

REVIEW

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

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

3rd Department of Psychiatry, School of Medicine, Aristotle University, Thessaloniki, Greece (Dr Fountoulakis); Paracelsus Medical University, Salzburg, Austria (Dr Grunze); Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain (Dr Vieta); Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK (Dr Young); Department of Psychiatry, University of British Columbia, Mood Disorders Centre of Excellence, Djavad Mowafaghian Centre for Brain Health, Vancouver, Canada (Dr Yatham); The Royal Institute of Mental Health Research, Department of Psychiatry, University of Ottawa, Ottawa, Canada (Dr Blier); Department of Psychiatry and Psychotherapy, Medical University Vienna, MUV, AKH, Vienna, Austria (Dr Kasper); Psychiatric Department, Ludwig Maximilians University, Munich, Germany (Dr Moeller).

Correspondence: Konstantinos N. Fountoulakis, MD, 6 Odysseos str (1st Parodos Ampelonon str.), 55535 Pylaia, Thessaloniki, Greece (kfount@med.auth.gr).

Abstract

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

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

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

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

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Introduction

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

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

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

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

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

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

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

Existing Evidence for the Treatment of BD

As shown and discussed in detail in the previous manuscripts of the CINP BD guidelines, there are a significant number of studies

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

Concept and Structure of the Clinical Guidelines

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

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

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

Clinical Guidelines to Treat Bipolar Disorder

General Guidelines

The first priority when dealing with a BD patient is the assessment of risks to the patient or others, and whether there is a need for immediate hospitalization, even involuntary. It is important to provide a tranquil environment with reduced stimuli for patients in an acute manic or hypomanic episode. Both the patient and the family should be advised that all important decisions including family matters, professional issues, and finances should be postponed until the resolution of the acute symptomatology. On the other hand, during an acute depressive or mixed episode, the patients are at a higher risk to commit suicide, and every measure to protect the life of the patient should be taken.

Establishing a therapeutic alliance with the patient and his/her family and caregivers is of utmost importance, although it could be difficult especially during periods of acute mania and in the presence of psychotic features. Involuntary admission might be unavoidable when the health and the life of the patient or others might be at risk; however, the dignity, human rights, and personal space of the patient should be respected, as law dictates.

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

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

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

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

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

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

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

and mixed patients response to treatment could take longer and improvement may be more subtle.

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

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

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

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

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

Clinical Guidelines for the Treatment of Acute Mania/Hypomania

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

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

In the absence of reliable data, hypomania should be treated similarly to full mania, although higher doses may be required for the latter. Besides the specific medication recommendations as depicted in Table 1, there are some general principles that should be obeyed:

Table 1. Level of Recommendation Concerning Monotherapy in Acute Mania/Mixed and Recommended Dosages for Medication Options

Agent/modality	Acute Mania					Mixed Episode				Recommended dosage (mg/d)	
	Mono therapy	Combination				Monotherapy		Combination with MS			
		MS	Li	Val	Cbz	FGAs	Manic component	Depressive component	Manic component		Depressive component
Aripiprazole	1	2	-	-	-	-	3	3	-	-	15-30
Asenapine	1	2	-	-	-	-	3	3	-	-	10-20
Cariprazine	1	-	-	-	-	-	-	-	-	-	3-12
Paliperidone	1	5	-	-	-	-	3	5	-	-	3-12
Quetiapine	1	2	2	-	-	-	5	-	-	-	400-800
Risperidone	1	2	-	5	-	-	3	-	5	5	2-6
Valproate	1	-	-	-	-	2	3	4	-	-	1200-3000 (loading dose 20-30 mg/kg body weight; serum level 75-150 mg)
Carbamazepine	2	-	-	-	-	-	3	3	-	-	600-1200 (serum level 4-15 mg/l)
Haloperidol	2	2	2	2	2	-	-	-	5	5	5-20
Lithium	2	-	-	-	2	-	5	-	-	-	600-1200 (serum level 0.8-1.3 mmol)
Olanzapine	2	2	-	2	5	-	3	3	2	2	10-20
ECT	3	-	-	-	-	-	-	-	-	-	-
Oxcarbazepine	3	-	2	-	-	-	-	-	-	-	900-1800
Chlorpromazine	4	-	-	-	-	-	-	-	-	-	300-1000
Pimozide	4	-	-	-	-	-	-	-	-	-	2-16
Tamoxifen	4	4	4	-	-	-	-	-	-	-	40-80
Ziprasidone	4	5	-	-	-	-	4	4	-	-	80-160
OFC	-	-	-	-	-	-	4	4	-	-	6 and 25, 6 and 50, 12 and 50
Medroxyprogesterone	-	2	-	-	-	-	-	-	-	-	20
Allopurinol	-	5	2	-	-	5	-	-	-	-	300-600
Celecoxib	-	-	-	-	-	-	-	-	5	5	-
Eslicarbazepine	5	-	-	-	-	-	-	-	-	-	-
Gabapentin	5	5	-	-	-	-	-	-	-	-	-
Lamotrigine	5	-	-	-	-	-	-	-	-	-	-
Licarbazepine	5	-	-	-	-	-	-	-	-	-	-
rTMS	5	-	-	-	-	-	-	-	-	-	-
Topiramate	5	5	-	-	-	-	-	-	-	-	-
Verapamil	5	-	-	-	-	-	-	-	-	-	-
FEWP	-	-	-	-	5	-	-	-	-	-	-

