Review
https://doi.org/10.9758/cpn.2022.20.3.403 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2022;20(3):403-414

Lithium and Valproate in Bipolar Disorder: From International Evidence-based Guidelines to Clinical Predictors

Calogero Crapanzano[1], Ilaria Casolaro[2], Chiara Amendola[3], Stefano Damiani[4]

[1]Azienda Sanitaria Provinciale di Agrigento, Centro Salute Mentale Licata, Licata, [2]Azienda Socio Sanitaria Territoriale Ovest Milanese, Milano, [3]Azienda Unità Sanitaria Locale Toscana Centro, Centro Salute Mentale Scandicci, Firenze, [4]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

Since decades, lithium and valproate remain the pharmacological cornerstone to treat bipolar disorder. Different response patterns occur according to the phases of illness. At same time, individual pretreatment variables may concur to determine a specific drug-response. Our narrative review focuses on these two key clinical aspects to summarize the state of art. Information from i) clinical trials and ii) the most relevant international guidelines is collected to assess the clinical and preclinical factors that may guide the use of lithium rather than valproate. Lithium may be effective in treating acute mania, and lithium efficacy is maximized when used to prevent both manic and depressive episodes. Lithium may be a better treatment choice in patients with: positive family history for bipolar disorder, mania-depression-interval pattern, few previous affective episodes/hospitalizations, high risk for suicide, no comorbidities. Valproate may be more effective as antimanic rather than prophylactic agent. Valproate might be a better choice in patients with many previous affective episodes/hospitalizations and psychiatric comorbidities. Finally, neither lithium nor valproate are suggested for the treatment of acute mixed states or bipolar depression. To consider clinical and preclinical factors may thus be useful to select the best treatment strategy.

KEY WORDS: Bipolar disorder; Lithium; Valproate.

INTRODUCTION

Bipolar disorder (BD) is a multifactorial disabling mental illness characterized by alternation of recurrent depressive, hypomanic, mixed episodes with euthymia [1]. The complex pharmacological treatment of BD prioritizes mood stabilizers, some of the most commonly psychotropic drugs prescribed worldwide. Despite wide evidence supporting the efficacy of lithium use in the treatment of BD, studies show that the use of this pharmacological tool is progressively declining in favour of valproate (VPA), the most common alternative to lithium [2-7]. The choice between these two therapeutic options as the main strategy of treatment for Bipolar Disorder is not immediate and must consider several factors.

The two major sources of information for clinicians' decision-making are scientific studies and clinical guidelines, which often provide complementary information and have thus to be integrated. Randomized controlled trials (RCTs), post-hoc analyses and international guidelines all agree on the overlap between lithium and valproate in terms of short [8-13] and long-term efficacy [12,14-16]. However, RCTs can be characterized by weak external validity that may not take into account the full clinical phenomenology of bipolar disorder; in view of this it seems useful to include evidence from studies with different designs, such as observational studies, to better report on a broader field of research, closer to real-world clinical practice [17].

Mood stabilizers, antipsychotics, and antidepressants are commonly prescribed treatments for BD. However, patterns of drug response to these medications can be different between patients and in the same patient at different stages along the disease course. This explains the in-

Received: January 6, 2022 / **Accepted:** February 9, 2022
Address for correspondence: Calogero Crapanzano
Azienda Sanitaria Provinciale di Agrigento, Centro Salute Mentale Licata, C/da Cannavecchia c/o Ospedale San Giacomo D'Altopasso, 92027 Licata, Italy
E-mail: calogerocrapanzano87@gmail.com
ORCID: https://orcid.org/0000-0001-6006-1268

terest of research in identification of phenotypic variables that can be used clinically to predict response, or non-response, to a specific treatment. Knowing and recognizing the specific pathophysiological domains of BD that are predictive of treatment response is crucial to personalize treatment. Clinical and pharmacogenomic studies have investigated this research field. However, pharmacogenomic studies, despite enormous potential to improve our understanding of the mood stabilizer-responding subtype of BP, are unlikely to have immediate application in clinical practice [18,19].

The goal of this paper is to provide a clinic-oriented review to support the choice between lithium and valproate among the different phases and pre-treatment variables of illness expression.

METHODS

We performed an extensive review of the major publications in English language about lithium and valproate on Web of Science (all databases). Due to the wide number and the heterogeneity of the available studies, a narrative review was preferred to a systematic one to condense clinically relevant information. At same time we conducted a comprehensive synthesis of selected international guidelines on treatment of BD I: World Federation of Societies of Biological Psychiatry (WFSBP) 2003/2010/2013/2018 [13,16,20,21], National Institute for Health and Care Excellence (NICE) 2014 [22], The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017) [23], Canadian Network for Mood and Anxiety Treatments (CANMAT)/International Society for Bipolar Disorders (ISBD) 2018/2021 [12,24], British Association for Psychopharmacology (BAP) 2016 [25] (Tables 1, 2).

RESULTS

Treatment of Acuta Mania

Lithium and valproate are considered as initial treatment selection in the CANMAT/ISBD 2018 and guidelines WFSBP 2003 [12,13], second choice in the BAP 2016 guidelines [25]. Valproate first and lithium second choice in CINP 2017 guidelines [23]. NICE guidelines do not recommend valproate and lithium as treatment of acute mania [22] (Table 3).

