



Review

New treatment guidelines for acute bipolar mania: A critical review

Alessandra M.A. Nivoli ^{a,b}, Andrea Murru ^a, José M. Goikolea ^a, José M. Crespo ^c, José M. Montes ^d, Ana González-Pinto ^e, Paz García-Portilla ^f, Julio Bobes ^f, Jerónimo Sáiz-Ruiz ^g, Eduard Vieta ^{a,*}

^a Bipolar Disorders Program, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

^b Institute of Psychiatry, Department of Neuroscience, University of Sassari, Italy

^c Department of Psychiatry, Hospital de Bellvitge, CIBERSAM, Barcelona, Spain

^d Department of Psychiatry, Hospital del Sureste, CIBERSAM, Madrid, Spain

^e Department of Psychiatry, Hospital Santiago Apóstol, CIBERSAM, Vitoria, Spain

^f Department of Psychiatry, University of Oviedo, CIBERSAM, Oviedo, Spain

^g Department of Psychiatry, Hospital Ramón y Cajal, Universidad de Alcalá, CIBERSAM, Madrid, Spain

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ABSTRACT

A number of treatment guidelines for bipolar disorder have been published and updated in the last few years. They are aimed at providing a synthesis of the best available scientific knowledge, and their application to every-day work should be helpful to clinicians. The aim of this report is to critically review recent guidelines focusing on the treatment of manic/hypomanic and mixed episodes. Guidelines are quite heterogeneous in methodology and conclusions, but they all agree that the treatment of manic/hypomanic and mixed episodes should generally be initiated with a medication such as lithium (Li), valproate (VPA) or atypical antipsychotics (AAP), including aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone as monotherapy. All guidelines agree on stopping ongoing antidepressant medication during mania. Combination therapy including Li or VPA with an AAP is suggested usually as second-line choice, sometimes as first-choice treatment for severe mania. Carbamazepine is mostly suggested as second line and not recommended in combination. Other antiepileptic drugs are not recommended for the treatment of mania, although lamotrigine may be maintained if it was prescribed previously for the prevention of depressive episodes. Main sources of discrepancies among guidelines include benefit–risk ratio issues (how much priority is given to efficacy over safety and tolerability), starting with combination versus monotherapy, and how to deal with treatments which are more experience-based than evidence-based (i.e.: electroconvulsive therapy).

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* Corresponding author. Tel.: +34 93 227 5400x3130; fax: +34 93 227 57 95.

E-mail address: evieta@clinic.ub.es (E. Vieta).

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1. Introduction

Bipolar disorder (BD) is a complex condition of major health relevance and chronic course, with a lifetime prevalence estimates of 1.0% for BP-I, 1.1% for BP-II, and 2.4% for subthreshold BPD (Merikangas et al., 2007) and important rates of disability and poor quality of life (Rosa et al., 2009; Sanchez-Moreno et al., 2009; Sierra et al., 2005). Despite the availability of many efficacious pharmacological agents for treating mania and hypomania, their management in clinical settings remains a challenge. Fountoulakis et al. (2005) reviewed twenty-seven guidelines on treatment of BD and concluded that at the first stage of the mania/hypomania algorithm, monotherapy with lithium, valproate or olanzapine was generally recommended, with the most recent guidelines at that time starting to support the use of other atypical antipsychotics as well.

Since 2005, many guidelines have been updated or revised, including those of the World Federation of Societies of Biological Psychiatry (WFSBP) (Grunze et al., 2009, 2010), the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) (Yatham, et al., 2009), the British Association for Psychopharmacology (BAP) (Goodwin and Consensus Group of the British Association for Psychopharmacology 2009), the National Institute for Health and Clinical Excellence (NICE, 2009) and the Clinical Practice Recommendation for bipolar disorder (Malhi et al., 2009).

The application of well-designed guidelines may be helpful to clinicians in reducing the variability of clinical practice and may carry substantial benefits to bipolar patients (Dennehy et al. 2005; Perlis 2007). However, they quickly become obsolete and are often difficult to translate to every-day practice (Vieta, 2009a,b). The final aim of this work is to critically review recently updated guidelines focusing exclusively on the treatment of manic/hypomanic episodes and, when available,

mixed episodes, in order to stress existing areas of consensus or controversy, highlight their limitations and strengths, and provide starting points for future research.

2. Methods

An extensive search for relevant national and international treatment guidelines, consensus statements and comprehensive reviews published since 2005 was undertaken. The publications were obtained from the following electronic databases: MEDLINE/PubMed/Index Medicus, PsycINFO/PsycLIT, Excerpta Medica/EMBASE, the Science Citation Index at Web of Science (ISI), and the Cochrane library. The literature search was performed using the MeSH heading “bipolar disorder” and using “bipolar”, “manic-depression”, “manic-depressive” “mania” with “treatment”, “treatment guidelines” and “treatment algorithms” – and their combination – as key words. The search was updated until August, 1st, 2010. Only articles written in English were considered as eligible. The general methodology of this review has been described in detail elsewhere when applied to bipolar depression (Nivoli et al., 2010).

We additionally included in the present review the Clinical Practice Recommendations for Bipolar disorder (Malhi et al., 2009), which categorized treatments as follows: *first-line* treatments, including drugs or interventions defined at Level I and II; *second-line* treatments, including Levels III–IV and V (Table 1). In the present manuscript, treatment options were classified according to previously described methods (Nivoli et al., 2010), as shown in Table 2. When available, data concerning treatment discontinuation and special clinical features (i.e. mixed episodes, psychotic mania) are specified.

3. Results

3.1. Results of the literature search

The search returned 409 articles. After excluding redundancies, reviews and letters, 28 papers concerning structured treatment algorithms and/or guidelines proposed by *official scientific societies and groups of experts* were kept. The final manual selection for new and recently updated guidelines returned 5 papers. All major guidelines and treatment algorithms updated after 2005 are summarized in Table 2. Guidelines and treatment algorithms not updated in the last 5 years have been previously and extensively reviewed elsewhere (Fountoulakis et al., 2005; Vieta et al., 2005).

3.2. Results of the analyses of current guidelines

3.2.1. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorder: update 2009 on the Treatment of Acute Mania (Grunze et al., 2009)

The task force of the World Federation of Societies of Biological Psychiatry (WFSBP) updated the first edition of previous guidelines (Grunze et al., 2003), by distinguishing, when possible, between acute mania, dysphoric, mixed states, psychotic mania and hypomania. In contrast with previous guidelines, this update is structured by medication class rather than by subtypes of mania. Six *categories of evidence* (CE, from A to F) describe the scientific rigor of treatment options. From these categories of evidence and from additional aspects such as safety, tolerability and interaction potential ("effectiveness"), different *grades of recommendation* (RG, from 1 to 5) are finally assigned. These guidelines propose monotherapy as first-choice, at least in mild and moderate mania, before switching to combination, in order to minimize side effects and medical risks. Combinations (atypical antipsychotic plus lithium or valproate) should be reserved for severe mania or as a subsequent step in mild and moderate mania after switching medication.