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

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

First step:

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

Second step:

If the interventions recommended during the first step fail or the response is unsatisfactory, then apply:

- Olanzapine, lithium, carbamazepine, haloperidol, or ziprasidone monotherapy
- Combinations of lithium or valproate plus asenapine, aripiprazole, haloperidol, olanzapine
- Lithium plus allopurinol*
- Valproate plus a first-generation antipsychotic (FGA)
- Valproate plus celecoxib*

Third step:

- Combination treatment of lithium or valproate with quetiapine or risperidone

Fourth step:

- Apply ECT on top of pharmacological treatment or switch to oxcarbazepine monotherapy
- The fourth step includes monotherapy with chlorpromazine, pimozide, tamoxifen options are also combination treat-

ments of lithium or valproate plus tamoxifen, or the combination of risperidone plus lithium. In patients with residual manic/hypomanic symptoms, oxcarbazepine addition to lithium may be helpful.

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

Fifth step:

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

Not recommended:

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

Note:

* no wide clinical experience

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

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

Clinical Guidelines for the Treatment of Acute Bipolar Depression

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

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

First step:

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

Second step:

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

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

1st step	<ul style="list-style-type: none"> • Discontinue treatment with antidepressants • Take into consideration the previous history of psychotic features • Start with aripiprazole, quetiapine, cariprazine, paliperidone, quetiapine, risperidone, valproate, or asenapine monotherapy • Consider IPSRT as add-on to medication according to clinical judgement, patient preferences and availability. Never utilize IPSRT as monotherapy
2nd step	<p>Apply</p> <ul style="list-style-type: none"> • Olanzapine, lithium, carbamazepine, or haloperidol monotherapy • Combinations of lithium or valproate plus aripiprazole, haloperidol, olanzapine, quetiapine, or risperidone • Lithium plus allopurinol or oxcarbazepine • Valproate plus a FGA • A mood stabilizer plus medroxyprogesterone • Valproate plus celecoxib
3rd step	<ul style="list-style-type: none"> • ECT on top of pharmacological treatment • Oxcarbazepine monotherapy.
4th step	<ul style="list-style-type: none"> • Monotherapy with chlorpromazine, pimozide, tamoxifen, or ziprasidone. • Combination of lithium or valproate plus tamoxifen • Combination of risperidone plus lithium • OFC or ziprasidone monotherapy in mixed episodes
5th step	<ul style="list-style-type: none"> • Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist • ECT if not applied earlier
Not recommended	<p>Monotherapy with eslicarbazepine, gabapentin, lamotrigine, licarbazepine, rTMS, topiramate, verapamil, and combination therapy of lithium or valproate plus paliperidone, ziprasidone, gabapentin, topiramate or FEWP and the combination of allopurinol plus a mood stabilizer (other than lithium) or an FGA</p>

Third step:

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

Fourth step:

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

Fifth step:

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

Not recommended:

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

- Memantine plus lamotrigine
- Lithium plus aripiprazole, donepezil, or imipramine
- Risperidone or ziprasidone for concomitant anxiety

