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Lithium treatment of Bipolar disorder in adults: A systematic review of randomized trials and meta-analyses

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Abstract

The aim of the study was to systematically review the hard evidence alone, concerning lithium efficacy separately for the phases and clinical facets of Bipolar disorder (BD).

The PRISMA method was followed to search the MEDLINE for Randomized Controlled trials, Post-hoc analyses and Meta-analyses and review papers up to August 1st 2020, with the combination of the words ‘bipolar’, ‘manic’, ‘mania’, ‘manic depression’ and ‘manic depressive’ and ‘randomized’.

Trials and meta-analyses concerning the use of lithium either as monotherapy or in combination with other agents in adults were identified concerning acute mania (N=64), acute bipolar depression (N=78), the maintenance treatment (N=73) and the treatment of other issues ($N = 93$). Treatment guidelines were also identified. Lithium is efficacious for the treatment of acute mania including concomitant psychotic symptoms. In acute bipolar depression it is efficacious only in combination with specific agents. For the maintenance phase, it is efficacious as monotherapy mainly in the prevention of manic while its efficacy for the prevention of depressive episodes is unclear. Its combinations increase its therapeutic value. It is equaly efficacious in rapid and non-rapid cycling patients, in concomitant obsessive-compulsive symptoms, alcohol and substance abuse, the neurocognitive deficit, suicidal ideation and fatigue

The current systematic review provided support for the usefulness of lithium against a broad spectrum of clinical issues in Bipolar disorder. Its efficacy is comparable to that of more recently developed agents

Keywords

Lithium; Systematic review; Bipolar disorder

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1. Introduction

Lithium is still the gold standard of bipolar therapies, and it is still widely used, in spite of recent advances in the field and the increased use of antipsychotics and specific antiepileptics,. However, it is true that its use is steadily declining (Karanti et al., 2016; Kessing et al., 2016; Parabiaghi et al., 2015), but peculiarly, it tends to be used for longer times than most alternatives (Baldessarini et al., 2008, 2007, 2019)

Lithium is a rare chemical element with atomic number 3 and its symbol is ‘Li’. It belongs to the alkali metal group, is the lightest metal and the least dense solid element. Two stable lithium isotopes can be found in nature. It is soft, silver-white and highly reactive and inflammable. In nature, it can be found in pegmatitic minerals, or in ocean water, but is usually obtained from brines and clays.

The main use of lithium is for the treatment of Bipolar disorder (BD), although it seems to be also useful in the augmentation of antidepressants in refractory unipolar depression, in the treatment of schizophrenia as well as in a variety of disorders characterized by impulsivity and aggression. The general idea is that lithium manifests a robust efficacy for all treatment phases of BD. It seems also to be useful for preventing suicidal behavior in patients with bipolar or major depressive disorder.

Although trace amounts exist in all organisms, there are no known physiological functions for lithium and live organisms can survive without it. In spite of this, lithium has been used as medication already since the late 19th century.

The specific biochemical mechanism of lithium action in mania is unknown. Interestingly unlike many other psychoactive drugs, it does not have any psychotropic effect in normal individuals at therapeutic concentrations. Treatment with lithium demands regular serum level tests and monitoring of thyroid and kidney function. Dehydration can result in increasing lithium levels. Serum lithium concentrations are recommended to be in the 0.4–1.2 mmol/l range (lower end of the range for maintenance therapy and the elderly, higher end for children) on samples taken 12 h after the preceding dose (Amdisen, 1977; Chen et al., 2004; Perlis et al., 2002; Solomon et al., 1996).

Lithium treatment for BD was approved in 1961 in France, in 1966 in the UK, in 1967 in Germany, and in 1970 in Italy and the US. In 1974, this application was extended to its use as a preventive agent for manic-depressive illness.

A list of references for further study on the history of lithium as a treatment option in psychiatry is included in the webappendix (weblist 1)

The **aim** of the current manuscript was to perform a systematic review of lithium for the treatment of BD. To this day a dedicated up-to-date review of the hard evidence concerning lithium efficacy separately for the phases and clinical facets of Bipolar disorder (BD) is lacking. There are several reviews and meta-analyses that examine it alone or together with other agents, however the conclusions on the basis of similar data seem to be rather different

and this is reflected in the different way treatment guidelines refer to lithium, and they also fail to synthesize a comprehensive picture.

The safety and tolerability of lithium were not among the main aims of the current paper.

2. Material and methods

The PRISMA method was followed to search the literature (for references see weblist 2). The method included the search for three kinds of publications:

- **a.** Randomized Controlled trials (RCTs; placebo controlled as well as clinical trials with an active comparator with the compounds used as monotherapy or add-on therapy).
- **b.** Post-hocan alyses of RCTs
- **c.** Meta-analyses and review papers
- **d.** Only English language papers were considered

For this purpose, the MEDLINE was searched up to August 1st 2020 in order to locate RCTs with the combination of the words ‘bipolar’, ‘manic’, ‘mania’, ‘manic depression’ and ‘manic depressive’ and ‘randomized’. Also, relevant review articles were scanned and their reference lists were utilized. A list of these articles is included in weblist 3 of the webappendix. No other databases were searched.

Combination were distinguished from add-on trials and were considered separately because combination trials include the initiation of combination treatment from the beginning in unselected patients, while add-on trials refer to patients more or less resistant to initial treatment and the adjunct agent is added at a subsequent point in order to improve this unsatisfactory result.

Combination and add-on treatment trials who considered lithium in an arm which included ‘mood stabilizers’ or ‘lithium or valproate’ or treatment as usual’ (TAU) are discussed separately from the others.

The search and selection of studies was completed by one of the authors (KNF) and verified by the other two. The results of the PRISMA search, and the selection of studies step by step are shown in Fig. 1.

3. Results on the efficacy of lithium in the treatment of bd

3.1. Acute mania (N=64)

3.1.1. Monotherapy (*N* = 5)—In total, there are 5 RCTs investigating the efficacy of lithium in comparison to placebo in acutely manic or mixed BD patients. Their details are shown in table 1. All of them are positive, and thus the conclusions are strong. The first study which was conducted in 1971 did not follow a methodology which is accepted today as scientific standard (Stokes et al., 1971). The next four followed a modern methodology. The results suggested a response rate versus placebo of 49% vs. 22–25% (Bowden et al.,

1994, 2005) and 45.8% vs. 34.4% (Keck et al., 2009). Remission rates were (49% vs. 22.1%) (Bowden et al., 2005) and 40% vs. 28.2% (Keck et al., 2009). The changes in the YMRS score from baseline in comparison to placebo were −15.2 vs. −6.7 (Bowden et al., 2005), −12.9 vs. −7.7 and −13.8 vs, −8.4 (Kushner et al., 2006) and −12.0 vs. −9.0 (Keck et al., 2009). These results suggest a rough number needed to treat (NNT) equal to 5–6 with onset of therapeutic effect at day 7 (Bowden et al., 1994, 2005; Keck et al., 2009; Kushner et al., 2006). One interesting finding in one of these studies was that lithium was even efficacious in the treatment of concomitant psychotic symptoms and equal to quetiapine (Bowden et al., 2005), but not on concomitant depressive symptoms, which today would most likely be labelled as mixed features according to DSM-5. While the drop-out rate was comparable to placebo, more patients on placebo dropped out because of lack of efficacy while in the lithium arm more dropped out because of adverse events, the most common being nausea, vomiting, dizziness headache, insomnia, asthenia, constipation, diarrhea, tremor and weight gain.

