

REVIEW

The CINP Guidelines on the Definition and Evidence-Based Interventions for Treatment-Resistant Bipolar Disorder

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Abstract

Background: Resistant bipolar disorder is a major mental health problem related to significant disability and overall cost. The aim of the current study was to perform a systematic review of the literature concerning (1) the definition of treatment resistance in bipolar disorder, (2) its clinical and (3) neurobiological correlates, and (4) the evidence-based treatment options for treatment-resistant bipolar disorder and for eventually developing guidelines for the treatment of this condition

Materials and Methods: The PRISMA method was used to identify all published papers relevant to the definition of treatment resistance in bipolar disorder and the associated evidence-based treatment options. The MEDLINE was searched to April 22, 2018.

Results: Criteria were developed for the identification of resistance in bipolar disorder concerning all phases. The search of the literature identified all published studies concerning treatment options. The data were classified according to strength, and separate guidelines regarding resistant acute mania, acute bipolar depression, and the maintenance phase were developed.

Discussion: The definition of resistance in bipolar disorder is by itself difficult due to the complexity of the clinical picture, course, and treatment options. The current guidelines are the first, to our knowledge, developed specifically for the treatment of resistant bipolar disorder patients, and they also include an operationalized definition of treatment resistance. They were based on a thorough and deep search of the literature and utilize as much as possible an evidence-based approach.

Keywords: treatment resistant, refractoriness, anticonvulsants, antidepressants, antipsychotics, bipolar disorder, evidence-based guidelines, lithium, mania, mood stabilizers, treatment

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Introduction

Bipolar disorder (BD) has been described since the times of Hippocrates and Areteus, but recently the subtypes BD-I and BD-II were proposed with a combined prevalence rate of up to 2.4% (Merikangas et al., 2011). The treatment of BD is probably the most challenging of all mental disorders with the unique characteristic that each phase needs a different treatment approach (Vieta and Goikolea, 2005).

Such complex mental disorders are those that are expected to benefit more by the development of treatment guidelines, which during the last few decades are becoming an ever more important part of medical reality. This is especially since the translation of research findings to everyday clinical practice is becoming increasingly difficult with the accumulation of complex and often conflicting research findings, which are thereafter also included in meta-analysis. Guidelines aim to assist clinicians but also policymakers to arrive at decisions concerning the treatment and care of patients. They set the standard of care and training for health professionals, and they identify priority areas for further research since they are based primarily on the available evidence, but also, in areas where evidence is not available, on expert opinion.

The literature suggests that depression rather than mania is the most challenging phase (Manning, 2005). If subsyndromal, the presence of residual symptoms impose a greater risk of relapse (Keller et al., 1992), greater disability, and poorer overall outcome (Tohen et al., 1990a, 1990b, 2006). Therefore, full remission and recovery should be the ultimate treatment goal. A significant proportion of patients, however, do not fully respond to treatment, and their long-term course is characterized by frequent relapses and residual symptoms, causing significant disability and functional impairment (Esan et al., 2017).

To fulfil this need for expert translation of research findings into clinical practice and for the benefit of patients, the International College of Neuropsychopharmacology (CINP) launched an effort to critically appraise the literature and provide guidance to clinicians in the form of a treatment algorithm and guidelines as precise as the data allow. It is hoped that they will help the clinician to follow the state-of-the-art evidence, thus enabling their clinical practice to be based on informed decision-making process. They have been commissioned by the CINP, and the working group consisted of experts with extensive research and clinical experience in the field of BD. There was no funding from any source for the development of the guidelines and the activities of the working group.

All the members of the working group were psychiatrists who are in active clinical practice and were selected according to their expertise with the aim to cover a multitude of different cultures. All of them were involved in research and other academic activities, and therefore it is possible that through such activities some contributors have received income related to medicines discussed in this guideline. All conflicts of interest are mentioned at the end of this paper, which is the introductory paper to the CINP BD guidelines. It should also be noted that some drugs recommended in the guideline may not be available in all countries, and labeling and dosing might vary.

This project has already developed treatment algorithms and guidelines for BD (Fountoulakis et al., 2017a, 2017b, 2017c, 2017d), and the next step would be to search for data in the area of BD resistant to treatment.

Aim of the Current Study

The aim of the current study was to perform a PRISMA systematic review of the literature concerning (1) the definition of treatment resistance in BD, (2) its clinical and (3) neurobiological correlates, and (4) the evidence-based treatment options for treatment-resistant BD.

Materials and Methods

The PRISMA method (Hopewell et al., 2008; Liberati et al., 2009; Moher et al., 2009) was followed in the search of the literature. We searched MEDLINE to April 22, 2018 with the combination of keywords “refractory” or “refractoriness” or “resistant” with “mania,” “manic,” “bipolar,” “manic-depressive,” or “manic-depression.” The PRISMA flowchart is shown in Figure 1.

The following inclusion criteria were utilized:

1. Papers in English language
2. Papers reporting specifically on BD, not on affective disorders in general. If the paper concerned affective disorders in general then there should be a specific elaboration on BD.
3. Concerning the definition of treatment resistance in BD: any paper that included a description or any kind of definition.
4. Papers considering resistant bipolar depression on the basis of failure of antidepressant treatment were not included. An exception was made for those specific antidepressants with a proven efficacy in the treatment of BD according to the CINP Bipolar Disorder Treatment Guidelines.
5. For clinical and neurobiological correlates we considered only papers with original data.
6. Concerning treatment options, all papers with original data, systematic reviews, and meta-analyses as well as post-hoc analyses were included.
7. Case reports and case series (including retrospective chart reviews) were not included (either referenced as such or according to the author's judgement).

Relevant review papers were scanned to locate additional studies (Poon et al., 2012; Hui Poon et al., 2015; Fountoulakis et al., 2017a; Grunze et al., 2018). The data concerning the treatment of resistant BD were ranked according to the method previously developed by the authors (Fountoulakis et al., 2017d) and shown in Table 1.

Results

Definitions of Treatment Resistance in BD (n = 37)

There are several approaches to define “response,” “remission,” “recovery,” “relapse,” and “recurrence” in mental disorders. Although these definitions have been used in observational studies (Tohen et al., 1990a, 1990b, 2003a, 2003b), a common starting point is that these definitions apply to patients who received treatment with an adequate dosage of an effective treatment modality for a sufficient duration of time. Patients unable to tolerate such an adequate therapeutic trial for any reason as well as noncompliant patients are usually considered as “pseudorefractory” (Table 2).

Some authors suggest that the basis is an inadequate response to a therapeutic trial of lithium or an inability to tolerate lithium's side effects (Barton and Gitlin, 1987; Aronson

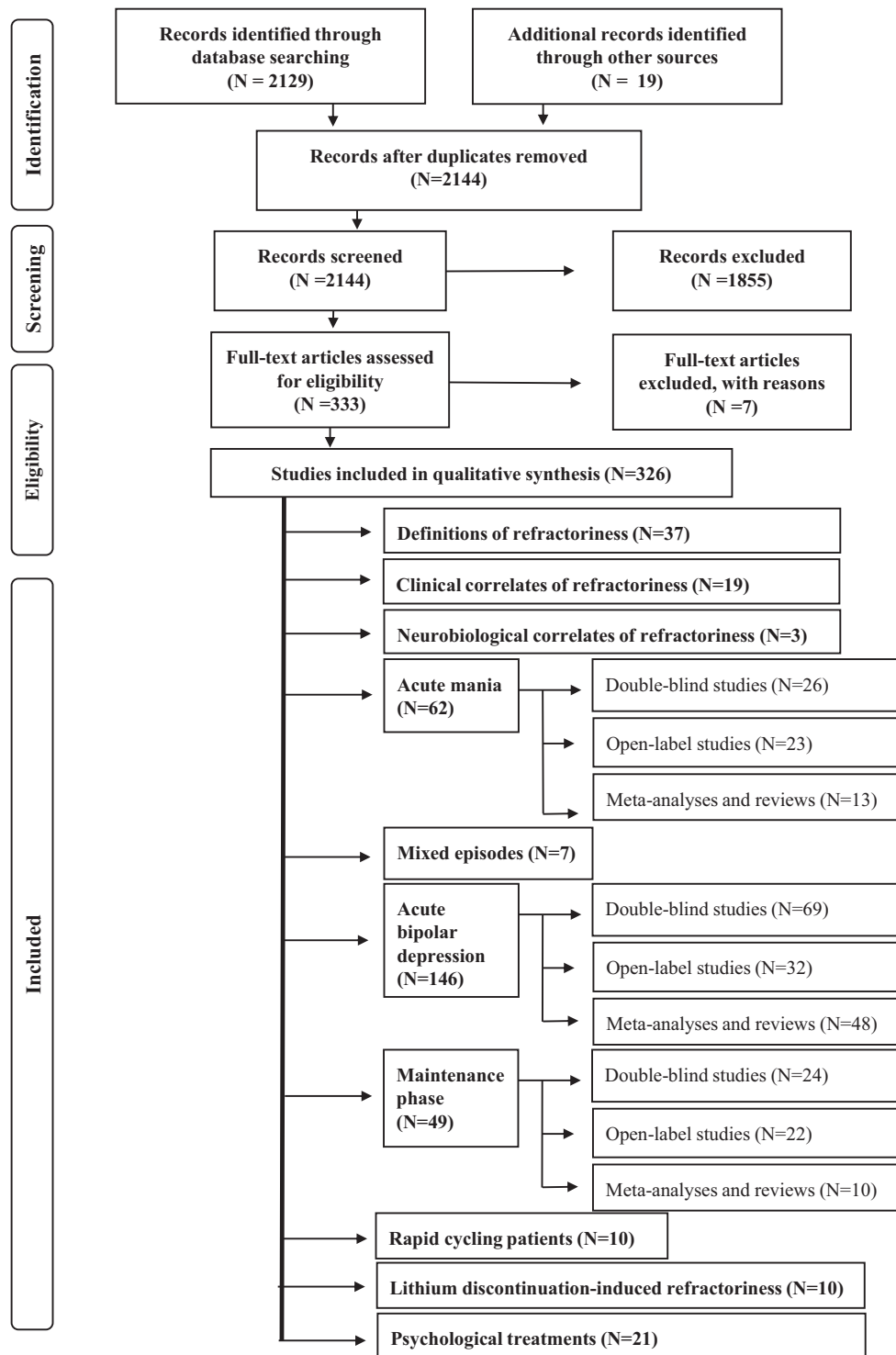


Figure 1. The PRISMA flowchart.

