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Lithium therapy and weight change in people with bipolar disorder: A systematic review and meta-analysis

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ABSTRACT

Lithium remains the gold standard maintenance treatment for Bipolar Disorder (BD). However, weight gain is a side effect of increasing relevance due to its metabolic implications. We conducted a systematic review and meta-analysis aimed at summarizing evidence on the use of lithium and weight change in BD. We followed the PRISMA methodology, searching Pubmed, Scopus and Web of Science. From 1003 screened references, 20 studies were included in the systematic review and 9 included in the meta-analysis. In line with the studies included in the systematic review, the meta-analysis revealed that weight gain with lithium was not significant, noting a weight increase of 0.462 Kg ($p = 0158$). A shorter duration of treatment was significantly associated with more weight gain. Compared to placebo, there were no significant differences in weight gain. Weight gain was significantly lower with lithium than with active comparators. This work reveals a low impact of lithium on weight change, especially compared to some of the most widely used active comparators. Our results could impact clinical decisions.

1. Introduction

Bipolar Disorder (BD) is a chronic disorder characterized by recurrent mood fluctuations. It is associated with both high morbidity and mortality (Carvalho et al., 2020), hence long-term prophylactic maintenance treatment is recommended (Vieta et al., 2011). Lithium, introduced in 1949 (Cade, 1949), remains probably the most effective drug for long-term therapy in BD, preventing both depressive and manic recurrences and reducing the risk of suicide, dementia and all-cause mortality (Geddes et al., 2004; Del Matto et al., 2020; Severus et al., 2014; Miura et al., 2014). It is consequently recommended as first line treatment in most guidelines (Yatham et al., 2018; Malhi et al., 2015; Grunze et al., 2013; Verdolini et al., 2020), either as monotherapy or combination (Wingård et al., 2019).

Despite the long-term effectiveness of lithium, there are concerns regarding its safety profile. Aside from the narrow therapeutic index, the need for monitoring, and some frequent side effects such as diarrhea, polydipsia and tremor, lithium's toxicity profile includes an increased risk of renal failure and reduced urine-concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain (McKnight et al., 2012; Tondo et al., 2017).

Weight gain is among the most distressing lithium-associated side effects for patients (Gitlin, 2016). In one study, despite ranking third in frequency, it ranked first among patients' rating of bothersome side effects of lithium use and second amongst bothersome side effects leading to lithium discontinuation (Gitlin et al., 1989). Nevertheless, weight gain remains as one of the less studied complications related with lithium treatment. Besides this, there is a high prevalence of weight gain

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and weight-related conditions due to other medications used to treat BD. Among these, metabolic syndrome (around 37 %) (Vancampfort et al., 2013), obesity (around 21 %) (Krishnan, 2005), type 2 diabetes mellitus (around 14 %) and non-alcoholic fatty liver disease (22–42 %,) are prominent (Soto-Angona et al., 2020; Vancampfort et al., 2016). These associated comorbidities lead to cardiovascular disease and higher premature mortality in BD patients (Correll et al., 2017; Staudt Hansen et al., 2019; Kessing et al., 2015; Hayes et al., 2015). People with BD who suffer weight-gain and related comorbidities also have a worse clinical course, more depression, associated physical comorbidities, and higher suicide rates (Hayes et al., 2015; Fagiolini et al., 2003; Torrent et al., 2008).

To date, findings about lithium-induced weight gain are controversial and inconsistent (Gitlin, 2016; McKnight et al., 2012). In fact, definitions of weight change and duration of observation differ across studies, precluding any simple averaging of lithium-induced weight gain. From the available studies, it is also unclear whether weight gain correlates with lithium dose or levels (Gitlin, 2016). Furthermore, the majority of studies include BD patients concurrently treated with psychotropic medications other than lithium, such as antipsychotics, valproate, and some antidepressants, which might contribute to weight gain (Torrent et al., 2008). Finally, genetic factors may be much more relevant than lithium itself (Bopp et al., 2019).

In this context, lithium-induced weight change is of increasing scientific and clinical interest for both patients and practitioners, considering that weight gain is usually one of the most dreaded side effects for patients and that in many occasions, it is the main reason for treatment discontinuation (Gitlin et al., 1989).

To provide evidence-based information for decision-making and accurate information to patients and professionals, the primary aim of this study is to systematically investigate whether lithium induces weight change and, if so, to quantify the magnitude of this association, compared to active comparators or placebo. The secondary aim of this study is to examine whether lithium-induced weigh change is moderated by duration of lithium therapy.

2. Methods

This review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher et al., 2009) followed by the Meta-analyses of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000); the review protocol was registered on PROSPERO database (Registration number: CRD42020144702).

2.1. Search strategy

A search strategy was developed based on the research question, according to the PICO format (Table 1) (Miller, 2001).

Studies were identified using the following databases: MEDLINE/PubMed, Scopus, and Web of Science from any time to August 1st 2019. The systematic search was performed by four independent researchers blinded to each other's results (SGC, AGP, MPC, and FGA).

The following search strategy was used in PubMed and then adapted for Scopus and Web of Science: (bipolar disorder[Mesh] OR bipolar disorder*[TI] OR bipolar I disorder[TI] OR bipolar II disorder[TI] OR bipolar-I[ti] OR bipolar-II[ti] OR mania[TI] OR manic[TI]) AND (lithium[Mesh] OR lithium[TI]) AND (weight[ALL] OR triglyceride* [ALL] OR cholesterol[ALL] OR HDL[ALL] OR VLDL[ALL] OR LDL[ALL] OR glycated hemoglobin OR glycated haemoglob* OR BMI OR body mass index OR blood glucose OR plasma glucose OR plasma lipids OR blood lipids OR serum lipids); no restrictions were applied. Finally, the reference lists of relevant identified papers were hand-searched for further relevant studies.

Table 1
Search strategy based on the research question, according to the PICO format.

Parameter	Criteria
Population	Human participants clinically diagnosed with Bipolar Disorder.
Intervention	Lithium monotherapy.
Comparator	Placebo or active comparator.
Outcomes	Weigh change and related metabolic measures.

After completing the searches, duplicate studies were removed, four independent investigators (SGC, AGP, MPC and FGA) screened independently the titles and abstracts for eligibility. A list of potentially eligible studies was developed by consensus, and the full texts were assessed by the above two teams. Both teams then applied eligibility criteria and developed a final list of studies to include. A fifth investigator (FC) supervised the process; any divergences were dealt through consensus.

2.2. Study selection

We included longitudinal studies evaluating the effect of lithium on weight change. Randomized controlled trials (RCTs) comparing lithium with placebo, or other active comparators in patients with BD were included. Prospective cohort studies comparing patients with and without lithium treatment and cross-over studies were also considered. No restriction on study time length or language were applied. Studies including parameters related to weight were sought (i.e., BMI, weight in kg or lb; the latter was converted to kg).

We excluded animal, *in vitro,* and cell culture studies, as well as those on the effects of drugs on body weight involving lithium, but not reporting results for each drug separately, absence of a lithium monotherapy arm, or lithium administered only as adjunctive therapy. Other exclusion criteria were reviews, editorials, opinion papers, letters-to-the-editor providing no original data, studies reporting on the same sample as other published studies, selective data reporting, duplicates, congress/conference abstracts, non-peer reviewed journals or papers, studies not reporting effects on body weight and related measures or studies involving other diagnoses than BD. Meta-analyses and reviews were used as evidence to support information that could not be drawn from individual studies.