Overall, the data are in support of the usefulness of lithium as first choice in the treatment of acute mania, including cases with psychotic symptoms. An important problem is that except from the Stokes et al., 1971 study, all the others were using lithium as an active comparator and therefore they did not focus on reporting its results in detail. The proportion of patients under lithium who failed to achieve therapeutic levels is unknown and no secondary analysis concerning different Li plasma levels exists.

3.2. Comparison of agents (*N* = 16)

Overall the data suggest that in terms of efficacy, lithium is equivalent to valproate (Bowden et al., 1994; Freeman et al., 1992) and carbamazepine (Lerer et al., 1987; Okuma et al., 1990; Small et al., 1991). However, there are some data suggesting that lithium has a broader effect in mania while the effect of the two antiepileptics might be restricted to subgroups of BD patients (Bowden et al., 1994; Freeman et al., 1992; Lerer et al., 1987). Lithium was reported to have fewer adverse effects in comparison to carbamazepine but more in comparison to valproate.

Its comparison with haloperidol suggested that haloperidol was more efficacious and faster acting, especially in severely psychotic patients (Garfinkel et al., 1980; Shopsin et al., 1975). Chlorpromazine also acted faster and might be more efficacious in more agitated patients (Platman, 1970; Prien et al., 1972; Shopsin et al., 1975). In comparison to both antipsychotics, lithium had again a broader effect on the core manic symptomatology. It was found to have equal efficacy to olanzapine in a small underpowered study (Berk et al., 1999; Shafti, 2010) and also to quetiapine (Bowden et al., 2005; Li et al., 2008) and aripiprazole (Keck et al., 2009), but was inferior to olanzapine in a larger and adequately powered study (Niufan et al., 2008). Concerning the comparison with aripiprazole, a small more recent study in males only, suggested that lithium was superior (Shafti, 2018).

Overall, lithium is similar in efficacy to the other compounds used against acute mania, but maybe with a broader efficacy at the cost of slower onset of action.

3.3. Combination treatment (*N* = 17)

Combination of lithium (600 to 1800 mg/day) and quetiapine XR (400 to 800 mg/day) was superior to quetiapine plus placebo (Bourin et al., 2014) in the treatment of acute mania. The combinations of lithium with haloperidol, lorazepam, carbamazepine, tamoxifen, and allopurinol are superior to lithium alone, but not the combination of lithium plus ziprasidone or dipyridamole. Most of these combinations had more adverse events in comparison to monotherapy (Amrollahi et al., 2011; Bowden, 2005; Garfinkel et al., 1980; Lenox et al., 1992; Machado-Vieira et al., 2008; Small et al., 1995; Weisler et al., 2003).

Three studies that reported on combinations of mood stabilizing agents (including lithium) with haloperidol vs. haloperidol monotherapy were equivocal as the outcome depended on the haloperidol dosage (Chou et al., 1999; Garfinkel et al., 1980; Klein et al., 1984). The addition of asenapine, olanzapine, risperidone, haloperidol and tamoxifen but not gabapentin and medroxyprogesterone on lithium or valproate was superior to lithium or valproate alone (Kulkarni et al., 2014, 2006; Pande et al., 2000; Sachs et al., 2002; Szegedi et al., 2012; Xu et al., 2015; Yatham et al., 2003).

Taking into consideration the data concerning combination treatment, it seems that only specific combinations of lithium (with asenapine, olanzapine, risperidone, quetiapine, carbamazepine, tamoxifen, lorazepam, allopurinolare more efficacious than monotherapy. Combinations with haloperidol seem to depend on the dosage of the antipsychotic.

3.4. Add-on treatment (*N* = 17)

In patients refractory to lithium, adding 600–1200 mg/day carbamazepine or oxcarbazepine improved the outcome (Juruena et al., 2009). However, it is of note that this study had several limitations, including that it did not specify the benefits clearly by phase of the disorder, and also did not specify an a-priory defined primary outcome.

In patients resistant to lithium, valproate, or carbamazepine, it is beneficial to add olanzapine, quetiapine, aripiprazole, asenapine or donepezil (Chen et al., 2013; Eden Evins et al., 2006; Sachs et al., 2004; Szegedi et al., 2012; Tohen et al., 2002; Vieta et al., 2008; Yatham et al., 2007), but not ziprasidone, topiramate, paliperidone, gabapentin or lovastatin (Berwaerts et al., 2011; Ghanizadeh et al., 2014; Pande et al., 2000; Roy Chengappa et al., 2006; Sachs et al., 2012a; Sachs et al., 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/day of carbamazepine) (Kramlinger and Post, 1989). Findings for the adding of allopurinol were inconclusive (Fan et al., 2012; Machado-Vieira et al., 2008).

Overall, in refractory to lithium patients, the addition of carbamazepine, oxcarbazepine, olanzapine, quetiapine, aripiprazole, asenapine or donepezil improved the outcome. The list of references is included in the webappendix (weblist 4)

3.5. Post-hoc analyses and meta-analytic studies (*N* = 16)

Overall, post hoc (Yatham et al., 2004) and meta-analytic studies (Emilien et al., 1996; Perlis et al., 2006; Scherk et al., 2007; Tamayo et al., 2010) confirm the superiority of

antipsychotics versus lithium in the treatment of acute mania. However, they also confirm that this higher efficacy comes with the cost of more frequent adverse events, mainly extrapyramidal symptoms and signs, weight gain and somnolence (Correll et al., 2010; Tarr et al., 2011a). Lithium might not be efficacious against concomitant depressive features (Ostacher et al., 2015).

Meta-analytic studies also suggest that combination treatment is superior to monotherapy, again at the cost of more frequent adverse events; however, these meta-analyses do not distinguish between add-on and combination studies and populations (Ogawa et al., 2014; Scherk et al., 2007; Smith et al., 2007; Tarr et al., 2011b).

One meta-analysis reported that the ranking in terms of efficacy for acute mania was haloperidol, risperidone, olanzapine, lithium, quetiapine, aripiprazole, carbamazepine, asenapine, valproate, and ziprasidone. According to that meta-analysis, antipsychotics were significantly more effective than mood stabilizers, however the results of that analysis do not fully support such a conclusion (Cipriani et al., 2011) and additionally it has been criticized both concerning the overall methodology but also concerning the incomplete list of RCTs which was utilized (Fountoulakis and Siamouli, 2012). A more balanced meta-analysis confirmed that the response to antipsychotics was greater and more rapid in comparison to lithium, valproate, or carbamazepine, but it did not confirm any difference between haloperidol and second generation antipsychotics (Yildiz et al., 2011). A more recent network meta-analysis did not support the superiority of any agent vs. another except for risperidone vs. aripiprazole and valproate (Yildiz et al., 2015). A fourth more recent meta-analysis reported that based on data from 1707 patients and 6 studies, in comparison to placebo, lithium was highly efficacious with OR=2.13 (95% CI: 1.73–2.63) for response and OR=2.16 (95% CI: 1.73–2.69). On the basis of data from 36 trials, lithium was more likely than placebo to cause only tremor and somnolence, and there were only limited data to suggest it is inferior only to quetiapine (OR 0.66, $N = 355$), olanzapine (OR 0.44, $N = 140$) and risperidone (MD 7.28, $n = 241$) (McKnight et al., 2019).