Lithium is first choice treatment and superior to valproate in a meta-analysis of 12 RCTs (n = 658) [26], second choice but again superior to valproate in a more recent meta-analysis of 68 RCTs (n = 16,073) [27]. In three 3 RCTs (n = 36; n = 179; n = 377) valproate is superior to placebo [8,28,29], not significantly different from lithium in 2 RCTs (n = 179; n = 300) [8,9], less efficacious than lithium in another RCT (n = 27) [30]. Finally, two open-label RCTs (n = 300; n = 268) and 2 systematic reviews of 10 (n = 1,427) and 25 (n = 3,252) RCTs, report a comparable

Table 1. Guidelines

Acronym	Guidelines
WFSBP 2003	The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders, Part II: Treatment of mania
WFSBP 2010	The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression
WFSBP 2013	The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder
WFSBP 2018	The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder
NICE 2014	Bipolar Disorder: The National Institute for Health and Care Excellence (NICE) Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care
CINP 2017	The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 2: Review, grading of the evidence, and a precise algorithm
CANMAT/ISBD 2018	Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 Guidelines for the Management of Patients with Bipolar Disorder
CANMAT/ISBD 2021	Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) recommendations for the management of patients with bipolar disorder with mixed presentations
BAP 2016	Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology (BAP)

Table 2. Grading of the categories/levels of evidence

Guidelines	Category	Description
WFSBP	Category A	Evidence from controlled studies
	Category B	Limited positive evidence from controlled studies
	Category C	Evidence from uncontrolled studies or case reports/expert opinion
	Category D	Inconsistent results
CINP	Level 1	Evidence from controlled studies
	Level 2	Limited positive evidence from controlled studies or meta-analysis
	Level 3	Evidence from controlled studies without placebo arm or from post hoc analyses
	Level 4	Inconsistent results or poor quality of RCTs
CANMAT/ISBD	Level 1	Evidence from controlled studies or meta-analysis
	Level 2	Limited positive evidence from controlled studies or meta-analysis
	Level 3	Evidence from controlled studies (n = 10−29 in each active treatment arm) or health system administrative data
	Level 4	Uncontrolled trial, anecdotal reports, or expert opinion
BAP	Category I	Treatment studies: evidence from controlled studies or meta-analysis Observational studies: Large representative population samples
	Category II	Treatment studies: limited positive evidence from controlled studies or evidence from at least one other type of quasi-experimental study Observational studies: small, well designed but not necessarily representative samples
	Category III	Treatment studies: evidence from uncontrolled studies Observational studies: non-representative surveys, case reports
	Category IV	Expert committee reports or opinions and/or clinical experience of BAP expert group

WFSBP, World Federation of Societies of Biological Psychiatry; CINP, The International College of Neuro-Psychopharmacology; CANMAT/ISBD, Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders; BAP, British Association for Psychopharmacology; RCTs, randomized controlled trials.

Table 3. Acute mania treatment phase

Guidelines	1° choice	2° choice	Categories of evidence
WFSBP 2003	Li		Level A
	VPA		Level A
CANMAT/ISBD 2018	Li		Level 1
	VPA		Level 1
BAP 2016		Li	Level I
		VPA	Level I
CINP 2017	VPA		Level 1
		Li	Level 1

WFSBP, World Federation of Societies of Biological Psychiatry; CANMAT/ISBD, Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders; BAP, British Association for Psychopharmacology; CINP, The International College of Neuro-Psychopharmacology; VPA, favour of valproate; Li, lithium.

efficacy between lithium and valproate [9,10,31,32].

Treatment of Acute Bipolar Depression

Lithium is first and valproate second choice in CANMAT 2018 guidelines [12]. Lithium fourth and valproate third choice in CINP 2017 guidelines [23]. Lithium third and valproate second choice in WFSBP 2010 guidelines [20]. NICE 2014 and BAP 2016 guidelines do not recommend valproate and lithium as treatment of bipolar depression [22,25], although in one of these lithium may be considered second choice if depressive symptoms are less severe [25] (Table 4).

Maintenance Treatment of BD

Lithium is the initial treatment choice in CANMAT 2018, WFSBP 2013, NICE 2014, CINP 2017, BAP 2016 guidelines [12,16,22,23,25]. Valproate is suggested as first initial treatment choice in CANMAT 2018 and (limited to prevention of depression) in WFSBP 2013 guidelines, second choice in NICE 2014 and BAP 2016 guidelines [12,16,22,25] (Table 5).

Lithium prophylaxis is associated with fewer mood relapses of any type in a nationwide cohort study involving 14,616 patients [33]. In 2 meta-analyses of 5 (n = 770) and 7 (n = 1,580) RCTs, lithium shows efficacy for manic relapse/recurrence, while prophylaxis for depressive relapse/recurrence was considered respectively equivocal or dependent on the type of analyses [34,35]. In 3 meta-analysis of six (n = 876), 48 (n = 9,821) and 21 studies (n = 9,240) no significant differences are found between lithium and valproate in terms of long-term efficacy [14,36,37], although lithium appears more efficacious and overall evidence of efficacy for lithium versus placebo appears

Table 4. Acute bipolar depression treatment phase

Guidelines	1° choice	2° choice	3° choice	4° choice	Categories of evidence
CANMAT/ISBD 2018	Li				Level 2
		VPA			Level 2
CINP 2017				Li	Level 4
			VPA		Level 3
WFSBP 2010			Li		Category D
		VPA			Category B
BAP 2016		Li[a]		-	Level 3

CANMAT/ISBD, Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders; CINP, The International College of Neuro-Psychopharmacology; WFSBP, World Federation of Societies of Biological Psychiatry; BAP, British Association for Psychopharmacology; VPA, favour of valproate; Li, lithium; –, not available.
[a]If depressive symptoms are less severe.