et al., 1989; Kramlinger and Post, 1989; Bauer, 1990; Pope, 1991; Schaff et al., 1993; McElroy et al., 1998; Altshuler et al., 1999; Calabrese et al., 1999; Green et al., 2000). Others consider a different definition on the basis of nonresponse to carbamazepine (Kramlinger and Post, 1989; Bauer, 1990; Schaff et al., 1993) or valproate (Calabrese et al., 1999), and their definition of failure also included intolerance. A more restrictive definition of treatment resistance demands failure to respond to at least

2 agents (McElroy et al., 1991; Kimmel et al., 1994; Calabrese et al., 1996), while other authors defined wider degrees of treatment nonresponse (tertiary resistance) (Vieta et al., 1998; Ciapparelli et al., 2000; Green et al., 2000; Suppes et al., 2003; Sajatovic et al., 2006).

The first comprehensive attempt defined treatment-resistant mania as mania without remission despite adequate therapy with at least 2 antimanic agents (lithium, antipsychotic,

Table 1. Summary of the method for grading data and recommendation on the basis of both efficacy and safety/tolerability

Grading on basis of efficacy	
Level 1	Good research-based evidence, supported by at least 2 placebo controlled studies of sufficient magnitude and good quality. In case of the presence of negative RCTs, positive RCTs should outnumber negative ones
Level 2	Fair research-based evidence, from 1 randomized, double-blind placebo controlled trial Also in case 1 or more trials exist, however, they fail to fulfil all the criteria above (e.g., very small sample size or no placebo control) as well as in case of positive meta-analysis alone
Level 3	Some evidence from comparative studies without placebo arm or from post-hoc analyses
Level 4	Inconclusive data or poor-quality RCTs
Level 5	Negative data
Grading on the basis of safety and tolerability	
Level 1	Very good tolerability, few side effects that are not enduring, do not cause significant distress, and are not life-threatening and do not compromise the overall somatic health of patient
Level 2	Moderate tolerability, many side effects that could be enduring, and cause significant distress but are not life-threatening, although they could compromise the overall somatic health of the patient Agents with very good overall tolerability but with rare life-threatening adverse events, could be classified here only if the lethality risk can be essentially considered to be negligible with application of procedures and protocols (e.g., laboratory testing, titration schedules, etc.)
Level 3	Poor tolerability, many side effects that are enduring, cause significant distress, compromise the overall somatic health of patient, or are life-threatening Agents with moderate overall tolerability and rare, life-threatening adverse events should be classified here even in case the lethality risk can be essentially considered to be negligible with the application of procedures and protocols (e.g., laboratory testing, titration schedules, etc.)
Recommendations for treatment (combination of efficacy and safety/tolerability)	
Level 1	Level 1 or 2 for efficacy and 1 for safety/tolerability
Level 2	Level 1 or 2 for efficacy and 2 for safety/tolerability
Level 3	Level 3 for efficacy and 1 or 2 for safety/tolerability
Level 4	Level 4 for efficacy or 3 for safety/tolerability
Level 5	Level 5 for efficacy (not recommended)

Abbreviation: RCT, randomized controlled trial.

Table 2. Issues to be addressed in order to label a patient as "resistant"

1. Correct diagnosis
2. Disorder not secondary to an organic disorder
3. Poor response to treatment not due to somatic or mental comorbidity
4. Poor response to treatment not due to a somatic condition that might not constitute a disorder by itself (e.g., genetic factors, smoking, alcohol use, gender, race, etc.)
5. Failure of therapy not due to nontolerability
6. Patient complies with recommended treatment and poor response not a consequence of lack of adherence

anticonvulsant, etc.) for at least 6 weeks on each agent in the absence of antidepressants or other mood-elevating agents (Sachs, 1996). For resistant bipolar depression, an extrapolation of the definition for unipolar to bipolar depression would be appropriate, which means no remission despite 2 adequate trials of standard antidepressant agents (6 weeks each), with or without augmentation strategies (Sachs, 1996). However, this definition is currently not supported by the data in a fundamental way since antidepressants are not considered to be efficacious in the treatment of bipolar depression, although they are among the most commonly used agents (Baek et al., 2014; Bjorklund et al., 2016; Kessing et al., 2016). Treatment-resistant mood cycling (resistance in the long term) was defined as continued cycling despite maximal tolerated lithium in combination with valproate or carbamazepine for a period of 3 times the average cycle length, or 6 months, whichever is longer, in the absence of antidepressants or other cycle-promoting agents (Sachs, 1996).

This definition is not in accord with the data concerning the efficacious treatment of these conditions (Sachs, 1996).

The only attempt to grade treatment resistance of a stratified response/refractoriness graduation suggested the clustering of resistant cases into 3 groups: (1) primary resistance, that is, inadequate response to a therapeutic trial of lithium (>0.7 mmol/L), valproate, or carbamazepine; (2) secondary resistance, that is, inadequate response to sequential therapeutic trials of 2 mood stabilizers or an antipsychotic and a mood stabilizer; and (3) tertiary resistance, that is, inadequate response to sequential therapeutic trials of 3 agents: any antipsychotics, 2 mood stabilizers and an antipsychotic, 2 antipsychotics and a mood stabilizer, or 3 mood stabilizers (Keck and McElroy, 2001).

Another definition was based on the assumption that lithium at serum levels of 0.8 mmol/L or greater for at least 6 weeks should be the first line of treatment for bipolar depression if a patient is not already on a mood stabilizer and if lithium fails, the addition of lamotrigine, carbamazepine, valproate, antidepressants (not tricyclic antidepressants), or an atypical antipsychotic such as olanzapine might be a reasonable second-line options (Yatham et al., 2003a; Tohen et al., 2004; Taylor et al., 2014). This is in partial agreement with the data currently available. In the STEP-BD study, treatment-resistant depression was defined as no response to treatment after 12 weeks of treatment or a well-documented failure to respond to at least 2 trials of antidepressants or an antidepressant and a mood stabilizer (Nierenberg et al., 2006).

A more sophisticated 4-level system for the staging of resistance from resistance to a single agent to resistant to 3 agents plus neurostimulation has been proposed, but its clinical relevance is unclear since it puts the emphasis on the number of

Table 3. The CINP definitions of response, remission, recovery, and resistance for BD

	Phase	Scale scores	Treatment duration according to CINP guidelines
Response	Acute mania	<25%, 25–49%, 50–74%, 75–100% reduction in YMRS or MRS scores No significant increase in MADRS or HDRS scores and MADRS and HDRS scores stay below 6	8–10 weeks
	Acute Bipolar depression	<25%, 25–49%, 50–74%, 75–100% reduction in MADRS or HDRS scores No significant increase in YMRS or MRS scores and YMRS and MRS scores stay below 5	10–12 weeks
Remission	Maintenance	Significant change in the frequency of episodes	1 year
	Acute mania	YMRS and MRS scores stay below 5 No significant increase in MADRS or HDRS scores and MADRS and HDRS scores stay below 6	8 weeks
	Acute Bipolar depression	MADRS and HDRS scores stay below 6 No significant increase in YMRS or MRS scores and YMRS and MRS scores stay below 5	8 weeks
	Maintenance	Very rare new episodes, and MADRS/HDRS scores <6 and YMRS/MRS scores <7 between episodes	2–3 years?
Recovery	Acute mania	YMRS and MRS scores stay below 5 No significant increase in MADRS or HDRS scores and MADRS and HDRS scores stay below 6	8 weeks
	Acute Bipolar depression	MADRS and HDRS scores stay below 6 No significant increase in YMRS or MRS scores and YMRS and MRS scores stay below 5	8 weeks
	Maintenance	No new mood episodes and MADRS/HDRS scores <6 and YMRS/MRS scores <7 between episodes	3–5 years
Resistance	Acute mania	No significant reduction in YMRS or MRS scores, or significant increase in MADRS or HDRS scores or MADRS and HDRS scores exceed 6	8–10 weeks
	Acute Bipolar depression	No significant reduction in in MADRS or HDRS scores or significant increase in YMRS or MRS scores or YMRS and MRS scores exceed 5	10–12 weeks
	Maintenance	No change in the frequency of episodes, or MADRS/HDRS scores >6 or YMRS/MRS scores >7 between episodes	1 year

Abbreviations: BD, bipolar disorder; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MRS, Mania Rating Scale; YMRS, Young Mania Rating Scale.

treatment options used but ignores other important details, including duration. It includes the following stages: Stage I: failed monotherapy trial of lithium, anticonvulsant, or atypical antipsychotic of adequate dose and for adequate duration (FDA-approved treatment based on mood episode); Stage II: Stage I plus failed trial of combination of 2 medications, lithium, or anticonvulsant and atypical antipsychotic; Stage III: Stage II plus failed trial of several different evidence-based adjunctive pharmacological compounds; and Stage IV: Stage III plus neurostimulation (Gajwani, 2009). Resistant BD-I or BD-II depression was defined in a stepped way as failure to reach remission with adequately dosed lithium (0.8 mEq/L) or to other adequate ongoing mood-stabilizing treatment, plus lamotrigine (50–200 mg/d) or with full dose (600 mg/d or more) of quetiapine as monotherapy (Pacchiarotti et al., 2009).