3.2.1.1. First-line. Lithium (A; 1–2) is recommended, especially in pure euphoric mania rather than in mania with dysphoric or depressive symptoms. Given its slow onset of action, scarce sedative properties, the narrow safety margin and the need to exclude some medical conditions, lithium monotherapy achieves a RG of "2" in acute mania. Lithium alone or in combination may be the primary choice when maintenance treatment is considered at the time of acute treatment initiation (A, 1). Valproate (A, 1) and carbamazepine (A, 2) are suggested for mixed states or dysphoric mania. Use of carbamazepine is limited in clinical practice because of its interactions with other psychotropic medications and some tolerability issues in rapid titration. Valproate is recommended both in pure mania (with or without psychotic symptoms) and mania with dysphoric/depressive features. However, considering its teratogenicity and high risk of a polycystic ovary syndrome (PCOS), its RG for women in child-bearing age is "2". Among atypical antipsychotics, aripiprazole (A, 1), is recommended across different subtypes of mania, both for pure mania and mixed or psychotic episodes and has a good tolerability profile. Risperidone (A, 1) is recommended in severe and psychotic

mania, but only limited data support its use in mixed states. Ziprasidone (A, 1) is recommended, both in mixed and psychotic mania, even if its use is restricted in some countries (RG "2"), due to the potential cardiovascular concerns at high doses. Olanzapine has shown a broad efficacy profile in acute mania (euphoric, dysphoric/mixed and psychotic) (CE "A"), but due to potential metabolic issues it reaches the RG of "2". Other atypical antipsychotics are suggested in acute mania, such as quetiapine (A, 2) and asenapine (A, 2). Quetiapine receives a RG "2" because of its weaker efficacy in direct comparison to haloperidol, lack of data supporting its efficacy on mixed states and the role of metabolic issues in maintenance treatment. Asenapine received a "2" because at the time of writing the guideline it had not been marketed yet, and therefore clinical experience was absent. Among typical antipsychotics haloperidol is suggested (A), especially in psychotic mania, for its antimanic efficacy, but it may exacerbate depressive and dysphoric symptoms, especially in mixed mania. Its RG is "2" due to the risk of acute extrapyramidal motor symptoms and tardive dyskinesia.

3.2.1.2. Second-line. If a lack of response is observed or if response is considered insufficient, the authors suggest to replace one medication (the potentially less effective for the current symptoms) of the combined treatment with another CE "A" or "B" (Level IV) or, if appropriate, CE "C" or "D", or clozapine or electroconvulsive therapy (ECT) if severe mania (Level V). Second-line choices include combination of lithium and/or an anticonvulsant plus antipsychotics. Oxcarbazepine is a low-profile option (C1, 4), and topiramate, gabapentin and lamotrigine are not recommended (E). Phenytoin has demonstrated its antimanic properties (CE "B"), but with important cognitive side effects and cerebellar atrophy (RG "3"). Other anticonvulsants such as levetiracetam, zonisamide, retigabine are poorly evidence-based (C1,4), as well as pregabalin and tiagabine (CE,"F"). Clozapine (C1,4) is recommended in refractory mania, both euphoric and dysphoric. Several other atypical antipsychotics are recommended as second choices, such as amisulpride (C1,4), paliperidone (B,3), zotepine (C1,4). Among typical antipsychotics chlorpromazine is suggested (B,3), even if the task force highlights that its widespread use in mania is not reflected by this rating, due to lack of rigorous evidence-based data. Clonazepam and lorazepam (C1,4) are suggested as add-on treatments to cope with agitation and relieve anxiety and insomnia. *Other agents* with antimanic action are tamoxifen (B,3) whose clinical use is limited due to its anti-estrogen nature; calcium antagonists (C1–D,4–5) and biophysical treatments such as repetitive transcranial magnetic stimulation (rTMS) (E).

3.2.1.3. Discontinuation. It is unclear how long clinicians should wait before changing or amending medication (Murru et al., 2011). In controlled studies, most successful drugs start to separate from placebo within 1 week or even less. The task force recommends that a treatment trial should not last more than 2 weeks. In case of insufficient response, what to do next is also based more 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. The question on which is the best strategy

Table 1

Comparison of different levels of evidence criteria and recommendation grades across guidelines: definition of first line and second line agents.

	WFSBP Grunze et al. (2009)	CANMAT ISBD Yatham et al. (2009)	BAP Goodwin et al. (2009)	NICE National Institute et al. (2009)	NHMRC National Health and Medical Research Council Malhi et al. (2009)
<i>Levels/categories of evidence (CE)</i>					
First line	Category A <i>Full Evidence from Controlled Studies</i> 2 or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo' in a study with adequate blinding) and 1 or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists.) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 2 more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfill established methodological standards. The decision is based on the <i>primary efficacy measure</i>.	Level 1 Meta-analysis or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo Level 2 At least one DB-RCT with placebo or active comparison condition	Level I <i>For causal relationships and treatment</i> Evidence from meta-analysis of RCTs, at least one large, good quality, RCTa or replicated, smaller RCTs <i>For non-causal relationships</i> Evidence from large representative population samples Level II Evidence from small, non-replicated RCTs at least one controlled study without randomisation or evidence from at least one other type of quasi-experimental study <i>For non-causal relationships</i> Evidence from small, well designed but not necessarily representative samples	1++: High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. 1+: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. 1–: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias	Level I Systematic review of all relevant randomized controlled trials Level II One or more properly designed randomized controlled trial.
Second line	Category B <i>Limited positive evidence from controlled studies</i> 1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo') or a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial. In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least 1 more positive study or a meta-analysis of all available studies showing superiority to placebo or at least one more randomized controlled comparison showing non-inferiority to an established comparator treatment	Level 3 Prospective uncontrolled trial with at least 10 or more subjects	Level III Evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies <i>Non-causal relationships</i> evidence from non-representative surveys, case reports	2++: High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal. 2+: Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal. 2–: Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal	Level III Well-designed prospective trial (non-randomized controlled trial); comparative studies with concurrent controls and allocation not randomized; case-controlled or interrupted time series with a control group. Level IV Case series, either post-test or pre-test/post-test. Level V Expert opinion

Category C <i>Evidence from uncontrolled studies or case reports/expert opinion C1: uncontrolled studies</i> 1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients) or a comparison with a reference drug with a sample size insufficient for a non-inferiority trial and no negative controlled studies exist <i>C2: Case Reports</i> 1 or more positive case reports and no negative controlled studies exist <i>C3: Based on the opinion of experts in the field or clinical experience</i>	Level 4 Anecdotal reports or expert opinion	Level IV Evidence from expert committee reports or opinions and/or clinical experience of respected authorities <i>Non-causal relationships</i> evidence from expert committee reports or opinions and/or clinical experience of respected authorities	3: Non-analytic studies (for example, case reports, case series)
Category D <i>Inconsistent results</i> Positive RCTs are outweighed by an approximately equal number of negative studies			4: Expert opinion, formal consensus
Category E <i>Negative evidence</i> 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			
Category F <i>Lack of evidence</i> Adequate studies proving efficacy or non-efficacy are lacking.			
<i>Recommendation grades (RG)</i>			
1 Category A evidence and good risk–benefit ratio	First line Level 1 or Level 2 evidence plus clinical support for efficacy and safety	A Directly based on category I evidence	Very likely to be clinical significant (CS1)
2 Category A evidence and moderate risk–benefit ratio	Second line Level 3 evidence or higher plus clinical support for efficacy and safety	B Directly based on category II evidence or extrapolated recommendation from category I evidence	
3 Category B evidence	Third line Level 4 evidence or higher plus clinical support for efficacy and safety	C Directly based on category III evidence or extrapolated recommendation from category I or II evidence	Likely to be clinical significant (CS2)
4 Category C evidence	Not recommended Level 1 or Level 2 evidence for lack of efficacy	D Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence Standard of good practice	Unlikely to be clinical significant (CS3)
5 Category D evidence			Inconclusive (CS4)

Table 2

Comparison of the updated guidelines for the treatment of acute mania.