Note:

* no wide clinical experience

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

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

Clinical Guidelines for the Treatment during the Maintenance Phase

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

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

	CINP 2017	WFSBP 2013 ^a	CANMAT and ISBD 2013	NICE 2014 ^b	BAP 2016 ^b
Aripiprazole	1	1	1	-	3
Asenapine	1	2	1	-	3
Cariprazine	1	-	3	-	3
Paliperidone	1	3	1	-	3
Quetiapine	1	2	1	1	1
Risperidone	1	1	1	1	1
Valproate	1	1	1	1	2
Carbamazepine	2	2	2	-	3
Haloperidol	2	2	2	1	1
Lithium	2	2	1	1	3
Olanzapine	2	2	1	1	1
ECT	3	4	2	-	3
Oxcarbazepine	3	4	3	-	-
Chlorpromazine	4	3	3	-	3
Pimozide	4	3	-	-	3
Tamoxifen	4	3	3	-	-
Ziprasidone	4	1	1	-	3
Eslicarbazepine	NR	-	-	-	-
Gabapentin	NR	NR	NR	NR	-
Lamotrigine	NR	NR	NR	NR	-
Licarbazepine	NR	-	-	-	-
rTMS	NR	-	-	-	-
Topiramate	NR	NR	NR	NR	-
Verapamil	NR	-	-	-	-
Phenytoin	-	3	-	-	-
Clozapine	-	4	3	-	3
Amisulpride	-	4	-	-	3
Clonazepam	-	4	-	-	-
Leviracetam	-	4	-	-	-
Lorazepam	-	4	-	-	-

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

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

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

^b Step 2 in the WFSBP guideline would be a combination of two grade "1".

Table 4. Level of Recommendation Concerning Monotherapy and Combination Treatment in Acute Bipolar Depression and also for Comorbid Anxiety

Agent/modality	Monotherapy				Combination					Recommended Dosage (mg/d)
	Overall	BD-I	BD-II	Comorbid anxiety	MS	Cbz	Lam	Li	Val	
Quetiapine	1	3	3	3	-	-	-	-	-	300–600
OFC	2	3	-	-	2	-	-	-	-	6 + 25; 6 + 50; 12 + 50
Lurasidone	2	-	-	3	2	-	-	-	-	20–120
Escitalopram	2	-	3	-	-	-	-	-	-	10
Fluoxetine	2	-	3	-	-	-	-	4	-	20–80
Valproate	3	3	5	3	-	-	-	-	-	500–2500 (50–100 mcg/mL)
Aripiprazole	3	3	-	-	-	-	-	5	-	5–30
Imipramine	3	-	-	-	-	-	-	5	-	75–300
Phenelzine	3	-	-	-	-	-	-	-	-	15–90
Olanzapine	4	4	-	-	-	-	-	-	-	5–20
Lamotrigine	4	4	4	-	-	-	-	4	-	50–200
Tranylcypromine	4	4	4	-	-	-	-	-	-	20–30
Venlafaxine	4	4	4	-	-	-	-	-	-	75–225
Carbamazepine	4	-	-	-	-	-	-	-	-	300–800
Lithium	5	-	4	5	-	-	2	-	-	600–1800
Paroxetine	5	5	5	3	5	5	-	5	5	20
Gabapentin	5	-	-	-	-	-	-	-	-	-
rTMS	5	-	4	5	-	-	-	-	-	-
Ziprasidone	5	5	-	5	5	-	5	5	5	-
FEWP	-	-	-	-	-	1	-	-	-	36 g/d
Levothyroxine (L-T4)	-	-	-	-	2	-	-	-	-	300 mcg/d
Modafinil	-	-	-	-	2	-	-	-	-	100–200
Pioglitazone	-	-	-	-	-	-	-	2	-	30
Pramipexole	-	-	-	-	2	-	-	-	-	1–3
Armodafinil	-	-	-	-	4	-	-	-	-	150
Ketamine	-	-	-	-	4	-	-	-	-	0.5 mg/kg i.v. (single dosage)
L-sulpiride	-	-	-	5	-	-	-	3	-	50–75
Oxcarbazepine	-	-	-	3	-	-	-	2	-	600–1200
Agomelatine	-	-	-	-	5	-	-	5	5	-
Imipramine	-	-	-	-	-	-	-	5	-	-
Memantine	-	-	-	-	-	-	5	-	-	-
Levetiracetam	-	-	-	-	5	-	-	-	-	-
Bupropion	-	-	-	-	5	-	-	-	-	-
Celecoxib	-	-	-	-	5	-	-	-	-	-
Risperidone	-	-	-	5	5	-	-	-	-	-

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

Recommended dosages for medication options are also shown.