The list of references is included in the webappendix (weblist 5)

3.6. Acute bipolar depression (N=78)

3.6.1. Monotherapy (N=11)—Older studies provided some positive data but their methodology is not according modern standards and thus the results are difficult to interpret (Baron et al., 1975; Donnelly et al., 1978; Goodwin et al., 1969, 1972; Greenspan et al., 1970; Mendels, 1976; Noyes and Dempsey, 1974; Noyes et al., 1974; Srisurapanont et al., 1995; Stokes et al., 1971). There is only one recent and rigorously conducted 8-week trial (EMBOLDEN I). It randomized 136 patients to lithium, 265 to quetiapine and 133 to placebo. The mean age was 42.2 years, and the majority of patients were females (59.3%). The results were negative for lithium but positive for quetiapine. In that study, the mean lithium serum levels were 0.61 mEq/lt. Many patients had low lithium levels with 34.9% having levels below 0.6 mEq/lt. A post-hoc analysis reported that the results were negative in patients with lithium levels >0.8 mEq/lt and also in completers, which suggests that even in the subgroup of patients with adequate serum levels, and in those who completed the

study, lithium was not efficacious. Additionally, lithium level did not correlate with change in depression rating scores (Young et al., 2010).

In conclusion, these data do not support the use of lithium as monotherapy in acute bipolar depression

3.6.2. Comparison of treatment options (N=3)—Only recently, comparison studies involving lithium in acute bipolar depression were conducted. In one of them, 12-weeks of lithium treatment was found to result in an inferior improvement to venlafaxine monotherapy in BD-II depression, concerning both response (67.7% vs. 34.4%; $p<0.001$) and remission (58.5% vs. 28.1%; $p<0.001$) rates. In addition, there were no significant or clinically meaningful differences in the emergence of hypomanic symptoms between treatments (Amsterdam et al., 2016b). Prior treatments with antidepressants reduced the odds for response and remission equally in both arms, which means enrichment for antidepressant failure might not have favored those randomized to lithium (Amsterdam et al., 2016a). The results suggested that venlafaxine is efficacious and safe as monotherapy in BD-II depression. A second 16-week study again in BD-II depression compared lithium vs. sertraline and reported that the treatment response rate was 62.7% without significant differences between groups after accounting for dropout. Mood shifts did not differ among groups (Altshuler et al., 2017).

3.6.3. Combination treatment (N=4)—The previously mentioned study had a third arm, which was a combination of lithium plus sertraline and it did not differ in any outcome in comparison to either monotherapy (Altshuler et al., 2017).

According to a small 6 week study in BD-II depression, adding pramipexole (vs. placebo) to lithium or valproate improved the outcome (60% vs. 9%; $p = 0.02$) (Zarate et al., 2004). Another small study compared the adding of inositol or placebo for 6 weeks to lithium or valproate; the results were numerically in favor of inositol in terms of response rates (44% vs. 0%; $p = 0.053$) (Eden Evins et al., 2006). On the contrary, adding paroxetine or bupropion to a mood stabilizer (including lithium) did not improve the outcome after 26 weeks in terms of recovery rates or transient remission (Sachs et al., 2007).

Taken these data together there are some but rather weak results suggesting that combination of lithium with pramipexole or inositole but not antidepressants might improve the outcome.

3.6.4. Add-on treatment (N=44)—Overall, the data suggest that for bipolar depressed patients who experience depression while receiving lithium treatment, it is appropriate to add lamotrigine (van der Loos et al., 2010, 2011; van der Loos et al., 2009), the D2 antagonist L -sulpiride (Bocchetta et al., 1993), possibly oxcarbazepine (Juruena et al., 2009) but not imipramine (Nemeroff et al., 2001). The data on adding paroxetine and amitriptyline on lithium are equivocal (Bauer et al., 1999; Bocchetta et al., 1993; Pilhatsch et al., 2010; van der Loos et al., 2010). A small placebo-controlled adjunctive study of aripiprazole to lithium and citalopram was negative. However, that study was underpowered; the study sample was too small to detect any differences (Quante et al., 2010). One small

study on the efficacy of the antidiabetic agent pioglitazone as add-on to lithium in bipolar patients without diabetes mellitus was positive (Zeinoddini et al., 2015).

In BD patients experiencing depression during treatment with lithium or valproate, ketamine or lurasidone could be considered. In these patients lurasidone improves also anxiety and ketamine improves suicidality. However, there is one unpublished failed study with lurasidone as add-on to lithium or valproate (Sanford and Dhillon, 2015; Suppes et al., 2013) and one negative study (Suppes et al., 2016). The data are negative concerning the addition of the melatonergic antidepressant agomelatine on lithium or valproate (Yatham et al., 2016b). Response to a single ketamine infusion appears within minutes but does not last more than 3–4 days (Diazgranados et al., 2010; Loebel et al., 2014; Xu et al., 2015a; Young et al., 2000; Zarate et al., 2012).

The data are positive concerning adjunctive modafinil (a wake-promoting agent; mean dose 177 mg/day) but with a low risk of switching to mania or hypomania. Both the response and remission rates were significantly higher in the modafinil group (44% and 39%) compared with the placebo group (23% and 18%) (Frye et al., 2007). Although that study did not report a higher risk for manic switches, it has been reported that modafinil could cause subclinical switches (Fountoulakis et al., 2008). Additionally, one published study for the treatment of acute BD-I depression with adjunct armodafinil (the longer lasting isomer of modafinil; dosage 150 mg/day; $N = 128$)) on lithium, valproate or olanzapine was positive (Calabrese et al., 2014; Calabrese et al., 2010). However two other studies were negative (Ketter et al., 2015; Ostacher, 2014). A very small placebo controlled trial 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). The data on the options to treat BD patients who experience a depressed episode during treatment with mood stabilizers suggest that it is not appropriate to add ziprasidone (Sachs et al., 2011) and the data are negative also concerning bipolar spectrum depressed patients (Patkar et al., 2015). Imipramine and venlafaxine increased the risk of switching to the opposite pole without any visible therapeutic benefits in comparison to other antidepressants (Altshuler et al., 2009; Post et al., 2001; Post et al., 2006; Sachs et al., 1994; Saricicek et al., 2011; Schaffer et al., 2006; Shelton and Stahl, 2004). The literature is also negative concerning the addition of celecoxib (400 mg/day)(Nery et al., 2008) and pregnenolone (titrated to 500 mg/day) (Brown et al., 2014). Some data support the usefulness of omega-3 fatty acids as adjunctive therapy in bipolar depression, but not mania. However, the data are conflicting and inconclusive (Chiu et al., 2005; Frangou et al., 2006; Frangou et al., 2007; Keck et al., 2006; Murphy et al., 2012; Sarris et al., 2012; Stoll et al., 1999; Sylvia et al., 2013)