	World Federation of Societies of Biological Psychiatry WFSBP	Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders CANMAT ISBD	British Association for Psychopharmacology BAP	National Institute of Clinical Excellence 2009 NICE	National Health and Medical Research Council NHMRC
	Grunze et al. (2009)	Yatham et al. (2009)	Goodwin et al. (2009)	Nice (2009)	Malhi et al. (2009)
First line	<i>Monotherapy:</i> Li ^{1–2} , VPA ^{1–2} , AAPs (ARP, OLZ ² , RSP, QTP ² , ZPD ²) Hal ² CBZ ² ASN ² <i>Combination:</i> Li/VPA + AAPs	<i>Monotherapy:</i> Li, VPA, AAPs (ARP, OLZ, QTP, QTP xr, RSP, ZPD) <i>Combination:</i> Li/VPA + HAL/RSP/QTP/OLZ/ARP <i>If severe agitation:</i> im ARP, im OLZ.	<i>Not on AM:</i> If severe Mania: AAPs, VPA. If mild–mod Mania: Li, CBZ <i>On AM:</i> AM + AAPs Optimization of doses	<i>Not on AM:</i> <i>Severe Mania:</i> AAPs <i>Less severe:</i> Li, VPA <i>On AM:</i> Li/VPA + AAPs VPA + OLZ, QTP, RSP <i>If severe agitation:</i> im ARP, im OLZ Li/VPA + AAPs ECT rTMS (?)	<i>Monotherapy:</i> Li, VPA, AAPs: OLZ, ARP, QTP, RSP, ZPD, PLP. Hal <i>Combination:</i> Li + VPA, Li + CBZ, Li/VPA + AAPs Li/VPA + OLZ <i>If severe agitation:</i> im ARP, im OLZ Adjunctive CLZ/RSP HAL, CBZ ECT
Second line	CBZ, Li + VPA, PAL, ASN, Li + ASN OXC, TPR, GBP, LMT; AAPs: CLZ, AMS, PLP, zotepine; HAL; ECT Others: Levetiracetam, zosinamide, retigabine, pregabalin, tiagabine.	CBZ, ASN, PLP, ECT, Li + VPA, Li/VPA + ASN; Others: HAL, CLP, Li/VPA + HAL, Li + CBZ, CLZ, OXC, tamoxifen GBP, TPR, LMT, VPA, TGB, RSP + CBZ, OLZ + CBZ.	Li/VPA + AAPs CLZ, ECT		
Not recommended	Monotherapy: GBP, TPR, LMT, VRP, TGB			Monotherapy: CBZ, GBP, LMT, TPR	GBP, LMT, TPR, OXC, PHT.

AD = antidepressant; AM = antimanic agent; AMS = amisulpride; AAPs = atypical antipsychotic; ARP = aripiprazole; ASN = Asenapine; CBZ = carbamazepine; CLZ = clozapine; ECT = electroconvulsive therapy; HAL = haloperidol; im: intramuscular; Li = lithium; LMT = lamotrigine; OLZ = olanzapine; OXC = oxcarbamazepine; PHT = phenytoine; PLP = paliperidone; QTP = quetiapine; RPD = risperidone; TPR = topiramate; VPA = valproate (the generic term of “valproate”, which includes sodium valproate, valproic acid and valproate semisodium); ZPD = ziprasidone; On AM: patient on treatment with anti manic medication; Not on AM: patient not on treatment with anti manic medication; rTMS: repetitive transcranial stimulation; GBP: gabapentin.

to deal with partial response (i.e., switching from one drug to another or adding one drug to another) remains unanswered.

3.2.2. *The Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (CANMAT and ISBD) (Yatham et al., 2009)*

The current guideline is the result of a collaborative effort between the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) updating previous CANMAT guidelines (Yatham et al., 2005, 2006), for the treatment of patients with bipolar disorder. Overall, the recommendations for the management of acute mania remain mostly unchanged. In this update, adjunctive aripiprazole has been added as first-line option, as well as the extended release formulation of quetiapine, while asenapine, alone or in combination, and paliperidone as monotherapy have been added as second-line choices.

3.2.2.1. First-line. First-line treatment options are lithium, valproate, and several atypical antipsychotics in monotherapy, such as aripiprazole, olanzapine, quetiapine risperidone, and ziprasidone (level 1). Aripiprazole is suggested in patients with more or less severe illness, mixed or manic episodes, with or without psychotic symptoms. The combination of lithium/divalproex with olanzapine, risperidone, quetiapine and aripiprazole is considered as a first-line combination treatment in BD. For severely agitated inpatients with acute mania intramuscular (i.m.) aripiprazole can be considered as a first choice treatment, as well as i.m. olanzapine.

3.2.2.2. Second and third-line. Asenapine, alone or in combination with lithium or divalproex, is mentioned given the positive data, but the lack of experience with the compound at the time of writing the guidelines places it in second-line. Even if it has not yet been approved for BD, paliperidone monotherapy is recommended as a second-line option based on reported efficacy data and safety profile. Recommendations for carbamazepine, ECT and lithium and/or divalproex are maintained. Tamoxifen is suggested as an augmentation option. Haloperidol, both in monotherapy and in association with lithium/divalproex, is recommended as a third-line option. Oxcarbazepine, previously indicated as a second choice treatment, is now considered as a third-line option. Chlorpromazine and clozapine monotherapy are still recommended.

3.2.2.3. Not recommended. Combinations of olanzapine or risperidone with carbamazepine are not recommended. Monotherapy with gabapentin, topiramate, lamotrigine, verapamil, or tiagabine is not recommended either.

3.2.2.4. Discontinuation. Change of treatment or combination therapy with 1st line treatments is the suggested step, but no time-limit for treatment trial is given.

3.2.3. *National Institute for Health and Clinical Excellence (NICE) Guidelines: The Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care (National Collaborating Centre of Mental Health, update 2009)*

The NICE guidelines have been commissioned by the National Institute for Health and Clinical Excellence (NICE)

and developed within the National Collaborating Centre for Mental Health (NCCMH). The NICE guidelines, revised in 2006 (National Institute for Health and Clinical Excellence, 2006) granted the National Guideline Clearinghouse (NGC) permission to include summaries of their clinical guidelines for identification, treatment and management of bipolar disorder in adults, children and adolescents in primary and secondary care. This was made with the purpose of disseminating and facilitating the implementation of that guidance. Although NICE has not yet verified this content to confirm that it accurately reflects the original NICE, this can be considered some sort of update of NICE. All NICE clinical guidelines are prepared in relation to the National Health Service in England and Wales, with no adaptation for use in any other country. The NGC summary was completed on June 19, 2006 and the NGC summary was updated on April 1, 2009. The term 'mood stabilizer' is avoided, because of lack of agreement on its definition. The terms 'antimanic agent' or 'antimanic medication' are preferred when referring to the treatment of an acute episode. NICE guidelines state that the pharmacological treatment of an acute manic or hypomanic episode depends on the severity of symptoms and whether patients are currently taking antimanic drugs. If the patient is taking an antidepressant (AD) at the onset of an acute manic episode, the AD should be abruptly or gradually stopped.

3.2.3.1. For patients not taking antimanic medication. The suggestion is to prescribe an antipsychotic if there are severe manic symptoms or marked behavioral disturbance; prescribing valproate or lithium is recommended if there is a good compliance and a positive response to these drugs in previous episodes; if symptoms are not severe it is reasonable to use lithium, given its slower onset of action. The addition of short-term use of BDZ, such as lorazepam, may help with behavioral disturbances and agitation. Monotherapy with an antipsychotic such as olanzapine, quetiapine and risperidone should be considered. If an antipsychotic proves to be ineffective, augmentation with valproate or lithium is suggested.

3.2.3.2. For patients taking antimanic medication. The dose of the ongoing treatment should be verified and eventually increased. If there is no improvement, the addition of lithium or valproate should be considered. For patient taking lithium, plasma levels should be checked, and if there is a true inadequate response, adding an antipsychotic to lithium may be effective. For patients taking valproate it can increase in the current dose is suggested and, if there is no improvement, adding olanzapine, quetiapine or risperidone is recommended. For patients on carbamazepine, increasing the dose is not recommended: clinicians should consider adding an antipsychotic. For severe behavioral disturbances it is suggested to treat patient with lorazepam, antipsychotics or a combination of both, first with oral intake. Risperidone and olanzapine are available also in orodispersible formulations. If a rapid tranquilisation is needed, consider intramuscular olanzapine (10 mg, up to 20 mg/day), lorazepam (2 mg, up to 4 mg/day) or haloperidol (2–10 mg, up to 18 mg/day), where possible as single agent. Electroconvulsive therapy (ECT) is recommended only in order to achieve rapid and short-term improvement of severe symptoms, and it is suggested in a prolonged or severe manic episode.