Table 5. Maintenance treatment phase

Guidelines	1° choice	2° choice	Categories of evidence
WFSBP 2013	Li		Category A
	VPA[a]		Category B
NICE 2014	Li		-
		VPA	-
BAP 2016	Li		Level 1
		VPA	Level 1
CINP 2017	Li[b]		Level 1
			Level 4
CANMAT/ISBD 2018	Li		Level 1
	VPA		Level 1

WFSBP, World Federation of Societies of Biological Psychiatry; NICE, The National Institute for Health and Care Excellence; BAP, British Association for Psychopharmacology; CINP, The International College of Neuro-Psychopharmacology; CANMAT/ISBD, Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders; VPA, favour of valproate; Li, lithium; –, not available.
[a]Limited to prevention of depression. [b]If manic predominant polarity.

more robust [14]; analogous results are found in a post-hoc RCT (n = 159) [15]. In a systematic review of 9 (n = 14,271) studies and in a network meta-analysis 33 RCTs (n = 6,846) comparing the different stabilizers including valproate, the evidence for the prevention is stronger for lithium than valproate [38,39]. Observational studies (n = 120; n = 57) [40,41], a randomized open label (n = 330) [42] and 3 cohort studies (n = 4,268; n = 5,089; n = 4,990) [17,43,44] report the same results. In a (n = 372) RCT, neither valproate nor lithium show clear prophylactic effect compared with placebo during 1-year follow-up [45]. Instead, in a post hoc analysis from 2 RCTs (n = 1,326), lithium is associated with a higher recurrence risk of manic relapse than placebo plus valproate [46].

Dysphoric Mania

Dysphoric mania, mixed mania, depressive mania and manic episode with mixed features in the Diagnostic and Statistical Manual of Mental Disorders 5th edition are overlapping terms that have been used to define mania and co-occurring depressive symptoms [47]. The evidence related to this condition is reported in the "Mixed states" section.

Acute Mixed States

No recommendations were given for lithium in WFSBP 2018, NICE 2014, CINP 2017, CANMAT 2021, BAP 2016 guidelines and for valproate in NICE 2014 and BAP 2016 [21-25]. In CANMAT 2021 guidelines, valproate is considered as the initial treatment choice to treat mixed mania and second choice to treat mixed depression and mixed episodes [24]. In WFSBP 2018 and CINP 2017 guidelines, valproate is the third choice to treat mixed mania [21,25] and mixed episodes [23] (Table 6).

In mixed mania results from 3 retrospective studies (n = 19; n = 84; n = 155) report a poor response to lithium [48-50] while in another retrospective study (n = 120) lithium is efficacious and comparable to valproate [51]. In 2 RCTs (n = 27) are reported suggestive data to superiority of valproate in mixed episodes [11,30]. In a post hoc RCT (n = 179) no differences are found in treatment efficacy between lithium and placebo in the subgroup of patients with mixed mania [52]. Finally, a systematic review of 32 (n = 8,891) studies reports that in mixed mania valproate is more efficacious than lithium [53].

Prevention of Mixed Relapses

In the WFSBP 2018 guidelines valproate and lithium

Table 6. Acute mixed states treatment phase

Guidelines	1° choice	2° choice	3° choice	Categories of evidence
CANMAT/ISBD 2021	VPA[a]			Level 3 [M], Level 3 [D]
		VPA[b]		Level 4 [D], Level 4 [M]
		VPA[c]		Level 3 [M], Level 4[D]
WFSBP 2018			VPA	Category C
CINP 2017			VPA	Level 3

CANMAT/ISBD, Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders; WFSBP, World Federation of Societies of Biological Psychiatry; CINP, The International College of Neuro-Psychopharmacology; VPA, favour of valproate; D/M, levels of evidence for mania [M] and depressive [D] symptoms; DSM, diagnostic and statistical manual of mental disorders.
[a]Manic episodes with mixed features (DSM-5). [b]Depressive episodes with mixed features (DSM-5). [c]Mixed episodes (DSM-IV).

Table 7. Mixed state prevention treatment

Guidelines	1° choice	2° choice	3° choice	Categories of evidence
WFSBP 2018		Li		Category D
	VPA			Category B
BAP 2016	Li			Category I
CANMAT/ISBD 2021		Li		Level 2
			VPA	Level 4

WFSBP, World Federation of Societies of Biological Psychiatry; BAP, British Association for Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Treatments; VPA, favour of valproate; Li, lithium.

are respectively first and second treatment choice (with low evidence) for preventing mixed episodes [21]. In the BAP 2016 guidelines lithium is the first treatment choice on mixed relapse [25]. Lithium is the second and valproate the third choice in prevention of mixed relapses in CANMAT 2021 guidelines [24] (Table 7). In a RCT (n = 117) and in 3 retrospective studies (n = 100; n = 300; n = 645), anamnesis of mixed episodes is associated to poor response to lithium [54-57], while in one of these studies and in a naturalistic observational study (n = 102) valproate is not related to poor response [57,58].

Frequency of Episodes

As regards rapid cycling course, lithium is the first line treatment (category of evidence Level 2), while valproate is not recommended in CINP 2017 [23]. In 3 prospective studies (n = 101; n = 336; n = 442) rapid cycling course is predictive of poor response to lithium [59-61], but not to valproate in one of these [59]. History of rapid cycling is associated with poor outcome to lithium in 2 meta-analyses and in a review of respectively 20 (n = 2,054), 71 (n = 17,396), 34 (n = 12,602) studies [62-64]. Body of evidence is considered too inconsistent in a systematic review of 43 (n = 4,280) studies [65]. In a RCT and in a post hoc RCT (n = 179; n = 929) valproate is not related to poor outcome [8,66] and shows lower risk for relapses and recurrences than lithium [66].

Number of Previous Episodes and Hospitalizations

In a post hoc RCT (n = 154), lithium but not valproate are related to poor response if > 10 previous affective episodes are reported in medical history [67]. In a post hoc RCT (n = 165) analysis of the relationship between treatment response and the number of previous affective episodes find that > 3 depressive and > 11 maniac episodes are associated with poor lithium response but not to valproate response [68]. History of previous hospitalizations is considered predictive to poor outcome to lithium in a meta-analysis and in 2 systematic reviews [63-65], in prospective (n = 402) and RCT (n = 372) studies [61,69], related to an inferior outcome than valproate in one of these studies [69].