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

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

To enhance treatment adherence it is important to recognize the contributing factors (Sajatovic et al., 2004) and involve both the patient and his/her family in the decision making with psychoeducational support (van Gent and Zwart, 1991; Sajatovic et al., 2004). In this context, the collaboration between the patient and his/her family with the therapist concerning the monitoring of symptoms can lead to the identification of

periods with a high risk of relapse, and if necessary to adjustments in treatment or to early targeted interventions to reduce the intensity and duration of an emerging acute episode.

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

A difficult question is whether it is wise to continue the index medication used for the acute episode. This is an option adopted by many guidelines. The position of the CINP guidelines

Table 5. Clinical Guideline to Treat Acute Bipolar Depressive Episodes

1st step	<ul style="list-style-type: none"> • Start with quetiapine, lurasidone, or OFC • Consider add-on CBT. Never consider CBT as monotherapy
2nd step	<ul style="list-style-type: none"> • Monotherapy with valproate or lithium • Combination of a mood stabilizer with lurasidone, modafinil, or pramipexole • Lithium plus pioglitazone • Carbamazepine plus FEWP • Add escitalopram or fluoxetine on ongoing therapy • For the treatment of comorbid anxiety add paroxetine, quetiapine, valproate, or lurasidone, and consider mindfulness-based interventions as add-on ongoing therapy
3rd step	<ul style="list-style-type: none"> • Aripiprazole, imipramine, or phenelzine monotherapy • Lithium plus oxcarbazepine or L-sulpiride
4th step	<ul style="list-style-type: none"> • Olanzapine, lamotrigine, tranylcypromine, or carbamazepine monotherapy • Venlafaxine preferably in combination with an antimanic agent • Armodafinil or ketamine on a mood stabilizer • Lithium plus fluoxetine or lamotrigine
5th step	<ul style="list-style-type: none"> • ECT • Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
Not recommended	Monotherapy with donepezil, paroxetine (except for comorbid anxiety), ziprasidone, gabapentin, lithium and rTMS, combination of any mood stabilizer with agomelatine, paroxetine, ziprasidone, bupropion, celecoxib, leviracetam, lisdexamfetamine or risperidone, Memantine plus lamotrigine and lithium plus aripiprazole, donepezil or imipramine. Not recommended also risperidone or ziprasidone for the treatment of concomitant anxiety

Abbreviations: CBT, cognitive behavioral treatment; Cbz, carbamazepine; ECT, electroconvulsive therapy; FEWP, Free and Easy Wanderer Plus; IPSRT, interpersonal and social rhythms therapy; Lam, lamotrigine; MS, mood stabilizer; OFC, olanzapine fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.

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

	CINP 2017	WFSBP 2013 ^a	CANMAT and ISBD 2013	NICE 2014 ^b	BAP 2016 ^b
Lurasidone	1	-	2	-	1
OFC	1	3	1	1	1
Quetiapine	1	1	1	1	1
Valproate	2	3	2	1	-
Lithium	2	5	1	1	3
Escitalopram	2	-	-	-	3
Fluoxetine	2	3	-	-	3
Aripiprazole	3	-	NR	-	-
Imipramine	3	-	-	-	4
Phenelzine	3	-	-	-	-
Carbamazepine	4	5	3	-	-
Lamotrigine	4	3	1	1	2
Olanzapine	4	3	3	1	1
Tranylcypromine	4	-	-	-	4
ECT	5	4	3	-	5
Gabapentin	NR	-	NR	-	-
Leviracetam	-	-	NR	-	-
L-thyroxine	-	4	-	-	-
Paroxetine	NR	-	-	-	3
Risperidone	-	-	NR	-	-
rTMS	NR	-	-	-	-
Ziprasidone	NR	-	NR	-	-

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

^a WFSBP: Recommendation reflects only monotherapy not considering evidence derived from combination treatment (except OFC).