The list of references is included in the webappendix (weblist 6)

3.6.5. Post-hoc review and meta-analytic studies (N=17)—A 12-weeks post hoc analysis in BD-II patients suggested that while venlafaxine was superior to lithium concerning both anxiety and depressive symptoms there were no difference in quality of life (Lorenzo-Luaces and Amsterdam, 2018; Lorenzo-Luaces et al., 2018). The analysis of data from 3 double-blind (DB), placebo-controlled, 6-week studies in adults with bipolar I

depression, reported that the proportion of patients who did not meet criteria for metabolic syndrome at baseline but developed them at week 6 was similar for lurasidone plus lithium or valproate vs. monotherapy with lithium or valproate (Tocco et al., 2020). A 6-week trial reported that the combination of lurasidone plus lithium or valproate was superior in terms of response of depression and quality of life compared to lithium or valproate monotherapy (Rajagopalan et al., 2016).

A number of meta-analyses reported negative results for lithium in acute bipolar depression (Citrome et al., 2014; Cruz et al., 2010; De Fruyt et al., 2012; Gao et al., 2011; Kemp et al., 2011; Mukai et al., 2014; Silva et al., 2013; Suttajit et al., 2014; Tamayo et al., 2010; Vieta et al., 2010). One meta-analysis which focused on depressed patients with BD-II reported that there was some support for its efficacy (Swartz and Thase, 2011). A more recent one reported equal efficacy between lithium and lamotrigine and superiority to placebo (Solmi et al., 2016), while an even more recent Cochrane one was negative for lithium monotherapy (Bahji et al., 2020).

The list of references is included in the webappendix (weblist 7)

3.7. Maintenance treatment (N=72)

3.7.1. Monotherapy (N=21)—Older studies reported positive findings on the efficacy of lithium during the maintenance phase of BD but their methodology is obsolete and according to modern standards their results are difficult to interpret (Baastrup et al., 1970; Christodoulou and Lykouras, 1982; Cundall et al., 1972; Dunner et al., 1976; Fieve et al., 1976; Fyro and Petterson, 1977; Hullin et al., 1972; Kane et al., 1982; Klein et al., 1981; Mander and Loudon, 1988; Margo and McMahon, 1982; Melia, 1970; Persson, 1972; Post et al., 1992; Prien et al., 1973a, 1973b; Small et al., 1971).

More recently, four randomized placebo controlled studies concerning the efficacy of lithium in the maintenance treatment of BD were published. The first one of them was negative/ failed. The three treatment groups did not differ concerning the time to manifestation of any mood episode and this was also the case concerning manic or depressive episodes alone. The median times to 50% survival without a mood episode were 24, 40 and 28 weeks respectively. (Bowden et al., 2000). The next three were positive (Bowden et al., 2003; Calabrese et al., 2003; Weisler et al., 2011). The first of them utilized patients who maintained response for 4 consecutive weeks, and reported both lithium and lamotrigine were superior to placebo at prolonging the time to intervention for any mood episode. The median survival times were 292, 140 and 85 days, respectively. Lamotrigine was superior to placebo at prolonging the time to a depressive episode while lithium was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode. The interpretation of this study is complex, because the study sample was enriched for response to lamotrigine, although lamotrigine is not efficacious against acute manic or mixed episodes. Thus, one interpretation could be that the study sample comprised of patients which manifested spontaneous remission (Bowden et al., 2003). The next study utilized patients who maintained response for 4 consecutive weeks. The results suggested that lamotrigine was significantly superior to placebo at prolonging the time to intervention for a depressive episode while lithium at prolonging the time to intervention for a manic or

hypomanic episode (Calabrese et al., 2003). Finally, there is also one study (NCT00314184 or trial 144, also named 'SPARCLE') which investigated the efficacy and safety of lithium vs. quetiapine vs. placebo as maintenance treatment in BD-I. The study was terminated early after planned interim analysis provided positive results. The results suggested that the time to recurrence of any mood event was significantly longer for lithium and for quetiapine vs. placebo. Both lithium and quetiapine significantly increased time to recurrence of both manic events and depressive events compared with placebo (Weisler et al., 2011). The details of these four studies are shown in table 2.

Two of the positive studies supported the usefulness of lithium in the prevention of manic but not depressive episodes irrespective of the polarity of the index episodes (Bowden et al., 2003; Calabrese et al., 2003). The third study supports its usefulness also in the prevention of depressive episodes (Weisler et al., 2011). It is important to note that the study samples were not enriched in favor of a response to lithium. On the contrary, one study had a sample enriched for response to quetiapine (Weisler et al., 2011), while two others had samples enriched for lamotrigine (Bowden et al., 2003; Calabrese et al., 2003) which, however, is not efficacious against acute mania.

In conclusion, the data so far support the usefulness of lithium in the prevention of manic and maybe for depressive episodes.

3.7.2. Comparison of treatments (N=20)—There are a number of studies comparing lithium with carbamazepine (Coxhead et al., 1992; Denicoff et al., 1997; Hartong et al., 2003; Lusznat et al., 1988; Placidi et al., 1986; Simhandl et al., 1993; Small et al., 1991; Stoll et al., 1989; Watkins et al., 1987), and, overall, the data suggested that both agents were comparable in terms of efficacy. There are some data in favor of a superiority of lithium in the treatment of more 'classic' patients, but in the rest of patients the two agents seem to be comparable. Lithium was also comparable to valproate (Bowden et al., 2000; Calabrese et al., 2005), to olanzapine in preventing deprssive episodes (but olanzapine was superior in preventing manic episodes) (Tohen et al., 2005, 2016) and also to aripiprazole (El-Mallakh et al., 2012) in terms of prevention of mood episodes.

There was a difference in the clinical profiles of lithium and lamotrigine. Lamotrigine was more efficacious in the prevention of depressive episodes and lithium in the prevention of manic, hypomanic, and mixed episodes (Bowden et al., 2003; Calabrese et al., 2003).

When compared to antidepressants, the available data suggested that lithium was superior to imipramine for the prevention of depression in BD-I patients episodes (Prien et al., 1973b, 1984) but inferior to fluoxetine in BD-II patients (Amsterdam and Shults, 2010). Another maintenance study reported equal efficacy between venlafaxine and lithium in the prevention of depressive relapses although there was a tendency of better performance for venlafaxine (Amsterdam et al., 2015).

3.7.3. Combination treatment (N=9)—There are three early studies which investigated the combination of lithium with another agent. The lithium plus imipramine combination was not more efficacious than lithium monotherapy (Kane et al., 1982; Prien et

al., 1984), and lithium or carbamazepine monotherapy was not inferior to their combination (Denicoff et al., 1997).