Comorbidities

Comorbidities are related to poor response to lithium in a systematic review [64] while more data are needed to establish psychiatric comorbidities as a predictor response to lithium according to a systematic review [65]. Borderline symptoms are found predictive of favorable response to valproate in a RCT (n = 30) [70]. Comorbidity between

obsessive-compulsive personality disorder (OCD) and BD were related to favorable outcome to valproate in a retrospective study (n = 102) [58]. Alcohol use is found predictive of poor response to lithium in retrospective (n = 645), prospective (n = 248) studies and in a systematic review [57, 64,71]. In a RCT (n = 59) valproate is superior to lithium on reducing alcohol assumption [72]. A trend toward lithium non responsiveness in bipolar patients with comorbid anxiety disorders is shown in 2 prospective studies (n = 81; n = 94) [73,74] and an association with long-term treatment response to valproate in a naturalistic study (n = 102) [58].

Family History

Family history of bipolar disorder is significantly associated with a favorable response to lithium prophylaxis in prospective (n = 68), retrospective (n = 167), cohort (n = 54), RCT (n = 72) and meta-analysis studies (n = 68) [63,75-78]. Analogous outcomes are found in patients with family history of lithium response in a case-control study (n = 15) [79]. A family history of bipolar disorder was not related to a better outcome of lithium prophylaxis in 2 prospective studies (n = 402; n = 186) [61,80].

Later Age of Illness Onset

Later age of illness onset is related to better effect of lithium in systematic reviews and meta-analysis [63,65], in 3 retrospective studies (n = 100; n = 141; n = 161) [55,81,82] and in a prospective cohort study (n = 186) [80]. In 5 case control studies (n = 46; n = 55; n = 101; n = 111; n = 215) [83-87] and in a prospective cohort study (n = 69) [88] age of illness onset was not related to lithium response. Otherwise, in a naturalistic observation study (n = 120) later age of illness onset was related to better outcome to lithium [40].

Psychotic Features

Psychotic features are related to favorable outcome to lithium in 2 RCTs (n = 205; n = 66) [89,90], poor outcome in one retrospective (n = 120), 2 prospective studies (n = 75; n = 336) [60,91] and in a meta-analysis of 8 studies (n = 1,066) [63], while inconclusive results are found in a systematic review of 43 studies [65]. Psychotic features are related to favorable outcome to valproate in a retrospective study (n = 120) [40], poor outcome in a prospective study (n = 101) [59].

Suicidality

Two meta-analysis of 48 and 41 studies (n = 6,674; n = 9,821) report mixed findings on advantage of lithium over valproate [36,92], while very large population-based cohort studies (n = 51,535; n = 18,018) show that lithium is superior to valproate to decrease incidence rate of suicide [93,94].

Mania-Depression-Interval

An episodic pattern of mania-depression-interval (MDI) sequence is found as a predictor of good response to lithium in systematic review and meta-analysis studies [63,65]. This result is not observed in a 5-year prospective study (n = 402) [61].

Sex

In a post hoc analysis (n = 929) female patients appeared to be at a greater risk for relapse and recurrence with valproate but not with lithium maintenance treatment [66], while in a nationwide cohort study (n = 15,988) lithium and valproate are comparable between males and females patients for reducing rehospitalization rate [95].

DISCUSSION

BD is characterized by a heterogeneous clinical presentation which extends beyond the concepts of mania and depression. In addition, different phenotypes that have been characterized (classical, psychosis spectrum, and characterological) [96] are related to different history of disease and prognosis [18].

Since Cade [97] and Lempérière [98], pioneers in the field of psychopharmacology, published their findings on the use of lithium salts and valpromide in BD, several studies have been conducted to investigate and clarify which phases and clinical characteristics of BD are specifically addressed by lithium and valproate.

In acute mania lithium is reported as efficacious and superior to valproate in some studies [26,27], comparable to valproate in others [8-10,31,32], inferior to valproate in still other studies [30]. In 3 guidelines both lithium and valproate are efficacious and comparable [12,13,25], in another guideline lithium was inferior to valproate [23], while they were both not recommended in another one [22].

In bipolar depression there are lack of data or incon-

sistent results to encourage use of lithium or valproate according to 4 guidelines [20,22,23,25]; lithium is considered first and valproate second choice in another one [12], lithium third and valproate second choice in still another one [20].

Clinical effectiveness of lithium in maintenance phases is reported in several studies [17,33-35,99]. Lithium is superior to valproate in some studies [17,38-44], comparable to valproate [14,15,36,37,45] or placebo [45] in other studies; less efficacious than valproate in still others [46]. It is first line in 5 guidelines (in one only in manic predominant polarity) while VPA is first line in 2 of these (in one only for the prevention of depressive episodes) [12,16,22,23,25].

In acute mixed states lithium is historically related to poor response [48-50,52]. In some studies, it is comparable [51] or inferior to valproate [11,24,30,53]. No guidelines recommend lithium as initial treatment selection of mixed episodes [22-25] while in CANMAT 2021 valproate is first choice to treat mixed mania, second choice to treat mixed depression and mixed episodes [24].

History of mixed episodes is related to poor response to lithium [54-57] but not to valproate [57,58]. Lithium is reported as a preferential choice over valproate against mixed relapse in 2 guidelines [24,25], but not in another one [22].

History of rapid cycling is related to poor response to lithium in several studies [59-64,66] but not to valproate [8,59,66]. Lithium is considered as the first line and valproate is not recommended in CINP 2017 guidelines [23].

Few episodes [67,68] and hospitalizations in past psychiatric history are related to better outcome with lithium treatment [61,63-65,69] while a high number is related to a better response to valproate [67-69].

Family history of bipolar disorder [12,63,75-78], as well family history of lithium response [12,79], are related to favorable response to lithium. However, others do not find this correlation [61,80].

Later age of illness onset is related to favorable response to lithium [55,63,65,80-82]. Others do not report any correlation [83-88]; in a study it is related to poor outcome [40].

In general, the anti-suicidal effect of lithium, even unrelated to bipolar illness, has most consistent data and shows that lithium is superior to valproate [6,36,93,94,100].