For each outcome, all studies meeting inclusion criteria were assessed and tabulated for the narrative systematic review, but only the highest available form of evidence as RCTs were included in the formal meta-analysis.

2.3. Outcomes and data extraction

The main outcomes investigated were those related with body weight change: baseline and follow-up weight (kg or lb), baseline and follow-up BMI, weight change from baseline (kg or lb), BMI change from baseline, percentage of weight change (%), and clinically significant change in bodyweight (>7% total weight in kg).

An independent search and extraction of data according to an *a priori* data extraction checklist were performed independently and in duplicate by the aforementioned four investigators. The following information was extracted: first author; year of publication; study design; study duration; country where the study was conducted; bipolar disorder subtype (I or II) if stated; mood status; sample size; weight change in lithium and control groups after treatment (endpoint minus baseline weight); lithium doses and blood levels; duration of treatment; active comparator or placebo, active comparator doses and blood levels when applicable. For all measures, when available, standard deviation (SD) and standard error (SE) were extracted.

2.4. Quality assessment of the included studies

We rated the quality of eligible studies through the assessment of their risk of bias, using the Cochrane Collaboration Risk of Bias tool 2.0

(RoB) (Sterne et al., 2019). We classified each study into a high, low, unclear risk category arising from the randomization, intervention adherence (deviation from intended interventions), missing outcome data, outcome measurement, and selective reporting domains, which in turn affected the overall quality of the study.

2.5. Data synthesis and statistical analysis

The meta-analyses were conducted in Comprehensive Meta-Analysis 3.01 using a random-effects model to account for heterogeneity between studies. Effect sizes were presented as differences in means (Kg) (with 95 % confidence intervals (CI)). The following outcomes were explored in separate analyses: (i) The difference in weight in people with BD receiving lithium at follow up compared to baseline, (ii) The difference in weight change in people receiving lithium compared to placebo or other active treatments (only compared against active treatments that are recommended for maintenance treatment of BD). As an additional analysis, we also performed a subgroup analysis to study if trial duration influenced the treatment effect. Given the paucity of available data, we were unable to conduct the planned analysis on the effect of lithium treatment on other metabolic parameters as BMI, glucose, triglycerides and cholesterol. Heterogeneity was assessed with I^2 test. Significance was set at $p < 0.05$.

3. Results

3.1. Search strategy

The search flow-diagram and the main results are reported in Fig. 1. MEDLINE/Pubmed search produced 375 records, Scopus yielded 438 and Web of Science 467. Twelve additional records were identified through other sources/reference lists. All eligible studies were incidentally in English. Of 714 unduplicated records, after screening by title or abstract, 63 full-text articles were retrieved and assessed for eligibility. Of these, 43 articles were excluded. Reasons for exclusion are provided in Fig. 1.

The remaining 20 articles (Findling et al., 2019; Gao et al., 2018; Yaramala et al., 2020; Amsterdam et al., 2016; Hayes et al., 2016;

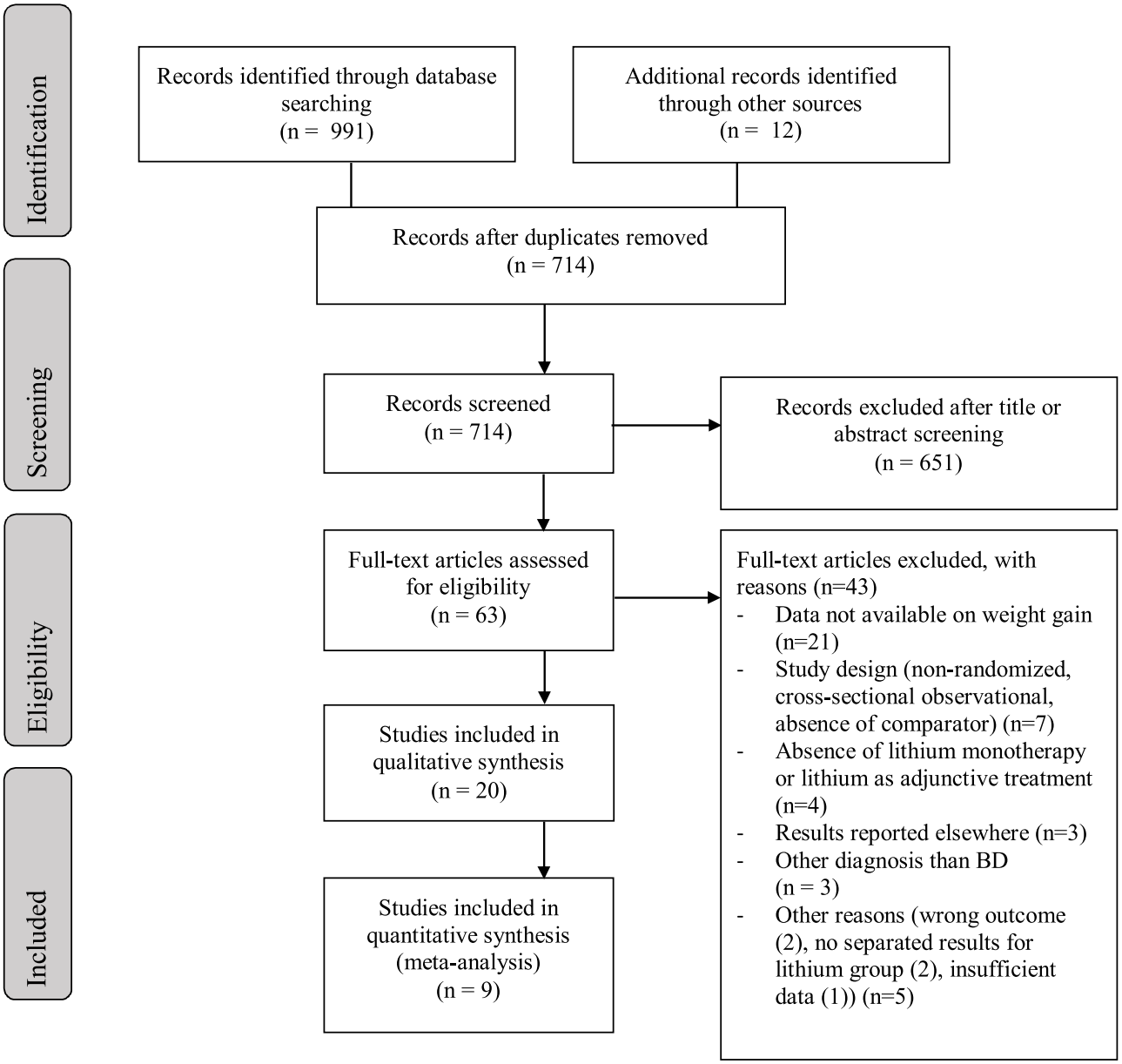

Fig. 1. PRISMA Flow diagram of the included studies.

Findling et al., 2015; Geller, 2012; McIntyre et al., 2011; Bowden et al., 2010; Keck et al., 2009; Amsterdam and Shults, 2008; Niufan et al., 2008; Bowden et al., 2008; Tohen et al., 2005; Bowden et al., 2005; Calabrese et al., 2005, 2003; Bowden et al., 2003, 2000; Peselow et al., 1980) reported qualitative information on weight change with lithium treatment compared to placebo and/or active comparator; these were suitable for the narrative synthesis. Of them, 9 articles (Findling et al., 2019; Gao et al., 2018; Yaramala et al., 2020; Amsterdam et al., 2016; Findling et al., 2015; Geller, 2012; Bowden et al., 2010; Keck et al., 2009; Tohen et al., 2005) were suitable for the meta-analysis and were included.