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

is that the acute-phase treatment should be continued for a minimum of 2 months after the achievement of full resolution of symptoms (and thus the patient has entered remission), and after this period treatment should gradually be changed into the recommended maintenance treatment.

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

these subthreshold or subsyndromal symptoms. However, it is obvious that this might lead to polypharmacy with little scientific support. As discussed in detail in the accompanying papers, BD is associated with frequent comorbidity that includes alcohol and substance abuse, anxiety disorders, personality disorders, and higher rates of general medical conditions. The management of these comorbid conditions and especially of those medical conditions that are associated with reduced life expectancy should be considered high priority.

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

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

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

If the treatment during the most recent episode needs to be completely different from the options that are suggested for the maintenance phase in the specific patient, keep it for the continuation phase and gradually taper it against one of the

recommended treatments for the maintenance phase. An overview of the data the clinical guideline is based on is shown in Table 7.

First step:

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

Second step:

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

Third step:

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

Fourth step:

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

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

Agent/modality	Monotherapy			Combination					Recommended dosage
	Manic	depressive	Mixed	MS	Cbz	Lam	Li	Val	
Quetiapine	2	2	-	1	-	-	-	-	300–800 mg/d
Olanzapine	2	2	2	4	-	-	-	-	5–20 mg/d
Lithium	2	3	-	-	-	-	-	-	0.6–1.2 mEq/L
Lamotrigine	4	4	-	-	-	-	-	-	50–400 mg/d
Psychoeducation	-	-	--	3	-	-	-	-	
Aripiprazole	1	5	-	2	-	5	-	5	10–30 mg/d
RLAI	1	5	-	2	-	-	-	-	25–50 mg/biweekly
Paliperidone	2	5	-	-	-	-	-	-	3–12 mg/d
Valproate	4	3	-	-	-	-	-	-	45–100 mg/L
Carbamazepine	4	4	-	-	-	-	-	-	4–12 mg/L
Ziprasidone	-	-	-	4	-	-	-	-	80–160 mg/d
Fluoxetine	-	2	-	-	-	-	-	-	10–40 mg/d
CBT	-	-	-	2	-	-	-	-	
Phenytol	-	-	-	2	-	-	-	-	Mean studied 380 mg/d (blood levels 10 microgram/mL)
Paroxetine	-	-	-	3	-	-	-	-	20 mg/d
N-acetyl cysteine	-	-	-	4	-	-	-	-	2 g/d
Imipramine	5	5	-	-	-	-	5	-	
Memantine	-	-	-	5	-	-	-	-	
Oxcarbazepine	-	-	-	-	-	-	5	-	
Perphenazine	-	-	-	5	-	-	-	-	

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

Fifth step:

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

Not recommended:

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

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

Duration of Maintenance Treatment

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

The only medical reasons for stopping maintenance treatment are poor tolerability, safety reasons, and continuous non-adherence. Also in some patients in whom medication does little or no difference, especially during the advanced stages of the disorder, a more palliative type rather than an aggressive

maintenance treatment might be preferable. This is a very sensitive issue and it is open to debate.

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

Special Cases and Populations**Agitation**

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

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

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

Combination of an antipsychotic with

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

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

1st step	<ul style="list-style-type: none"> • Start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine, or risperidone (including RLAI) monotherapy • Consider CBT or psychoeducation as add-on to medication. Never consider CBT or psychoeducation as monotherapy
2nd step	<ul style="list-style-type: none"> • Take predominant polarity (if present) into consideration • Add fluoxetine or lithium on the first-step option • Lithium plus carbamazepine • Quetiapine plus lithium or valproate • Olanzapine or aripiprazole plus a mood stabilizer
3rd step	Add RLAI, valproate, carbamazepine, lamotrigine, or N-acetylcysteine on second-step treatment
4th step	Take into consideration the predominant polarity and add an agent with proven efficacy against the acute phase no matter whether it has proven maintenance efficacy. Consider adding venlafaxine or haloperidol
5th step	Consider any combinations from steps 1–4 that have not been tried Consider maintenance ECT Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
Not recommended	Adding memantine or perphenazine on a mood stabilizer, aripiprazole plus lamotrigine or valproate, lamotrigine plus valproate, lithium plus lamotrigine, imipramine, or oxcarbazepine.