MDI pattern is reported as a favorable predictor of response to lithium in several studies [12,63,65]; others do not report any correlation [61].

Psychiatric comorbidities are related to poor response to lithium [12], including alcohol use [57,64,71,72], anxiety symptoms/disorders [73,74] and personality disorders [64], while valproate is related to good response with alcohol use [57], anxiety symptoms/disorders, OCD [58], borderline personality symptoms [12,70].

Psychotic features are related to good outcome to lithium in some studies [89,90], poor outcome in others [40,60,63,91], inconclusive results in still others [65]. Valproate is related to good outcomes in some studies, but not in others [40,59].

Finally, there are mixed results on sex-specific response to lithium and valproate [66,95].

LIMITATIONS

Many variables predict recurrence of illness or poor outcome independent of treatment and may not be crucial in the choice of medication: history of previous episodes, subsyndromal or residual symptoms [12,25,101,102], alcoholism/substance use [12,91], anxiety [12,103], psychotic features [12,104-106], early onset of illness, [107], mixed features [108-110], rapid cycling course [12,111,112], personality comorbidity [12,113].

CONCLUSION

Although it is effective in treating acute mania, the strong point of lithium treatment remains prophylaxis, mostly of manic recurrences/relapses in Bipolar Disorder, as shown by several studies reporting lower rehospitalization risks with lithium than valproate [17,42,99,114]. Moreover, lithium may be a more suitable choice when in presence of family history of BD, previous response to lithium, MDI pattern, low number of previous affective episodes and hospitalizations, active suicidality, lack of other medical comorbidities. Valproate prescription appears more advisable during acute mania than maintenance phases, and may be a more suitable choice in presence of high number of previous mood episodes/hospitalizations, other psychiatric comorbidities. Evidence appears not robust enough to support their use to treat or prevent mixed episodes and bipolar depression, while data on other pretreatment variables are too inconsistent to

be considered. Finally, although it may appear intuitive and marginal, there is consensus on the predictive value of a previous response to lithium and valproate across major guidelines [12,20,22,25].

■ **Funding**

None.

■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Conceptualization: Calogero Crapanzano. Supervision: Stefano Damiani. Writing-original draft: Calogero Crapanzano. Writing review & Editing: Calogero Crapanzano, Ilaria Casolaro, Chiara Amendola.

■ **ORCID**

Calogero Crapanzano https://orcid.org/0000-0001-6006-1268
Ilaria Casolaro https://orcid.org/0000-0002-6276-1732
Chiara Amendola https://orcid.org/0000-0002-0522-3022
Stefano Damiani https://orcid.org/0000-0002-5235-0788

REFERENCES

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Arlington:American Psychiatric Association;2013.*
2. Baldessarini R, Henk H, Sklar A, Chang J, Leahy L. *Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. Psychiatr Serv 2008;59:1175-1183.*
3. Zivanovic O. *Lithium: a classic drug-frequently discussed, but, sadly, seldom prescribed! Aust N Z J Psychiatry 2017; 51:886-896.*
4. Nivoli AM, Murru A, Vieta E. *Lithium: still a cornerstone in the long-term treatment in bipolar disorder? Neuropsychobiology 2010;62:27-35.*
5. Licht RW. *Lithium: still a major option in the management of bipolar disorder. CNS Neurosci Ther 2012;18:219-226.*
6. Post RM. *The new news about lithium: an underutilized treatment in the United States. Neuropsychopharmacology 2018;43:1174-1179.*
7. Ng VWS, Man KKC, Gao L, Chan EW, Lee EHM, Hayes JF, *et al. Bipolar disorder prevalence and psychotropic medication utilisation in Hong Kong and the United Kingdom. Pharmacoepidemiol Drug Saf 2021;30:1588-1600.*
8. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, *et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group. JAMA 1994;271:918-924. Erratum in: JAMA 1994; 271:1830.*
9. Bowden C, Göğüş A, Grunze H, Häggström L, Rybakowski J, Vieta E. *A 12-week, open, randomized trial comparing sodium valproate to lithium in patients with bipolar I disorder suffering from a manic episode. Int Clin Psychopharmacol 2008;23:254-262.*
10. Bowden CL, Mosolov S, Hranov L, Chen E, Habil H, Kongsakon R, *et al. Efficacy of valproate versus lithium in mania or mixed mania: a randomized, open 12-week trial. Int Clin Psychopharmacol 2010;25:60-67.*
11. Clothier J, Swann AC, Freeman T. *Dysphoric mania. J Clin Psychopharmacol 1992;12(1 Suppl):13S-16S.*
12. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, *et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord 2018;20:97-170.*
13. Grunze H, Kasper S, Goodwin G, Bowden C, Baldwin D, Licht RW, *et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part II: treatment of mania. World J Biol Psychiatry 2003;4:5-13.*
14. Cipriani A, Reid K, Young AH, Macritchie K, Geddes J. *Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. Cochrane Database Syst Rev 2013;2013:CD003196.*
15. Kang MG, Qian H, Keramatian K, Chakrabarty T, Saraf G, Lam RW, *et al. Lithium vs valproate in the maintenance treatment of bipolar I disorder: a post- hoc analysis of a randomized double-blind placebo-controlled trial. Aust N Z J Psychiatry 2020;54:298-307.*
16. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, *et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry 2013;14:154-219.*
17. Kessing LV, Hellmund G, Geddes JR, Goodwin GM, Andersen PK. *Valproate v. lithium in the treatment of bipolar disorder in clinical practice: observational nationwide register-based cohort study. Br J Psychiatry 2011;199:57-63.*
18. Coombes BJ, Markota M, Mann JJ, Colby C, Stahl E, Talati A, *et al. Dissecting clinical heterogeneity of bipolar disorder using multiple polygenic risk scores. Transl Psychiatry 2020; 10:314.*
19. O'Connell KS, Coombes BJ. *Genetic contributions to bipolar disorder: current status and future directions. Psychol Med 2021;51:2156-2167.*
20. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, *et al. The World Federation of Societies of*

Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry 2010;11:81-109.

21. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Azorin JM, *et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: acute and long-term treatment of mixed states in bipolar disorder. World J Biol Psychiatry 2018;19:2-58.*
22. National Collaborating Centre for Mental Health (UK). *Bipolar disorder. The NICE guideline on the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care. London:The British Psychological Society and The Royal College of Psychiatrists;2014.*
23. Fountoulakis KN, Yatham L, Grunze H, Vieta E, Young A, Blier P, *et al. The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), part 2: review, grading of the evidence, and a precise algorithm. Int J Neuropsychopharmacol 2017;20:121-179.*
24. Yatham LN, Chakrabarty T, Bond DJ, Schaffer A, Beaulieu S, Parikh SV, *et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) recommendations for the management of patients with bipolar disorder with mixed presentations. Bipolar Disord 2021;23:767-788.*
25. Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes T, Cipriani A, *et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2016;30:495-553.*
26. Poolsup N, Li Wan Po A, de Oliveira IR. *Systematic overview of lithium treatment in acute mania. J Clin Pharm Ther 2000;25:139-156.*
27. Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, *et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 2011;378:1306-1315.*
28. Pope HG Jr, McElroy SL, Keck PE Jr, Hudson JI. *Valproate in the treatment of acute mania. A placebo-controlled study. Arch Gen Psychiatry 1991;48:62-68.*
29. Bowden CL, Swann AC, Calabrese JR, Rubenfaer LM, Wozniak PJ, Collins MA, *et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. J Clin Psychiatry 2006;67:1501-1510.*
30. Freeman TW, Clothier JL, Pazzaglia P, Lesem MD, Swann AC. *A double-blind comparison of valproate and lithium in the treatment of acute mania. Am J Psychiatry 1992;149:108-111.*
31. Macritchie K, Geddes JR, Scott J, Haslam D, de Lima M, Goodwin G. *Valproate for acute mood episodes in bipolar disorder. Cochrane Database Syst Rev 2003;(1):CD004052.*
32. Jochim J, Rifkin-Zybutz RP, Geddes J, Cipriani A. *Valproate for acute mania. Cochrane Database Syst Rev 2019;10:CD004052.*
33. Sköld M, Rolstad S, Joas E, Kardell M, Pålsson E, Goodwin GM, *et al. Regional lithium prescription rates and recurrence in bipolar disorder. Int J Bipolar Disord 2021;9:18.*
34. Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. *Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004;161:217-222.*
35. Severus E, Taylor MJ, Sauer C, Pfennig A, Ritter P, Bauer M, *et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. Int J Bipolar Disord 2014;2:15.*
36. Kishi T, Ikuta T, Matsuda Y, Sakuma K, Okuya M, Mishima K, *et al. Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials. Mol Psychiatry 2021;26:4146-4157.*
37. Yee CS, Vázquez GH, Hawken ER, Biorac A, Tondo L, Baldessarini RJ. *Long-term treatment of bipolar disorder with valproate: updated systematic review and meta-analyses. Harv Rev Psychiatry 2021;29:188-195.*
38. Kessing LV, Bauer M, Nolen WA, Severus E, Goodwin GM, Geddes J. *Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review of evidence from observational studies. Bipolar Disord 2018;20:419-431.*
39. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, *et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 2014;1:351-359.*
40. Garnham J, Munro A, Slaney C, Macdougall M, Passmore M, Duffy A, *et al. Prophylactic treatment response in bipolar disorder: results of a naturalistic observation study. J Affect Disord 2007;104:185-190.*
41. Rosso G, Solia F, Albert U, Maina G. *Affective recurrences in bipolar disorder after switching from lithium to valproate or vice versa: a series of 57 cases. J Clin Psychopharmacol 2017;37:278-281.*
42. BALANCE investigators and collaborators, Geddes JR, Goodwin GM, Rendell J, Azorin JM, Cipriani A, *et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010;375:385-395.*
43. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. *Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. World Psychiatry 2016;15:53-58.*