To date, the International Society for Bipolar Disorders nomenclature and definitions are the most comprehensive and up to date and utilize both a syndromal (on the basis of DSM criteria) and symptomatic (on the basis of rating scales) approach. These definitions recommend the use of incremental steps for symptom improvement (<25%, 25–49%, 50–74%, 75–100%) to define response. They propose multiple cut-off points for the definition of remission, with the most stringent being <6 for Hamilton Depression Rating Scale (HDRS)-17 and Montgomery-Asberg Depression Rating Scale (MADRS) and <5 for the Young Mania Rating Scale (YMRS) in the case of depression and mania, respectively. These stringent criteria allow for inclusion of

subsyndromal states that are very important for failing functional recovery in BD (7–14 in HDRS or MADRS and 8–14 in YMRS). In essence, the definition of subsyndromal states is utilized also for the definition of Treatment Emergent Affective Switch. Non-criterion symptoms that are commonly associated with BD (usually during the depressive phase) such as anxiety, panic attacks, irritability, hopelessness, avoidance, or cognitive dysfunction should not be included in the definitions. These authors defined “recovery” as sustained remission after at least 8 weeks (Tohen et al., 2009), which is similar to the approach of the AMA (American Psychiatric Association, 2000). A modified version was proposed several years later (Fountoulakis, 2012).

Another proposal was that treatment-resistant BD should be conceptualized as failure to respond to at least 2 trials of dissimilar medication with presumably adequate doses and durations within a specific phase of bipolar illness (manic, depressive, or mixed) or for “breakthrough”; symptoms. These symptoms should emerge despite previous apparently effective maintenance treatment. There do not refer to patients who are intolerant (In table 4, the grading of treatment options according to safety issues is shown) of a treatment regimen and because of this they refrain from treatment and also to the extent possible, they do not refer to those patients who are not adherent to recommended treatment (Poon et al., 2012).

The most recent attempt was to define treatment resistance in terms of failure to reach sustained symptomatic remission for 8 consecutive weeks after 2 different treatment trials, at adequate

Table 4. Grading of treatment options according to safety issues following system shown in [Table 1](#)

Agent/modality	Grade	Comments
Agomelatine	2	Elevation of liver enzymes
Allopurinol	2	Swelling of mouth and lips, severe skin rashes, infections, eye irritation, hepatitis, appetite and weight loss, and painful or bloody urination
Amitriptyline	2	Many adverse effects, some risk for cardiovascular events
Aripiprazole	1	
Armodafinil/modafinil	2	Stimulant, risk for abuse
Asenapine	1	
Bupropion	1	
Carbamazepine	2	Hepatic enzymes induction, many adverse effects
Cariprazine	1	
Celecoxib	1	
Choline		Food supplement
Chromium		Food supplement
Clozapine	3	Potentially lethal agranulocytosis, metabolic syndrome
DBS	1	
Diltiazem	1	
Donepezil	1	
ECT	2	Not preferred by patients, mild cognitive problems
Folic acid		Food supplement
Gabapentin	1	
Galantamine		
Haloperidol	2	Extra-pyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, switch risk
Imipramine	2	Cardiac side effects, many adverse effects, switch risk
Inositol		
Ketamine	3	Transient dissociation and elevation of blood pressure
Lamotrigine	2	Good overall tolerability but potentially lethal skin reaction that can be avoided by slow titration
Levetiracetam	3	Induction of suicidality
Light therapy		
Lisdexamfetamine	3	High risk for abuse and dependence
Lithium	2	Many adverse effects, weight gain, toxicity
Lovastatin		
L-sulpiride	1	
l-thyroxine	2	Mild cardiovascular, skin and bone adverse effects
Lurasidone	1	
Magnesium		Food supplement
Memantine	1	
Modafinil	2	Stimulant, risk for abuse
n-3 fatty acids		Food supplement
N-acetyl cysteine	1	
Nimodipine	1	
Olanzapine	2	Metabolic syndrome
Omega 3 fatty acids	1	
Oxcarbazepine	1	
Paliperidone	1	
Paroxetine	1	Weight gain
Phenytoin	2	Many adverse effects
Pioglitazone	2	Not recommended in patients with diabetes mellitus type I and in liver disease Absolute contraindication in heart failure patients
Pramipexole	2	Adverse effects include the induction of compulsive behaviors and psychotic symptoms
Pregabalin	2	Risk of abuse, weight gain
Pregnenolone	2	Not well studied
Primidone		
Quetiapine	1	Weight gain
Ramelteon	1	
Risperidone/RLAI	1	Increased prolactin, weight gain
S-adenosyl-L-methione	2	Some adverse effects; long-term effects unknown
Sleep deprivation	1	
TMS	1	
Topiramate	3	Induction of depression and suicidality
Tranlycypromine	2	Many adverse effects
Tryptophan		Food supplement
Valnoctamide	1	
Valproate	1	Cautious use in women of childbearing age
Venlafaxine	2	Switch risk
Verapamil	1	
Ziprasidone	2	QTc prolongation, patient ECG recommended when used in combination

Abbreviations: DBS, deep brain stimulation; ECG, electrocardiogram; ECT, electroconvulsive therapy; EPS, extrapyramidal signs; RLAI, risperidone long acting injection; TMS, transcranial magnetic stimulation.

Table 5. Levels of recommendation concerning adjunctive treatment for resistant acute mania and recommended dosages for medication options

Treatment modality to add	Grading		Dosage
	In terms of efficacy	In terms of recommendation	
Aripiprazole	2	1	Up to 30 mg/d
Asenapine	2	1	Up to 20 mg/d
Quetiapine	1	1	Up to 800 mg/d
Valnoctamide	2	1	1200 mg/d
Haloperidol	2	2	Up to 12 mg/d
Olanzapine	2	2	Up to 40 mg/d
Phenytoin	3	3	400 mg/d
Allopurinol	4	4	600 mg/d
Carbamazepine	4	4	Up to 1200 mg/d
Clozapine	4	4	Up to 550 mg/d
ECT	4	4	–
Folic acid	4	4	3 mg/d
Leviracetam	4	4	2000–3000 mg/d
l-Thyroxine	4	4	Until FT4 higher than upper limit
Oxcarbazepine	4	4	Up to 1200 mg/d
Pregabalin	4	4	75–150 mg/d
Donepezil	NR	NR	
Gabapentin	NR	NR	
Lamotrigine	NR	NR	
Lovastatin	NR	NR	
Nifedipine	NR	NR	
Paliperidone	NR	NR	
Ramelteon	NR	NR	
Risperidone	NR	NR	
Topiramate	NR	NR	
Verapamil	NR	NR	
Ziprasidone	NR	NR	

Abbreviations: ECT, electroconvulsive therapy; FT4, free-T4; NR, not recommended.

therapeutic doses, with at least 2 recommended monotherapy treatments or at least 1 monotherapy treatment and another combination treatment. It also introduced the term “multi-treatment-resistant BD” after failure of additional trials with at least 1 trial with an antidepressant, a psychological treatment, and a course of electroconvulsive therapy (ECT) (Hidalgo-Mazzei et al., 2019).

Considering the above, the International Society for Bipolar Disorders definition is a good starting point, but the authors suggest that additional considerations are necessary. The key points the therapist needs to consider before suggesting a patient might be treatment-resistant are summarized in Table 2. The proposed CINP definitions of response, remission, recovery, and resistance for BD are shown in Table 3. According to the authors of the current paper, a key issue is that nonresponse should be considered only after treatment according to the best evidence available. At this time, the options recommended by the CINP guidelines for BD (Fountoulakis et al., 2017a, 2017b, 2017c, 2017d) and the CANMAT Guidelines (Yatham et al., 2018) provide the most up-to-date and comprehensive overview of treatment options.

Clinical Correlates of Treatment Resistance (n = 19)

A number of studies suggest that some kind of progression occurs over the long-term course of the illness, and this, in turn, contributes to treatment resistance (Berk et al., 2011b; Fries et al., 2012) with an association to number of mood episodes (Swann et al., 1999; Obrocea et al., 2002; Scott et al., 2006; Reinares et al., 2010; Berk et al., 2011a; da Costa et al., 2016) and hospitalizations (Nunez et al., 2018). This progression is not uniform (Swann et al., 1999; Scott et al., 2006).

