence from controlled studies is based on: one or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") *or* a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial *or* one or more sufficiently powered post-hoc analyses of RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo"). In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least one more positive study or a meta-analysis of all available studies showing superiority to placebo or non-inferiority to an established comparator treatment.

[4] C1 evidence is based on: one or more positive naturalistic open studies (with a minimum of five evaluable patients *or* a comparison with a reference drug with a sample size insufficient for a non-inferiority trial *and* no negative controlled studies exist).

[5] E: 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.

[6] F: Adequate studies proving efficacy or non-efficacy are lacking. If existing, open studies or case reports showed a total lack of efficacy.

another one using haloperidol as a comparator (Young et al. 2009). One (unpublished) study comparing aripiprazole with placebo was negative (McIntyre et al. 2007). A further head to head comparison against haloperidol with no placebo arm is difficult to interpret due to methodological limitations (Vieta et al. 2005a). In a placebo-controlled combination treatment study with either valproate or lithium, aripiprazole was also superior to valproate or lithium alone (Vieta et al. 2009c). In addition, an intramuscular injectable preparartion of aripiprazole has demonstrated antimanic efficacy in a controlled study (Sanford and Scott 2008).

Secondary analyses also confirmed the broad spectrum of efficacy of aripiprazole across subtypes of mania.

Effectiveness. More frequent side effects reported in the full publications were headache, somnolence and dizziness, but none of these was significant more frequent than with placebo. Akathisia appears to be more frequent with aripiprazole than with placebo (Keck et al. 2003a; Sachs et al. 2006)

Aripiprazole did not cause any significant QTc changes in controlled studies and was weight-neutral in the short-term. No significant changes in any blood parameter were observed. Specifically, no significant elevations in prolactin, cholesterol and fasting blood glucose levels were reported for aripiprazole.

Recommendation. Based on the available evidence, aripiprazole fulfils **CE** "**A**" for antimanic efficacy, with subanalyses supporting efficacy also in dysphoric/mixed states and psychotic mania. With the good tolerability profile, this would translate into a **RG** "**1**".

Olanzapine

Efficacy. Olanzapine has shown significant superiority over placebo in four double-blind placebo-controlled monotherapy studies (Tohen et al. 1999, 2000) including one in adolescent mania (Tohen et al. 2007) and one focussing on mild to moderate mania (Tohen et al. 2009b). Three of these studies had a duration of 3 weeks, and one of 4 weeks. It is of note that especially in the 4-week study (Tohen et al. 2000) a relatively large proportion of patients with mixed states (43%) were included, with olanzapine showing similar efficacy in secondary analysis to that in pure manic patients. In both of the early studies (Tohen et al. 1999, 2000), more than 50% of patients also had psychotic features. It is of clinical importance that the improvement, as measured by the drop in the Young Mania Rating Scale (YMRS) scores, did not differ between psychotic and non-psychotic manic patients. In addition, a randomized, controlled trial of injectable olanzapine in agitated mania has demonstrated significant superiority for olanzapine against placebo and lorazepam after 2 h (Meehan et al. 2001).

In addition to the placebo-controlled, randomized, controlled trials summarised above, several further head-to head comparison studies with olanzapine have been conducted. Three double-blind placebo-controlled trials compared olanzapine with valproate in acute mania. In the trial of Tohen et al. (2003b) olanzapine outperformed valproate on the primary outcome, the reduction of the YMRS after 3 weeks. However, this study may be criticized on the ground that valproate was likely to be underdosed; only 87% of the manic patients reached plasma levels above 350 mmol/l. In a second study comparing olanzapine and valproate, Zajecka et al. (2002) used higher doses of valproate (mean dose 2115 mg/day compared to 1401 mg/day in the previous study) but lower doses of olanzapine. In this study, no significant difference between groups was found for YMRS reduction; however, the study was not powered for efficacy but for weight gain, resulting in potential type II error (Vieta 2003). Finally, in a study comparing olanzapine and valproate in mild to moderate mania, olanzapine was significantly more efficacious than valproate after 12 weeks, but on the expenses of higher weight gain and more metabolic issues (Tohen et al. 2009b). Compared head-to-head with lithium, olanzapine had superior efficacy to lithium in the acute treatment of mania over a 4-week period. However, adverse events were experienced by a greater number of olanzapine patients than lithium patients which may limit olanzapine's clinical utility (Niufan et al. 2008). In a direct comparative study with risperidone, no difference in antimanic efficacy was observed (Perlis et al. 2006a). With haloperidol as comparator, haloperidol was significantly better at week 6 (primary endpoint), but at week 12 the efficacy of olanzapine and haloperidol were comparable (Tohen et al. 2003a).

Olanzapine had also been subject to controlled combination treatment studies. In the study of Tohen et al. (2002) patients were treated with either valproate or lithium for acute mania. Those not showing sufficient response after three weeks were then randomised and treated in a double-blind fashion with either olanzapine or placebo as an add-on. Olanzapine treated patients had a significant better outcome reflected by the YMRS total score after 6 weeks of treatment. In secondary analyses, a positive effect was also noted on the Hamilton Depression Rating Scale (HAM-D) scores,

especially in patients with mixed episodes with moderate or severe depressive symptoms. In terms of the YMRS, olanzapine outperformed placebo in patients with mixed mania and psychotic symptoms as was also the case in the placebo-controlled monotherapy trials (Baker et al. 2004).

A recent study conducted at the request of the regulatory authorities investigated olanzapine vs. placebo as add-on treatment to carbamazepine in acute mania. Olanzapine treated patients did not differ significantly from the placebo group in the primary outcome, the YMRS score reduction. However, this finding was not totally unexpected: due to induction of the olanzapine metabolism by carbamazepine, patients attained olanzapine blood levels that were considered insufficient (Tohen et al. 2008).

Finally, these positive results in controlled clinical studies were consistent with a large, pan-European naturalistic mania study (EMBLEM) which reported efficacy both for olanzapine monotherapy and olanzapine in combination with other medications in a broad spectrum of manic patients (Vieta et al. 2008).

Effectiveness. According to secondary analyses, olanzapine seems to be equally efficacious across the range of subtypes of mania (euphoric, dysphoric/mixed, psychotic).

As far as tolerability and safety are concerned, olanzapine showed a favourable profile in the acute treatment. In all controlled trials until 2003, the drop out rates due to adverse events were not significantly higher than in patients taking placebo, valproate or haloperidol (McCormack and Wiseman 2004). Somnolence and dizziness was associated significantly more frequently with olanzapine treatment than with placebo. EPS however, were not significantly more frequent when compared to placebo independent of dosage. Not surprisingly, in one head-to-head trial against haloperidol, all scales covering EPS showed significantly higher ratings for haloperidol than for olanzapine (Tohen et al. 2003a). Anticholinergic side effects like dry mouth or constipation occurred rarely in the controlled studies. Significant QTc prolongations have not been observed in any of the olanzapine trials. However, with intramuscular injections of olanzapine, there is an increased risk of respiratory arrest inpatients on concomitant benzodiazepines.