3.2. Characteristics of studies included in the systematic review

The characteristics of the included studies in the systematic review, together with a narrative synthesis of the study results and the quality assessment with the Cochrane Collaboration Risk of Bias tool 2.0 (RoB), of the appraised evidence are reported in Tables 2 and 3.

The 20 studies included a total of 10,812 participants with BD (3844 following treatment with lithium, 6372 with active comparator and 596 with placebo). Regarding BD subtype, 10 studies were on BD I, 2 studies on BD II and 8 studies on either both or undefined. Mood status was reported as manic or mixed episode in 13 studies, depressive in 3 studies and both or undefined in 4 studies (Table 2). Sample sizes for each study ranged from 31 to 6671 participants. The age of the participants ranged from 10 to 44 years.

Of the included studies, 18 studies were RCTs, some of them with an open label acute treatment phase prior to a double blind maintenance phase and 2 were prospective cohort studies (Hayes et al., 2016; Peselow et al., 1980). All but three studies, which focused on children and adolescents (Findling et al., 2019, 2015; Geller, 2012) were conducted in adult populations with BD. Active comparators included quetiapine (Gao et al., 2018; Yaramala et al., 2020; Hayes et al., 2016; Bowden et al., 2005), venlafaxine (Amsterdam et al., 2016; Amsterdam and Shults, 2008), divalproex or sodium valproate (Hayes et al., 2016; Geller, 2012; Bowden et al., 2010, 2008; Calabrese et al., 2005; Bowden et al., 2000), olanzapine (Hayes et al., 2016; Niufan et al., 2008; Tohen et al., 2005), risperidone (Geller, 2012), aripiprazole (McIntyre et al., 2011; Keck et al., 2009), and lamotrigine (Calabrese et al., 2003; Bowden et al., 2003).

The weight change measures from baseline were very heterogeneous among studies, including: 1) mean weight change from baseline 2) BMI; 3) body weight at different timepoints (baseline, end of the study, different weeks); 4) proportion of patients with clinically relevant (>7% from baseline) weight gain or loss, 5) proportion of patients with >15% weight gain, 6) proportion of patients presenting weight gain or loss as an adverse effect/event, 7) change in weight *z* score (change score is the week value minus the baseline value; baseline is defined as the first visit of the efficacy phase mean ± SD), 8) mean weight change by baseline BMI category (<23 kg/m^2, 23–27 kg/m^2 or >27 kg/m^2).

Most studies reported, to a variable extent, some degree of weight gain with lithium, but few stated the statistical significance of weight change. Eight studies showed a greater weight gain with the active comparator than with lithium therapy (Yaramala et al., 2020; Hayes et al., 2016; Geller, 2012; Bowden et al., 2010; Niufan et al., 2008; Tohen et al., 2005; Bowden et al., 2005, 2000), 4 studies did not show significant differences in weight gain between lithium and active comparators (McIntyre et al., 2011; Keck et al., 2009; Calabrese et al., 2005; Bowden et al., 2003), and 3 studies showed greater weight gain with lithium than active comparators (Amsterdam et al., 2016; Amsterdam and Shults, 2008; Bowden et al., 2003). Six studies found no statistically significant difference in weight gain between lithium and placebo (Findling et al., 2019, 2015; Bowden et al., 2005; Keck et al., 2009; Bowden et al., 2005; Calabrese et al., 2003; Bowden et al., 2000), while only one study found increased weight gain with lithium compared to placebo (Peselow et al., 1980).

3.3. Characteristics of studies included in the meta-analysis

The 9 studies included in the meta-analysis were all RCTs, and had a total of 2212 participants (991 following treatment with lithium, 1014 with active comparator and 207 with placebo). Sample sizes for each study ranged from 31 to 482 participants, and study durations varied from 8 to 52 weeks. The age of participants ranged from 10 to 43 years.

3.4. Results of the meta-analysis

We reported the results according to the different weight change comparisons investigated:

3.4.1. Weight change during lithium treatment

3.4.1.1. Weight change during lithium treatment: difference in means of kg, at follow up compared to baseline. A total of 9 studies, comprising 9 unique comparisons and 991 participants, were included for these meta-analyses, reported in Fig. 2, (Findling et al., 2019; Gao et al., 2018; Yaramala et al., 2020; Amsterdam et al., 2016; Findling et al., 2015; Geller, 2012; Bowden et al., 2010; Keck et al., 2009; Tohen et al., 2005). Details of the studies assessed can be found in Tables 2 and 3.

The difference in weight between lithium treated patients at follow up compared to baseline did not reach statistical significance, reporting weight gain of 0.462 Kg in the lithium group (Difference in means = 0.462, 95 % C.I.= -0.179 to 1.103, $p = 0.158$, n= 991). Heterogeneity for this outcome was high ($I^2 = 89$ %).

3.4.1.2. Weight change during lithium treatment according to trial length. A subgroup analysis was performed to examine whether lithium weight change was moderated by duration of lithium therapy and is reported in Fig. 3. Weight gain was significantly greater in those interventions with 12 weeks or shorter, (Difference in means = 0.552, 95 % C.I. = 0.010–1.095, p = 0.046).

3.4.2. Differences in weight change in people receiving lithium compared to active controls or placebo

3.4.2.1. Weight change with lithium compared to placebo. A total of 3 studies, comprising 3 unique comparisons and 437 participants (n = 230 lithium, n = 207 placebo), were included for these meta-analyses reported in Fig. 4 (Findling et al., 2019, 2015; Keck et al., 2009). Details of the studies assessed can be found in Tables 2 and 3.

The difference in weight between lithium and placebo at follow up from baseline did not reach statistical significance, favoring weight loss in the lithium group (Difference in means= -0.354, 95 % C.I.= -1.011 to 0.303, p = 0.291, n = 437). Heterogeneity for this outcome was $I^2 = 0.0$ %.

3.4.2.2. Weight change in lithium-treated groups compared with weight change in active comparators. A total of 5 studies, comprising 6 unique comparisons and 1411 participants (n = 663 lithium, n = 748 active comparators), compared weight change between lithium treatment and active comparators (Amsterdam et al., 2016; Bowden et al., 2010; Geller, 2012; Keck et al., 2009; Tohen et al., 2005). Details of the studies assessed can be found in Tables 2 and 3.

Considering that antidepressants are not considered as maintenance treatment in monotherapy for BD in general, a *sensitivity* analysis excluding the study with venlafaxine as active comparator (Amsterdam et al., 2016), was performed and reported in Fig. 5, resulting in a significant difference, favoring weight gain in the active comparator group of 1.446 kg, compared to lithium group (Difference in means= -1.446, 95 % C.I.= -2.489 to -0.404, p= 0.007, $I^2 = 86.8$, n= 1282).

Table 2
Summary of studies included in the systematic review and meta-analysis.