Also the combination of lithium, carbamazepine, or valproate with perphenazine was not better than mood stabilizer monotherapy; on the contrary, combination treatment was associated with a shorter time to depressive relapse, more drop-outs, and increased rates of dysphoria and depressive symptoms (Zarate and Tohen, 2004). Similarly negative were the results for the lithium or valproate combination with olanzapine (Tohen et al., 2004) while, on the contrary, the combination with quetiapine had significant advantages irrespective of index episode, mood stabilizer and rapid cycling status (Suppes et al., 2009; Vieta et al., 2008). Positive results were also reported for their combination with ziprasidone (Bowden et al., 2010). Lurasidone combination with lithium or valproate was superior to lithium or valproate alone after 28 weeks of treatment and concerning any mood episode but only in non-rapid cycling patients with an index episode of depression (Calabrese et al., 2017)

In conclusion, the data suggest that combination of lithium with quetiapine, lurasidone or ziprasidone but not with holanzapine, perphenazine, carbamazepine or imipramine.

3.7.4. Add-on treatment (N=7)—The data are negative for the addition of oxcarbazepine (Vieta et al., 2008a) and equivocal for lamotrigine (van der Loos et al., 2011) to lithium.

Two studies suggest that adding aripiprazole (Marcus et al., 2011) or ziprasidone (Citrome, 2010) to lithium or valproate significantly prolongs the time to relapse.

It is reported that patients who respond to treatment with lithium, valproate or carbamazepine plus antidepressants are more likely to maintain response with continuation of the combined treatment; however, those patients who manifest only a partial acute response are unlikely to further improve when the same treatment is continued (Altshuler et al., 2009). Also adjunctive asenapine to lithium or valproate was well tolerated for up to 52 weeks, but no efficacy data were reported from that trial (Szegedi et al., 2012). Risperidone or olanzapine adjunctive to lithium or valproate therapy for 24 weeks was beneficial but continuation of risperidone beyond this period does not reduce the risk of relapse (Yatham et al., 2016)

These studies suggest that in patients refractory to lithium, adding aripiprazole, risperidone, olanzapine or ziprasidone improves the outcome. The list of references is included in the webappendix (weblist 8)

3.7.5. Post-hoc, review and meta-analyses (N=24)—Concerning lithium, it has been reported that only at plasma levels between 0.6–1.2 mEq/lt is it efficacious in the prevention of both manic and depressive episodes (Nolen and Weisler, 2013). Another post-hoc analysis did not confirm its efficacy in the prevention of depressive episodes (Calabrese et al., 2003b; Goodwin et al., 2004). These results still held true when early relapses that occurred in the first 90 or 180 days were excluded from the analysis (Calabrese et al., 2006). The lack of efficacy of lithium in a subgroup of patients might be due to lithium-induced thyroid function abnormalities in a subpopulation of patients (Frye et al.,

2009). Overall, lamotrigine performed better in comparison to lithium in terms of remission and the persistence of subsyndromal symptoms (Frye et al., 2006).

Twenty-four weeks of combination of lithium with an atypical antipsychotic was superior to lithium monotherapy in preventing mania but not depression (Kang et al., 2020). In BD and MDD patients with lithium-induced nephrogenic diabetes insipidus randomized to atorvastatin or placebo, there found no significant differences in mood outcomes at 12-week follow-up (Fotso Soh et al., 2020)

Adjunctive risperidone treatment on mood stabilizer was observed to reduce the risk of manic episodes during the first 24 weeks, but not after 24 weeks. Treatment did not appear to reduce the risk of depressive episodes (Valdes et al., 2019). Two studies supported the usefulness of RLAI (Bobo and Shelton, 2010) and of ziprasidone for the maintenance treatment of BD-I disorder in adults as an adjunct to lithium or valproate (Citrome, 2010).

A fair number of meta-analyses focused on lithium. One confirmed its efficacy but failed to find sufficient evidence to prove that a lithium-withdrawal relapse phenomenon exists, that is patients relapse soon after stopping lithium and the symptomatology turns refractory to treatment (Davis et al., 1999). Three others confirmed the prophylactic anti-manic efficacy of lithium but were equivocal for the prophylactic efficacy against depressive episodes (Burgess et al., 2001; Geddes et al., 2004; Severus et al., 2014). One reported only a generic prophylactic effect, equal to that of lamotrigine (Oya et al., 2019). Another one supported its prophylactic efficacy against depressive episodes (Popovic et al., 2011), while a more recent one reported that maybe the prophylactic effect concerning depressive episodes might take longer to appear in comparison to that of manic episodes (Taylor, 2018). Antipsychotics were reported to be superior to lithium (Vazquez et al., 2015a; Vazquez et al., 2015b).

Interestingly, one meta-analysis calculated the relapse rate under lithium maintenance treatment. It reported that the recurrence of any mood episode within the first 18 months was 39.8% (95% CI: 32.8%-47.1%); depressive episodes, 25.6% (95% CI: 18.8%-34.0%); manic/hypomanic/mixed episodes, 18.5% (95% CI: 13.7%-24.7%); all-cause discontinuation rate, 67.0% (95% CI: 57.2%-75.5%); and discontinuation rate due to adverse events, 8.7% (95% CI: 5.1%-14.7%) (Kishi et al., 2020).

The issue of combination treatment has been at the focus of two meta analyses. They both reported negative conclusions for the addition of antidepressants on mood stabilizers (Beynon et al., 2009; Ghaemi et al., 2008). A third analysis suggested that no monotherapy was associated with a significantly reduced risk for both manic/mixed and depressive relapse, and only quetiapine plus lithium or divalproex was associated with a significantly reduced risk for relapse towards both the manic/mixed and depressive pole (Vieta et al., 2011). This specific meta-analysis also pointed out that the majority of studies included samples enriched for response to a specific agent during the acute phase.

The list of references is included in the webappendix (weblist 9)

3.8. Treatment of other issues (*N* = 93)

A complete list of the 93 papers concerning the usefulness of lithium in the treatment of other issues in Bipolar patients is included in the appendix

Mixed episodes—Mixed episodes are no longer accepted as a diagnostic entity by DSM-5; instead 'mixed features' is included as a specifier and this creates a degree of confusion for future treatment recommendations since the two concepts differ significantly. So far, mixed episodes have been combined with pure manic episodes in RCTs and results have been reported together.

3.8.1. Treatment of acute mixed episodes: The effect of lithium specifically on mixed episodes is unknown and a post-hoc analysis of one of these RCTs confirmed the efficacy of lithium only in classic manic but not mixed patients albeit the number of mixed patients was too small to allow a firm conclusion. The combination of olanzapine plus lithium or valproate has positive data concerning both components. The data concerning the combination of haloperidol or risperidone plus lithium or valproate were negative. A trial of celecoxib (400 mg/day) did not support its efficacy as an adjunct in the treatment of depressive or mixed episodes.