The most worrisome adverse effects of olanzapine are metabolic (Franciosi et al. 2005). The initial concern was weight: in the olanzapine short-term trials the mean weight gain from baseline to endpoint ranged from 1.65 to 4 kg. Unfortunately, blood glucose and lipid levels were not monitored consistently in these short-term studies, since problems in this area had not been anticipated. Although there is one report of death due to ketoacidosis in the trial by Zajecka and colleagues (Zajecka et al. 2002), only the bipolar depression study from Tohen et al. (2003c) reported on non-fasting blood glucose levels from the patients receiving olanzapine or the olanzapine/fluoxetine combination, and found them to be significantly higher than in patients taking placebo. The recent study in mild to moderate mania (Tohen et al. 2009b) also found increased glucose blood levels after 12 weeks in patients assigned to olanzapine compared to those with valproate. More information is available concerning cholesterol and triglyceride blood levels, which are more sensitive indicators of metabolic disturbance than glucose. The study of Zajecka and colleagues (Zajecka et al. 2002) in which olanzapine treated patients exhibited the highest weight gain also showed a significant increase in serum cholesterol in the olanzapine group (13.9 mg/dl for olanzapine compared with a small reduction of −1.69 mg/dl for valproate). This increase in lipids has been confirmed in other studies with olanzapine across indications and is supported by animal data (Ader et al. 2005). Metabolic problems are associated with the use not only of olanzapine, but also of the other atypical antipsychotics clozapine and quetiapine (van Winkel et al. 2008). The primary salience of the metabolic syndrome derives from its links to cardiovascular risk factors, and the attendant mortality risks of long-term treatment with atypical agents (Ray et al. 2009). This reinforces the general recommendation of regular fasting blood glucose checks after initiation of these atypical antipsychotics in particular, although no antipsychotic (including the older drugs) can be exempt with the possible exceptions of aripiprazole and ziprasidone.

Recommendation. In summary, the **CE** for antimanic efficacy of olanzapine is "**A**", but the **RG** "**2**" because of these potential metabolic issues.

Quetiapine

Efficacy. Two randomised, placebo- and comparator-controlled acute mania monotherapy studies have been published (Bowden et al. 2005; McIntyre et al. 2005). In addition, a placebo-controlled mania study evaluating an extended release formulation of quetiapine has recently been presented (Cutler et al. 2008). There is also a placebo and paliperidone-controlled trial in which quetiapine was used as the active control for assay sensitivity (Vieta et al. 2009a). All of these monotherapy studies demonstrated significant superiority of quetiapine over

placebo. Whereas quetiapine was as effective as lithium (Bowden et al. 2005), haloperidol showed a faster onset of action (McIntyre et al. 2005) and better efficacy than quetiapine (Scherk et al. 2007). These controlled studies did not enrol patients with mixed states, so it is only possible to make conclusions about pure mania (with or without psychotic symptoms).

Quetiapine was also tested in two placebo controlled combination studies as add on to lithium or valproate. Whereas one study showed superiority of the combination quetiapine/lithium or valproate (Sachs et al. 2004), the other failed to do so (Yatham et al. 2007).

Further evidence for the antimanic action of quetiapine stems from two controlled studies in adolescents, one placebo-controlled add on study to valproate (DelBello et al. 2002), and one head-to head comparison against valproate (DelBello et al. 2006). It has been suggested that quetiapine doses in the registration trials (up to 800 mg/day) had been too low, but the evidence from open studies whether higher dosages are more effective is conflicting (Pajonk et al. 2006; Khazaal et al. 2007).

Effectiveness. The drops out rates in these controlled studies due to side effects were comparable to placebo drop outs.

Although its incidence remained low, somnolence occurred two to six times more frequently than with placebo. Somnolence to that extent could have been due to the concomitant use of benzodiazepines, which may synergistically increase this adverse event. In both combination treatment trials (Yatham et al. 2004) somnolence occurred again to a significantly higher degree with quetiapine than with placebo, and additive effects of mood stabilizers and quetiapine on somnolence cannot be excluded.

Extrapyramidal side effects were assessed using the Barnes Akathisia and the Simpson Angus Rating Scale for Parkinsonism, but (as was the case for olanzapine) no significant differences between quetiapine, placebo or the comparator drugs in all trials with respect to EPS were observed (Bowden et al. 2005; Calabrese et al. 2005; McIntyre et al. 2005).

Cardiac tolerability was also favourable, and no significant QTc prolongation was observed when compared to placebo.

The mean weight gain was consistently higher in quetiapine treated patients compared to those on placebo, haloperidol or lithium, respectively. In three studies no significance is reported on the mean weight change. However, the absolute numbers show a weight gain with quetiapine (Bowden et al. 2005; Calabrese et al. 2005; McIntyre et al. 2005). Metabolic issues cannot be excluded when quetiapine is taken as long term medication, but do not appear significant with short-term use.

No other clinically relevant changes in laboratory parameters and vital signs significantly different from placebo have been observed in any of the quetiapine studies.

Recommendation. Based on the controlled date, the **CE** for acute antimanic efficacy can be graded "**A**". However, the task force feels that the **RG** should be only "**2**", for two reasons: quetiapine appeared weaker than (low dose) haloperidol in direct comparison and there is a lack of data supporting its use in mixed states. Finally, metabolic issues may become of importance if quetiapine is chosen as continuation or maintenance treatment.

Risperidone

Efficacy. Three double-blind, placebo-controlled monotherapy trials have been published so far (Hirschfeld et al. 2004; Khanna et al. 2005; Smulevich et al. 2005), one of them also having a haloperidol comparator arm (Smulevich et al. 2005). The results are uniform: risperidone (mean dosage 4–6 mg/day) was significantly better than placebo in all the studies. Comparison with haloperidol showed no difference in antimanic efficacy (Scherk et al. 2007). Additionally, a small head-to head comparison trial against lithium and haloperidol (Segal et al. 1998) and a larger comparison against olanzapine (Perlis et al. 2006a) support the antimanic efficacy of risperidone monotherapy.

Two placebo-controlled studies investigated risperidone as add on to valproate or lithium (Sachs et al. 2002) or as add on to lithium, valproate or carbamazepine (Yatham et al. 2003). Whereas the first study demonstrated the superiority of risperidone add-on, the second one failed due to lack of response in the patients receiving carbamazepine as primary treatment. This illustrates the problematic issues associated with carbamazepine as an inducer of cytochrome P450 enzyme in combination treatment.

Whereas mixed patients were seldom represented in these studies, the study by Khanna et al. (2005) supplies evidence for efficacy of risperidone in severe and psychotic mania (mean baseline YMRS score 37.2). A reduction of 21 points in the YMRS was observed in this study, an antimanic response hardly ever seen in any other controlled phase III trial.

Effectiveness. Risperidone demonstrated powerful antimanic action in one study with a mean daily dose of almost 6 mg (Khanna et al. 2005). However, this efficacy was at the expense of tolerability.

Approximately 50% of the patients in this study suffered also from EPS. In lower dosages as used in the other studies, the rate of EPS was also much lower. In four of the five trials (three in monotherapy and the two combination treatment studies), discontinuation due to EPS was similar to placebo (Sachs et al. 2002; Yatham et al. 2003; Hirschfeld et al. 2004; Khanna et al. 2005; Smulevich et al. 2005). However, three monotherapy trials found significant higher total Extrapyramidal Symptom Rating Scale (ESRS) ratings in the risperidone group than in the placebo group (Hirschfeld et al. 2004; Khanna et al. 2005; Smulevich et al. 2005). To place these results into perspective, a significant difference in the ESRS total score favoring risperidone in comparison to haloperidol was also found in one of these trials (Smulevich et al. 2005).