First author and publication year	Duration (weeks)	Treatment groups Drug, n	Mean (SD)/median/ [range] dose mg/d	Mean (SD)/median/ [range] serum concentration mEq/L	Diagnosis	Mood status	Age: mean (SD)	Gender: % Female
Studies entering the meta-analisis								
Yaramala et al., 2020	24 weeks	(1) LI + APT, n = 240 (2) QTP + APT, n = 242	(1,2) NA (secondary analysis of Bipolar CHOICE study)	(1,2) NA	BD I and BD II	Different mood status considered	38.6 (12.1) LI, 39.1 (12.2) QTP	58.3 LI, 59.1 QTP.
Findling et al., 2019	28 weeks	(1) LI, n = 17 (2) placebo, n = 14	(1) 1412 (428)	(1) 0.8–1.2	BD I	Manic or mixed episode	12 (2.5)	32
Gao et al., 2018	16 weeks	(1) LI, n = 18 (2) QTP, n = 24	(1) 600 (2) 327.78, [100–900]	(1) 0.5 [0.3–1.05] (n = 13), second lithium levels 0.8 [0.4–1] (n = 7)	BD I, BD II or subthreshold BD	Different mood status considered	39.48 (14.69)	52.4
Amsterdam et al., 2016	12 weeks	(1) LI, n = 64 (2) VLF, n = 65	(1) mean max dose 1180.85 (399.14), [300–1800] (2) mean max dose 256.55 (101.07), [75–375]	(1) mean max level 0.94 (0.38), [0.30–2.40]	BD II	Depressive episode	42.9 (13.6)	56.6
Findling et al., 2015	8 weeks	(1) LI, n = 53, (2) placebo, n = 28	(1)1483 (584), median (min-max) 1500 (300–3600)	(1) 0.98 (0.47)	BD I	Manic or mixed episode	11.5 (2.9) LI, 11.2 (3.0) placebo	58.5 LI, 46.4 placebo
Geller, 2012	8 weeks	(1) LI, n = 90 (2) RSP, n = 89 (3) VLP, n = 100	(1) NA (2) 2.57 (1.21) (3) NA	(1) 1.09 (0.34) (2) NA (3) 113.6 (23.0) µg/mL	BD I	Manic or mixed episode	10.1 (2.8)	50.2
Bowden et al., 2010	12 weeks	(1) LI, n = 135 (2) VLP, n = 122	(1) 969 (207) (2) 1394 (394)	(1) 0.8 (0.3) (2) 114 (136) ug/ml	BD I	Manic or mixed episode	38.5 (12.6)	63 LI, 54 VLP
Keck et al., 2009	12 weeks	(1) LI, n = 160, (2) APZ, n = 155 (3) placebo, n = 165.	(1) 1210.6 (2) 23.6	(1) 0.66 (0.27)	BD I	Manic or mixed episode.	39.6 (10.5) LI, 39.6 (10.6) APZ, 39.8 (11.3) placebo	48 LI, 49 APZ, 48 placebo
Tohen et al., 2005	52 weeks	(1) LI, n = 214 (2) OLZ, n = 217	(1) 1102.7 (270.3) (2) 11.9 (4.4)	(1) 0.76 (0.14)	BD	Manic or mixed episode	42.3 (12.3) LI, 42.5 (13.1) OLZ	53.7 LI, 52.1 OLZ.
Studies entering only the systematic review								
Hayes et al., 2016	18 years, Jan. 1995 to Dec. 2013	(1) LI, n = 2148, (2) VLP, n = 1670, (3) OLZ, n = 1477, (4) QTP, n = 1376.	(1,2,3,4) NA	(1,2,3,4) NA	BD	Mood status not defined	46.29 LI, 42.31 VLP, 41.01 OLZ, 38.08 QTP	59.92 LI, 54.55 VLP, 53.55 OLZ, 69.69 QTP
McIntyre et al., 2011	52 weeks (12+40)	(1) LI, n = 38 (2) APZ, n = 25	(1) [1119.5–1211.7] (2) 21.7 [20.8–23.9]	(1,2) NA	BD I	Manic or mixed episode	41.21 (9.84) LI, 37.20 (11.85) APZ	50 LI, 60 APZ
Amsterdam and Shults, 2008	12 weeks	(1) LI, n = 40 (2) VLF, n = 43	(1) 966.24 (410.9), [0–2400] (2) 185.6 (92.04), [0–450]	(1) 0.64 (0.265), [0.29–1.5]	BD II	Depressive episode	37.2 (13.4)	57
Niufan et al., 2008	4 weeks	(1) LI, n = 71 (2) OLZ, n = 69	(1) 1110 (257.4), median (IQR) 1114 (950.0–1296.4) (2) 17.8 (2.56), median (IQR) 18.8 (16.4–19.7)	(1,2) NA	BD	Manic or mixed episode	32.6 (13.21)	52.9
Bowden et al., 2008	12 weeks	(1) LI, n = 149 (2) VLP, n = 149	(1) 1052 (298), median (range) 1000 (400–1600) (2) 1618 (366), median (range) 1500 (750–3000)	(1) median (range) 0.68 (0.0–1.92) (2) median (range) 57,9 ug/ml (2.1–122)	BD I	Manic episode	43.6 (12.4)	54

(continued on next page)

Table 2 (*continued*)

First author and publication year	Duration (weeks)	Treatment groups Drug, n	Mean (SD)/median/ [range] dose mg/d	Mean (SD)/median/ [range] serum concentration mEq/L	Diagnosis	Mood status	Age: mean (SD)	Gender: % Female
Bowden et al., 2005	12 weeks	(1) LI, n = 98 (2) QTP, n = 107 (3) placebo, n = 95	(1) [400–800] (2) 586 prior to day 21 and 618 prior to day 84.	(1) mean target (0.6-1.4) Median 0.73 at day 14, 0.80 at day 21, and 0.80 at day 84.	BD I	Manic episode	Age (range): 38.8 (18–73) LI, 38 (18–72) QTP, 41.3 (18–70) placebo	40.8 LI, 43.9 QTP, 42.1 placebo
Calabrese et al., 2005	80 weeks	(1) LI, n = 32 (2) VLP, n = 28	(1) 1359, [900–2100] (2) 1571, [750–2750]	(1) 0.92 (2) 77 μg/ml	BD I or BD II disorder, rapid cycling	Hypomanic, manic, or a mixed episode	37.2 (9) LI, 37 (8.2) VLP	59 LI, 43 VLP
Calabrese et al., 2003	76 weeks	(1) LI, n = 120 (2) LTG, n = 169 (3) placebo, n = 121.	(1) median (range) 900 (450–1800) (2) median (range) 200 (100–285)	(1) 0.8 (0.3)	BD I	Depressive episode.	43.6 (12.3) LI, 44.1 (11.7) LTG, 42.1 (13) placebo	60 LI, 59 LTG, 50 placebo
Bowden et al., 2003	76 weeks	(1) LI, n = 46 (2) LTG, n = 58 (3) placebo, n = 69.	(1) NA (2) [100–400]	(1) [0.8–1.1]	BD I	Hypomanic or manic episode	41.9 (11.3) LI, 40.6 (12.6) LTG, 40.9 (11.0) placebo	52 LI, 55 LTG, 51 placebo
Bowden et al., 2000	52 weeks	(1) LI, n=90, (2) VLP, n=187, (3) placebo, n=92	(1,2,3) NA	(1) 1.0 (0.48), median (min-max) 0.9 (0.1–2.7) (2) 84.8 (29.9), median (min-max) 83.9 (0.6–156) ug/ml	BD I	Manic episode	40.3 ± 9.8 LI, 38.9 ± 12.7 VLP, 38.7 ± 11.9 placebo	52 LI, 50 VLP, 52 placebo
Peselow et al., 1980	48 weeks	(1) LI, n=21 (2) Placebo, n=12	(1,2) NA	(1,2) NA	BD	Mood status not defined	34.9 (10.7) LI, 39.8 (12.0) placebo	NA

APT: adjunctive personalized treatment (could not receive any adjunctive atypical antipsychotic drug), APZ: aripiprazole, LI: lithium, LTG: lamotrigine, NA: not available, OLZ: olanzapine, QTP: quetiapine, RSP: Risperidone, VLF: Venlafaxine, VLP: Valproate sodium or divalproex.