The related references are shown in weblist 10

3.8.2. Maintenance treatment of mixed bipolar episodes: Lithium had negative results in patients with a dysphoric manic index episode. On the other hand, the data are in support of the combination of quetiapine plus lithium or valproate but not for the addition of aripiprazole on lithium or valproate.

The related references are shown in weblist 11

3.9. Treatment of rapid cycling patients

3.9.1. Treatment of acute episodes in rapid cycling patients—It seems that lithium monotherapy has a week but positive effect in the treatment of acute episodes in rapid cycling patients. Lithium and venlafaxine had equal efficacy in terms of response (47%) in BD-II depression in rapid cycling patients in comparison to non-rapid cyclers

On the contrary, when the combination of lithium and divalproex was not effective, the further addition of lamotrigine did not seem to add anything in terms of efficacy

The related references are shown in weblist 12

3.9.2. Relapse prevention in rapid cycling patients—The data so far suggest that lithium and divalproex are equally efficacious and also that the combination of them is not better than lithium alone. One small study reported that the combination of lithium plus carbamazepine did better than either agent alone. Overall, the widely believed concept among clinicians that divalproex is more effective than lithium in the long-term management of rapid-cycling BD was not supported by a trial on 139 patients. Another study confirmed the efficacy and safety of quetiapine add-on to lithium or divalproex in the prevention of

mood episodes in rapid cycling BD-I patients with most recent episode manic/mixed or depressive. There was a North American study with a similar design as the previous one reporting similar results. The data were negative concerning the administration of 6 g/day of ethyl-eicosapentanoate (EPA) as augmentation of treatment with mood stabilizers in rapid cycling patients with bipolar depression.

One meta-analysis suggested that lithium is at least partially efficacious in rapid cycling patients, another one suggested there is no clear advantage of any treatment option vs. the others. The meta-analysis of 20 studies published from 1974 to 2002 comparing subjects with rapid and non-rapid cycling BD reported that in contrast to common beliefs, lithium prophylaxis has at least partial efficacy in a considerable number of rapid cyclers, especially when antidepressants are avoided. Hypothyroidism may be associated with mood destabilization in vulnerable patients.

The related references are shown in weblist 13

3.10. Treatment of special conditions

3.10.1. Treatment of comorbid substance abuse disorder—There are two placebo controlled trials suggesting that the combination of valproate and lithium in BD patients with co-occurring alcohol dependence improves both mood and alcohol use symptoms. Lithium might be useful in the treatment of concomitant substance and polysubstance abuse.

The related references are shown in weblist 14

3.10.2. Treatment of comorbid obsessive-compulsive disorder—Memantine was more efficacious than placebo when added on lithium plus olanzapine with 78.94% of patients in the memantine group vs. 36.84% patients in the placebo group demonstrating more than 34% decline in the Yale Brown Obsessive Compulsive Behavior Scale score ($p < 0.01$) at the 16-weeks endpoint. Similarly aripiprazole was efficacious as add-on to lithium with 91.30% patients in the aripiprazole group vs. 4.34% in the placebo group having $a >$ 34% decline in YBOCS score ($p < 0.01$) at the 8-weeks endpoint

The related references are shown in weblist 15

3.10.3. Treatment of neurocognitive disorder—The comparison of lithium vs. quetiapine maintenance treatment for 12 months suggested that there were greater improvements in performance in lithium-treated patients in comparison to quetiapine-treated in terms of phonemic fluency. Otherwise, there were no other significant differences between the two arms

The related references are shown in weblist 16

3.10.4. Suicide—There is much discussion concerning the potential anti-suicidal efficacy of specific drugs and especially of lithium. However almost all the data come from studies of naturalistic and epidemiological nature and no controlled studies exist.

There is only one post-hoc analysis which investigated suicidality in BD-I patients during treatment with olanzapine in combination with lithium or divalproex. In mixed patients with residual suicidality, suicidal thoughts were associated with somatic discomfort, agitated depression, and psychosis. It seems that combination therapy with olanzapine plus lithium ($N = 36$) vs. lithium alone ($N = 22$) significantly reduced the score in the suicidal item of the HAMD by 58% vs. 29% ($p<0.05$) within 1 week, and all associated symptoms within 2 weeks by averages of 31% vs. 12% ($p<0.05$). One trial on suicide attempters with BD confirmed reduction of suicidal thoughts with lithium or valproate treatment, and the two agents had equal efficacy.

One review concluded that there is no definitive evidence as to whether or not lithium has an anti-suicidal effect. Another recent meta-analysis confirmed the anti-suicidal effect of lithium vs. placebo but another one suggested it is superior only to carbamazepine. A meta-review did not add much to the discussion. The most recent meta-analysis reported a general beneficial effect of lithium on overall mortality in BD but not specifically concerning suicidality.

The related references are shown in weblist 17

3.10.5. Fatigue—The pooled analysis of two trials confirmed the efficacy of ketamine infusions for the treatment of fatigue in patients resistant to lithium or valproate monotherapy, but there are no data on the efficacy of lithium as monotherapy.

The related references are shown in weblist 18

4. Safety issues with lithium therapy (The related references are shown in weblist 19)

The discussion of safety was not part of the systematic review, but a brief elaboration on the subject would be important. It is well known that lithium plasma levels have a narrow therapeutic window (recommended plasma level 0.6–1.2 mmol/L; lower end of the range for maintenance therapy and the elderly, higher end for children) on samples taken 12 h after the preceding dose. Comprehensive guidelines concerning lithium treatment and optimal therapeutic serum levels are available and should be applied, and a recent review provides up-to-date information on its safety. However, it seems that only a small minority of patients is monitored according to these guidelines. Extensive and comprehensive reviews exist on the issue of safety and tolerability (Gitlin, 2016)

The place of lithium in the various treatment guidelines

A number of treatment guidelines are dealing with lithium were identified and their recommendations were registered. For the comparison of the value the most important of these guidelines attribute to lithium only the most recent (after 2005) were utilized. Because different guidelines utilize different systems of grading and recommendation, their comparison is difficult and incomplete. The comparison of the most important of them in terms of the recommendations of their latest versions concerning lithium, is shown in

table 3. The table is based on a translation by the authors of the current paper, of the recommendations these guidelines made.

The related references are shown in weblist 20

5. Discussion

One-hundred and fifty years after its first use in Psychiatry by Hammond, 75 years since the experiments of John Cade and 50 years after the works of Mogens Schou, Baastrup and others, lithium remains the golden standard in the treatment of Bipolar disorder, and has the reputation of a legendary, extraordinary and almost magic treatment option.

Of course, in medicine as well as in Psychiatry, nothing is magic. Lithium, like all other treatment options has indications as well as limitations, but accumulated data suggest it is highly efficacious against a broad spectrum of facets of Bipolar disorder, which is maybe the most multifacet mental illness with a complex treatment.