Even when including the study by Khanna et al. with its exceptional low-drop out rate, the overall drop out rates due to side effects of risperidone did not differ significantly from placebo. In two trials, somnolence was reported at least twice as often for risperidone as for placebo. Dizziness occurred slightly more often with risperidone than with placebo, but was not statistically significant in two trials (Sachs et al. 2002; Hirschfeld et al. 2004).

The cardiac tolerability of risperidone appears good, no significant or clinically relevant QTc prolongations were observed in controlled trials in bipolar disorder.

Weight gain was significantly higher with risperidone in both combination trials and in one monotherapy trial (Hirschfeld et al. 2004). The mean weight gain ranged from 1.7 to 2.4 kg at endpoint. In comparison, patients with placebo experienced weight loss (−0.25 kg) or gained weight to a maximum of 0.5 kg in both the studies in which risperidone has been combined with a mood stabilizer (Sachs et al. 2002; Yatham et al. 2003).

Despite the fact that some clinical trials show considerable weight gain for risperidone, cholesterol blood levels or non-fasting blood glucose levels have not been reported. Metabolic dysregulation should be anticipated in clinical practice.

Elevation of prolactin blood level occur that are even higher than with haloperidol (Smulevich et al. 2005). This may be a consequence of the relatively low brain penetration of risperidone and the relatively high plasma levels required for efficacy: these will preferentially elevate prolactin since the pituitary lies outside the blood–brain barrier. Adverse events possibly related to elevated prolactin levels occurred in six patients in the risperidone group and in two patients in the haloperidol group, respectively.

Recommendation. Based on the controlled date, the **CE** for acute antimanic efficacy can be graded "**A**". Overdosing of risperidone should be avoided as this clearly impacts effectiveness due to EPS and prolactin elevation. The **RG** would be "**1**". There is evidence for good efficacy in severe and psychotic mania, but only limited data supporting risperidone's use in mixed states.

Ziprasidone

Efficacy. Ziprasidone monotherapy was tested for antimanic efficacy in three double-blind placebo-controlled studies (Keck et al. 2003c; Potkin et al. 2005b; Vieta et al. 2009b), one of them also had haloperidol as an internal comparator (Vieta et al. 2009b). All these studies confirmed the antimanic efficacy of ziprasidone. However, in direct comparison, haloperidol was more effective (Warrington et al. 2007). Post-hoc analyses of these trials also provided evidence that ziprasidone is effective in dysphoric/mixed states and psychotic mania (Greenberg and Citrome 2007). Ziprasidone is also available as intramuscular injectable solution.

In one placebo-controlled add-on study to lithium or valproate, ziprasidone did not separate from placebo at end point, although it enhanced the initial antimanic response (Weisler et al. 2004a). Additionally, it separated from placebo at study end on several secondary measures.

Effectiveness. No significant differences compared to placebo were observed during these cited controlled studies in EPS related scales (Keck et al. 2003b; Potkin et al. 2005a). However, akathisia was reported twice as often for patients taking ziprasidone than for placebo (10.7 vs. 5.7%, respectively, albeit a non- significant difference (Keck et al. 2003c)).

Initial somnolence was reported about three to four times as often for ziprasidone than for placebo, and dizziness occurred to a significant degree in one published ziprasidone study (22.1 vs. 10% in the placebo group) (Keck et al. 2003b).

Ziprasidone's cardiovascular safety profile is of some concern. In the study by Keck et al. (2003b), ziprasidone treated patients experienced a mean QTc prolongation of 11 msec, although no prolongations beyond 500ms were observed. The main safety concern, torsades de pointe, has not been reported in post-marketing surveillance. Elevated blood pressure has been noted in 11.4% of the patients of the ziprasidone group compared to 2.9% of the placebo group. However, there were no changes in the measured median values for systolic or diastolic blood pressure or pulse observed from baseline to endpoint in either group.

Ziprasidone, together with aripiprazole, are the two aAP, which do not cause significant weight increase in controlled mania trials. No significant changes in levels of total cholesterol, HDL and LDL were detected when compared to placebo (Keck et al. 2004). Secondary analysis of short-term and long-term studies of ziprasidone in bipolar patients revealed even a decrease of lipid levels (Nasrallah et al. 2004).

Recommendation. Ziprasidone fulfils **CE "A"** for antimanic efficacy, with subanalyses supporting efficacy also in mixed states and psychotic mania. Therefore the **RG** is "**1**". However, due to the fear of potential cardiac toxicity, ziprasidone is not available in some countries or restricted in its use. For these countries, the **RG** is **"2"** as it should not be considered as first line treatment for legal reasons.

Other atypical antipsychotics

This section deals with those atypical antipsychotics, which have studies supportive of antimanic efficacy, but are not or not yet licensed in this indication, or are not yet marketed, but are likely to be in the close future (e.g., asenapine).

Amisulpride is a frequently used antimanic medication in some parts of the world; however, evidence for efficacy is so far based on one double blind, randomized, add-on trial to valproate vs. the combined treatment with haloperidol and valproate (Thomas et al. 2008), and one positive open, but randomized study (Vieta et al. 2005b). The add-on comparator study against haloperidol and valproate failed to proof the a priori defined hypothesis of superiority of amisulpride, and was underpowered for proofing equality. Thus, the **CE** for efficacy is "**C1**", and the **RG** "**4**". Until the emergence of recent atypicals it was an attractive off-label treatment. Amisulpride is not associated with weight gain or reports of new onset diabetes. However, high dosages of amisulpride usully as administered in acute mania do cause hyperprolactemia.

For *asenapine*, two placebo-controlled acute mania monotherapy randomized controlled trials (ARES 7501004 and 7501005) (McIntyre et al. 2008a) and one add-on study to lithium or valproate treatment (Apollo 7501008) (Calabrese et al. 2008) have been presented in scientific meetings as posters so far, with the monotherapy studies also including a comparator arm (olanzapine). In all three studies, asenapine demonstrated significant superiority over placebo. Olanzapine appeared numerically though not statistically superior to asenapine.

Asenapine was well tolerated in these cited studies; in particular the incidence of EPS was low. However, a small increase of weight was observed with asenapine in the two 3-week monotherapy studies and a moderate increase of weight and fasting glucose in the combination study after 12 weeks (Calabrese et al. 2008). Although there was no significant increase in patients with asenapine fulfilling criteria for metabolic syndrome in a 52-week extension of Ares 7501004 and 7501005 (McIntyre et al. 2008b), the limited data are insufficient to provide a conclusive statement regarding its metabolic risks.

Based on the available evidence, asenapine fulfils **CE** "**A**" of antimanic efficacy, with a subanalysis supporting also efficacy on depressive symptoms in mixed states. With the still limited clinical experience and a possible signal for metabolic concerns, it may be, once available, a **RG** "**2**" recommendation with further evidence for safety awaiting.

Clozapine can be considered as the archetypal atypical antipsychotic. Numerous case reports and several small investigator-initiated trials support its antimanic as well as mild antidepressive and good prophylactic efficacy in bipolar patients (Frye et al. 1998). Clozapine may in consequence be regarded as a last resort drug in treatment refractory bipolar patients (Calabrese et al. 1996; Green et al. 2000). However, all these data are derived from small and often poorly controlled investigator-initiated trials. The large-scale methodologically unambiguous studies are missing due to the lack of commercial interest and the potentially life threatening side effects of clozapine. Thus, **CE** for the antimanic efficacy of clozapine must be graded "**C1**", but the **RG** is only "**4**" despite the fact that it may be very helpful in treatment resistant mania.