3.2.3.3. For mixed episodes. Patients should be treated as if they have an acute manic episode, no antidepressants should be prescribed and a close (weekly) monitoring for suicide risk should be made.

3.2.3.4. Not recommended. Carbamazepine, gabapentin, lamotrigine and topiramate are not suggested as routinely used for treating acute manic episodes.

3.2.3.5. Discontinuation. NICE guidelines suggest the mood stabilizer plus antipsychotic if monotherapy does not control symptoms. They do not recommend a time limit for treatment trial.

3.2.4. British Association For Psychopharmacology: Evidence-Based Guidelines For Treating Bipolar Disorder Revised, Second Edition (Goodwin and Consensus Group of the British Association for Psychopharmacology, 2009)

The British Association for Psychopharmacology (BAP) guidelines are putting in particular emphasis on systematic review and randomized controlled trials, followed by a discussion of the important issues in order to identify consensus and areas of uncertainty. The guidelines refer to the methodology of the North England Evidence-based Guideline Development Project undertaken by the Centre for Health Services Research, University of Newcastle (Shekelle et al., 1996). Treatment options are provided for each phase of the illness. Treatment choices should be dictated by the clinical context and, when possible, by patient preference and experience.

3.2.4.1. First-line. First-line treatments for severe manic or mixed episodes among patients not already on long-term treatment for bipolar disorder are oral administrations of antipsychotics or valproate, because of their rapid anti-manic effect (A); for less severe episodes lithium or carbamazepine can be considered as a short-term treatment. Authors suggest preferring atypical antipsychotics because of their generally more favorable short-term adverse effect profile (A). Most patients with mania will require short-term treatment with medications in the appropriate clinical setting, such as hospitalization. Antidepressants should be tapered and discontinued. When agitated patients require parenteral treatment, suggestions include antipsychotic and benzodiazepines, such as clonazepam or lorazepam, if promoting sleep is necessary. For patients who suffer a manic or mixed episode while on long-term treatment, clinicians should ensure that the highest well-tolerated dose of the current treatment is offered (A) and promote adherence. The authors suggest a combination of aripiprazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone combined with lithium or valproate (A).

3.2.4.2. Second-line. If symptoms are inadequately controlled with optimized doses of the first-line medicine and/or mania is severe, the combination of lithium or valproate with an antipsychotic should be considered (A). Clozapine is an option in treatment refractoriness (B). ECT is suggested for resistant patients and women with severe mania during pregnancy. Atypical antipsychotic should be considered when psychotic symptoms are present (A).

3.2.4.3. Discontinuation. Short-term treatment of mania may be reduced in dose and discontinued (tapering over 2 weeks or more) after full symptomatic remission (B), and this will often occur within 3 months (I). Any medication aimed at immediate symptom relief, as hypnotics or sedatives, should be discontinued as soon as symptoms improve. Short-term treatments also effective in relapse prevention may be appropriately continued when long-term treatment is planned.

3.2.5. Clinical Practice Recommendations for bipolar disorder, National Health and Medical Research Council (Malhi et al., 2009)

The clinical practice recommendations (CPR) for bipolar disorder have been developed involving a large multidisciplinary team with national and international representation. These recommendations aim to provide a practical overview on the management of bipolar disorder by reflecting both evidence-based practice and real-world experience. The strength of recommendations reflects the National Health and Medical Research Council Levels of Evidence criteria (see Table 1).

3.2.5.1. First-Line. Antimanic agents suggested in monotherapy are: lithium, valproate, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone (level I). As a first line combination, lithium or valproate with short-term administration of atypical antipsychotics is suggested (level I). In order to manage behavioral disturbance, short-term use of benzodiazepines (e.g. lorazepam) or antipsychotics is recommended. Oral administration is preferable. If intramuscular administration is necessary, an injectable atypical (e.g., i.m. aripiprazole or olanzapine) or a combination of an injectable typical antipsychotic and benzodiazepines are mentioned. If cognitive disturbances are present, the guideline suggests to use antipsychotics as adjunctive treatment (level I), with preference for atypical antipsychotics over typical neuroleptics. Lithium plus valproate (level II), lithium plus carbamazepine (level II) and lithium or valproate plus olanzapine (level II) are suggested as eligible combination strategies.

3.2.5.2. Second-line. Adding clozapine or risperidone to ongoing treatment is suggested (level III). If acute manic symptoms or behavioral disturbance persists or becomes severe, ECT can be considered (level III). Haloperidol and, to a less extent, carbamazepine are also mentioned. As haloperidol is efficacious but its longer-term use carries an increased risk of extrapyramidal side-effects, it is not recommended unless other options have failed.

3.2.5.3. Not recommended. Gabapentin, lamotrigine, topiramate, phenytoin and oxcarbazepine are not recommended for the treatment of acute mania. Overall, the use of two antipsychotics concurrently is not advised.

4. Discussion

4.1. Diagnostic and scope issues

The guidelines considered in the present review focus on DSM-IV bipolar disorder, type I. CANMAT and ISBD guidelines

deal with the treatment of Bipolar II disorder too, and point out to the need of a better bipolar spectrum disorders detection, by considering the following: subthreshold hypomanic episodes in the context of multiple other signs of bipolarity, as well as multiple signs of bipolarity without hypomanic or manic episodes (the so defined *soft bipolar spectrum*). WFSBP guidelines distinguish, when data allow it, between pure mania, dysphoric mania, mixed states, psychotic mania and hypomania, and mention that the clinical relevance of different manifestations of mania should merit more attention in guidelines (e.g. mania with delirium, chronic mania, oligo-symptomatic mania, or mania in different phases of life). The BAP guidelines suggest considering the identification of core symptoms against a check list as in DSM-IV and the importance of second sources for collateral information (family members, caregivers etc.), suggesting the aid of a screening instrument such as the Mood Disorder Questionnaire (Hirschfeld et al., 2000). In conclusion, there is a widespread inconsistency in diagnostic assessment of different subtypes and definitions with respect to bipolar illness across different guidelines and, when specific diagnostic criteria are proposed as in DSM-IV and ICD-10, they seem to be insufficiently representative of the clinical complexity of the patient with BD. Great efforts have to be made in order to establish clinical definitions which enhance sensitivity in detection of subclinical presentations, combined with higher specificity of clinical characteristics. Nonetheless, steps in this direction have been taken, such as the ISBD Diagnostic Task Force consensus (Ghaemi et al., 2008) and the ISBD Nomenclature Task Force (Tohen et al., 2009a).