Lithium has a proven efficacy in many of these facets, and more important, its mode of function seems to be quite different from all the known psychopharmacological agents, although it is still largely unknown. Thus, it serves not only as a valuable treatment option but also as a different paradigm for the understanding of the neurobiology of BD, although unfortunately, during the recent years its use is declining. This decline in use is probably the result of the increasing use of atypical antipsychotics in the treatment of BD. These agents might have a slightly increased rate of adverse events in comparison to lithium, but they do not cause any long-term problems from the essential organs like the kidney, or the thyroid, although some of them do induce metabolic syndrome and diabetes melitus and rarely cardiomyopathy. Additionally, they do not demand the measuring of serum levels and their safe dose range is large. Essentially it seems unlikely to die because of atypical antipsychotics overdosage, which is not the case with lithium.

The current systematic review identified and registered all the available hard data. This led to a number of unexpected findings, including the efficacy of lithium against psychotic symptoms in acute mania as well as its efficacy in non-classic cases of mania. Overall, the literature suggests that there are some data favouring lithium in more ‘classic’ cases of euphoric mania, while antiepileptics and antipsychotics appear to have a better efficacy for patients with mixed features and those with comorbidity. This is not supported by more recent data.

Conclusively, the current systematic review provided support for the usefulness of lithium against a broad spectrum of clinical issues in BD. Overall, the data are in support of the usefulness of lithium in the treatment of acute mania, including cases with psychotic symptoms. It could be inferior to antipsychotics especially in the more severe cases, but with a more favourable adverse effects profile. It is especially efficacious against acute mania in combination with antipsychotics and antiepileptics. Its efficacy against acute bipolar depression is not proven either as monotherapy or in combinations although some encouraging data exist, especially with some combinations. Concerning the maintenance

phase, its efficacy as monotherapy or in combination is solidly proven in the prevention of manic episodes but not beyond doubt concerning the prevention of depressive episodes

Its efficacy is proven only in combination with olanzapine against acute mixed episodes and with quetiapine in their prevention. There seems to be equally efficacious in rapid in comparison to non-rapid cycling patients. It could be useful as monotherapy or in combination with valproate in the treatment of BD with concomitant alcohol and substance abuse and in combination with memantine or aripiprazole when there is a concomitant OCD

As a general picture, it is useful in the treatment of BD as monotherapy but also in combination with a significant variety of conventional and unconventional agents. Efficacy is comparable with that of more recently developed agents, while clinical experience suggests that a subgroup of patients respond so perfectly to lithium that it is as if they were suffering from a ‘lithium deficiency disorder’ (which is not the case of course in Bipolar disorder). With the availability of monitoring, the chance of problematic adverse events could be minimized and the achieving and sustaining of therapeutic blood levels is not a problem of access to laboratory or equipment any more for most of the world.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflict of interest

In the past Dr Fountoulakis has received grants and served as consultant, advisor or CME speaker or received support for participating in congresses by AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Pfizer, the Pfizer Foundation, Sanofi-Aventis, Servier, Shire and others

Since the beginning of 2020 he has no conflict of interest at all, and currently serves as director of Cochrane Greece.

Dr Tohen is a former full time employee at Lilly (1997 to 2008). He has been a consultant for AstraZeneca, Abbott, BMS, Lilly, GSK, J&J, Otsuka, Roche, Lundbeck, Elan, Alkermes, Allergan, Intracellular Therapies, Merck, Minerva, Pamlab, Alexza, Forest, Teva, Sunovion, Gedeon Richter, and Wyeth. His-spouse is a former employee at Lilly (1998–2013)

Dr. Zarate is a full-time U.S government employee. He is listed as a coinventor on a patent for the use of ketamine in major depression and suicidal ideation. Dr. Zarate is listed as a coinventor on a patent for the use of (2R,6R)-hydroxynorketamine, (*S*)-dehydronorketamine and other stereoisomeric dehydro and hydroxylated metabolites of (R,S)-ketamine metabolites in the treatment of depression and neuropathic pain. Dr. Zarate is listed as coinventor on a patent application for the use of (2R,6R)hydroxynorketamine and (2S,6S)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation and post-traumatic stress disorders. Dr. Zarate has assigned his patent rights to the U.S. government but will share a percentage of any royalties that may be received by the government.

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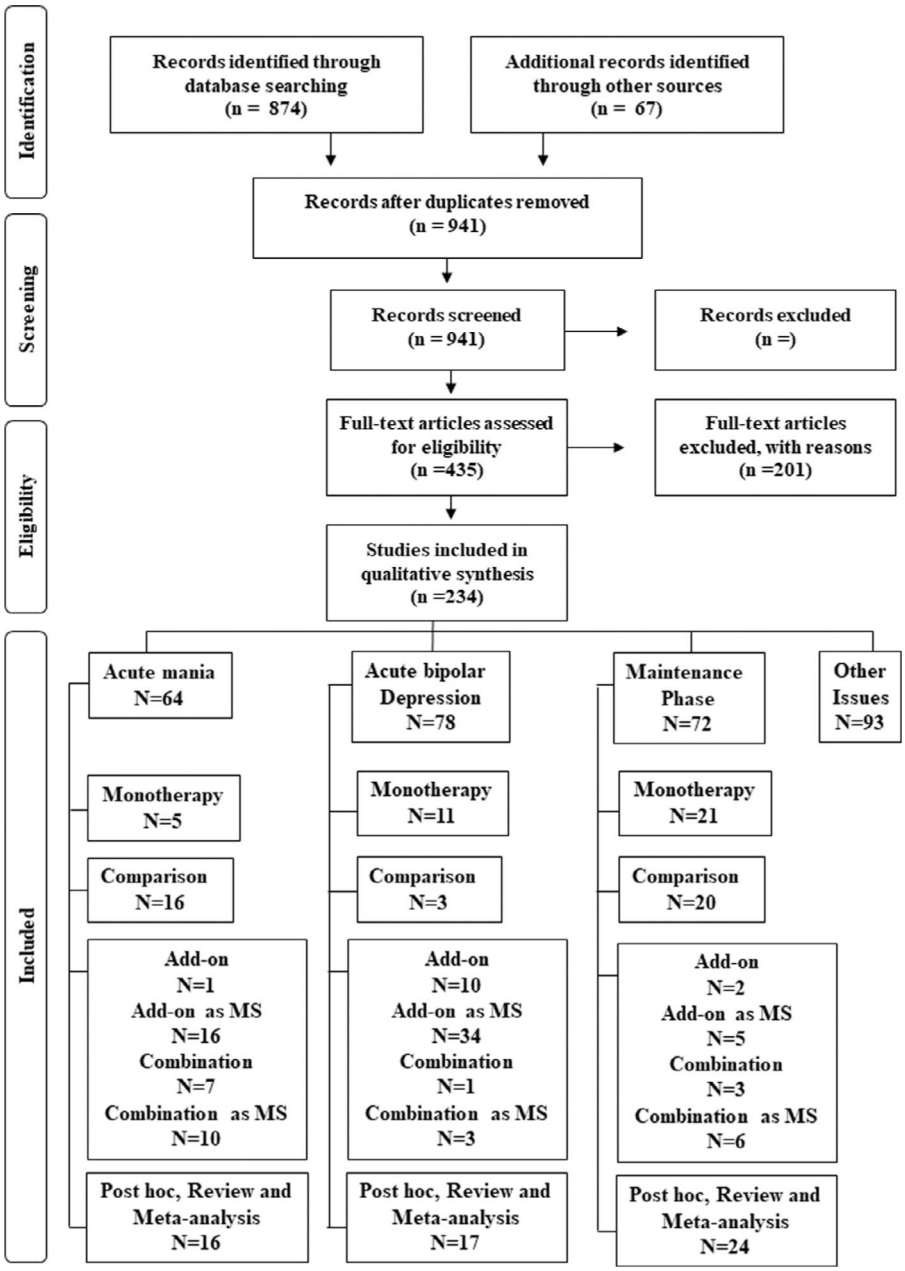

Fig. 1.