Recently, *paliperidone* monotherapy has been tested in two placebo-controlled monotherapy trials, one of them positive, with quetiapine as active comparator (Vieta et al. 2009a), and the other reaching significance only for the highest dose of paliperidone (12 mg/d; see www.clinicaltrial.gov, trial identifier NCT00299715). An add-on study of paliperidone to lithium or valproate was negative (see www.clinicaltrial.gov, trial identifier NCT0030 9686).

Paliperidone was generally well tolerated in these studies, but with increasing susceptibility to EPS with higher dosages. Other side effects occuring more frequently than with placebo included headache, somnolence, dizziness, sedation, akathisia, dystonia, and dyspepsia. Similar to risperidone, paliperidone caused an increase in prolactin both in male and female subjects.

Since paliperdione is a metabolite of risperidone, differences from the parent compound might be expected to be minimal.

At this stage, with two positive and one negative study, the **CE** for efficacy for paliperidone can be graded as "**B**", the corresponding **RG** would be "**3**". However, this grading is only true for the highest tested dosage, 12 mg/d; for lower tested dosages (6 and 3 mg/day) the evidence is inconsistent ("D").

The situation with *zotepine* is quite similar to that for clozapine. At least two open studies are in line with antimanic efficacy (Harada and Otsuki 1986; Amann et al. 2005) (**CE** "**C1**", **RG**"**4**") but mainly a lack of commercial interest prohibited further evaluation in randomized, controlled studies. As zotepine is capable of causing significant weight gain, its value may be limited with the emergence of weight neutral atypicals with proven antimanic efficacy.

Typical neuroleptics

Haloperidol

Efficacy. Although haloperidol has been the primary clinical choice in severe mania for decades, an adequate evidence base for its use has only recently emerged. It also used to be routinely administered at higher doses than were probably necessary. Haloperidol has been used as a comparator in randomized, placebo-controlled studies examining risperidone (Smulevich et al. 2005), quetiapine (McIntyre et al. 2005), ziprasidone (Vieta et al. 2009b), aripiprazole (Young et al. 2009) and in a combination study of risperidone with lithium or valproate (Sachs et al. 2002). In all these studies, haloperidol was significantly better than placebo. This conclusion is additionally supported by a metaanalysis of these studies (Cipriani et al. 2006). Direct head-to-head comparison studies of haloperidol exist with olanzapine (Tohen et al. 2003a), aripiprazole (Vieta et al. 2005a), valproate (McElroy et al. 1996a), carbamazepine (Brown et al. 1989) and lithium (Segal et al. 1998) and in combination with lithium vs. carbamazepine+lithium (Small et al. 1995). All these studies also support the antimanic efficacy of haloperidol across subtypes of mania.

Effectiveness. The use of haloperidol is clearly limited by its high propensity at commonly used doses (>10 mg/day) to induce acute extrapyramidal motor symptoms, and propably even more important, tardive dyskinesia. Naturalistic data suggest that bipolar patients may be even more prone than schizophrenic patients to these side effects (Mukherjee et al. 1986; Keck et al. 2000). It is likely, nevertheless, that doses of haloperidol may be chosen that are effective in mania and minimize the risk of EPS. In a study randomizing manic patients to three different doses of haloperidol, 10, 20 and 80 mg, no differences were shown in terms of efficacy, suggesting that the the optimal dose range might even be below 10 mg daily (Rifkin et al. 1994).

It has also been suggested that typical antipsychotics may be more likely to induce depressive symptoms than atypicals (Tohen et al. 2003a) and have no prophylactic efficacy (Zarate and Tohen 2004) but further prospective trials may be needed to prove these assumptions.

Recommendation. In summary, the **CE** for antimanic efficacy of haloperidol can be graded as "**A**". Due to its side effect burden, the **RG** is "**2**" for mania in general. However, at least in the emergency treatment of severe mania or in patients who do not respond to other therapies, haloperidol has its place and justification.

Chlorpromazine

One placebo-controlled randomised trial for chlorpromazine in acutely manic patients has been reported (Klein and Oak 1967). Other controlled studies involving chlorpromazine were head-to-head comparisons versus lithium (Platman 1970; Spring et al. 1970; Johnson et al. 1971; Prien et al. 1972; Shopsin et al. 1975; Takahashi et al. 1975) and carbamazepine (Okuma et al. 1979). Additional comparator trials include comparison of chlorpromazine against pimozide (Cookson et al. 1980), thiothixene (Janicak et al. 1988) and ECT (McCabe and Norris 1977b). The general impression from all these studies was of comparable efficacy for chlorpromazine and the respective comparator. However, in the large study by Prien et al. (1972), chlorpromazine was superior to lithium in a subgroup of highly active patients Similar dose considerations apply to the use of chlorpromazine as to haloperidol, although it is generally more sedative. The doses established for use in acute mania (200–800 mg/day) are associated with a high risk of EPS.

Other frequent side effects with chlorpromazine include pronounce sedation; tardive dyskinesia, hypersensitivity of the skin to sunlight and hepatotoxicity. With only one small placebo-controlled study with chlorpromazine in mania, the **CE** for efficacy is "**B**" and the **RG** "**3**". The task force is aware that this rating may not accurately reflect the usefulness of this medication which still has a widespread use in mania, especially in countries with limited access to newer medication, but at the time of its discovery RCTs according to todays standards were not considered as esssential.

Benzodiazepines

Clonazepam and lorazepam are quite frequently used in bipolar disorder. However, they are usually not considered as primary mood stabilising agents but are (lorazepam in particular) used as add-on treatment to calm the patient and relieve anxiety and insomnia. Nevertheless, there are some studies supporting true antimanic effects of these two drugs.

Clonazepam

Clonazepam is a high potency 1,4-benzodiazepine derivative. Besides effecting the GABA A receptor, clonazepam may also modulate the central serotonergic metabolism (Lima 1991). In a small double-blind study (Edwards et al. 1991), clonazepam was superior to placebo. However, since the duration of the trial was only 5 days and since considerable amounts of chlorpromazine were given in both groups, any true antimanic efficacy can not be inferred. The beneficial role of clonazepam in mania has also been supported in one randomized comparator trial against lithium (Clark et al. 1997) and in other, but inconclusive studies (Chouinard et al. 1983; Adler 1986; Chouinard 1987; Pande 1988; Chouinard et al. 1993; Bottai et al. 1995; Morishita and Aoki 1999) With no rigourous evidence from methodologically sound RCT's, but some comparator trials, a level "**C1**" **CE** for efficacy, corresponding to a **RG** "**4**". However, caution should be exerted in the light of its addictive potential.

Lorazepam

Lorazepam is often used as a standard rescue medication in controlled mania studies, but it may by itself influence the outcome of trials if used in an uncontrolled manner. In a small double-blind study lorazepam's efficacy was comparable to that of haloperidol as an add-on to lithium (Lenox et al. 1992). However, used as an add-on medication to haloperidol, lorazepam was less efficacious than lithium add-on treatment (Chou et al. 1999). In a small, double-blind, randomised monotherapy but not placebo-controlled 2-week comparison with clonazepam, lorazepam appeared more efficacious in treating acute mania (Bradwejn et al. 1990). Recently, lorazepam by intramuscular injection was compared with olanzapine and placebo in 201 acutely manic patients. At endpoint after 24 h lorazepam injections were better than placebo on several outcome parameters measuring agitated behaviour. However, the study was not powered to show significant differences between lorazepam and placebo (Meehan et al. 2001).