4.2. Methodological issues

4.2.1. Methodology of the development of the different guidelines

All guidelines were created without any financial support from pharmaceutical companies and experts of the task force were selected according to their expertise. Guidelines have been usually developed by multidisciplinary teams (consisting of health professionals as psychiatrists, psychologists, social worker, nurses, methodologists, pharmacologists, but patients and families as well), involving, as a general rule, experts from different cultures in order to facilitate their applicability in different countries. However, some exceptions exist, as the NICE guidelines, specifically tailored for the use in the United Kingdom (UK) Mental Health setting: their authors prioritized the evidence in that context, modifying recommendations accordingly. In all mentioned guidelines an extensive literature search was performed and data were extracted from standard mental health related bibliographic databases. NICE guidelines used the most elaborated literature review and data classification, following a step-wise, hierarchical approach based on methods set out in the *Guideline Development Methods: Information for National Collaborating Centres and Guidelines Developers*. Moreover, inclusion criteria of literature data vary across the different guidelines depending also on their date of publication: the CANMAT and ISBD guidelines include data published up to 2007, the WFSBP guidelines are based on evidence published up to the end of 2008 and the NICE guidelines include data up to March 2006, with an update published in 2009. The other

mentioned guidelines do not specify in their methods paragraph any time limit for the literature research. The second step of the guidelines development was the collection and classification of data and the discussion of consensus and areas of uncertainty. BAP guidelines, published in March 2009, are the result of an initial meeting in May 2007. Again, NICE guidelines are the most elaborated, developed during seventeen meetings (from March 2004 to March 2006) and two consensus conferences by a Guideline Consensus Group (GCG), in which smaller topic groups were formed in order to undertake the task on specific areas: service delivery, pharmacological and other physical treatment, psychological therapies and warning signs. The other guidelines do not describe their development process in detail. All the guidelines address the treatment of acute mania in adults and some of them mention special considerations: the WFSBP guidelines provide recommendations for the treatment of different mania subtypes, such as dysphoric and mixed mania. The CANMAT/ISBD guidelines expand the discussion to BD type II and includes a special section on safety and monitoring. The BAP guidelines specify treatment options for manic or mixed episodes for patients who are not already on long-term treatment and for patients who are already taking medication, including treatment recommendations for special populations (elderly patients, substance abuse comorbidities, and pregnancy). NICE guidelines also include a section for general recommendations for special populations (women and children) and are the only guidelines that take into account cost-effectiveness information, where available, in the generation of statements and recommendations. The WFSBP update and NICE guidelines are structured in term of groups of medications and summaries of treatments are provided for each compound, while other ones follow a structure based on illness phases.

4.2.2. Methodology of the definition of category of evidence (CE) and recommendation grades (RG)

Once the literature review was performed, the available data were evaluated and ranked using standardized and systematic methods; for each drug a grading was created and each compound was assigned to a category of evidence (CE), which basically describes the level of efficacy. Additional clinical aspects of safety and tolerability were subsequently integrated, leading to different recommendation grades (RG) finally assigned to each compound. As summarized in Table 1, all the guidelines refer to specific categories (or levels) of evidence, consequence of the different weight given to the design of the study included, the presence of meta-analyses or the presence of negative evidence.

The first main distinction across guidelines comes from the different weight given to the presence of meta-analyses: all guidelines but WFSBPs define the presence of positive results from meta-analyses as full evidence for the efficacy of a determined compound (the higher level of evidence) while WFSBP guidelines favor positive evidence from RCTs (CE: A) while considering results from meta-analyses as less compelling (CE: B), due to a number of shortcomings, i.e. the risk of overpowering results. WFSBP guidelines specify that when randomized, double-blind trials were not available, other sources of information were collected, such as open studies or case reports. The methodology of the rationale in choosing

the different CE and the derived RG has been already described in our previous review on bipolar depression (Nivoli et al., 2010). The authors made a distinction between “lack of evidence” (studies do not exist) and “negative evidence” (studies showing no-superiority of placebo or inferiority to an active comparison), suggesting that the lack of evidence for a specific drug, does not, under certain conditions, preclude its use in a non-responsive patient. On the other hand, this attempt should be avoided if the drug has negative evidence. Moreover, the definition of CE and RG greatly varies in BAP, in CPR and in CANMAT/ISBD guidelines, as in the latter an emphasis on existing systematic reviews and meta-analyses, besides the presence of RCTs, is put. NICE guidelines applied a very elaborated method to rank evidence data. Where possible, meta-analyses were used to synthesize the evidence and, if necessary, re-analyses of the data or sub-analyses were used to answer clinical questions not addressed in the original studies, while the methodology of the other guidelines did not allow for a systematic review or re-analysis of all possible data from primary sources. NICE guidelines provide tables with summaries of the characteristics of the studies and, where appropriate, forest plots, displaying the effect size and confidence intervals (CI) for each study. The quality of the evidence for each selected study was based on the quality assessment components, such as study design, limitations to study quality, consistency, directness, and effect sizes. The quality of evidence was graded using the following definitions of quality from *High* (further research is very unlikely to change our confidence in the estimate of the effect) to *Very Low* (any estimate of the effect is very uncertain). In order to formulate clinical recommendations, a decision tree was used to help determine the likelihood of the effect being clinically significant, and results are described as: “CS1 = very likely to be clinical significant”; “CS2 = likely to be clinical significant”; “CS3 = unlikely to be clinical significant”; and “CS4 = inconclusive”. Once the evidence profile tables and clinical summaries were extracted, the associated clinical recommendations were provided taking into account the trade-off between the benefits and risks, as well as economic factors. There is some imbalance between NICE guidelines structural quality (internal validity) and the quality of their content as regards to external validity, so that these guidelines are extremely complete and informative but are quite hard to interpret and to apply in every-day clinical practice.

4.2.3. The limits of the evidence-base in the treatment of acute mania

A common major methodological problem in dealing with evidence-based data comes from the nature and design of the majority of RCTs on treatment of mania. The first main issue is related to the *poor generalizability* of the results. The inclusion criteria define patients selected following the DSM-IV criteria for manic/hypomanic or mixed episodes, which are quite strict. These exclude patients with comorbidities, suicidal risk or need for complex treatment regimens, and fail in characterizing the variety and complexity of clinical manifestations of these phases of the illness. Moderately or severely ill manic patients, with impaired insight and lack of cooperativeness may not be selected to participate to the trial and, consequently, the discrepancies between highly selected patients and patients seen in clinical practice are

particularly broad in mania. Furthermore, the concept of mixed-mania or dysphoric mania is not well defined. Mixed states are notoriously difficult to distinguish from both mania and agitated depression and their identification is one of the main issues in the diagnosis of bipolar disorder (Vieta and Morralla 2010), with important outcome implications (González-Pinto et al., 2011). Some authors proposed that large, representative, well-designed observational studies, which include a wide range of patients from naturalistic setting, may be useful to describe the characteristic and course of patients and treatments, even if they carry limitations in assessing treatment outcomes (Reed et al., 2009). These trials may grant new insight on the effectiveness of compounds in a real-life clinical setting (Ghaemi, 2010), outlining the limits of drugs tested in double blind RCTs. For instance, this may be the case of valproate: its preferred use over lithium has been recently questioned on the basis of the BALANCE study, which could re-define its role as a first line antimanic and long-term treatment (Ghaemi, 2010). The second problem is related to the *interpretation of the outcome* (Licht, 2001). With regard to the definition of response/remission in RCTs, some authors highlighted the need to better describe response (Martinez-Arán et al., 2008), suggesting to redefine the reduction of 50% or more from baseline in either the total score at the Young Mania Rating Scale (YMRS) or the mania subscale score of the Schedule for Affective Disorders and Schizophrenia-Change version (SADS-C). Furthermore, a response definition based on a certain threshold in a score may be more valid and clinically useful than an abstract percentage reduction. Detailed analyses on response patterns to various treatments are not available: response may be delayed for some medication that need titration or are used in lower dosages (Grunze et al., 2009). One further remark raises from the patient's potential risk for switching to depression during an antimanic treatment, combined with the high proportion of manic patients with depressive symptoms: a weekly use of scales measuring degrees of depression in RCTs on mania is highly advisable. The *minimum duration of RCTs* in mania is crucial too, with the need to evaluate a response after 3 weeks (which is typically the duration of short-term RCTs for mania), allowing more complete information gathering for the duration of the acute episode and the risk of exacerbation of manic and depressive symptoms. The *high drop-out rate* can be one of the reasons of the short duration of RCTs in mania (Licht 2001). Consequently, the high drop-out rate may affect results, even though data are then analyzed using the intent-to-treat design, because reasons for drop-out are differently distributed in the treatment groups: patients in the placebo arm tend to drop out due to lack of efficacy, while patients in the active arm tend to drop-out for side effects, generally before response. Including the drop-out due to the lack of efficacy as a secondary outcome measure could be a solution to deal with this limitation. Due to the difficulty in recruitment of manic patients, RCTs have got relatively small sample sizes, leading to *limitations in statistical power* which often carry difficulties in interpreting study results. A last limitation is represented by *negative evidence*: negative studies are sometimes not published and information may not always be complete, thus biasing evidence for efficacy. Sponsor bias can affect the goodness of

guidelines: even if experts who formulate recommendations do their best to be objective, there are still views and attitudes towards specific drugs: readers should use guidelines as an indicative and suggestive tool but they should enhance their own knowledge of the original publications.