Abbreviations: ECT, electroconvulsive therapy; RLAI, risperidone long acting injectable.

Combinations of injectables with oral medication could also be an option depending on availability. In principle benzodiazepines should not be used as monotherapy beyond the acute emergency room setting in BD patients.

Pregnancy, Breast-Feeding, and the Use of Oral Contraceptives

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

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

If a decision in favor of medication treatment has been made, at least some patients might require higher doses of medication because of physiological changes related to pregnancy. Decrease in dosage might be advisable during the last few weeks before delivery (Altshuler and Hendrick, 1996). The agents with a known teratogenic effect are lithium, valproate, carbamazepine, and lamotrigine in doses >200 mg/d. Valproate and carbamazepine should be avoided in any case; continuation of lithium treatment might be justified in selected patients with their informed consent as the risk of heart malformations has been overestimated in the past (Burt and Rasgon, 2004;

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

Management of Somatic Problems in BD Patients

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

Increase in appetite, weight gain, and obesity are common problems in BD patients and are associated both with the

Table 9. Comparison of the CINP Guidelines to Other Previously Developed Guidelines for Maintenance Phase

	CINP 2017	WFSBP 2013 ^a	CANMAT and ISBD 2013	NICE 2014 ^b	BAP 2016 ^b
Aripiprazole	1	1	1	-	3
Lithium	1	1	1	1	1
Olanzapine	1	2	1	1	2
Paliperidone	1	3	2	-	3
Quetiapine	1	1	1	1	2
Risperidone	1	2	-	-	3
RLAI	1	-	1	-	2
OFC	2	-	2	-	-
Carbamazepine	2	4	2	-	2
Valproate	2	3	1	1	2
Lamotrigine	3	1	1	-	2
Haloperidol	4	-	-	-	3
Venlafaxine	4	-	-	-	-
ECT	5	4	3	-	-
Ziprasidone	5	3	-	-	3
Continue most recent episode treatment	NR	-	-	1	-
Antidepressants	-	3	NR	-	4
Asenapine	-	4	3	-	3
Gabapentin	-	4	NR	NR	-
Topiramate	-	4	NR	-	-

Abbreviations: ECT, electroconvulsive therapy; NR, not recommended; OFC, olanzapine-fluoxetine combination; RLAI, risperidone long-acting injectable.

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

^a WFSBP: Recommendation grades and subsequent positioning could be either based on efficacy in the prevention of mania, depression or any episode. Thus, numbers do not reflect the sequence of treatment in an individual patient.

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

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

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

Discussion

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

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

Although it is expected that, in principle, the development of algorithms obeys the rules of EBM and is based primarily on research data from studies conducted in a rigorous way, often expert opinion or clinical consensus supersede the evidence. In the last few years, the consumer opinion as well as economic issues have had increasing strength and importance and may play a significant role in the shaping of steps. The standard

approach in the development of algorithms as this has been shaped in the last 20 years is to utilize EBM standards for the earlier steps; however, as algorithms move from earlier to later steps, the evidence becomes more and more insufficient, and in most cases expert opinion or clinical consensus gradually take over. Socioeconomic forces from patient advocates, the industry, and the economic interests of the government and insurance companies exert pressure already from the first step and up to the end of the procedure or interventions.

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

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

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

It is evident that there are many issues that need further study, data are sparse and insufficient, and many questions remain unanswered. The most important and still unmet need is to be able to merge all the guidelines that concern different phases of the illness into a single one and in this way consider BD as a single unified disorder, which is the real world fact. However, to date the research data do not permit such a unified approach. It is also important to note that in spite of the publication of various treatment guidelines, clinicians do not seem to widely adopt any of them. Their impact on clinical practice

is quite limited even in the US. After the publication of the first [APA 1994](#) guidelines, only about 16% of manic patients without psychotic features, 38% with mania with psychotic features, 31% of bipolar depressed with psychotic features, and 17% of bipolar depressed without psychotic features were reported to be treated according to treatment guidelines ([Lim et al., 2001](#)).

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

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

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

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Statement of Interest

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