Algorithm for the treatment of resistant acute mania

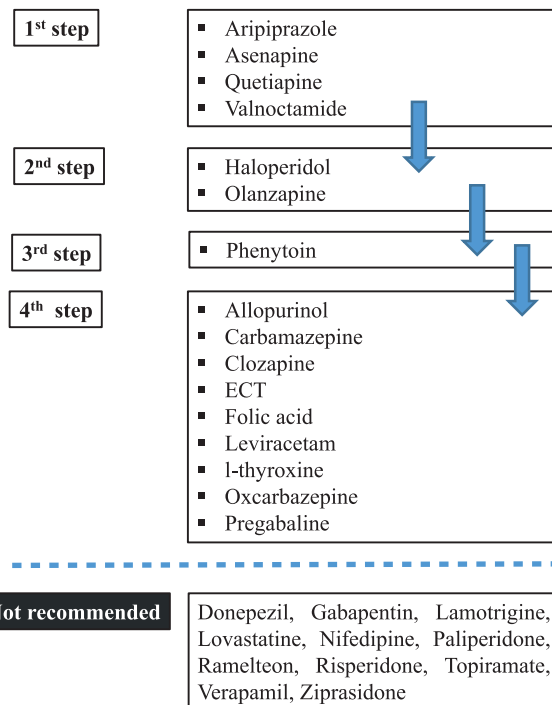


Figure 2. Algorithm for the treatment of resistant acute mania.

Clinical characteristics of treatment-resistant patients are the frequent presence of rapid cycling (37%), other forms of cycling (32%), chronic depression (26%), mixed states (6%) (Cole et al., 1993), and anxiety (Wooderson et al., 2014; Parker and Graham, 2017; Nunez et al., 2018). Other features include melancholia, comorbidity with social phobia, current suicidal risk and severe intensity of current depressive episode (Mendlewicz et al., 2010), cognitive difficulties, and sleep disturbance (Kessler et al., 2013; Wooderson et al., 2014). However, some studies failed to identify such clinical markers of resistance (Vo and Dunner, 2003; Amsterdam et al., 2016a; Sandu et al., 2017).

Other features that might distinguish between resistant and nonresistant BD include being female, older, older age at illness onset, a higher incidences of family depression, lower likelihood of being gainfully employed, a higher number of lifetime stressors, medical conditions, a different personality and temperament profile, and more regular use of benzodiazepines (Parker and Graham, 2017). It is believed that substance use and unhealthy lifestyle might contribute to treatment resistance, although data are lacking (Schaffer et al., 2017).

It is important that those clinical variables with supposed value in predicting response or resistance to lithium treatment and including the presence of elation, grandiosity, paranoia, irritability, delusions, and hallucinations did not predict treatment response to lithium (Miller et al., 1991).

Overall, the data are of low quality and it is unknown whether the clinical picture is useful in predicting treatment response.

Neurobiological Correlates of Treatment Resistance (n=3)

Only 3 studies reported on possible neurobiological correlations of treatment resistance and identified family history of affective disorder (Cole et al., 1993; Parker and Graham, 2017) and electroencephalographic abnormalities (Cole et al., 1993) as risk factors, while neuroinflammation mechanisms seem to promote the progression towards treatment resistance (Bauer et al., 2017).

Treatment of Resistant BD

Resistant Acute Mania (n=62)

Double Blind Studies in the Treatment of Resistant Acute Mania (n=26)
Valproate monotherapy (serum levels 50 and 100 mg/L), in 36 lithium-resistant manic patients (including patients who could not tolerate lithium), produced a 54% decrease in scores on the YMRS in the valproate arm vs a 5% decrease in the placebo arm (Pope et al., 1991).

In 1 underpowered study, 13 BD-I and 15 BD-II patients received 900–4800 mg/d gabapentin, lamotrigine, or placebo in a crossover design for 6 weeks, and at endpoint there was no difference between the 3 arms (Frye et al., 2000). In another study, 114 BD-I outpatients resistant to lithium, valproate, or their combination were randomized to adjunctive gabapentin (600–3600 mg/d) or placebo for up to 10 weeks, with placebo performing better (Pande et al., 2000).

There are positive data on add-on phenytoin in patients resistant to haloperidol treatment (Mishory et al., 2000) and of add-on 600–1200 mg/d carbamazepine or oxcarbazepine in patients resistant to lithium (Jurueña et al., 2009). The second study was of poor quality. A study adding lovastatin to lithium was negative (Ghanizadeh et al., 2014).

In patients resistant to lithium, valproate, or carbamazepine, it is beneficial to add olanzapine, quetiapine, aripiprazole, or asenapine (Tohen et al., 2002; Sachs et al., 2004; Yatham et al., 2007b; Vieta et al., 2008; Szegeedi et al., 2012) but not ziprasidone, topiramate, or paliperidone (Roy Chengappa et al., 2006;

Berwaerts et al., 2011; Sachs et al., 2012a, 2012b). For patients resistant to both lithium and carbamazepine monotherapy, their combination was reported to be beneficial (at dosages corresponding to lithium levels 0.7–1.2 mmol/L and up to 1600 mg/d of carbamazepine) (Kramlinger and Post, 1989).

One study provided inconclusive data for risperidone (Yatham et al., 2003b) as the results were likely confounded by the effects of carbamazepine on serum levels of risperidone.

There was only 1 sham-controlled trial of ECT as adjunctive treatment to chlorpromazine (600 mg/d) in 30 acutely manic patients and supported the efficacy of ECT with a faster rate of improvement (Sikdar et al., 1994).

One placebo-controlled 4-week random controlled trial in 180 acutely manic patients supported the efficacy and safety of allopurinol (600 mg/d) and dipyrindamole (200 mg/d) as adjunctive to lithium (Machado-Vieira et al., 2008). However, a previous study was negative in patients resistant to lithium, valproic acid, carbamazepine, or atypical antipsychotic medications (Fan et al., 2012). Findings for valproate are inconclusive (Fan et al., 2012; Jahangard et al., 2014).

Folic acid was reported useful as an adjunct to valproate; however, the study is problematic concerning its methods of analysis and the reporting of results (Behzadi et al., 2009). Valnoctamide (the valproic acid precursor) plus risperidone combination was more effective than risperidone plus placebo (Bersudsky et al., 2010), while a pilot 8-week study in 21 acutely manic outpatients on the usefulness of adjunctive ramelteon states failed (McElroy et al., 2011) and another 2 on donepezil were negative (Eden Evins et al., 2006; Chen et al., 2013).

Open Label Studies in the Treatment of Resistant Acute Mania (n=23)
Treating resistant manic patients with olanzapine 5–40 mg/d monotherapy resulted in remission in three-quarters of patients (McElroy et al., 1998; Chen et al., 2011), and several small studies support the efficacy of up to 550 mg/d clozapine with three-quarters of the patients responding after prolonged treatment (Kimmel et al., 1994; Calabrese et al., 1996; Ciapparelli et al., 2000; Green et al., 2000). The combination of aripiprazole with clozapine in BD patients that failed to respond to other atypical antipsychotics returned a positive result in psychotic manic patients (Benedetti et al., 2010). Results concerning risperidone are equivocal (Sajatovic et al., 1996; Vieta et al., 1998).

Adding gabapentin or pregabalin (600–3600 mg/d) resulted in response in three-quarters of resistant manic patients (McElroy et al., 1997; Altshuler et al., 1999; Schaffer et al., 2013). Only one-quarter of rapid cycling patients responded (Altshuler et al., 1999). Adding 100–300 mg/d topiramate resulted in a response rate of almost 60% (Chengappa et al., 1999; Vieta et al., 2002b) but titrating up to 1300 mg/d did not increase the response (Calabrese et al., 2001). Adding leviracetam (500–1000 mg/d) produced response or remission in one-half of patients (Post et al., 2005); data concerning verapamil (up to 240 mg/d) were negative (Barton and Gitlin, 1987) while for nifedipine 120 mg/d were unimpressive (De Beaurepaire, 1992). Some positive findings exist for diltiazem (Silverstone and Birkett, 2000). Adding l-thyroxine to lithium or carbamazepine resulted in a 50% response rate (Bauer and Whybrow, 1990).

Three-quarters of resistant manic patients respond to ECT (Perugi et al., 2017) with equal efficacy for unilateral vs bilateral ECT (Mukherjee et al., 1988), and bifrontal ECT was as efficacious as bitemporal ECT and better tolerated (Barekattain et al., 2008; Hiremani et al., 2008).

Meta-Analytic and Review Studies in the Treatment of Resistant Acute Mania (n=13)

Meta-analytic studies also suggest that combination treatment is superior to monotherapy at the cost of more frequent adverse events; however, these meta-analyses do not distinguish between add-on studies (which utilize patients resistant to monotherapy) and combination studies (which utilize general patient populations) (Scherk et al., 2007; Smith et al., 2007; Tarr et al., 2011; Ogawa et al., 2014). Due to the insufficient evidence base, earlier reviews provide only vague conclusions (Gitlin, 2001, 2006; Keck and McElroy, 2001). Overall, there is a striking paucity of research concerning resistant cases, and existing studies are small and insufficiently controlled and findings remain preliminary. ECT is generally considered as an option for resistant patients. In acute manic patients who are partial responders to lithium/valproate/carbamazepine, adding an antipsychotic is a reasonable choice. Encouraging results have been reported by adding aripiprazole, clozapine, and pregabalin in resistant mania (Hui Poon et al., 2015). The analysis of the data for the cholinesterase inhibitors galantamine and donepezil as well as the glutamate receptor antagonist memantine was negative (Veronese et al., 2016). One meta-analysis of combination studies confirmed the higher rate of adverse events compared with monotherapy (Galling et al., 2015). One review of open studies supported the usefulness of clozapine (Li et al., 2015).

There are a few randomized controlled trials of ECT in mania, and they consistently report clinically meaningful efficacy, with a majority of pharmacotherapy-resistant patients responding to ECT. Evidence for the use of other brain stimulation therapies in treating bipolar mood states is preliminary and limited (Loo et al., 2011; Versiani et al., 2011).