In conclusion, the discrepancies in recommendations of guidelines based on evidence data may be related to the methodology of RCTs in mania. Specific attention is needed to overcome limits in generalizability of study results with the implementation of large, well-designed, randomized, open studies on naturalistic populations using broader inclusion criteria, improving evaluation of the outcome and duration of trials.

4.3. Treatment recommendations

The mentioned guidelines reach different conclusions in the treatment of acute manic episodes, usually resulting from different weights placed on the available evidence and, to some extent, due to different cultural traditions in treatment and attitudes towards particular agents. However, all the guidelines included in the present review agree on first treating manic/hypomanic and mixed episodes with a medication fulfilling the highest criteria for efficacy and, when possible, having the highest clinical recommendation grade, like lithium (Li), valproate (VPA) or atypical antipsychotics (AAPs) as monotherapy, in order to minimize side effects and medical risks. Combinations (atypical antipsychotic plus lithium or valproate) should be reserved for severe mania as first line choice or as a subsequent step in mild and moderate mania in which another first line medication (second option) failed. Dealing with antidepressants in BD is a delicate business: despite the widespread use of these agents, all guidelines agree on stopping the ongoing antidepressant medication during a manic/mixed episode.

4.3.1. Monotherapy

Lithium monotherapy is recommended by almost all guidelines as first-line treatment in acute mania, on the basis of positive results from three-arm, placebo-controlled trials (Bowden et al., 1994, 2005) and a meta-analysis (Smith et al., 2007). In WFSBP guidelines this statement is also supported by additional data coming from three-arm, placebo-controlled trials versus topiramate (Kushner et al., 2006) and aripiprazole (Keck et al., 2009). WFSBP recommends lithium especially in pure euphoric mania rather than in mania with dysphoric or depressive symptoms but, given its slow onset of action, scarce sedative properties, the narrow safety margin and the need to exclude some medical conditions, monotherapy achieves a RG of “2” (A, 2) in acute mania. On the other hand, the authors suggest that lithium alone or in combination may be the primary choice when maintenance treatment is considered at the time of the acute treatment initiation (A, 1). Given its slower onset of action, English guidelines (BAP and NICE) recommend this compound as first-line only for less severe acute episodes, when there are good compliance and evidence of a positive response in previous episodes.

Valproate monotherapy is recommended as a first line choice in all guidelines, with some slight differences. In WFSBP it is recommended as first-line (A, 1) both in pure mania (with or without psychotic symptoms) and in mania

with dysphoric/depressive features, on the basis of positive results from double-blind, placebo-controlled trials (Bowden et al., 2006; Pope et al., 1991), three-arm, placebo controlled trials (Bowden et al., 1994, 2005) and head-to-head studies compared to lithium (Bowden et al., 2008; Freeman et al., 1992), haloperidol (McElroy et al., 1996) and olanzapine (Zajacka et al., 2002). However, considering its teratogenicity and high risk of polycystic ovary syndrome (PCOS), its RG for women in child-bearing age is “2” (A, 2). Valproate recommendations are dissimilar in the two English guidelines: while in BAP it is recommended as first-line treatment for severe manic or mixed episodes among patients not already on long-term treatment because of its rapid anti-manic effect (I, A), the NICE recommend to prescribe valproate in less severe mania and, as in the case of lithium, if good compliance and positive response in previous episodes are present. This difference may be explained by the fact that NICE guidelines, due to the rigorous methodological selection of studies, consider as inconclusive or unlikely to be clinically significant (CS3–4) some results from RCTs which are interpreted as positive in BAP guidelines, such as results from the head-to-head study versus olanzapine (Zajacka et al., 2002), which actually was not powered for efficacy (Vieta, 2009b). *Carbamazepine* shows heterogeneity on its recommendations too. In WFSBP guidelines it is recommended for mixed states or dysphoric mania (CE, A) on the basis of its efficacy demonstrated in two double-blind, placebo-controlled trials (Weisler et al., 2004a, 2005). The guidelines authors also say, though, that the use of carbamazepine is limited in clinical practice by some tolerability issues and interactions with other psychotropic medications, which make it a RG of “2”. BAP guidelines also recommend it as first line treatment, but in less severe mania. In general, it is mostly considered as second line and not recommended in combination.

Monotherapy with atypical antipsychotics is recommended as a first line choice in all the guidelines included in the present review because of positive data from controlled studies and their short-term adverse effect profile. One further factor that influences the choice of antipsychotics includes properties like sedation, which according to almost of the guidelines may be desirable in the short term treatment of manic episodes. *Aripiprazole* is recommended as a first line choice in all guidelines. In WFSBP it is recommended across different subtypes of mania, both for pure mania and mixed or psychotic episodes, showing superiority to placebo (Keck et al., 2003a; Sachs et al., 2006) and equivalent efficacy in three-arm, placebo controlled studies compared to lithium (Keck et al., 2009) and haloperidol (Young et al., 2009), even if the authors highlight the presence of a negative placebo-controlled study (El Mallakh et al., 2010) and in NICE one head-to-head study with haloperidol is considered as inconclusive probably due to some methodological issues (Vieta et al., 2005). *Olanzapine* monotherapy is recommended as a first line choice in all guidelines. Its high level of evidence is justified by results from meta-analyses (Bowden et al., 2005; Smith et al., 2007) and on the basis of a broad evidence of positive results in double-blind, placebo controlled studies (Tohen et al., 1999, 2000), in three-arm studies versus valproate (Tohen et al., 2009b) and in its intramuscular formulation compared to lorazepam (Meehan et al., 2001), as well as in head-to-head comparative studies with valproate

(Tohen et al., 2003a; Zajecka et al., 2002), lithium (Niufan et al., 2008), risperidone in manic and mixed patients (Perlis et al., 2006a) and haloperidol (Tohen et al., 2003b). It has shown a broad efficacy profile in acute mania (euphoric, dysphoric/mixed and psychotic), but due to potential metabolic issues it reaches the RG of “2” in WFSBP guidelines. *Quetiapine* is recommended as first line monotherapy in all guidelines in pure mania, mixed and rapid cycling, on the basis of two placebo-controlled RCTs (Cutler et al. 2008; McIntyre et al., 2005) and three-arm placebo controlled trials with lithium (Bowden et al., 2005), haloperidol (McIntyre et al. 2005) and paliperidone ER in manic and mixed patients (Vieta et al., 2010a). While in BAP and CANMAT/ISBD guidelines it received the highest RG, WFSBP assigned quetiapine a RG of “2” (A,2) because of its weaker efficacy in direct comparison to haloperidol (McIntyre et al., 2005) and the potential role of metabolic issues in maintenance treatment. This warning is confirmed in NICE guidelines where two studies are interpreted as inconclusive due to methodological issues (Bowden et al., 2005; McIntyre et al., 2005). *Risperidone* also reaches the higher level of evidence in all guidelines on the basis of positive results from meta-analyses (Perlis et al., 2006b; Rendell et al., 2006; Smith et al., 2007), double-blind, placebo-controlled studies (Hirschfeld et al., 2004; Khanna et al. 2005), three-arm placebo controlled studies with haloperidol (Smulevich et al. 2005) and a comparative study versus lithium (Segal et al. 1998). WFSBP recommends risperidone in severe and psychotic mania (A, 1) but only limited data support its use in mixed states. *Ziprasidone* is recommended throughout the guidelines and WFSBP suggests its efficacy both in mixed and psychotic mania (A,1), basing on double-blind, placebo-controlled studies (Keck et al. 2003b; Potkin et al. 2005), and a three-arm placebo controlled study with haloperidol (Vieta et al., 2010b) in which, it proved to be superior to placebo but inferior to haloperidol. WFSBP stresses that, due to ziprasidone potential cardiovascular concerns at high doses, its use is restricted in some countries (RG “2”). *Asenapine* is only recommended by WFSBP and CANMAT/ISBD guidelines because of its very recent approval. In WFSBP asenapine is recommended in manic episodes and also in mixed states (CE of A) on the basis of recent positive results from RCTs (McIntyre et al., 2010) but due to the limited experience and little data on safety and tolerability it received a RG of “2”. For *haloperidol*, despite its widespread use in mania, controlled data has only recently become available and this compound reached a CE of A in WFSBP guidelines, especially in psychotic mania, but it may exacerbate depressive and dysphoric symptoms, especially in mixed mania. Its RG is “2” due to the risk of acute extrapyramidal motor symptoms and tardive dyskinesia.