Given the lack of placebo-controlled studies or sufficiently powered comparator trials the **CE** for antimanic efficacy of lorazepam can be graded"**C1**" with a **RG** "**4**".

Because of fears of potential dependency, the continous use of lorazepam cannot be recommended; thus, its main clinical value remains as an add-on in the acute state of mania.

Investigational agents

Tamoxifen

On placebo-controlled, double blind study gave evidence for the antimanic efficacy of the protein kinase C inhibitor tamoxifen (Yildiz et al. 2008), although some methodological issues may raise concerns about the generalisability of the result (Tohen 2008). In addition, two smaller placebo-controlled studies (Kulkarni et al. 2006; Hah and Hallmayer 2008) and one single blind study (Zarate et al. 2007) also found significant improvement of mania with tamoxifen. On this basis and in the absence of comparator trials, tamoxifen has "**B**" **CE** of efficacy. However, despite a formal **RG** of "**3**", its clinical utility is clearly limited due to its nature as an antioestrogen and it should rather be considered as an experimental approach. From its unique mode of action tamoxifen appears quite interesting; a better tolerated protein kinase C inhibitor could be an antimanic agent of the future.

Calcium antagonists

An open study suggests antimanic efficacy of *nimodipine* (Brunet et al. 1990) (**CE** for efficacy "**C1**", **RG** "**4**"). One placebo-controlled, but methodologically flawed small study with a cross-over design suggested some antimanic efficacy for *verapamil* (Dubovsky et al. 1986), but two larger, parallel group studies could not confirm this finding (Walton et al. 1996; Janicak et al. 1998) (**CE** for efficacy "**D**", **RG** "**5**")**.** The viability of these calcium antagonists as antimanic agents, however, is limited due to the effect on blood pressure (verapamil) or their short half-life necessitating multiple dosing per day (nimodipine).

Physical treatments

For *electroconvulsive therapy* (ECT)**,** randomized, controlled studies have not been completed in mania. Numerous case reports and chart reviews support the utility of ECT in severe mania (McCabe and Norris 1977a; Soares et al. 2002; Volpe and Tavares 2004; Neve et al. 2007). A comprehensive review of open studies and case reports pertaining to

ECT in acute mania describes improvement in approximately 80% of patients (Mukherjee et al. 1994), thus being greater than for any pharmacological intervention.

Retrospective comparison of ECT against several pharmacological interventions revealed similar efficacy of neuroleptics or lithium and ECT in mania (McCabe and Norris 1977b; Thomas and Reddy 1982). In another retrospective chart review, however, ECT outperformed lithium significantly (Black et al. 1987). So far, there are only two prospective studies: One study compared initial ECT, followed by lithium continuation with lithium as exclusive treatment from initiation. After 8 weeks patients who had initially a course of ECT showed a significantly higher responder rate than those who started on lithium (Small et al. 1988). In the other prospective study, combined treatment with ECT and chlorpromazine was more effective than chlorpromazine alone (Sikdar et al. 1994).

Recent work suggests that bifrontal ECT is at least as efficacious as bitemporal ECT in severe mania and better tolerated (Hiremani et al. 2008; Barekatain et al. 2008).

Given the lack (and impracticality) of randomized, sham-controlled studies, the **CE** for ECT in acute mania is "**C1**", the **RG** "**4**". However, in the opinion of the WFSBP task force, ECT is still a valuable last resource in severe delirious mania which is otherwise treatment refractory (Karmacharya et al. 2008).

A possible alternative to ECT as a physical treatment, *repetitive transcranial magnetic stimulation* (rTMS) has not been shown to have unequivocal antimanic efficacy in a single blind study against sham-rTMS (Kaptsan et al. 2003) (**CE** "**E**").

Dosages and duration of treatment

Recommended dosages for the different medication in monotherapy are given in Table V. These dosages are derived from studies in acute mania. They do not necessarily reflect the whole dosage range that is approved for a given medication: dosages as supplied here are mostly in the upper approved dosage range. In the case of combination treatment, a reduction of the daily dosage may be necessary when side effects of two medications are additive or potentiating. Most combination treatment trials used lower dosage of the investigational drug than in the corresponding monotherapy studies. However, in some instances, e.g., combination treatment with enzyme inducers like carbamazepine (Spina et al. 1996), dosages of the investigational drug need a modest increase compared to monotherapy. Therapeutic drug monitoring (TDM) is particularly advisable in patients who do not respond to combination treatment regimens (Baumann et al. 2004).

Antimanic treatment has to be continued at least until full remission, syndromal and functional, has been achieved. Persistence of subsyndromal mania is associated with a significantly increased risk of relapse (Tohen et al. 2003d, 2006a). Most guidelines recommend continuation therapy for 6–12 months after remission from an acute mood episode has been achieved; this recommendation is based upon evidence for unipolar depression, and controlled data in mania from discontinuation trials are only available for lithium (Goodwin 1994), olanzapine (Tohen et al. 2006b) and aripiprazole (Keck et al. 2006) supporting this approach with a grade "**B**" **CE** for these medications. But for many substances, this recommendation is based upon expert advice and clinical reasoning (**CE** "**C3**"). Also based on clinical experience, doses may me reduced at some point after remission has been achieved, depending on tolerability. For lithium, this is mandatory for safety reasons, since the renal clearence of this agent diminish after an acute episode has resolved and since antimanic serum-levels in the continuation therapy may be too risky.

Therefore, based on these considerations, and unless there is doubt as to whether the manic episode may have had an external trigger, e.g., steroids, alcohol, other drugs of abuse, all patients should be offered continuation and maintenance regimens (for the indication, see (Grunze et al. 2004)). Accordingly, in selection of a drug or regimen for treatment for acute mania an important consideration should be the overall efficacy and tolerability of the regimen in long term treatment, thereby minimizing switchs of medication which may be associated with an increased relapse risk.

Dealing with non-response

Treatment should generally be initiated with a medication fulfilling the criteria for CE for efficacy "A" and having a RG of "1" (see Table V and Figure 1). If this first choice medication is inefficacious or leads only to partial response, it is unclear how long clinicians should wait before changing or amending medication. In controlled studies, most successful investigational drugs start to separate from placebo within 1 week. Early partial response whether on active drug or placebo (Pappadopulos et al. 2008), predicts later response at study endpoint. However, detailed analyses on various response patterns are, so far, not available. Response may be delayed with some medication that need titration (e.g., lithium and quetiapine) or are used in lower dosages (e.g.,

Table V. Categories of evidence (CE) and grade of recommendation (RG) for pharmacological and non-pharmacological treatments used in acute mania (in alphabetical order within one category of evidence).