44. Bohlken J, Riedel-Heller S, Bauer M, Kostev K. *Bipolar disorder and outcomes of monotherapy with lithium, valproate, quetiapine, olanzapine, venlafaxine, and citalopram. Pharmacopsychiatry 2021;54:126-130.*
45. Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, *et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. Arch Gen Psychiatry 2000;57:481-489.*
46. Suppes T, Vieta E, Gustafsson U, Ekholm B. *Maintenance treatment with quetiapine when combined with either lithium or divalproex in bipolar I disorder: analysis of two large randomized, placebo-controlled trials. Depress Anxiety 2013;30:1089-1098.*
47. McElroy SL, Keck PE. *Dysphoric mania, mixed states, and mania with mixed features specifier: are we mixing things up? CNS Spectr 2017;22:170-176.*
48. Secunda SK, Katz MM, Swann A, Koslow SH, Maas JW, Chuang S, *et al. Mania. Diagnosis, state measurement and prediction of treatment response. J Affect Disord 1985;8: 113-121.*
49. Himmelhoch JM, Mulla D, Neil JF, Detre TP, Kupfer DJ. *Incidence and signficiance of mixed affective states in a bipolar population. Arch Gen Psychiatry 1976;33:1062-1066.*
50. Keller MB, Lavori PW, Coryell W, Andreasen NC, Endicott J, Clayton PJ, *et al. Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. JAMA 1986;255:3138-3142.*
51. Goldberg JF, Garno JL, Leon AC, Kocsis JH, Portera L. *Rapid titration of mood stabilizers predicts remission from mixed or pure mania in bipolar patients. J Clin Psychiatry 1998;59: 151-158. Erratum in: J Clin Psychiatry 1998;59:320.*
52. Swann AC, Bowden CL, Morris D, Calabrese JR, Petty F, Small J, *et al. Depression during mania. Treatment response to lithium or divalproex. Arch Gen Psychiatry 1997;54:37-42.*
53. Fountoulakis KN, Kontis D, Gonda X, Siamouli M, Yatham LN. *Treatment of mixed bipolar states. Int J Neuropsychopharmacol 2012;15:1015-1026.*
54. Prien RF, Himmelhoch JM, Kupfer DJ. *Treatment of mixed mania. J Affect Disord 1988;15:9-15.*
55. Backlund L, Ehnvall A, Hetta J, Isacsson G, Agren H. *Identifying predictors for good lithium response - a retrospective analysis of 100 patients with bipolar disorder using a life-charting method. Eur Psychiatry 2009;24:171-177.*
56. Sportiche S, Geoffroy PA, Brichant-Petitjean C, Gard S, Khan JP, Azorin JM, *et al. Clinical factors associated with lithium response in bipolar disorders. Aust N Z J Psychiatry 2017;51: 524-530.*
57. Woo YS, Yoon BH, Song JH, Seo JS, Nam B, Lee K, *et al. Clinical correlates associated with the long-term response of bipolar disorder patients to lithium, valproate or lamotrigine: a retrospective study. PLoS One 2020;15:e0227217.*
58. Lee J, Baek JH, Lee D, Ahn SW, Yang SY, Choi Y, *et al. Defining phenotypes of long-term lithium and valproate response, including combination therapy: a modified application of the Alda scale in patients with bipolar disorders. Int J Bipolar Disord 2020;8:36.*
59. Calabrese JR, Woyshville MJ, Kimmel SE, Rapport DJ. *Predictors of valproate response in bipolar rapid cycling. J Clin Psychopharmacol 1993;13:280-283.*
60. Pfennig A, Schlattmann P, Alda M, Grof P, Glenn T, Müller-Oerlinghausen B, *et al. Influence of atypical features on the quality of prophylactic effectiveness of long-term lithium treatment in bipolar disorders. Bipolar Disord 2010;12:390-396.*
61. Maj M, Pirozzi R, Magliano L, Bartoli L. *Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 1998;155:30-35.*
62. Kupka RW, Luckenbaugh DA, Post RM, Leverich GS, Nolen WA. *Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies. J Clin Psychiatry 2003;64:1483-1494.*
63. Hui TP, Kandola A, Shen L, Lewis G, Osborn DPJ, Geddes JR, *et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. Acta Psychiatr Scand 2019;140:94-115.*
64. Grillault Laroche D, Etain B, Severus E, Scott J, Bellivier F; ISBD-IGSLI Joint Task Force on Lithium Treatment. *Socio-demographic and clinical predictors of outcome to long-term treatment with lithium in bipolar disorders: a systematic review of the contemporary literature and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. Int J Bipolar Disord 2020;8:40.*
65. Kleindienst N, Engel R, Greil W. *Which clinical factors predict response to prophylactic lithium? A systematic review for bipolar disorders. Bipolar Disord 2005;7:404-417.*
66. Degenhardt EK, Gatz JL, Jacob J, Tohen M. *Predictors of relapse or recurrence in bipolar I disorder. J Affect Disord 2012;136:733-739.*
67. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. *Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry 1999;156:1264-1266.*
68. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. *Mania: differential effects of previous depressive and manic episodes on response to treatment. Acta Psychiatr Scand 2000;101:444-451.*
69. Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, *et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 2003;28:1374-1382.*
70. Frankenburg FR, Zanarini MC. *Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. J Clin Psychiatry 2002;63:442-446.*