4.3.2. Combinations

Combination therapy including Li or VPA with an AAP is suggested on the basis of positive results from meta-analyses (Bowden et al., 2005; Smith et al., 2007). Some guidelines prioritize monotherapy, but others give it a first-line grade in the treatment for severe mania. Positive combination data is available for aripiprazole (Vieta et al., 2008a), olanzapine (Tohen et al., 2008), also in mixed and psychotic episodes (Tohen et al., 2002) and with positive results from

naturalistic studies only mentioned in WFSBP guidelines (Vieta et al., 2008b), quetiapine (Sachs et al., 2004; Yatham et al., 2007), risperidone (Rendell et al., 2006; Sachs et al., 2002; Yatham et al., 2003), ziprasidone (Weisler et al., 2004b), and haloperidol (Sachs et al., 2002; Small et al., 1995). Asenapine is also recommended by WFSBP and CANMAT/ISBD guidelines as first choice in combination with lithium and valproate on the basis of positive evidence from one still unpublished, add-on, placebo controlled study (Calabrese et al., 2008), although it has a RG of “2”. In NICE, if an antipsychotic proves to be ineffective, augmentation with valproate or lithium is suggested. English guidelines (BAP and NICE) also give first-line recommendations for patients already taking medication during a manic/hypomanic/mixed episode: if the patient is taking lithium or valproate, they suggest adding an atypical antipsychotic. In the case of carbamazepine they do not recommend combination with other agents, but they suggest changing the ongoing medication for another first-line treatment. Only the GCP guidelines suggest combination of lithium with carbamazepine as first-choice treatment. If severe agitation, CANMAT/ISBD, BAP and NICE guidelines all suggest the use of i.m. aripiprazole or olanzapine as first choice on the basis of three-arm, placebo-controlled studies (Zimbroff et al., 2007; Meenhan et al., 2001).

4.4. Clinical issues

4.4.1. Monotherapy versus combination

In all mentioned guidelines, safety and practicability issues favor monotherapy as first line approach, making best use of the dosage range available for a given medication, since combined treatment is potentially associated with higher frequency and greater severity of side effects (Vieta, 2009a,b). Combination is recommended for severe mania as first-line treatment (in WFSBP, CANMAT/ISBD and BAP) and as a second choice in mild and moderate mania after switching from unsuccessful medication in all guidelines. This is quite in contrast with clinical practice, where most patients are treated with combinations of two or more antimanic agents (Haro et al., 2010) due to illness complexity, comorbidity, lack of adherence, side effects. Indeed, despite the overwhelming evidence for efficacy of several monotherapies (Yildiz et al., 2011), in clinical practice a small proportion (less than 10%) of acutely manic patients receive monotherapy (Ghaemi, 2006; Wolfspenger et al., 2007) due to comorbid conditions or severity of illness. In a meta-analysis of co-therapy and monotherapy in acute bipolar mania (Smith et al., 2007) the authors analyzed eight RCTs (1124 participants) and found that significant reductions in mania, as measured by at least 50% improvement from baseline at YMRS scores, were shown for haloperidol, olanzapine, risperidone and quetiapine as co-therapy compared with monotherapy with a mood stabilizer, even if combination were less well tolerated than monotherapy. These results confirm the advantage on adding an antipsychotic if a patient is not fully responding to a mood stabilizer alone. In conclusion, even if the first-line approach in all mentioned guidelines is monotherapy, with combination approach reserved for severe cases or as a second choice, a proper algorithm regarding different medications, phase of the illness and specific clinical presentations is lacking. An effort in this direction has been made during the ECNP consensus meeting,

when Goodwin et al. (2009a) faced the problem of advantages and disadvantages of combination therapy with antipsychotics. They highlighted that the use of antipsychotics in combination has been poorly studied by industry supported trials as well as by independent studies and proposed a summary and discussion of the existing data and the possible study designs that could underpin future use of drug combinations. They also mentioned the lack of a distinction between patients responding insufficiently to an acute antimanic treatment with lithium (or valproate) and patients suffering from breakthrough mania during prophylaxis in add-on studies on lithium/valproate plus antipsychotics. This can significantly limit the selection of patients in the study and, consequently, the generalizability of the results. The authors also suggest that conventional two-arm trial designs could benefit from a third antipsychotic monotherapy arm in order to improve data from studies which compare and quantify the efficacy of antipsychotics in monotherapy or in combination.

It is worth mentioning a recent meta-analysis (Cipriani et al., 2011) of randomized, double-blind trials comparing one active antimanic drug with another or with placebo, including also combination and augmentation studies. The authors highlighted that, overall, antipsychotics were significantly more effective than mood stabilizers, with risperidone, olanzapine and haloperidol showing the best efficacy profile in the treatment of acute manic episodes while lamotrigine, topiramate and gabapentin were not significantly better than placebo. In terms of drop-outs, olanzapine, risperidone and quetiapine showed more efficacy than haloperidol. These results have potential clinical implication that should be considered in the development of future guidelines, even if extrapolation of data from mania trials to clinical practice should be done with caution.

4.4.2. Discontinuation of the ongoing treatment

The question on which is the best strategy to face partial response (i.e., switching from one drug to another or adding one drug to another) remains unanswered by the published guidelines. There is no agreement in current guidelines on specific criteria for stopping ineffective treatment and for the time frame necessary to interrupt/switch a medication in acute mania. Most guidelines recommend continuation of treatment for 6–12 months after remission from an acute mood episode. Controlled data for discontinuation in mania are only available for lithium (Goodwin 1994), olanzapine (Tohen et al., 2006) and aripiprazole (Keck et al., 2006). In the absence of firm evidence about when to stop a medication if the first choice drug is inefficacious or leads only to a partial response, the WFSBP recommends that a treatment trial should not last more than 2 weeks, and the continuation or discontinuation of a given initial antimanic agent should be decided upon the basis of full, partial or no response. In case of insufficient response, what to do next is based on expert opinion and clinical experience rather than on evidence. The BAP guidelines recommend that discontinuation of short-term treatment for mania can be considered after full remission of symptoms. The required duration will be often after 12 weeks, although higher doses of antipsychotics may be reduced earlier. NICE and CANMAT/IFSBP guidelines do not recommend a time limit for treatment trial. All guidelines agree with stopping ongoing antidepressant medication

either abruptly or gradually, depending on clinical factors (current clinical need, previous discontinuation symptoms and specific discontinuation risk for each antidepressant). While this is one of the few matters of agreement across guidelines, clinicians continue to prescribe antidepressants in as many as 15% of the manic and mixed patients (Rosa et al., 2010). In the event of partial response, it is suggested to optimize dosage of first-choice treatments, check patient's adherence to treatment. If there is still no response, switching to another first choice medication or considering combination with two first-choice agents are recommended.