3.5. Quality of studies and risk of Bias

As shown in Table 2, most studies were rated as high quality (low risk category) according to the Cochrane Collaboration Risk of Bias tool 2.0 (RoB), with just one study (Peselow et al., 1980) rated as medium-low quality (medium-high risk of bias category).

4. Discussion

4.1. Summary of evidence

To our knowledge, this is the first systematic review and meta-analysis to investigate the impact of lithium treatment on weight gain in BD. We systematically reviewed 20 studies that compared weight change with lithium and its comparators. Subsequently, our meta-analysis on a subset of these studies suggests that weight gain with lithium is not significant, notwithstanding a trend to weight increase of less than 0.5 Kg, with greater weight gain in shorter studies. Weight gain with lithium was significantly lower than with active comparators. Finally, overall baseline-to-endpoint weight gain differences between lithium and placebo were not significant.

The parsimonious conclusion is that weight gain with lithium treatment is far less significant than previously thought. A further possible explanation for this lack of statistically significant differences in weight gain with lithium or between lithium and placebo, could be the increased risk of being overweight related to BD itself, possibly associated to genetic factors or lifestyle habits (Keck and McElroy, 2003). Patients with BD appear to be at greater risk than the general population for overweight and obesity (Keck and McElroy, 2003; Tully et al., 2020; Fagiolini et al., 2008). This seems to be related, beyond treatment with medications associated with weight gain, alone or in combination, to factors including comorbid binge-eating disorder, the number of depressive episodes, greater propensity to atypical depressive symptoms with increased appetite (Mitchell et al., 2001), excessive carbohydrate consumption, and low rates of exercise (Wildes et al., 2006; Shah et al., 2006). The greater weight gain in shorter studies could be due to initial fluid retention that stabilizes with time, it is also possible that people who have more weight gain early on are more likely to drop out. Moreover a shorter duration of illness may be associated with higher weight gain possibly because the receiving patients have not yet achieved sustained remission, thus requiring polypharmacy; one other explanation could be that patients may have not yet taken full advantage of psychoeducation intervention to enhance dietary habits and reduce the overall number of medications besides the cornerstone treatment represented by lithium. (Fornaro et al., 2016). Regarding the greater weight gain with the active comparators, this is in line with the evidence of an important impact in weight gain of different pharmacologic options for BD (Torrent et al., 2008). It should be noted that some included studies compared lithium to treatment alternatives known for their low metabolic impact, such as lamotrigine (Grootens et al., 2018), which may influence these results (Calabrese et al., 2003; Bowden et al., 2003).

Considering the systematic review, only one study reported that lithium was associated with more weight gain than placebo, while 6 studies found no significant differences in weight gain between lithium and placebo. Furthermore, three studies with venlafaxine and lamotrigine as active comparators reported greater weight gain with lithium than with active comparators, while four studies using aripiprazole, lamotrigine and valproic acid as active comparators found no significant difference compared to lithium. Finally, eight studies showed greater weight gain with the active comparator than with lithium; these used atypical antipsychotics (quetiapine, olanzapine, and risperidone) and valproate as active comparators. These agents are known to increase body weight.

This data is mostly in line with the literature, where weight gain with

Table 3
Weight outcomes and quality of included studies.

First author and publication year	Definition of weight gain	Outcomes relating to weight gain	Study quality
Studies entering the meta-analisis			
Yaramala et al., 2020	(a) mean (SD) weight gain kg	(a) LI, 1.8 (3.5); placebo, 1.7 (4.1). NS	High
Findling et al., 2019	(a) mean (SD) weight change kg (b) mean (SD) BMI change kg/m^2	(a) LI, -1.6 (3.6); QTP, 1.2 (3.7). (b) LI, -0.6 (1.4); QTP, 0.6 (1.4). NS, despite small decreases in (a) and (b) in LI group.	High
Gao et al., 2018	(a) patients with >7% weight increase from baseline (b) body weight LS-mean (SE) at 2,6, 8, 12, 16, 20, 24 weeks (c) BMI kg/m^2 LS-mean (SE) at 2,6, 8, 12, 16, 20, 24 weeks	(a) at 24 weeks occurred in 21 (8.8 %) subjects treated with QTP + APT and 29 (12.3 %) of those treated with LI + APT (p = 0.8). (b),(c) QTP and LI based pharmacotherapy produced modest but significant increases in body weight and BMI regardless of binge-eating status. QTP + APT group experienced greater increases in (b) y (c) than LI + APT. Significant increases in (b) y (c) at all time points in QTP + APT group, but only at 20 and 24 weeks in the LI + APT group.	High
Amsterdam et al., 2016	(a) mean (SD) weight gain, [range] observed kg (b) mean (SE) weight gain, [95 % CI] predicted kg	(a) LI, -0.24 (2.49), [-7.26 to 5.90]; VLF -1.31 (3.85), [-14.97 to 9.98]. (b) LI, 0.37 (0.31), [0.24 to 0.98]; VLF -1.20 (0.42), [-2.02 to -0.37]. Modest, albeit statistically significant between-group difference, small weight loss in VLF group relative to the LI group	High
Findling et al., 2015	(a) mean (SD) change in weight z score[1] kg.	(a) LI, 0.9 (1.6); placebo 1.2 (1.7). NS	High
Geller, 2012	(a) mean (SD) weight gain kg (b) mean (SD) increase in BMI kg/m^2	(a) RSP, 3.31 (1.75) vs LI, 1.42 (1.62), p = 0.001. RSP, 3.31 (1.75) vs VLP, 1.67 (1.92), p = 0.001. In RSP group (a) was significantly greater than in LI and VLP group. (b) RSP, 1.37 (0.77) vs LI, 0.37 (1.24), p = 0.001. RSP, 1.37 (0.77) vs VLP, 0.35 (0.82), p = 0.001. In RSP group (b) was also significantly greater than in LI and VLP group.	High
Bowden et al., 2010	(a) mean weight change from baseline (analysis of variance). (b) patients with >7% weight gain from baseline	(a) LI, 0.2 (3.3); VLP, 1.1 (2.9), p = 0.04. Mean weight gain was greater in the VLP group than in the LI group. (b) LI, 9 %; VLP, 7 %, p = 0.20.	High
Keck et al., 2009	(a) mean (SE) change in weight from baseline OC (b) mean (SE) change in weight from baseline LOCF (c) mean weight change by baseline	(a) APZ (n = 40), 1.34 (0.63); LI (n = 53), 0.62 (0.55), p = 0.39. NS (b) APZ, 1.4 (0.56); LI, 0.31 (0.54), p = 0.113. NS (c) NS (d) mid-BMI subgroup (23–27kg/m2), LI, 0.12	High

Table 3 (*continued*)