Conclusion Concerning the Treatment of Resistant Acute Mania

Controlled data suggest that in patients resistant (principally) to lithium, valproate, or carbamazepine, it is beneficial to add aripiprazole, asenapine, folic acid, quetiapine, or valnoctamide. The next choice should be adding haloperidol, olanzapine, or phenytoin on lithium, valproate, or carbamazepine. The data are inconclusive concerning allopurinol, carbamazepine, clozapine, ECT, leviracetam, l-thyroxine, oxcarbazepine, and pregabalin.

According to controlled data, the agents not recommended include donepezil, gabapentin, lamotrigine, lovastatin, paliperidone, ramelteon, risperidone, topiramate, and ziprasidone, while additionally, on the basis of open data, nifedipine and verapamil are also not recommended (Table 5; Figure 2).

Mixed Episodes (n=7)

Adding olanzapine or placebo to divalproex-resistant mixed patients for 6 weeks returned positive results both for the manic as well as for the depressive component (Houston et al., 2009).

One open study of adjunct gabapentin (300–2000 mg/d) reported an almost 50% response rate but this concerned exclusively the depressive component (Perugi et al., 1999).

There were no randomized trials of ECT in mixed episodes (Loo et al., 2011). The results of open trials concerning the usefulness of ECT suggest that approximately 40% to two-thirds of patients responded and 30% remitted, and the response concerned both the manic and the depressive components (Medda et al., 2010, 2015; Perugi et al., 2017). One study concerning repetitive transcranial stimulation (rTMS) reported a lower response rate (around 40%) and response restricted to the depressive component (Pallanti et al., 2014).

Treatment-Resistant BD (n=145)

Double Blind Studies in the Treatment of Resistant Acute BD (n=69)

In bipolar depressed patients who experience depression while under lithium treatment, it is appropriate to add lamotrigine (van der Loos et al., 2009, 2010, 2011), the D2 antagonist L-sulpiride (Bocchetta et al., 1993), pramipexole (Goldberg et al., 2004), or possibly oxcarbazepine (Jurueña et al., 2009) but not imipramine (Nemeroff et al., 2001). The data on adding paroxetine and amitriptyline are equivocal (Bocchetta et al., 1993; Bauer et al., 1999; Young et al., 2000; Pilhatsch et al., 2010; van der Loos et al., 2010). Imipramine and venlafaxine might pose the patients at an increased risk of switching without a superior benefit compared with other antidepressants (Nemeroff et al., 2001; Vieta et al., 2002a); however, 1 study suggests quite the opposite (Amsterdam et al., 2016b). One study suggested that the addition of lamotrigine to quetiapine treatment improved outcomes, but folic acid seems to nullify the effect of lamotrigine (Geddes et al., 2016).

In BD patients experiencing depression during treatment with lithium or valproate, ketamine or lurasidone could be added. Lurasidone also improves anxiety (Loebel et al., 2014) and ketamine improves suicidality. Response to a single ketamine infusion may appear within hours but does not last more than 3 to 4 days (Diazgranados et al., 2010; Zarate et al., 2012; Lally et al., 2014; Loebel et al., 2014; Xu et al., 2015). One study reported negative results (Xu et al., 2015). Besides reducing suicidality, ketamine has been reported to be efficacious especially against anhedonia (Lally et al., 2014) and fatigue (Saligan et al., 2016). Repeated administration of ketamine studies have not been carried in BD (Murrugh et al., 2013; Phillips et al., 2019). There is 1

Algorithm for the treatment of resistant acute bipolar depression

1st step

- Lithium plus lamotrigine
 - ECT
 - Light therapy
 - Modafinil
 - Pramipexole
 - TMS
- Add CBT or psychoeducation if possible to the above

2nd step

- Pioglitazone

3rd step

- Amitriptyline
- Bupropion
- Clozapine
- Diltiazem
- Gabapentin
- L-sulpiride
- N-acetyl cysteine
- Ketamine
- l-thyroxine
- Lurasidone
- Omega-3 fatty acids
- Oxcarbazepine
- Paroxetine
- Pramipexole
- Sleep deprivation
- Tranylcypromine
- Venlafaxine

Not recommended

- Agomelatine, aripiprazole, celecoxib, DBS, galantamine, imipramine, inositol, leviracetam, lisdexamfetamine, memantine, pregnenolone, S-adenosyl-L-methionine, topiramate, and ziprasidone

Figure 3. Algorithm for the treatment of resistant acute bipolar depression.

failed study with lurasidone as add-on to lithium or valproate (Suppes et al., 2013, 2016).

An underpowered placebo-controlled adjunctive study of aripiprazole to lithium and citalopram was negative (Quante et al., 2010).

For a depressed episode during treatment with mood stabilizers, it is not beneficial to add ziprasidone (Sachs et al., 2011; Patkar et al., 2015). Topiramate and levetiracetam should be avoided because of a risk of worsening depression and inducing suicidality (CIT0371). Imipramine and venlafaxine increased the risk of switching without superior benefits compared with other antidepressants (Sachs et al., 1994, 2011; Post et al., 2001, 2006; Shelton and Stahl, 2004; Schaffer et al., 2006; Altshuler et al., 2009; Saricicek et al., 2011).

The data are negative concerning the addition of memantine on lamotrigine (Anand et al., 2012) or valproate (Lee et al., 2014a, 2014b), ketamine on ECT (Abdallah et al., 2012), lisdexamfetamine to treatment as usual (TAU) (McElroy et al., 2015), and agomelatine to lithium or valproate (Yatham et al., 2016).

A study in 85 patients with adjunctive modafinil (mean dosage 177 mg/d) was positive without switching to mania or hypomania. Response and remission rates were higher in the modafinil group (44% and 39%) compared with the placebo group (23% and 18%) (Frye et al., 2007). However, modafinil could cause subclinical switches (Fountoulakis et al., 2008b). One published study for the treatment of acute BD-I depression with adjunct armodafinil (dosage 150 mg/d; n=128) to lithium, valproate, or olanzapine was positive (Calabrese et al., 2010, 2014). However, 2 other studies were negative (Ostacher, 2014; Ketter et al., 2015).

One small study on pioglitazone as add-on to lithium in bipolar patients without diabetes mellitus was positive (Zeinodini et al., 2015). A trial of celecoxib (400 mg/d) was negative in the treatment of depressive or mixed episodes (Nery et al., 2008). One study with add-on pregnenolone (titrated to 500 mg/d) was negative (Brown et al., 2014). While a very small report without an a priori defined primary outcome suggested that adding supraphysiologic doses of levothyroxine (L-T4) to a mood stabilizer improves the outcome (Bauer et al., 2016), a previous, more complete report on the same placebo-controlled dataset was negative (Stamm et al., 2014). That study reported positive findings in females but not in males. A small quasi-placebo-controlled study was positive concerning the addition of inositol (Chengappa et al., 2000).

A 24-week trial on the efficacy of N-acetyl cysteine (NAC, 1 g twice daily) adjunctive to usual medication in subsyndromal but treatment-resistant depressive symptoms was positive (Berk et al., 2008); however, a more recent study was negative (Berk et al., 2019a, 2019b). The data on omega-3 fatty acids are conflicting and inconclusive (Stoll et al., 1999; Frangou et al., 2006, 2007; Keck et al., 2006; Murphy et al., 2012). One negative study exists concerning S-adenosyl-L-methionine up to 1400 mg/d (Murphy et al., 2014).

ECT may be more effective than pharmacotherapy for treatment-resistant bipolar depression (Schoeyen et al., 2015) but TMS is poorly investigated in bipolar depression (Dell'Osso et al., 2009). Active deep TMS was superior to sham at end point ($P=.03$) but not at follow-up (Tavares et al., 2017). One study on transcranial direct current stimulation reported that the cumulative response rates were higher in the active vs sham groups (67.6% vs 30.4%; $P=.01$) but not remission rates (37.4% vs 19.1%; $P=.18$) (Sampaio-Junior et al., 2018).

Sleep deprivation and other noninvasive circadian-related interventions could be useful add-on treatments to accelerate

and sustain the antidepressant response (Wu et al., 2009). A study on bright light therapy in bipolar depression was negative (Dauphinais et al., 2012), whereas other controlled studies were positive (Sit et al., 2018; Yorguner Kupeli et al., 2018; Zhou et al., 2018).

Open Label Studies in Treatment of Resistant Acute Bipolar Depression (n=32)

One study reported a 31% response rate with add-on levetiracetam titrated to a target dose of 2000 mg/d (Post et al., 2005). Another study supported the adjunctive therapy with diltiazem (Silverstone and Birkett, 2000).

Adding bupropion to ongoing treatment after 4 weeks yielded a 60% response (Erfurth et al., 2002) while adding tranlycypromine in imipramine-resistant patients resulted in a 75% response (Thase et al., 1992).

Resistant depressive patients from the STEP-BD trial were randomly assigned to open-label adjunctive treatment with lamotrigine, inositol, or risperidone for up to 16 weeks without any significant between-group differences. However, the recovery rate with lamotrigine was 23.8% vs 17.4% with inositol and 4.6% with risperidone (Nierenberg et al., 2006). Another STEP-BD subgroup received adjunctive aripiprazole, but the response rate was as low as 27% (Ketter et al., 2006).

Adjunctive gabapentin for 12 weeks (mean dose 1725 mg/d) resulted in a 55% response (Wang et al., 2002) and for 8 weeks with mean dosage 1270 ± 561 mg in a 42% response rate (Perugi et al., 2002). A third very small trial (n=5) reported that all patients responded to adjunctive gabapentin (Altshuler et al., 1999).

