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

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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-
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 Acute 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) |
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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 or meta-analysis |
|                     | 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 |
|                     | Category II | Treatment studies: limited positive evidence from controlled studies or evidence from at least one other type of quasi-experimental study |
|                     | Category III | Treatment studies: evidence from uncontrolled studies |
|                     | 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 1                |
|                     | VPA       |           | Level 1                |
| CINP 2017           | VPA       |           | 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; 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        | VPA       |           |           | Level 2                |
| CINP 2017          |           | VPA       | Li        |           | Level 4                |
| WFSBP 2010         |           | VPA       | Li        |           | Category D             |
| BAP 2016           |           | VPA       | Li        |           | Category B             |

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.

*If depressive symptoms are less severe.

Table 5. Maintenance treatment phase

| Guidelines         | 1° choice | 2° choice | Categories of evidence |
|--------------------|-----------|-----------|------------------------|
| WFSBP 2013         | Li        | VPA       | Category A             |
| NICE 2014          | Li        | VPA       | Category B             |
| BAP 2016           | Li        | VPA       | Level 1                |
| CINP 2017          | Li        | VPA       | Level 1                |
| CANMAT/ISBD 2018   | Li 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.

*Limited to prevention of depression. *If manic predominant polarity.

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 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].
Table 6. Acute mixed states treatment phase

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

CANNMAT/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.

*Manic episodes with mixed features (DSM-5). *Depressive episodes with mixed features (DSM-5). *Mixed episodes (DSM-IV).

Table 7. Mixed state prevention treatment

| Guidelines          | 1° choice | 2° choice | 3° choice | Categories of evidence |
|---------------------|-----------|-----------|-----------|------------------------|
| WFSBP 2018          | VPA       | Li        |           | Category D              |
| BAP 2016            | Li        |           |           | Category I              |
| CANMAT/ISBD 2021    | Li        | VPA       |           | Level 2, 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 choice treatment 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 [62-64], but 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 valproamide 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-
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Consistent 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].

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**Conflicts of Interest**

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

**Author Contributions**

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