First author and publication year	Definition of weight gain	Outcomes relating to weight gain	Study quality
	BMI^2 OC (d) mean weight change by baseline BMI^2 LOCF (e) patients with >7% weight gain from baseline OC (f) patients with >7% weight gain from baseline LOCF	(0.48); APZ 1.57 (0.50), p = 0.041. (e) APZ, 14.6 % (6/41); LI 3.7 % (2/54), p = 0.059, NS (f) NS	
Tohen et al., 2005	(a) mean (SD) weight change kg (b) patients with >7% weight increase from baseline (c) patients presenting weight increase or decrease as an adverse event	(a) OLZ, 1.8 (5.8); LI, -1.4 (5.0), p < 0.001. Significantly greater for the OLZ group than in the LI group. (b) OLZ (n = 64), 29.8 %; LI (n = 21), 9.8 %, p < 0.001. Significantly greater for the OLZ group than in the LI group. (c) weight increase: OLZ, 6.5 %; LI, 4.7 %, p = 0.53, weight decrease: OLZ, 3.2 %; LI, 5.1 %, p = 0.35.	High
Studies entering only the systematic review			
Hayes et al., 2016	(a) increase in body weight ≥ 7% from baseline (b) increase in body weight ≥ 15% from baseline	(a) and (b) significantly higher in individuals taking VLP, OLZ, or QTP compared to LI. (b) VLP HR 1.62; 95 % CI 1.31–2.01; p < 0.001; OLZ HR 1.84; 95 % CI 1.47–2.30; p < 0.001; QTP HR 1.67; 95 % CI 1.24–2.20; p < 0.001), after adjustment, rates of weight gain were higher with VLP, OLZ, and QTP than LI.	High
McIntyre et al., 2011	(a) mean weight change from baseline LOCF kg (b) mean weight change from baseline OC kg (c) patients with >7% weight gain or loss from baseline	(a) LI, 0.74; APZ, 0.97, p = 0.60. (b) LI (n = 9), 2.71; APZ (n = 7), 5.66, p = 0.46. (c) LI vs APZ, weight gain (20.0 % vs 42.9 %, p = 0.323) or weight loss (10.0 % vs 0 %, p = 0.403). Weight gain was moderate and NS, except patients with a baseline BMI < 25 kg/m^2, that showed a greater increase in mean weight with APZ.	High
Amsterdam and Shults, 2008	(a) weight gain as an adverse effect	(a) LI, 20 % (8/40); VLF, 9.3 % (4/43)	High
Niufan et al., 2008	(a) mean increase in weight kg (b) mean BMI increase kg/m^2 (c) patients with >7% weight gain from baseline	(a) OLZ, 1.85; LI, 0.73, p = 0.014; (b) OLZ, 0.69; LI, 0.27, p = 0.012. (c) OLZ, 16.2 %; LI, 2.9 %, p = 0.009 Mean increases were statistically significantly higher in the OLZ treatment group. In addition, significantly more OLZ patients had a clinically significant weight increase compared to LI.	High

(*continued on next page*)

Table 3 (*continued*)

First author and publication year	Definition of weight gain	Outcomes relating to weight gain	Study quality
Bowden et al., 2008	(a) patients with >7% weight gain from baseline	(a) LI, 4 % (6/150); VLP, 8.7 % (13/149)	High
Bowden et al., 2005	(a) mean (SD) weight change LOCF and OC kg (b) patients with >7% weight increase from baseline, adjusted for baseline BMI category (c) patients presenting weight increase or decrease as an adverse event	(a) QTP, 2.6; placebo, –0.08 (LOCF). QTP, 3.3; placebo, 0.3 (OC). LI, 0.7 (LOCF); LI, 1.0 (OC). Significantly higher in QTP than placebo($p < 0.001$). LI not significantly different from placebo. (b) BMI < 25 (placebo: 9.2 %, QTP: 33.3 %, and LI: 16.9 %) BMI ≥ 25 (placebo: 6.3 %, QTP: 24.4 %, and LI: 12.1 %). Significantly more frequent in the QTP group than in the placebo group ($p = 0.008$). Most patients who gained ≥7% of their weight belonged to the group with baseline BMI < 25 while a smaller proportion belonged to the group with baseline BMI ≥ 25. (c) Weight increase: LI, 6.1 %; QTP, 15 %; Placebo, 1 %. Weight decrease: LI, 6 %; QTP, 1.9 %; Placebo, 1 %.	High
Calabrese et al., 2005	(a) patients presenting weight gain as an adverse event.	(a) LI, 3 %; VLP, 4 %.	High
Calabrese et al., 2003	(a) mean weight change kg (b) patients with >7% weight increase from baseline	(a) placebo, 1.2; LI, 4.2; LTG, -2.2 (LTG vs LI: $p < 0.1$; comparisons with placebo were not significant). (b) placebo, 6 %; LI, 10 %; LTG, 7 %.	High
Bowden et al., 2003	(a) patients with >7% weight increase from baseline	(a) LTG, 11 %; LI, 10 %; placebo, 2 %.	High
Bowden et al., 2000	(a) patients presenting weight increase as an adverse event	(a) LI, 13 %; VLP, 21 %; placebo, 7 %. VLP > placebo, $p < 0.004$. Significantly higher incidence of tremor and weight gain in VLP than in the placebo group.	High
Peselow et al., 1980	(a) average (SD) weekly and cumulative weight change from baseline	(a) LI, 3.97 (2.81) kg; placebo, 1.06 (1.49), $p < 0.01$. Statistically significant between-group difference.	Medium-low

APT: adjunctive personalized treatment (could not receive any adjunctive atypical antipsychotic drug), APZ: aripiprazole, BMI: body mass index, LI: lithium, LOCF: last observation carried forward, LS: least squares, LTG: lamotrigine, NS: No statistically significant between-group difference, OC: observed cases, OLZ: olanzapine, QTP: quetiapine, RSP: Risperidone, VLF: Venlafaxine, VLP: Valproate sodium or divalproex. 1. Change score is the week value minus the baseline value; baseline is defined as the first visit of the efficacy phase mean ± SD, 2. BMI baseline category: <23 kg/m^2, 23–27 kg/m^2 or >27 kg/m^2.

some second generation antipsychotics like quetiapine, risperidone, and olanzapine (Kim et al., 2008; Huhn et al., 2019; Bak et al., 2014) as well as with valproate (Grootens et al., 2018) is well established. In contrast, aripiprazole (Bak et al., 2014) and lamotrigine (Grootens et al., 2018; Sachs et al., 2006) have a more neutral metabolic profile, and in some studies, they were even associated with weight loss (Bowden et al., 2006), although with aripiprazole, data are inconsistent in other disorders and in pediatric populations (Schoemakers et al., 2019). Finally, venlafaxine appears to be associated with weight loss (Kraus et al., 2002; de Oliveira et al., 2004). Nevertheless avoiding concurrent prescription of antidepressant with lithium in the long-term management of bipolar depression should, in theory, minimize the impact of mood-de-stabilizers (antidepressants), thus further reducing the need for otherwise higher mean doses of lithium or complex polypharmacy with concurrent antipsychotic treatments. Polypharmacy may otherwise affect long-term weight gain in BD. Some of these results are also consistent with previous studies where obesity and overweight in BD are considered to be partly related to prescribed drugs (Torrent et al., 2008).

Although the biological mechanisms that lead to lithium-related weight gain are not entirely clear, researchers speculate that several processes are likely to be involved and different hypotheses have been proposed. These processes may work alone or in combination to cause weight gain in people on lithium therapy (Gitlin, 2016; Mangge et al., 2019).