Adding lamotrigine 75–100 mg/d resulted in an approximately 50–70% response (Kusumakar and Yatham, 1997; Nierenberg et al., 2006; Kagawa et al., 2014).

Adding levetiracetam up to 3000 mg/d resulted in 31% remission (Post et al., 2005). Approximately 23% of patients from the Stanley Foundation Bipolar Network long-term follow-up study responded after adding 8.7 mg/d of tiagabine (Suppes et al., 2002) and one-half of patients responded to topiramate (Vieta et al., 2002b). Two-thirds of patients responded to 0.95 mg/d pramipexole (Lattanzi et al., 2002).

There were 3 positive papers (2 on the same dataset) on the utilization of a single infusion of ketamine (0.5 mg/kg) over 40 min resulting in a 50% response (Rybakowski et al., 2013, 2017; Ionescu et al., 2015). One small study was positive for omega-3 fatty acids (Chiu et al., 2005).

More than one-half of patients and two-thirds of those with BD-I are reported to respond to ECT (Medda et al., 2009, 2010; Perugi et al., 2012, 2017; Schoeyen et al., 2015) while one-fourth manifest remission (Medda et al., 2010). One study, however, reported similar remission rates with an algorithm-based pharmacological treatment (34.8% vs 30.0%) (Schoeyen et al., 2015). Another study with nonconvulsive electrotherapy reported 73% response and 55% remission rates (Regenold et al., 2015).

Early rTMS studies reported a 60% response rate (Dell'Osso et al., 2009; Wozniak-Kwasniewska et al., 2015). One study of sequential bilateral rTMS vs sham treatment was negative with both arms having a 10% response rate (Fitzgerald et al., 2016), but another with high-frequency repetitive transcranial magnetic stimulation reported 35% response and 30% remission rates (Poleszczyk et al., 2018).

The results with deep brain stimulation in a very small study were rather poor (<20% acute response and remission rates) (Holtzheimer et al., 2012), and similarly a study with deep (H1-coil) transcranial magnetic stimulation (deep TMS) vs sham

Table 6. Levels of recommendation concerning adjunctive treatment for resistant acute bipolar depression and recommended dosages for medication options

Treatment modality to add	Grading		Dosage
	In terms of efficacy	In terms of recommendation	
Lamotrigine (on lithium)	1	2	Up to 200 mg/d
Light therapy	1	1	
ECT	2	2	
Modafinil	2	2	Up to 200 mg/d
Pramipexole	2	2	Up to 2.5 mg/d
TMS	2	2	
Pioglitazone	3	3	30 mg/d
Amitriptyline	4	4	Up to 150 mg/d
Bupropion	4	4	Up to 375 mg/d
Clozapine	4	4	Up to 600 mg/d
Diltiazem	4	4	Up to 240 mg/d
Gabapentin	4	4	600–2400 mg/d
L-sulpiride	4	4	50–75 mg/d
N-acetyl cysteine	4	4	2000 mg/d
Ketamine	1	4	Intravenous infusion 0.5 mg/kg
l-Thyroxine	4	4	300 mcg/d
Lurasidone	4	4	Up to 120 mg/d
Omega-3 fatty acids	4	4	Various
Oxcarbazepine	4	4	Up to 1200 mg/d
Paroxetine	4	4	Up to 40 mg/d
Pramipexole	4	4	3 mg/d
Sleep deprivation	4	4	–
Tranlycypromine	4	4	30–60 mg/d
Venlafaxine	4	4	75–225 mg/d
Agomelatine	NR	NR	
Aripiprazole	NR	NR	
Celecoxib	NR	NR	
DBS	NR	NR	
Galantamine	NR	NR	
Imipramine	NR	NR	
Inositol	NR	NR	
Leviracetam	NR	NR	
Lisdexamfetamine	NR	NR	
Memantine	NR	NR	
Pregnenolone	NR	NR	
S-adenosyl-L-methione	NR	NR	
Topiramate	NR	NR	
Ziprasidone	NR	NR	

Abbreviations: DBS, deep brain stimulation; ECT, electroconvulsive therapy; NR, not recommended; TMS, transcranial magnetic stimulation.

was superior at week-4 in HDRS but not at follow-up at week-8. There was no difference in response and remission rates (Tavares et al., 2017). An earlier H1-Coil rTMS study reported that two-thirds of patients responded and one-half of them remitted (Harel et al., 2011).

Total sleep deprivation plus light therapy for 1 week resulted in a 44% response in resistant patients (Benedetti et al., 2005).

Post-hoc, Review, and Meta-Analytic Studies (n=48)

The problems in the literature concerning the treatment of resistant bipolar depression are described in several reviews and meta-analytical studies. The overall conclusion is that the available hard data are extremely scarce and most of the strategies remain essentially experimental; however, there seem to be some that are potentially efficacious and promising (Aan Het Rot et al., 2012; Poon et al., 2012; Sienaert et al., 2013; Hui Poon et al., 2015). In addition, combination studies confirmed the higher rate of adverse events compared with monotherapy (Galling et al., 2015).

Existing papers suggest minimal effects of lamotrigine, risperidone, inositol (Parikh et al., 2010), or lurasidone (Sanford and Dhillon, 2015) and that the addition of an antidepressant does not increase efficacy (Parikh et al., 2010; Van Lieshout and MacQueen, 2010). The combination with best data in resistant acute bipolar depression is lithium plus lamotrigine (Fountoulakis et al., 2012c). Antidepressant reviews provide conflicting conclusions (Gijsman et al., 2004; Sidor and MacQueen, 2011; Vazquez et al., 2013; Zhang et al., 2013); 1 meta-analysis was negative regarding the usefulness of galantamine, donepezil, and memantine (Veronese et al., 2016) while another concluded that second-generation antidepressants produced a significant but small score change but had no effect in response and remission rates. There was also no increased risk of treatment-emergent mania or hypomania during the acute phase while there was some risk in the long term (McGirr et al., 2016a).

Some studies support the efficacy of stimulants, especially modafinil and armodafinil (Corp et al., 2014), ketamine (Corp et al., 2014; Fond et al., 2014; McGirr et al., 2015), and

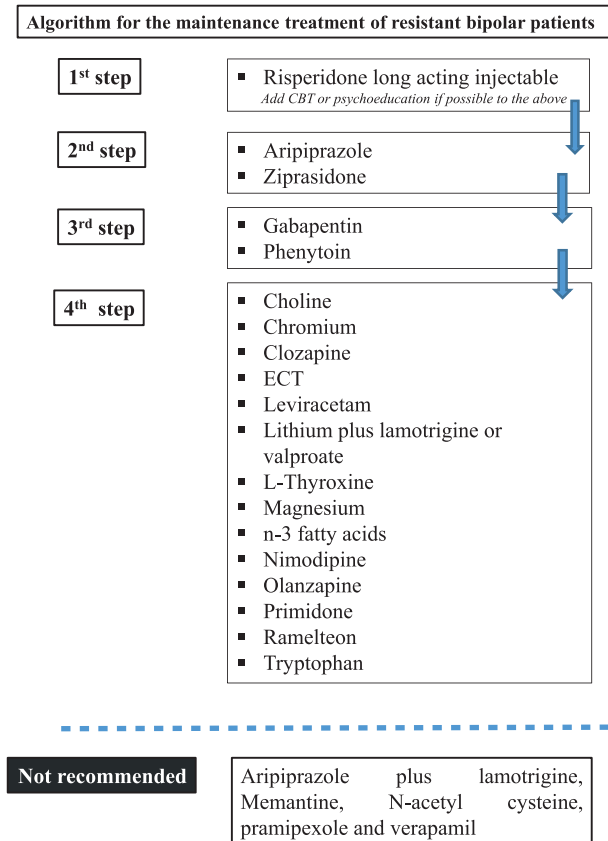


Figure 4. Algorithm for the treatment of resistant cases of bipolar disorder (BD) during the maintenance phase.

antiinflammatory agents (Rosenblat et al., 2016). A meta-analytic study supported the efficacy of dopaminergic drugs (Szmulewicz et al., 2017). The review of pramipexole data suggested that two-thirds of patients respond (Dell'Osso and Ketter, 2013; Tondo et al., 2014).

The meta-analysis of ketamine studies supported its efficacy but also suggested the data are conflicting as to whether the therapeutic effect extends beyond day 4 and up to day 7 (Sienaert et al., 2013; Caddy et al., 2014; Fond and Boyer, 2014; Fond et al., 2014; Tondo et al., 2014; Coyle and Laws, 2015; Lee et al., 2015; McGirr et al., 2015; Newport et al., 2015; Parsaik et al., 2015; Romeo et al., 2015; Bobo et al., 2016; Kishimoto et al., 2016; Saligan et al., 2016; Xu et al., 2016; Kraus et al., 2017).

One meta-analysis was positive concerning the usefulness of light therapy (Tseng et al., 2016).

Reviews and meta-analyses are positive concerning omega-fatty acids, but they do not include all trials (Sarris et al., 2012; Sylvia et al., 2013; Grosso et al., 2014; Ciappolino et al., 2017). Another meta-analysis was negative for adjunctive inositol (Mukai et al., 2014) and another one supported the usefulness of clozapine (Li et al., 2015).