Medication	Category of evidence (CE)	Recommendation Grade	Typically recommended daily dose for adults (variations may occur due to different approvals)
Aripiprazole	A	1	1530 mg
Asenapine	A	2	10–20 mg
Carbamazepine	A	2	600–1200 mg (serum level 4–15 mg/l)
Haloperidol	A	2	5–20 mg
Lithium	A	2[7]	600–1200 mg (serum level 0.8–1.3 mmol)
Olanzapine	A	2	10–20 mg[8]
Quetiapine	A	2	400–800 mg
Risperidone	A	1	2–6 mg
Valproate	A	1[9]	1200–3000 mg (loading dose 20–30 mg/kg body weight; serum level 75–100 mg)
Ziprasidone	A	1[10]	80–160 mg
Chlorpromazine	B	3	300–1000 mg
Paliperidone	B	3	3–12 mg; only 12 mg/d achieves "B" level
Phenytoin	B	3	300–400 mg
Pimozide	B	3	2–16 mg
Tamoxifen	B	3	40–80 mg
Amisulpride	C1	4	400–800 mg
Clonazepam	C1	4	2–8 mg
Clozapine	C1	4	100–300 mg
Levetiracetam	C1	4	500–1500 mg
Lorazepam	C1	4	4–8 mg
Nimodipine	C1	4	240–480 mg
Oxcarbazepine	C1	4	900–1800 mg
Retigabine	C1	4	600–1200 mg
Zonisamide	C1	4	100–500 mg
Zotepine	C1	4	200–400 mg
Verapamil	D	5	480 mg
Lamotrigine	E	–	50–200 mg
Topiramate	E	–	200–600mg
Gabapentin	E	–	900–3600 mg
Tiagabine	F	–	20–40 mg
Pregabalin	F	–	1800 mg
ECT	C1	4	*Reserved for treatment refractory mania and special issues (e.g., as alternative option in pregnancy)*
rTMS	E	–	

[7]If long-term treatment is considered at the same time, the RG for lithium is "1".
[8]A fixed dose of 20 mg olanzapine was sufficient to demonstrate significant antimanic effects in females with moderate to severe mania (Bech et al. 2006). However, females achieve significantly higher plasma concentrations of olanzapine than males (Kelly et al. 1999, 2006). This may imply that higer doses are needed in males with moderate to severe mania (Goodwin and Jamison 2007).
[9]Valproate is not recommended as first choice treatment (RG "1") in women of child-bearing age.
[10]The RG for ziprasidone is "2" in countries where its use is restricted due to regulatory order.

the first olanzapine monotherapy study: Tohen et al. 1999). On the other hand, as acute mania constitutes a significant burden to patients and to everyone involved, clinicians may not want to wait for too long to tap the last potential of a medication. Hence, in the absence of firm evidence, the task force recommends that a treatment trial should not last more than 2 weeks. Adressing what to do next, in case of insufficient response after e.g., 2 weeks, is also more based on expert opinion and clinical experience than driven by evidence. The suggestion of the task force is that the continuation or discontinuation of a given initial antimanic treatment should be decided upon the basis of full, partial or no response (see Figure 1). However, it is an open question, whether an only partly sufficient treatment should be replaced by another treatment or whether another treatment should be added. The latter approach can, besides assuming a synergistic effect, be justified as maximizing the likelihood of effect, since the first-line drug, albeit insufficient after the first 2 weeks then still may have a chance to work on its own over time. The former approach can be justified from a perspective on tolerability and by facilitating a proper monotharapy continuation therapy. The use of standardized rating scales as the YMRS to determine and document is encouraged. Clinical studies usually use a 50% reduction of the YMRS, MRS or MAS as response criterion (Goodwin and Jamison 2007): however, more detailed increments

for partial response may be helpful in making clinical decisions (Tohen et al. 2009a).

Monotherapy or combination treatment?

In reality, less than 10% of acutely manic patients receive monotherapy; the avarage number of medication in acutely manic patients is apprpximately three (Wolfsperger et al. 2007). Clinical routine appears to be based on polypharmacy in bipolar patients (Lin et al. 2006; Ghaemi et al. 2006; Wolfsperger et al. 2007; Peh and Tay 2008). This underlines the difficulties in treating naturalistic samples compared to selected samples in clinical studies; less than 20% of a screened naturalistic patient cohort fulfills all inclusion criteria for entering a randomized, controlled trial (Licht et al. 1997). Modifying factors mostly include comorbid conditions and severity of illness. In line with this clinical practice are observations from randomized, controlled trials that addition of an antipsychotic drug to patients with persistent manic symptoms despite treatment with lithium or valproate has shown greater rates of acute efficacy than has continuation of lithium or valproate alone (Tohen et al. 2002; Sachs et al. 2002; Sachs et al. 2004; Vieta et al. 2009c): However, the obtainable clinical information from these trials are limited. Firstly, there is no distinction between subjects responding insufficiently to an acute antimanic treatment with

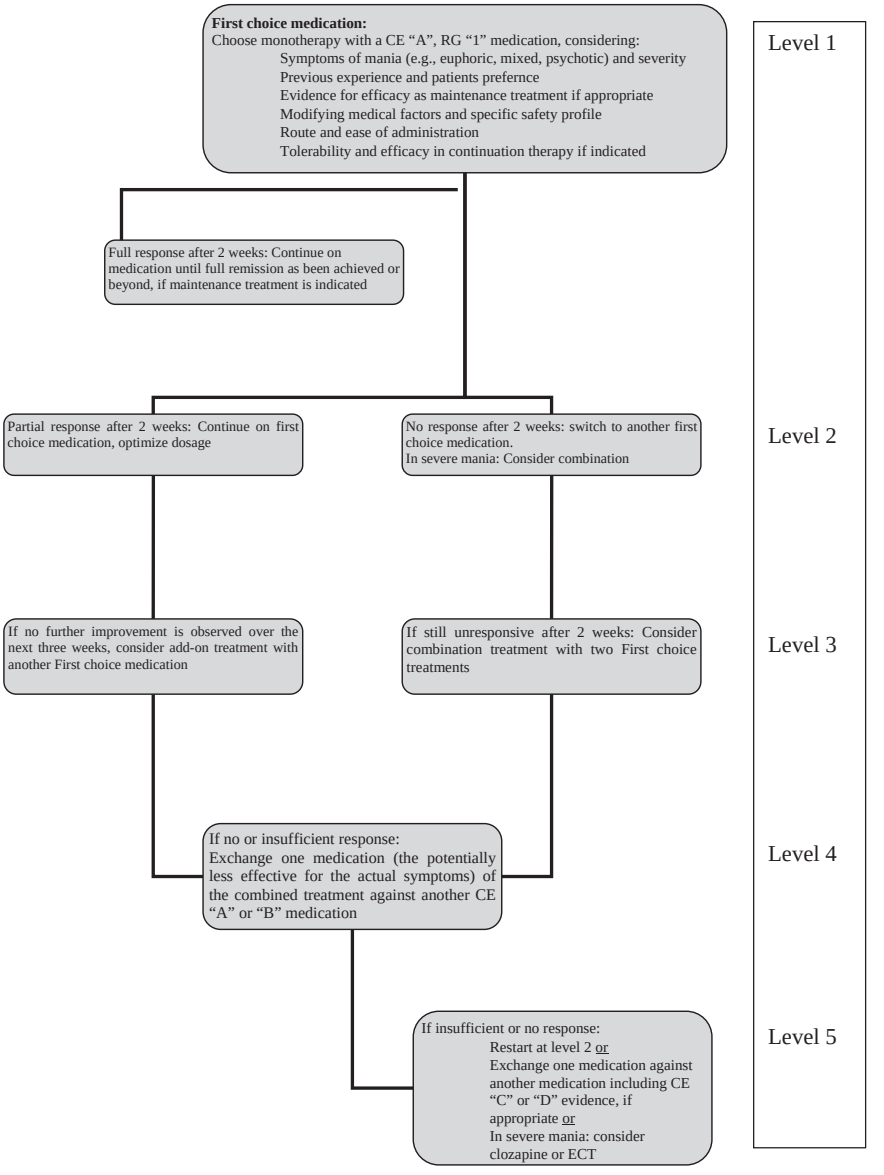

Figure 1. Treatment algorithm as suggested by the WFSBP taskforce. CE, category of evidence; RG, recommendation grade (see Tables IV and V).

lithium or valproate and subjects suffering from a break-through mania with ongoing prophylactic treatment. Secondly, clear and valid definitions and assessments of insufficient response are often lacking. As to the important clinical question whether an antipsychotic and lithium (or valproate) combined from the beginning (a de novo combination) are better than the antipsychotic or the lithium or valproate given alone there is very limited data. Actually, only the risperidone trial (Sachs et al. 2002) gave to some extens such information, indicating that the de novo combination did not do better than the lithium or valproate alone. However, Müller-Oerlinghausen et al. (2000) showed that valproate added to a typical neuroleptic (mainly haloperidol) is superior to the neuroleptic given alone in severely ill patients, most of them probably receiving the combination from the beginning.