Hypothetically, early weight gain after starting lithium therapy could lead in regaining weight that was previously lost unintentionally. Another mechanism related with weight gain could possibly result from the increased thirst caused by lithium, leading to the ingestion of high-calorie drinks (Peselow et al., 1980). Lithium might also cause sodium and water retention in people who consume a high-salt diet, which can lead to added body weight (Demers and Heninger, 1970); however, this finding is controversial. Other authors support that weight gain in lithium-treated patients is due not to an increase in fluid retention but rather to an increase in fat and other solid tissues (Peselow et al., 1980). Unrecognized hypothyroidism, leading to a reduced metabolic rate which in turn leads to weight gain may play a role in a small minority of patients (Cayköylü et al., 2002; Shine et al., 2015) considering that skilled clinicians do routinely monitor thyroid functioning and easily fix hypothyroidism in most of the cases.

However, it seems likely that, for most patients, lithium alters other core mechanisms that can cause weight gain (Ackerman and Nolan, 1998). Many studies have shown lithium to have insulin-like properties, influencing carbohydrate metabolism in a variety of ways, some of which may form the basis for the increased weight gain, while other studies have described effects in lipids metabolism (Peselow et al., 1980). The mechanisms of action implicated in lithium-induced weight gain include an increased glucose uptake into the cells through stimulation of hexokinase and pyruvate kinase and inhibition of muscle protein kinase. Valproate and lithium also feature weight gain as a side effect and both interact with HDACs (histone deacetylases), which are important enzymes for epigenetic modulation by catalyzing the deacetylation of histones. The deacetylation of histones induces a tighter wrapping of proteins around the DNA and blocks transcription by physically limiting the access of transcription factors (Gracious and Meyer, 2005).

Lithium may also have direct effects on mitochondrial energy generation both alone and in combination with other agents (Bortolasci et al., 2020; Maurer et al., 2009). In addition to insulin-like properties (Peselow et al., 1980), lithium may have direct appetite stimulating effects in the hypothalamus (Keck and McElroy, 2003). Also, recent studies associated leptin with weight gain during lithium augmentation (Bopp et al., 2019; Ricken et al., 2016).

The risk of gaining weight while taking lithium is greatest during the first two years of treatment (Gitlin, 2016) and in addition to pharmacotherapy, several factors can influence the likelihood of gaining weight while taking lithium treatment (Gitlin, 2016), including treatment duration, sex or baseline weight for example. One study evaluating mean weight change found no significant difference between placebo, aripiprazole and lithium at week 3, nor between aripiprazole and lithium at week 12 in any subgroup "adjusted by baseline BMI category" (BMI b23 kg/m^2, 23–27 kg/m^2 or N 27 kg/m^2) (Keck et al., 2009).

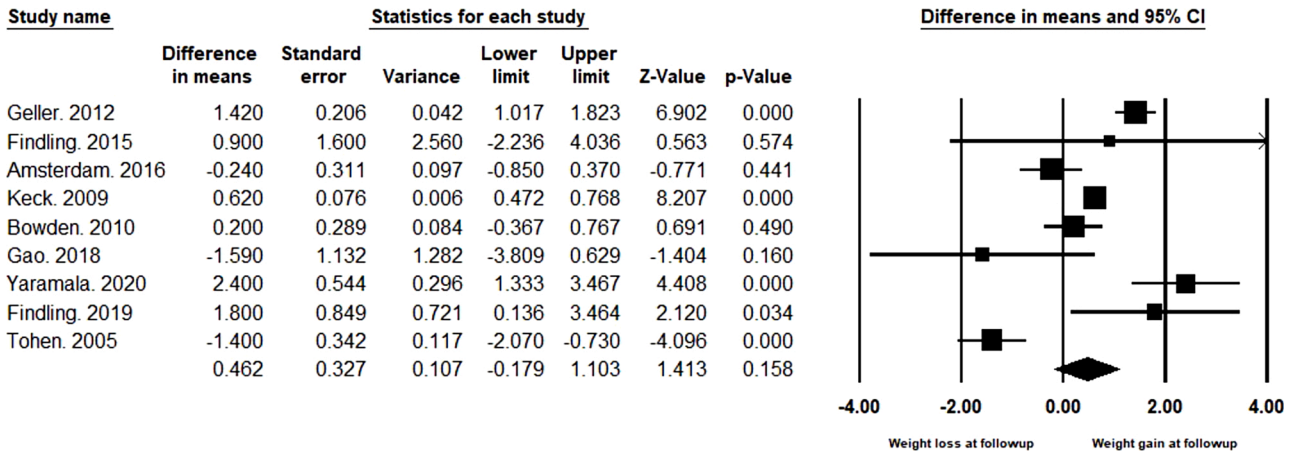

Fig. 2. Weight change during lithium treatment – Forest plots with the summary effect size (Difference in means) of weight gain, between lithium treated patients at follow up compared to baseline. Studies ordered based on trial length (small to large).

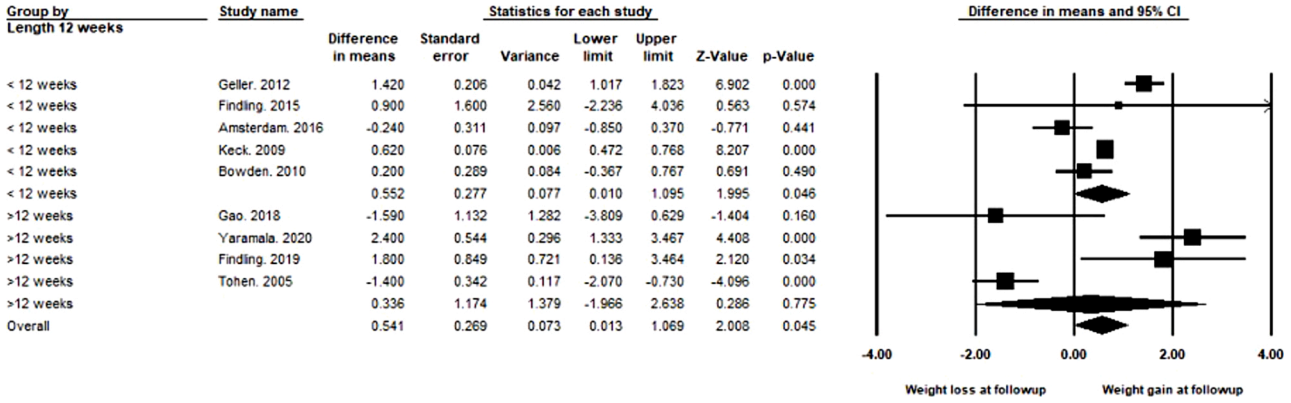

Fig. 3. Weight change during lithium treatment according trial length – Forest plots with the summary effect size (Difference in means) of weight gain, between patients treated with lithium in 2 subgroups: shorter than 12 weeks and longer than 12 weeks.