71. O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE. *Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry 1991;159:123-129.*
72. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. *Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. Arch Gen Psychiatry 2005;62:37-45.*
73. Young LT, Cooke RG, Robb JC, Levitt AJ, Joffe RT. *Anxious and non-anxious bipolar disorder. J Affect Disord 1993;29: 49-52.*
74. Keller MB, Lavori PW, Kane JM, Gelenberg AJ, Rosenbaum JF, Walzer EA, *et al. Subsyndromal symptoms in bipolar disorder. A comparison of standard and low serum levels of lithium. Arch Gen Psychiatry 1992;49:371-376.*
75. Maj M, Arena F, Lovero N, Pirozzi R, Kemali D. *Factors associated with response to lithium prophylaxis in DSM III major depression and bipolar disorder. Pharmacopsychiatry 1985; 18:309-313.*
76. Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, *et al. Is response to prophylactic lithium a familial trait? J Clin Psychiatry 2002;63:942-947.*
77. Grof P, Alda M, Grof E, Zvolsky P, Walsh M. *Lithium response and genetics of affective disorders. J Affect Disord 1994;32:85-95.*
78. Mendlewicz J, Fieve RR, Stallone F. *Relationship between the effectiveness of lithium therapy and family history. Am J Psychiatry 1973;130:1011-1013.*
79. Duffy A, Alda M, Milin R, Grof P. *A consecutive series of treated affected offspring of parents with bipolar disorder: is response associated with the clinical profile? Can J Psychiatry 2007;52:369-376.*
80. Coryell W, Akiskal H, Leon AC, Turvey C, Solomon D, Endicott J. *Family history and symptom levels during treatment for bipolar I affective disorder. Biol Psychiatry 2000; 47:1034-1042.*
81. Yazici O, Kora K, Uçok A, Tunali D, Turan N. *Predictors of lithium prophylaxis in bipolar patients. J Affect Disord 1999; 55:133-142.*
82. Masui T, Hashimoto R, Kusumi I, Suzuki K, Tanaka T, Nakagawa S, *et al. A possible association between missense polymorphism of the breakpoint cluster region gene and lithium prophylaxis in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:204-208.*
83. Sarantidis D, Waters B. *Predictors of lithium prophylaxis effectiveness. Prog Neuropsychopharmacol 1981;5:507-510.*
84. Dunner DL, Fieve RR. *Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 1974;30:229-233.*
85. Yang YY. *Prophylactic efficacy of lithium and its effective plasma levels in Chinese bipolar patients. Acta Psychiatr Scand 1985;71:171-175.*
86. Rybakowski JK, Suwalska A, Skibinska M, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Hauser J. *Response to lithium prophylaxis: interaction between serotonin transporter and BDNF genes. Am J Med Genet B Neuropsychiatr Genet 2007;144B:820-823.*
87. Okuma T. *Effects of carbamazepine and lithium on affective disorders. Neuropsychobiology 1993;27:138-145.*
88. Maj M, Starace F, Nolfe G, Kemali D. *Minimum plasma lithium levels required for effective prophylaxis in DSM III bipolar disorder: a prospective study. Pharmacopsychiatry 1986;19: 420-423.*
89. Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, *et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. J Clin Psychiatry 2005;66:111-121.*
90. Rosenthal NE, Rosenthal LN, Stallone F, Fleiss J, Dunner DL, Fieve RR. *Psychosis as a predictor of response to lithium maintenance treatment in bipolar affective disorder. J Affect Disord 1979;1:237-245.*
91. Tohen M, Waternaux CM, Tsuang MT. *Outcome in mania. A 4-year prospective follow-up of 75 patients utilizing survival analysis. Arch Gen Psychiatry 1990;47:1106-1111.*
92. Cipriani A, Hawton K, Stockton S, Geddes JR. *Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ 2013;346:f3646.*
93. Song J, Sjölander A, Joas E, Bergen SE, Runeson B, Larsson H, *et al. Suicidal behavior during lithium and valproate treatment: a within-individual 8-year prospective study of 50,000 patients with bipolar disorder. Am J Psychiatry 2017;174: 795-802.*
94. Antolín-Concha D, Lähteenvuo M, Vattulainen P, Tanskanen A, Taipale H, Vieta E, *et al. Suicide mortality and use of psychotropic drugs in patients hospitalized due to bipolar disorder: a Finnish nationwide cohort study. J Affect Disord 2020;277:885-892.*
95. Ragazan DC, Eberhard J, Berge J. *Sex-specific associations between bipolar disorder pharmacological maintenance therapies and inpatient rehospitalizations: a 9-year Swedish national registry study. Front Psychiatry 2020;11:598946.*
96. Alda M. *The phenotypic spectra of bipolar disorder. Eur Neuropsychopharmacol 2004;14 Suppl 2:S94-S99.*
97. Cade JF. *Lithium salts in the treatment of psychotic excitement. Med J Aust 1949;2:349-352.*
98. Lempérière T. *[Brief history of the development of valproate in bipolar disorders]. Encephale 2001;27:365-372. French.*
99. Lähteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E, *et al. Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. JAMA Psychiatry 2018;75:347-355. Erratum in: JAMA Psychiatry 2022. doi: 10.1001/jamapsychiatry.2022.0241. [Epub ahead of print]*
100. Del Matto L, Muscas M, Murru A, Verdolini N, Anmella G, Fico G, *et al. Lithium and suicide prevention in mood disorders and in the general population: a systematic review.*

Neurosci Biobehav Rev 2020;116:142-153.

101. Judd LL, Schettler PJ, Solomon DA, Maser JD, Coryell W, Endicott J, *et al. Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. J Affect Disord 2008;108:49-58.*
102. Perlis RH, Ostacher MJ, Patel JK, Marangell LB, Zhang H, Wisniewski SR, *et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006;163:217-224.*
103. Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, *et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2004;161:2222-2229.*
104. Coryell W, Leon AC, Turvey C, Akiskal HS, Mueller T, Endicott J. *The significance of psychotic features in manic episodes: a report from the NIMH collaborative study. J Affect Disord 2001;67:79-88.*
105. Ozyildirim I, Cakir S, Yazici O. *Impact of psychotic features on morbidity and course of illness in patients with bipolar disorder. Eur Psychiatry 2010;25:47-51.*
106. Canuso CM, Bossie CA, Zhu Y, Youssef E, Dunner DL. *Psychotic symptoms in patients with bipolar mania. J Affect Disord 2008;111:164-169.*
107. Post RM, Leverich GS, Kupka RW, Keck PE Jr, McElroy SL, Altshuler LL, *et al. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. J Clin Psychiatry 2010;71:864-872.*
108. Hantouche EG, Akiskal HS, Azorin JM, Châtenet-Duchêne L, Lancrenon S. *Clinical and psychometric characterization of depression in mixed mania: a report from the French National Cohort of 1090 manic patients. J Affect Disord 2006;96:225-232.*
109. Perugi G, Micheli C, Akiskal HS, Madaro D, Socci C, Quilici C, *et al. Polarity of the first episode, clinical characteristics, and course of manic depressive illness: a systematic retrospective investigation of 320 bipolar I patients. Compr Psychiatry 2000;41:13-18.*
110. Kupfer DJ, Frank E, Grochocinski VJ, Luther JF, Houck PR, Swartz HA, *et al. Stabilization in the treatment of mania, depression and mixed states. Acta Neuropsychiatr 2000;12:110-114.*
111. Maj M, Magliano L, Pirozzi R, Marasco C, Guarneri M. *Validity of rapid cycling as a course specifier for bipolar disorder. Am J Psychiatry 1994;151:1015-1019.*
112. Tondo L, Hennen J, Baldessarini RJ. *Rapid-cycling bipolar disorder: effects of long-term treatments. Acta Psychiatr Scand 2003;108:4-14.*
113. Patel RS, Manikkara G, Chopra A. *Bipolar disorder and comorbid borderline personality disorder: patient characteristics and outcomes in US hospitals. Medicina (Kaunas) 2019;55:13.*
114. Simhandl C, König B, Amann BL. *A prospective 4-year naturalistic follow-up of treatment and outcome of 300 bipolar I and II patients. J Clin Psychiatry 2014;75:254-262; quiz 263.*