5. Future directions

The range of treatments for acute mania has significantly increased over the last years, leading to the possibility of better tailoring a specific treatment for a given patient, but also generating the need to standardize the broad range of treatments now available. Treatment guidelines can be useful tools in reducing the variability of clinical practice, improving diagnostic and therapeutic skills for complex disorders, highlighting the gaps of the evidence-base, and promoting consensus expert opinions about scientific topics which lack sufficient evidence-based data. Moreover, treatment guidelines are useful instruments to adapt evidence-based medicine to every-day clinical practice, and improve cost-effectiveness of treatment options.

Future guidelines should distinguish between the different clinical presentations of mania, hypomania and mixed states with particular attention to some clinical specifiers such as mixed episode and rapid cycling, currently not adequately studied as a distinct subtype in BD (Vieta et al., 2004). New antimanic drugs should show additional benefits besides being merely effective, and should have an established long-term, prophylactic efficacy not only against manic episode, but also in the prevention of depressive episodes, as well as a safe, well tolerable and practical profile in order to improve adherence to treatment. Finally, it also appears crucial to conduct large, prospective trials in unselected populations in a methodological rigorous manner, in order to improve evidence-based data and to increase the confidence that a given treatment is also effective in real word settings. Such data would substantially enrich treatment guidelines, which to date fail in addressing important issues in the treatment of mania such as when to discontinue the treatment, which drug should be discontinued first in case of combination therapy, how to treat first-episode patients, or how to deal with chronic and treatment-resistant cases. Furthermore, comparative information between different therapeutic options almost does not exist and this makes prioritizing one option over another much more difficult.

6. Conclusions

In conclusion, we systematically reviewed guidelines, consensus meeting and treatment algorithms which concern with bipolar mania/hypomania and mixed treatment, published or updated since 2005. Pharmacotherapy remains the treatment of choice for acute bipolar mania. Despite their heterogeneity, all guidelines agree with interrupting an ongoing antidepressant medication and recommend monotherapy with lithium, valproate or atypical antipsychotics as first-line

choice, showing good homogeneity about what *not* to use as a treatment for acute mania. Combination therapy is generally suggested as second-line treatment, even if BAP guidelines recommend it as first-line treatment for severe mania.

The problem of which guideline is better is not completely solved by the present review. The selected guidelines showed high scientific standards and adequate methodological approaches. However, some differences can be mentioned in order to assist clinicians in orientating themselves in the use and application of guidelines within the clinical practice. On the opinion of the writers, WFSBP and NICE guidelines are the most comprehensive ones by a scientific point of view: the authors evaluate a broad range of research evidence, including different types of recent RCTs, supporting the definition of their categories of evidence and recommendation grades. Furthermore, in NICE a very rigorous statistical method is applied in order to quantify the quality of evidence. This is extremely informative for a researcher, but very difficult to interpret and to translate into clinical practice. NICE guidelines also reflect local health care needs and the nature of existing services in UK, and this can limit their use in other countries. The CANMAT/ISBD guidelines are also very comprehensive, especially for atypical antipsychotics, but lack informations about lithium and anticonvulsants (they merely refer to meta-analyses or recent reviews). The authors provide schematic algorithms for assessing the choice of the best treatment approach for every phase, something which is particularly useful for clinicians, and provides information on BD type II. BAP and CGP guidelines are more clinically-oriented, providing practical approaches for the assessment and management of BD. Particularly the BAP guidelines discuss key uncertainties across a broad range of problems that clinicians have to face while dealing with patients affected by BD. On the other hand, they are less comprehensive when mentioning evidence based data, prioritizing results from meta-analyses and reviews over RCTs. In conclusion, all the guidelines revised hereby meet standards, but perhaps the WFSBP poses as the most comprehensive on the basis of the following characteristics: a very detailed summary of evidence based data on efficacy of each compound; the inclusion of well-designed, large, open studies; detailed explanations on how a particular CE and RG is assigned to each compound; the integration of tolerability and safety issues in the assignment of every drug in a specific RG; the presence of special considerations for the treatment of different subtype of mania; the outline of the pharmacological approach in an algorithm. A common flaw presented by all of the guidelines hereby reviewed is that none weighted in the levels of evidence the eventual presence of long-term trials on the compounds considered, an issue which is specific of the course of the bipolar illness as the acute treatment is often given in the perspective of a long-term treatment; this is only mentioned in the WFSBP mania guidelines, even if this concept is fully developed in the WFSBP maintenance guidelines.

In conclusion, to evaluate the implementation of clinical guidelines is an important component for their further improvement. However, advances in clinical and methodological issues still are needed to fill the gap with clinical practice, while genetic and neurobiological research can still point out new drug targets, better profile responders and no-responders, thus bringing new possibilities to the difficult management of this illness.

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Conflict of interest

Dr. Alessandra MA, Nivoli have been a speaker for Astra-Zeneca and have served as advisor for Bristol-Myers. Dr. Andrea Murru have served as advisor for Bristol-Myers. Dr. Manuel Goikolea has been a speaker of advisory board for Astra-Zeneca, Bristol Myers-Squibb, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Merck Sharpe and Dohme, Otsuka, Pfizer, Sanofi-Aventis. Dr. Jose M Crespo has received research grants and/or honoraria as consultant or speaker from Astra-Zeneca, Bristol-Myers-Squibb, Eli Lilly, Janssen, Novartis, Pfizer, Otsuka Pharmaceutical Sanofi-aventis, the Spanish Ministry of Health and the Spanish Ministry of Science and Innovation (CIBERSAM). Dr. José Manuel Montes have collaborated with the following companies: Grants from Astra-Zeneca, Pfizer, Servier; Speaker Board: Astra-Zeneca, BMS. Advisory Board: Lundbeck, Pfizer. Dr. Ana González-Pinto has received grant support, acted as consultant, or given presentations for the following pharmaceutical companies: Almirall (Barcelona, Spain), Astra-Zeneca (Madrid, Spain), Eli Lilly (IN,USA), Glaxo-Smith-Kline (Madrid, Spain), Lundbeck (Barcelona, Spain), Pfizer (Madrid, Spain), Sanofi-Aventis (Paris, France), MSD, BMS, Janssen and Boehringer Ingelheim (Barcelona, Spain). Dr. Paz García-Portilla has no conflict of interest. Dr. Julio Bobes has received consulting fees and honoraria within the last 3 years from AstraZeneca, Bristol-Myers-Otsuka, GlaxoSmithKline, Janssen-Cilag, Lilly, Pfizer, Sanofi-Aventis, Schering-Plough. Dr. Jeronimo Saiz-Ruiz, has been a speaker for and on the advisory boards of Lilly, GlaxoSmithKline, Lundbeck, Janssen, Servier and Pfizer; and has received grant/honoraria from Lilly, Astra-Zeneca, Bristol-Myers and Wyeth. Dr. Eduard Vieta has received research grants and served as consultant, advisor or speaker for the following companies. Grants: Almirall, Astra-Zeneca, Bristol-Myers-Squibb, Eli Lilly, Generalitat de Catalunya, Glaxo-Smith-Kline, Janssen-Cilag, Novartis, Pfizer, Sanofi-Aventis, Servier, Seventh European Framework Program, Spanish Ministry of Science and Innovation. Consultant: Astra-Zeneca, Bristol-Myers-Squibb, Eli Lilly, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Lundbeck, Merck Sharpe and Dohme, Novartis, Otsuka, Pfizer, Sanofi, Servier, Shering-Plough, Takeda, and United Biosource Corporation. Advisory Board: Astra-Zeneca, Bristol-Myers-Squibb, Eli Lilly, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Lundbeck, Merck Sharpe and Dohme, Novartis, Otsuka, Pfizer, Sanofi, Servier, Shering-Plough, Takeda, and United Biosource Corporation.

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