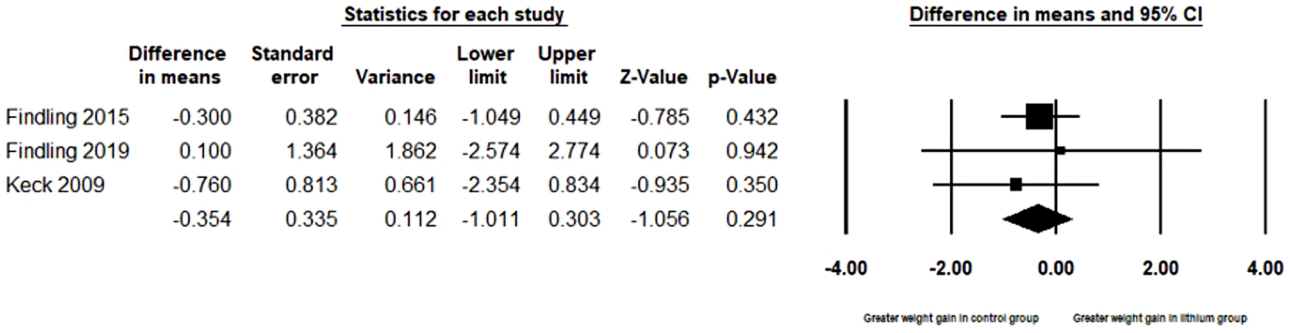

Fig. 4. Weight change in lithium treatment compared to placebo – Forest plots with the summary effect size (Difference in means) of weight gain, between patients treated with lithium versus placebo.

Another study evaluated the impact of baseline binge eating, showing that the largest increases over 24 weeks in body weight and BMI, and waist circumference in women occurred in quetiapine-treated patients with baseline binge-eating, relative to quetiapine-treated patients without binge eating and lithium-treated patients with or without baseline binge-eating (Yaramala et al., 2020). Patients with obesity showed greater weight gain while on lithium compared to patients without obesity (Bowden et al., 2006). Other studies showed that baseline body weight predicted greater weight gain (Vendsborg et al., 1976; Vestergaard et al., 1988). Finally, unhealthy lifestyle such as smoking, substance/alcohol use, poor dietary habits, and sedentary life can also contribute to weight gain as well as to the development and severity of medical comorbidity and clinical symptoms in BD (Fagiolini et al., 2008; Sylvia et al., 2013a, b).

Taken together, our results suggest an unexpectedly low impact of lithium on weight gain. This is important new data when choosing pharmacological maintenance treatment options in patients with BD. Even though weight gain with lithium did not reach statistical significance, the trend to weight increase with lithium, and particularly with other active comparators, suggests that careful monitoring of weight changes in patients before and after drug prescription should be implemented in clinical practice. Drugs which potentially cause weight

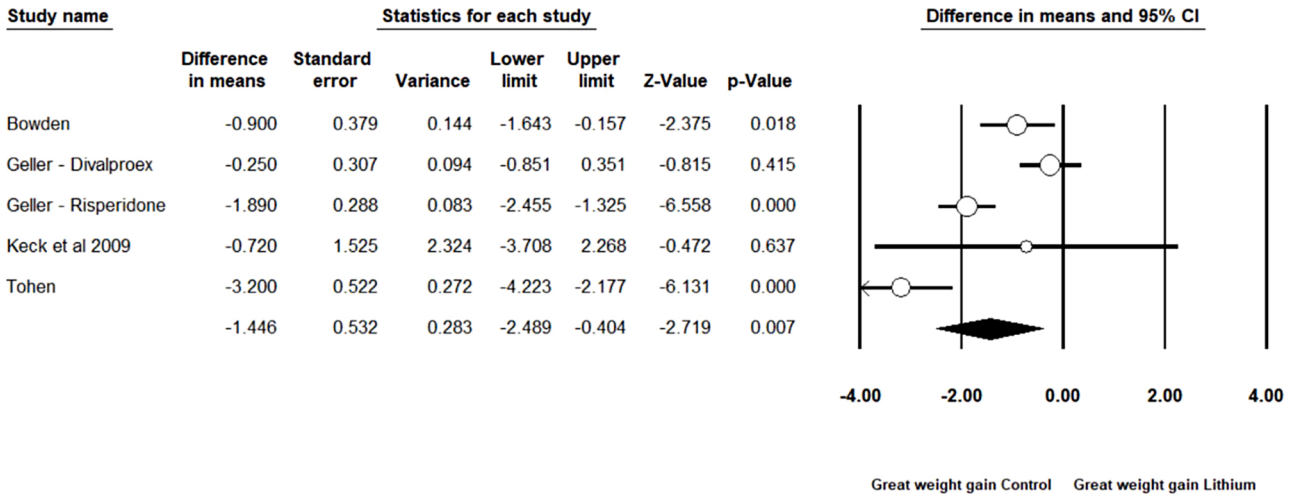

Fig. 5. Weight change in lithium treatment compared to active comparators – Forest plots with the summary effect size (Difference in means) of weight gain, between patients treated with lithium versus active comparators.

gain should be avoided, if possible, in overweight patients with BD. Furthermore, eating habits and daily activities should be targeted as they may also have a significant impact on overall health and weight-related issues (Torrent et al., 2008), as seen in the placebo groups, where independently from drug treatment, weight gain is prone to occur.

4.2. Strengths and limitations

As far as we know, our is the first systematic review and meta-analysis focusing on weight-related change with lithium treatment. Our study analyzed several weight measures across different studies by comparing weight change during lithium treatment as well as comparing weight change with placebo and/or active comparators. Thus, we were able to identify trends in weight change with lithium, placebo and active comparators that are used in drug treatment of BD.

Limitations include a generally high level of statistical heterogeneity in our meta-analyses; due to the limited studies, comprehensive subgroup analysis to detect factors that may affect heterogeneity was not feasible. Potential factors that may be affecting this between group differences are different trial durations, assessment measures used, and variable medications and dosing employed as well as a previous open label phase, in some studies, where patients could receive other treatments that were discontinued in extension phases. However, most included studies were of high quality and had a low risk of bias. Also, we were not able to meta-analyze nor perform a systematic review of the outcome on other metabolic measures such as lipid or glycemic profiles due to dearth of data. For similar reasons, we were unable to perform subgroup analysis by lithium dosage or age. Additionally, we grouped all studies together, regardless of mood state. It is possible that the participants with a depressive mood status had a different diet composition compared to a manic episode or prior to an acute episode, and this might have influenced the results. However, the included studies did not describe diet composition or lifestyle habits of the participants; thus it is not possible to say to which extent the weight gain is due to drug treatment, to lifestyle changes or pathophysiology inherent to BD itself. Moreover a sizeable proportion of the studies could not control for other potential confounding factors, e.g., concurrent hypothyroidism induced by lithium administration, what can leads to weight gain, reducing metabolic rate as described above.

4.3. Conclusions

This is the first systematic review and meta-analysis to examine weight change with lithium treatment in people with BD. According to our results, weight gain with lithium did not reach statistical significance and was clinically irrelevant. Weight gain was greater in shorter studies. Weight gain with lithium was significantly lower than with active comparators, with no significant differences compared to placebo. This meta-analysis can inform clinical decisions and avoid potential delay in first line treatment initiation due to potential weight gain concerns of which we found no sound evidence.

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Declaration of Competing Interest

SGC has received CME-related honoraria, or consulting fees from Janssen-Cilag, Italfarmaco, Angelini and Lundbeck and reports no financial or other relationship relevant to the subject of this article.

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck and Angelini with no financial or other relationship relevant to the subject of this article.

EV has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbvie, Angelini, Celon, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research. Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda.

IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag and Lundbeck (unrelated to the present work).

MB has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work.

AGP has received CME-related honoraria, or consulting fees from Janssen-Cilag, Angelini and Lundbeck and reports no financial or other relationship relevant to the subject of this article.

All other authors report no biomedical financial interests or potential conflicts of interest related to the present article.

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