There are no studies with adequate methodology on ECT (Loo et al., 2011; Versiani et al., 2011). One meta-analysis compared the efficacy of ECT in unipolar vs bipolar depression and identified 6 relevant studies. It reported a similar rate of response in both disorders (50.9% vs 53.2%) (Dierckx et al., 2012).

A meta-analysis of rTMS in bipolar depression, although based overall on a smaller number of participants, supported efficacy (McGirr et al., 2016b).

One post-hoc study pooled the data from transcranial direct current stimulation (transcranial direct current stimulation) trials and reported significant positive results (D'Urso et al., 2017) while a review suggested that Vagus nerve stimulation is promising for bipolar depression (Cimpianu et al., 2017). Another review focused on surgical interventions but without any conclusion (Lipsman et al., 2010).

Conclusion Concerning the Treatment of Resistant Acute Bipolar Depression

Controlled data suggest that in resistant bipolar depressive patients, it is beneficial to use lithium plus lamotrigine or adding lamotrigine, modafinil, or pramipexole. Ketamine is also another option but carries the risk of transient dissociation and increased blood pressure. The data are inconclusive concerning L-sulpiride, amitriptyline, bupropion, clozapine, diltiazem, ECT, gabapentin, l-thyroxine, lurasidone, NAC, omega-3 fatty acids, oxcarbazepine, paroxetine, pramipexole, sleep deprivation, TMS, tranlycypromine, and venlafaxine.

According to either controlled or open data, the interventions not recommended include agomelatine, aripiprazole, celecoxib, deep brain stimulation, galantamine, imipramine, inositol, leviracetam, lisdexamfetamine, memantine, pregnenolone, S-adenosyl-L-methionine, topiramate, and ziprasidone (Table 6; Figure 3).

BD Resistant to Maintenance Treatment (n=49)

Double-Blind Studies in Maintenance Treatment of Resistant BD (n=24)
A small study supported the adding of phenytoin to TAU (Mishory et al., 2003) as did another small one for gabapentin (but not on top of antipsychotics) (Vieta et al., 2006). One study suggested a beneficial effect of clozapine on a small subsample of nonpsychotic BD (Suppes et al., 1999). Data are equivocal for the addition of lamotrigine to lithium (van der Loos et al., 2011) and negative for adjunctive pramipexole to TAU in stabilized BD patients with the aim to improve neurocognition (Burdick et al., 2012). Two studies suggest that Risperidone Long Acting Injectable (RLAI) on TAU significantly prolongs the time to relapse (Macfadden et al., 2009; Quiroz et al., 2010), as did adding aripiprazole (Marcus et al., 2011) or ziprasidone (Citrome, 2010) to lithium or valproate. Adding aripiprazole to lamotrigine did not improve long-term outcome (Carlson et al., 2012). Patients who responded to treatment with lithium, valproate, or carbamazepine plus antidepressants were more likely to maintain response with continuation of the combined treatment; however, those patients who manifested only a partial acute response were unlikely to further improve when the same treatment was continued (Altshuler et al., 2009). Adjunctive asenapine to lithium or valproate was well tolerated for up to 52 weeks, but no efficacy data were reported from that trial due to lack of statistical power (Szegedi et al., 2012).

One trial in 75 BD patients reported that NAC treatment caused a significant improvement on the MADRS score compared with placebo ($P=.002$) during maintenance. There was no effect of NAC on time to a mood episode and no significant between-group differences in adverse events (Berk et al., 2008). Another study in 14 BD-II patients from the previous study reported a superiority of the NAC group vs placebo in terms of remission ($P=.031$) (Magalhaes et al., 2011a). Data were conflicting concerning ramelteon (Norris et al., 2013; Mahableshwarkar et al., 2017) and negative results for memantine in patients on valproate treatment (Lee et al., 2014b).

Table 7. Levels of recommendation concerning adjunctive treatment for resistant patients during maintenance phase and recommended dosages for medication options

Treatment modality to add	Grading		Dosage
	In terms of efficacy	In terms of recommendation	
RLAI	1	1	Up to 100 mg/mo
Aripiprazole	2	2	Up to 30 mg/d
Ziprasidone	2	2	Up to 160 mg/d
Gabapentin	3	3	Up to >2500 mg/d
Phenytoin	3	3	380 mg/d
Choline	4	4	–
Chromium	4	4	–
Clozapine	4	4	Up to 600 mg/d
ECT	4	4	–
Leviracetam	4	4	Up to 3000 mg/d
Lithium plus lamotrigine or valproate	4	4	Usual recommended dosages
L-Thyroxine	4	4	500 µg/d
Magnesium	4	4	–
n-3 fatty acids	4	4	–
Nimodipine	4	4	Up to 360 mg/d
Olanzapine	4	4	Up to 30 mg/d
Primidone	4	4	Up to 250 mg/d
Ramelteon	4	4	8 mg/d
Tryptophan	4	4	
Aripiprazole plus lamotrigine	NR	NR	
Memantine	NR	NR	
N-acetyl cysteine	NR	NR	
Pramipexole	NR	NR	
Verapamil	NR	NR	

Abbreviations: DBS, deep brain stimulation; ECT, electroconvulsive therapy; NR, not recommended; TMS, transcranial magnetic stimulation.

There are some studies suggesting that there is a role for various nutritional supplements such as n-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid), chromium, choline, magnesium, and tryptophan alone or in combination with pharmacotherapies for the treatment of BD, but the data are of low quality (Sylvia et al., 2013).

Open-Label Studies in Maintenance Treatment of Resistant BD (n=22)

Open studies support the usefulness of adding clozapine (Suppes et al., 1999; Ciapparelli et al., 2000, 2003), gabapentin (Schaffer and Schaffer, 1999), lamotrigine (Calabrese et al., 1999), levitiacetam (Post et al., 2005), RLAI (Yatham et al., 2007a), and the anticonvulsant primidone (Schaffer et al., 1999) with approximately 30–40% of patients responding, while a higher than 40% response rate was reported for olanzapine (McElroy et al., 1998; Vieta et al., 2001), higher than 50% with L-thyroxine T(4) (Bauer et al., 2002), and higher than 70% for the N-methyl-D-aspartate antagonist memantine (Koukopoulos et al., 2010).

One-third of participants responded well to the combination of lithium plus valproate (Denicoff et al., 1997), but the BALANCE study neither supported nor refuted the superiority of the combination of lithium plus valproate over monotherapy (Geddes et al., 2002; Rendell et al., 2004; Investigators et al., 2010). Results were somewhat positive also for the combination of carbamazepine plus nimodipine, but negative for adding the calcium channel blocker verapamil (Pazzaglia et al., 1998). For overweight patients, adding topiramate (McElroy et al., 2000; Lykouras and Hatzimanolis, 2004; Gabriel, 2007) or zonisamide (Wang et al., 2008) could be an option. However, mood destabilization was observed in another study with the addition of zonisamide.

Using maintenance ECT for more than 18 months, with a treatment at approximately monthly intervals, resulted in an up to 80% response rate (Vanelle et al., 1994).

Post-hoc, Review, and Meta-Analytic Studies (n=10)

Meta-analyses support the efficacy of antidepressants added to mood stabilizers in the long-term treatment of bipolar patients without increasing risk of new manic/hypomanic episodes (Liu et al., 2017). Ziprasidone plus lithium or valproate treatment showed modest to moderate remission rates at week 24 based on 4 different remission criteria in terms of symptomatic and sustained remission (Pae et al., 2012).

The addition of an atypical antipsychotic-antimanic agent in some BD patients might help to reduce suicidal ideation (Houston et al., 2006). Efficacy of NAC was also supported by 2 post-hoc analyses (Magalhaes et al., 2011b, 2013), which, however did not include more recent negative data. Two other studies supported the usefulness of RLAI (Bobo and Shelton, 2010) for the maintenance treatment of BD-I disorder in adults as an adjunct to lithium or valproate. One paper supported the usefulness of the dopamine agonist pramipexole (Dell'Osso and Ketter, 2013). Overall, the review papers support the usefulness of ECT (Vaidya et al., 2003; Fountoulakis et al., 2012c), the combination of antiepileptics with antipsychotics (Fountoulakis et al., 2012c), and clozapine (Li et al., 2015) for the maintenance treatment of resistant patients.

Conclusion Concerning Treatment for Resistant Patients During Maintenance Phase

Controlled data suggest that in resistant patients (principally to lithium, valproate, or carbamazepine), it is beneficial to add antidepressants, RLAI, aripiprazole, or ziprasidone to the ongoing treatment. The next choice should be adding gabapentin or phenytoin. The data are inconclusive concerning clozapine, ECT, leviracetam, lithium plus lamotrigine or valproate, L-thyroxine, the calcium blocker nimodipine, olanzapine, primidone, ramelteon, and the food supplements choline, chromium, magnesium, n-3 fatty acids, and tryptophan.

According to either controlled or open data, the nonrecommended agents include memantine, NAC, pramipexole, and verapamil. Aripiprazole plus lamotrigine was also not effective (Table 7; Figure 4).

It is important to note that the scarcity of the data does not permit a differential choice between agents and treatment options to prevent the relapse into a manic or depressive episode preferentially.

Resistant Rapid Cycling Cases (n = 10)

The data on resistant patients with rapid cycling course are very few. Overall, they suggest that the combination of lithium plus divalproex for up to 16 weeks leads to only 14% stabilization with no additional value of adjunct lamotrigine (Kemp et al., 2012). One small trial of clorgyline 2.5–10.0 mg/d, alone or in combination with lithium carbonate, was positive (Potter et al., 1982), while clozapine was found to be less efficacious in resistant rapid cycling patients (Suppes et al., 2004; Li et al., 2015). On the contrary, lamotrigine as an add-on therapy exerted a similar effect in rapid and non-rapid cycling patients (Bowden et al., 1999). A small cross-over, double blind study was positive for adjunctive nimodipine (Pazzaglia et al., 1993).