A greater efficacy of combination treatment is also supported by a meta-analysis of Smith et al. (2007a). Eight eligible add-on studies were included with a total of 1124 subjects. Significant reductions in YMRS scores were demonstrated for haloperidol, olanzapine, risperidone and quetiapine as co-therapy compared with monotherapy with lithium or valproate. For atypical antipsychotics combined, the pooled difference in mean scores was 4.41 (95% CI: 2.74, 6.07). In addition, significantly more participants on co-therapy met the response criterion (at least 50% reduction in YMRS score, RR 1.53 (1.31, 1.80)). However, this metaanalysis again mingles trials with de novo combinations and add-on combination in insufficiently responsive patients.

Taken together, there is not enough unambiguous evidence that supports combination therapy as a general first line treatment. Additionally, safety and practicability issues would clearly favour monotherapy as first line approach making best use of the dosage range available for a given medication. Combined treatments are potentially associated with higher frequency or greater severity of side effects (Smith et al. 2007a; Vieta et al. 2008) putting patients at a potentially unnecessary risk and perhaps disrupting the therapeutic alliance. A recent guideline (Yatham et al. 2006) recommend combination treatment as a possible first line choice (not restricted a special grade of severity of mania); however, the WFSBP task force feels that clinicians in general should be encouraged to make best use of a diligently chosen monotherapy before switching to combinatons in order to minimize side effects and medical risks. Monotherapy should be the primary choice at least in mild and moderate mania; although polytherapy has proven to be potentially more efficacious in certain combinations (atypical antipsychotic + lithium or valproate vs. lithium or valproate alone) it should be reserved for severe mania or as a subsequent step in mild and moderate mania after switching (unsuccessful) medication.

How do antimanics compare?

Direct comparative trials between these antimanic substances are still limited, especially between different atypicals, the one exception being olanzapine vs. risperidone (Perlis et al. 2006a). Others are either inconclusive (olanzapine–valproate (Zajecka et al. 2002; Tohen et al. 2003b; Tohen et al. 2009b), aripiprazole–haloperidol (Vieta et al. 2005a)), not powered for comparing investigational drug and comparator, or the relevant statistical comparison has not been made (the various studies using lithium as comparator, or olanzapine as comparator for asenapine (Hirschfeld et al. 2007)). There are three exceptions, showing that haloperidol is more powerful in the short term treatment of acute mania than olanzapine (Tohen et al. 2003a), quetiapine (McIntyre et al. 2005) and aripiprazole (Young et al. 2009) (see also Scherk et al. 2007). Comparison of atypicals across trials, however, did not hint towards pronounced differences in efficacy (Perlis et al. 2006b).

Although haloperidol may be more powerful than some atypicals, but is still a RG "2" medication, as the use of typical neuroleptics in higher dosages should be restricted to emergencies where parenteral administration is the only choice, and should be limited to a maximum of a few weeks, to avoid the risk of tardive dyskinesia (TD) (Kasper et al. 2006). TD may have an increased incidence in bipolar patients (Hamra et al. 1983; Mukherjee et al. 1986; Kane 1999). The aetiology of TD remains uncertain but is believed to result from long-term blockade of dopamine receptors. The true risks for atypical antipsychotics with a high degree of D2 receptor occupancy are not yet firmly established, but appear lower (Remington 2007). The key message from the introduction of the atypical drugs is that it is possible to achieve antipsychotic and anti-manic action without inducing severe extra-pyramidal side effects. This may imply that low-dose typical neuroleptics are still a reasonable alternative to atypical antipsychotics in selected patients (Geddes et al. 2000; Lieberman et al. 2005). This may apply as much to mania as to schizophrenia. In this respect, it has also beeen demonstrated that chlorpromazine is more powerful in excited manic patients than lithium (Prien et al. 1972).

Taken together, the choice of the primary treatment depends mainly on previous responsiveness,

patient's preference, safety and tolerability profile, including medical conditions or co-medication that may interfere with the chosen drug, route of administration and future need of maintenance treatment.

Special considerations for treatment depending on the subtype of mania

Dysphoric mania and mixed states

These two manifestations of mania are summarised under one heading. According to DSM-IV, mixed states imply that diagnostic criteria for a manic episode and a depressive episode (except for the duration criterion) are fulfilled simultaneously. Dysphoric mania describes mania with some depressed and dysphoric features that are either not pronounced enough or insufficiently lasting enough to fulfil the criteria for a major depressive episode (see also section on *Diagnostic issues in bipolar I disorder*). Women appear more often affected than men, both in bipolar I (Arnold et al. 2000) and II disorder (Suppes et al. 2005). As dysphoric (or mixed) mania and mixed states have not been the subject of intensive primary studies and prospective controlled trials so far, we have only a limited amount of evidence for efficacy and even less for the superiority of one drug over another. Another issue is that when antimanic efficacy has been indicated in mixed states, this does not necessarily imply efficacy on depressive symptoms and may be far from efficacy on core depressive symptoms. In fact, depression rating scales usually used in clinical trials also capture some manic symptoms. Secondary analysis of the influential valproate efficacy study (Swann et al. 1997) as well as some older studies (Himmelhoch and Garfinkel 1986; Secunda et al. 1987) indicated that lithium may not be very effective, and that valproate, carbamazepine, olanzapine and risperidone may be more efficacious than lithium in these patients (Freeman et al. 1992; Swann et al. 1997; Goldberg and Harrow 1998; Tohen et al. 2000; Benabarre et al. 2001). Post hoc analyses of the pivotal phase III studies with olanzapine (Baker et al. 2003), ziprasidone (Vieta 2005; Greenberg and Citrome 2007) and aripiprazole (Sachs et al. 2006) demonstrated comparable efficacy for mixed states and pure mania. In contrast, the evidence for risperidone and carbamazepine is mostly based on open studies. Although there is no direct evidence for lack of efficacy, the use of typical neuroleptics (especially in higher dose) may exacerbate dysphoric or depressive symptoms and should probably be avoided (Whitlock and Evans 1978; Tohen et al. 2003a).

Psychotic mania

Psychotic mania has only recently been designated as a subtype of bipolar mania. It is unclear whether secondary grandiose delusions – the commonest clinical manifestation of "psychosis" merits qualitative distinction since it looks much more like an expression of severity. On the other hand, first rank symptoms also occur in mania and confuse the distinction from schizophrenia. "Psychotic mania" is a diagnosis that conflates these perhaps different clinical conditions.