The PRISMA flowchart. Some studies belong to multiple groups, therefore the partial numbers do not equal the number of studies in top category. ‘as MS’ means that in these studies, lithium was utilized in a treatment arm together with valproate and carbamazepine.

Table 1.

Placebo-controlled monotherapy studies of lithium in the treatment of acute mania.

Study	Duration	N (males)	Age in yrs	Lithium dosage	Li levels (mEq/lt)	Results
Stokes et al., 1971	More than a year of alternating 7–10 day periods	38 (17) inpatients	10–79	0–5 meq/kg	0.93	Significant improvement during periods of lithium treatment vs. periods with placebo
Bowden et al., 1994	3 wks	Li: 36 (26) Val: 69 (36) Plc: 74 (42)	39.1 ± 11.2 40.4 ± 10.8 39.0 ± 10.0	1950 mg/day	1.2	Li was equal to Val-and superior to plc
Bowden et al., 2005	12 wks	Li: 98 (58) Quet: 107 (60) Plc: 95 (55)	38.8 (18–73) 38.0 (18–72) 41.3 (18–70)		0.80	Li was equal to Quet and superior to plc
Kushner et al., 2006 PDMD 004	3 wks	Li: 113 (46) Tpm 200: 110 (48) Tpm 400:110 (58) Plc: 111 (57)	43±14 42±14 43±14 42±13	1258±221 mg/day	0.8–1.2 mEq/L	Li was superior to both Tpm and plc
Kushner et al., 2006 PDMD 008	3 wks	Li: 114 (41) Tpm 400:116 (42) Plc: 112 (45)	42±11 40±12 41±12			Li was superior to both Tpm and plc
Keck et al., 2009	3 wks	Li: 160 (84) Ari: 155 (79) Plc: 165 (86)	39.6 ± 10.5 39.6 ± 10.6 39.8 ± 11.3	≤1500 mg/day	0.76 (0.6–1.2 mEq/L)	Li was equal to Ari and superior to plc

Ari: Aripiprazole; Li: Lithium; Tpm: Topiramate; Quet: Quetiapine; Val: valproate/divalproax.

Table 2

Placebo-controlled monotherapy studies of lithium in the maintenance treatment of BD.

Study	Duration	N (males)	Age in yrs	Lithium Dosage (mg/day)	Li levels (mEq/lt)	Comments and results
Bowden et al., 2000	52 wks	Li: 91 (43) Val: 187 (93) Plc: 94 (48)	40.3 ± 9.8 38.9 ± 12.7 38.7±11.9		0.8–1.2	Neither lithium nor divalproex did better than placebo (failed study)
Bowden et al., 2003	18 months	Li: 46 (22) Lam: 59 (26) Plc: 70 (34)	41.9± 11.3 40.6 ± 12.6 40.9±11.0		0.8–1.1	Lamotrigine was superior to placebo at prolonging the time to a depressive episode while lithium was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode.
Calabrese et al., 2003	18 months	Li: 121 (48) Lam: 221 (91) Plc: 121 (60)	43.6 ± 12.3 44.1 ± 11.7 42.1 ± 13.0	900 (450–1800)	0.8–1.1	Most recent episode depressive. Lamotrigine was significantly superior to placebo at prolonging the time to intervention for a depressive episode while lithium at prolonging the time to intervention for a manic or hypomanic episode
Weisler et al., 2011	104 wks	Li: 364 (155) Quet: 404 (182) Plc: 404 (210)	38.4 ± 12.5 39.9 ± 12.3 40.0 ± 12.9		0.63±0.45 (0.6–1.2)	Lithium and quetiapine significantly increased time to recurrence of both manic events and depressive events compared with placebo.

Lam: Lamotrigine; Li: Lithium; Plc: placebo Quetiapine; Val: valproate/divalproax.

a incalculable * estimated by the authors.

Table 3

Comparison of the place of lithium in the most important treatment guidelines

	CANMAT/ ISBD (Yatham et al., 2018)	WFSBP (Grunze et al., 2018, 2009, 2010, 2013)	CINP (Fountoulakis et al., 2017a, 2017b, 2020)	BAP (Goodwin et al., 2016)	Korean (Woo et al., 2018)	NICE (NICE, 2020)	RANZCP (Malhi et al., 2018)	Current review
Acute mania	1	3	2	2	1	1*	1	M, IC
Acute classic mania	1	2	2		1			M, IC
Acute mixed episodes (DSM-IV)	NR	NR	1 IC	IC	1			IC
Acute mania with mixed features (DSM-5 like)	NR	NR	NR		1			no
Acute mania with psychotic features	IC	NR	3		IC			M, IC
Acute Bipolar depression	1	5	4	2	1	1*	1	IC
Acute Bipolar depression with mixed features (DSM-5 like)		NR			IC			
Acute bipolar depression with psychotic features								
BD-II acute depression	2							
Prevention of any episode	1	1	1	1	1	1*		M, IC
Prevention of Manic episodes	1	1	1				1	M, IC
Prevention of depressive episodes	1	4	1					maybe
Prevention of Mixed episodes		5						IC
BD-II Hypomanic episode			1		1			
BD-II maintenance phase	1		1		1			
Rapid cycling patients	1	6	2					M, IC
Acute treatment of concomitant anxiety								
Treatement of consomitant Obsessive compulsive symptoms	1							IC
Alcohol abuse	1 IC, 2 MN		IC					M
Substance use disorder	1							IC
Neurocognitive disorder								IC
Suicide ideation	1	yes	1					M, IC
Fatigue								IC

	CANMAT/ ISBD (Yatham et al., 2018)	WFSBP (Grunze et al., 2018, 2009, 2010, 2013)	CINP (Fountoulakis et al., 2017a, 2017b, 2020)	BAP (Goodwin et al., 2016)	Korean (Woo et al., 2018)	NICE (NICE, 2020)	RANZCP (Malhi et al., 2018)	Current review
Safety during acute treatment	+	+	+	+	+	+	+	+
Tolerability during acute treatment	+	+	+	+	+	+	+	+
Safety during maintenance	++	++	++	++	++	++	++	++
Tolerability during maintenance	++	++	++	++	++	++	++	++

Numbers correspond to the respected intervention step by the guideline, as extracted by the authors (not all guidelines utilize steps).

IC: in combination,.

M: monotherapy,.

NR: not recommended,.

* but not in primary care.

+: good.

++: very good.