Adding mexiletine 200–1200 mg/d led to 46% remission and 15% partial response (Schaffer et al., 2000) while levothyroxine improved only depressive symptoms (Bauer and Whybrow, 1990). Vagus nerve stimulation was associated with a 38.1% mean improvement in overall illness over a 12-month study period (Marangell et al., 2008). Adding chromium resulted in an acute response in one-third of patients, but only regarding depression. The high drop-out rate made it impossible to test for maintenance efficacy (Amann et al., 2007).

Lithium Discontinuation-Induced Treatment Resistance (n = 10)

Treatment resistance possibly induced by lithium discontinuation was suggested for the first time by Post et al following a systematic life-chart methodology in the study of 4 patients with BD in whom long periods (6–15 years) of effective lithium prophylaxis were followed by relapses on lithium discontinuation. Once the drug was reinstated, it was no longer effective (Post et al., 1992). However, the reason for discontinuation in these 4 cases was not reported, and the discussion of these cases clearly leaves room for a progression of the illness rather than a specific lithium-related cause as the most probable explanation.

Case reports and selected reviews support this (Post et al., 1993; Bauer, 1994; Murray, 1994; Koukopoulos et al., 1995; Maj et al., 1995; Tondo et al., 1997; Post and Leverich, 2008; Post, 2012) but the arguments are scientifically weak.

The only existing systematic review and meta-analysis of the literature identified the existence of 212 patient data relevant to this question and the meta-analysis returned negative results, suggesting there is no convincing evidence that lithium is less effective when treatment is discontinued and restarted compared with uninterrupted treatment (de Vries et al., 2013).

Psychological Treatments (n = 21)

There are some but overall limited data of problematic quality concerning the usefulness of specific adjunctive psychotherapies (Reinares et al., 2014; Miziou et al., 2015).

Although the overall data for the long-term efficacy of cognitive-behavioral therapy (CBT) either as monotherapy or as add on to TAU are negative concerning relapse prevention, there are some positive results for the acute depressive phase in BD (Ball et al., 2006; Scott et al., 2006; Zaretsky et al., 2008; Costa et al., 2011; Gomes et al., 2011; Meyer and Hautzinger,

2012; Gonzalez Isasi et al., 2014). The effectiveness of psychotherapy for resistant patients was reported to increase with time, and this improvement was not significant until 12 months of follow-up (Gonzalez-Isasi et al., 2010, 2012; Isasi et al., 2010). A post-hoc analysis suggested that CBT could be more effective than TAU in patients with less than 12 previous episodes but less effective in those with more episodes (Scott et al., 2006). In BD patients with insomnia, CBT for insomnia was superior to psychoeducation concerning manic relapses (Harvey et al., 2015).

The data on adjunctive psychoeducation suggest that compared with TAU or nonspecific intervention, it prevents relapse to both poles if administered to patients in clinical remission (Perry et al., 1999; Colom et al., 2003; Colom et al., 2009; Lobban et al., 2010; de Barros Pellegrinelli et al., 2013), but it has no effect on biological rhythms (Cardoso Tde et al., 2015). Again, a post-hoc analysis suggested that patients with more than 7 episodes did not show significant improvement with group psychoeducation for time to recurrence, and those with more than 14 episodes did not benefit from the treatment in terms of time spent ill (Colom et al., 2010). A systematic review confirmed the above (Bond and Anderson, 2015).

There are no data to support the usefulness of interpersonal and social rhythm therapy, family focus treatment, intensive psychosocial intervention, cognitive remediation and functional remediation, mindfulness-based interventions (MBCT), or internet-based interventions in the treatment of resistant BD patients.

Overall, there are limited data to suggest that any kind of psychotherapy is useful in resistant BD patients; some data suggest that it could be useful in resistant patients at the early stages of the disorder.

Algorithm for Treatment of Resistant BD

A visual representation of the recommended steps in the treatment of resistant cases during each phase is shown in Figures 2–4. As already mentioned, this specific algorithm is based on the materials collected to develop a general algorithm for BD by the CINP (Fountoulakis et al., 2017a, 2017b, 2017c, 2017d).

The authors decided that although mixed episodes are not included in DSM-5, it would be important to include a guidance option for them since some relevant data do exist. Also, they decided to include a recommendation for adding CBT and/or psychoeducation at a level higher than the evidence suggests, because, if available, they could be added without problems to existing pharmacotherapy. However, the recommendation is that this addition should not interfere with the application of the algorithm itself, that is, the first step of the algorithm concerning pharmacotherapy should always be initialized and pseudo-resistance should have been ruled out (Schaffer et al., 2017).

Discussion

The current guidelines are the first to our knowledge developed specifically for the treatment of resistant bipolar patients, and they also include an operationalized definition of treatment resistance.

The key issue is the definition of “response,” since this is a prerequisite for the definition of “resistant.” There are several papers defining response, remission, and resistance in mental disorders, and it seems that all the definitions are

characterized by a rather narrow and vague approach. With BD, these definitions face a particular problem. They perform well with disorders with a predominantly linear course, characterized by exacerbations and remissions and with a single major factor or constellation of symptoms (e.g., unipolar melancholic depression). They also perform relatively well with complex disorders like schizophrenia that, in spite of the large variability of the clinical picture (to the extent it is possible 2 patients with schizophrenia not sharing a single symptom), their treatment is more or less unimodal (antipsychotics) and the course of the disease is monotonous. In BD, however, the course is characterized by episodes of distinct clusters of symptoms while the resulting accumulated stress has a profound adverse effect on neurocognition and general functioning with the neurobiology of the patient to change under the pressure of what is called “allostatic load,” leading eventually to treatment resistance, disability, high comorbidity, and preterm mortality (Vieta et al., 2013).

When it comes to BD, things are quite different from other mental disorders. The reliability and validity of usual approaches are questionable because both the clinical picture and the treatment are complex and interrelated. Also, the course is not monotonous but, on the contrary, it manifests with unpredictable switches with a complex and unique relationship between clinical symptoms and impairment. Another issue is the problematic interplay of the clinical picture with psychometric scale scores when the longitudinal course of the disorder is complex, as in the case of BD. For example, the use of the MADRS scale to assess response to treatment with a tricyclic antidepressant could lead to erroneous conclusions in case this depressive BD patient becomes mixed or rapid cycling emerges. The MADRS will probably classify him as being a “responder,” but whether this is true is a matter of debate. Accepting simplistic approaches cannot serve as a real solution.

The current study developed a definition of treatment resistance in BD and an algorithm for its treatment. These were based on a thorough and deep search of the literature. During the last couple of decades, our knowledge concerning the treatment of BD has changed radically (Grande et al., 2016; Vieta et al., 2018), and a rather narrow therapeutic effect for most agents is accepted, so narrow that the very existence of the term “mood stabilizer” is under question. Further, the collapse of the “class effect” approach to BD treatment (Rosa et al., 2011) raises important questions as to which patients are truly resistant and which were simply treated in a suboptimal way.

The review of the literature suggested that there are some evidence-based options for the treatment of resistant acute mania but much fewer for the treatment of resistant depression, mixed states, and rapid cycling cases. Thus, the relative shortage of hard data (Poon et al., 2012) leaves the clinician in many cases with the heavy burden to decide on the basis of clinical experience and wisdom. The current treatment guidelines on one hand rely on hard data; however, they provide a limited number of options for the treatment of a variety of cases, and without the ability to tailor treatment to the clinical picture and the specific needs of the individual patient. Future specific and targeted research is essential and necessary to test possible treatment approaches for resistant patients of all kinds.

Most of the problems concerning the interplay of clinical features with definitions of response and resistance, especially for the maintenance phase, have been discussed elsewhere (Ghaemi et al., 2004; Fountoulakis, 2010; Vieta and Garriga, 2016; Fountoulakis et al., 2017b, 2017c, 2017d). Clinical wisdom is also of high importance in the planning of long-term treatment of

BD patients. In this frame, the concept of “predominant polarity” and the “polarity index” of a given agent are of great importance since it guides the clinician to tailor treatment to the specific needs of the specific patient (Nivoli et al., 2011; Popovic et al., 2012, 2013, 2014; Sentissi et al., 2019).

Better knowledge of the underlying neurobiological substrate of treatment resistance in BD would be important, since the failure of physiological compensatory mechanisms over time, accompanied by neuroprogression and cross-sensitization of episode recurrence, trauma exposure, and substance use could constitute modifiable factors both in the prevention but also in the treatment of such cases (da Costa et al., 2016). So far, however, our knowledge does not permit a reliable prediction or assessment of resistant cases since no neurobiological or clinical variables have proven reliable (Gonzalez-Isasi et al., 2012). However, the observation that psychoeducation is preferentially efficacious in patients with less than 7 episodes, while it has no effect in those with more than 14 episodes, provides us with a first clue of the stages and the timetable of the development of resistance (Colom et al., 2010; Bond and Anderson, 2015; van der Markt et al., 2019). On the other hand, while the stage of the progression of the disorder has been proposed as a factor that should be taken into consideration in the planning of treatment especially in resistant cases (Passos and Kapczinski, 2017), in essence this might reflect a cyclical logic with treatment resistance defining the stage and vice versa.

Statement of Interest

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