Psychotic mania has been so little studied in clinical trials that recommendations regarding drug regimens are based principally on inferential criteria. Typical neuroleptics, in this case *pimozide*, may be superior to lithium as shown by the Northwick Park functional psychosis study (Johnstone et al. 1988) **(CE "B", RG "3").** However, this may not be directly related to their antipsychotic properties, but to greater efficacy in severe manic states which are regularly accompanied by psychosis (Licht 2006). Some older guidelines also favoured anticonvulsants over lithium when psychotic symptoms are present, e.g., (Kusumakar et al. 1997), others recommended the combination of either valproate or lithium with an antipsychotic right from the start (McElroy et al. 1996b). In the single randomized comparison of two efficacious drugs in a sample of patients with acute psychotic mania *valproate* and *haloperidol* were similarly efficacious. Limitations of the study included an open design and a small sample ((McElroy et al. 1996a), **CE "C1", RG "4"**). With the emergence of atypical antipsychotics, monotherapy options may increase, but unambiguous prospective, controlled trials are still lacking. However, post hoc analysis of Phase III studies of *olanzapine*, *risperidone* and *ziprasidone* showed similar response rates in psychotic versus nonpsychotic mania.

Severity of mania

Recent treatment recommendations have almost uniformly advocated the preferential use of lithium, valproate ("mood stabilisers") or atypical antipsychotics for the first-line treatment of mania. Despite this, typical neuroleptics are still very widely used in manic patients (Tohen et al. 2001; Wolfsperger et al. 2007). As long as care is taken to avoid EPS, long experience supports this strategy, even if formal controlled evidence for the group of most severe manic patients is limited. However, as outlined previously, haloperidol is usually not considered a first line drug for tolerability reasons. Randomised studies comparing atypicals with the typical neuroleptic haloperidol were conducted without specification of severity of mania as long as the inclusion

threshold was achieved, and supplied varying results (Smulevich et al. 2005; McIntyre et al. 2005; Vieta et al. 2005a; Young et al. 2009). It is, however, noteworthy that a retrospective chart review of manic patients in a hospital setting showed advantages of atypical antipsychotics over typical neuroleptics (Letmaier et al. 2006).

Obviously, the severity of behavioural disturbance is also an important factor in deciding on first-line treatment in acute mania. Most treatment algorithms are based on controlled trials in moderately manic patients who are still able to give informed consent. In clinical practice, severity of mania and speed of onset of action are the primary arguments in favour of a particular drug. In the ultra-short treatment of acutely manic and highly excited or violent patients, typical neuropleptics still have their place (Cipriani et al. 2006) and are superior to lithium (Prien et al. 1972; Garfinkel et al. 1980) and some atypical antipsychotics (Scherk et al. 2007). In patients who are severely manic but still willing to take medication, loading with valproate (Hirschfeld et al. 1999) or carbamazepine (Dose and Emrich 1995) may be alternatives, whereas lithium loading is effective (Keck et al. 2001), but associated with higher risks of accidental overdosing. Recent trials in severly manic patients, e.g., a randomized, controlled trial with risperidone (Khanna et al. 2005), and post hoc subgroup analyses of severly manic patients in randomized, controlled trials with other atypical antipsychotics support the usefulness of *risperidone*, *ziprasidone*, *aripiprazole* and *olanzapine* in this patient group. C**lozapine** has also shown efficacy in refractory mania, both euphoric and dysphoric, in open prospective trials **(CE "C1")** (Müller and Heipertz 1977; Suppes et al. 1992; Antonacci and Swartz 1995; Calabrese et al. 1996; Green et al. 2000). Finally, the efficacy of electroconvulsive therapy in severe and delirious manic states is supported by numerous case series **(CE "C1")** (Grunze and Scharfetter 2004).

Hypomania

Hypomania may be known to be the prelude to full-blown mania in individual patients, in which case treatment should be as for mania. Otherwise hypomania is not a common point for the initiation of new treatment. In case the patient is receiving prophylactic treatment with an antimanic agent, the best recommendation is to check the plasma level of the medication and, depending on the result, increase the dosage. If the patient is not currently receiving an antimanic medication, an appropriate drug could be introduced that should, if indicated, also be the drug of choice for prophylaxis.

It is unclear whether the controlled positive results for olanzapine and valproate in mild to moderate mania (Tohen et al. 2009b) can be extrapolated to hypomania. In addition, there is some uncontrolled evidence for the usefulness of risperidone in hypomania (Vieta et al. 2001). If no further prophylaxis is planned, short-term treatment with either valproate or an atypical antipsychotic may be the best choice **(CE "C3"),** as both are well tolerated, have a good safety profile and a relatively rapid onset of action, minimising the danger that hypomania develops into mania within the next days. In this respect, it is also important to intervene early against sleep loss as this may be an important factor for developing full blown mania.

In contrast to more severe manic states, hypomania may be still manageable to some extent by behavioural interventions in combination with pharmacotherapy. These inventions may center around modifications of daily routines, e.g., maintaining a natural sleep wake cycle, stress avoidance, and some elements of cognitive behavioural therapy (CBT) (Basco and Rush 1996). However, so far no psychological intervention has shown efficacy in controlled studies in comparison to a "placebo" intervention in mania (Gutierrez and Scott 2004). The domain of psychotherapy in bipolar disorder largly remains in bipolar depression and relapse preventiona.

Future perspectives

The treatment portfolio for acute mania has significantly increased over the last years, and new agents are currently in the pipeline. Additionally, new targets for drug development will emerge; Proteinkinase C inhibition is one example of a mechanism with some recent evidence of efficacy. However, given the substantial number of medications available, it will become more essential that new medications show additional benefits besides being effective antimanic agents. Most clinicians are likely to prefer antimanic drugs which also have established long term, prophylactic efficacy not only against manic relapse, but also against depressive episodes or even more challenging, substances that also have antidepressant activity. With the expanding range of drugs with evidence of efficacy in mania, psychiatrists as well as patients may reasonably place safety, tolerability, and evidence of good persistence over time on equal footing with efficacy in selecting and continuing a regimen. Similarly, tolerability and ease of adhering to the prescribed dosage can benefit from selection of drug formulations with extended release properties and/or once daily dosing. In a highly competive field, future research and

development will have to take that into account at an earlier stage than in the past; it will not be enough if you have "just another antimanic drug" to be clinically accepted. In addition, regulators may query increasingly what the advantage of a new mediction is compared to those available and place more extreme demands on safety studies before licensing. Novel mechanisms of action, coupled with an at least as favourable benefit/risl profile than current drugs, are two components that may become desirable, if not essential for regulatory approval in the future.

Due to the fact that patients enrolled in most randomised trials are highly selected, it also appears important to conduct large, prospective trials in unselected populations in a methodological more rigourous manner as previously done in schizophrenia. This will not necessarily improve the evidence base, but increase the confidence that a given evidence based treatment is also effectice in real world settings. Likewise, systematic data adressing the issue of dealing with patients not responding to first-step treatments is highly needed.

Conclusions

This update of the original WFSBP guideline from 2003 has been compiled to aid clinician's choice when treating patients with acute mania, as the scientific evidence for established agents has significantly increased over the last five years, and new medications have become available. Recommendations given in this guideline are based, wherever possible, on randomized, controlled, double-blind trials. However, such studies do not always reflect clinical realities and have their shortcomings, e.g., the exclusion of comorbid, suicidal, or medically ill patients, which may in turn lead to disappointment with some medictation in clinical practice. Accordingly, adherence to these guidelines can be far from ensuring a successful outcome in every case. However, it may be a helpful framework for the educated psychiatrist, planning the individual treatment of a patient, taking all sources of information and all available treatment options into account.

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