Journal of Psychiatric Research 143 (2021) 230–238

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Repurposed drugs as adjunctive treatments for mania and bipolar depression: A meta-review and critical appraisal of meta-analyses of randomized placebo-controlled trials

Francesco Bartoli [a,1], Daniele Cavaleri [a,*,1], Bianca Bachi [a], Federico Moretti [a], Ilaria Riboldi [a], Cristina Crocamo [a], Giuseppe Carrà [a,b]

[a] Department of Medicine and Surgery, University of Milano-Bicocca, via Cadore 48, 20900, Monza, Italy
[b] Division of Psychiatry, University College London, 149 Tottenham Court Rd, Bloomsbury, London, W1T 7BN, United Kingdom

ARTICLE INFO

Keywords:
Meta-review
Repurposed drugs
Adjunctive treatment
Bipolar disorder
Mania
Bipolar depression

ABSTRACT

Several drugs previously tested in clinical trials and approved for different indications have been repurposed for bipolar disorder. We carried out a systematic meta-review of meta-analyses of randomized placebo-controlled trials investigating repurposed drugs as adjunctive treatments for mania and bipolar depression. We performed a critical appraisal using 'A MeaSurement Tool to Assess systematic Reviews' Version 2 (AMSTAR 2). We synthesized results on efficacy, tolerability, and safety, assessing evidence quality according to the 'Grading of Recommendations, Assessment, Development and Evaluations' (GRADE) approach. Our systematic search identified nine eligible studies investigating 12 drugs, four for mania and eight for bipolar depression. The quality of reporting was heterogeneous according to AMSTAR 2. In mania, allopurinol (for symptoms reduction and remission at 4–8 weeks) and tamoxifen (for response and symptoms reduction at 4–6 weeks) showed higher efficacy than placebo, with low and very low quality of evidence, respectively. Concerning bipolar depression, modafinil/armodafinil (for response, remission, and symptoms reduction at 6–8 weeks) and pramipexole (for response and symptoms reduction at 6 weeks) were superior to placebo, despite the low quality of evidence. Results on the efficacy of celecoxib and N-acetylcysteine were of low quality and limited to certain outcomes. Overall, the lack of evidence of high and moderate quality does not allow us to draw firm conclusions on the clinical utility of repurposed drugs as adjunctive treatments for mania and bipolar depression, highlighting the need for additional research.

1. Introduction

Bipolar disorder (BD) is a severe illness, affecting about 2% of the population worldwide, with significant disease burden, marked impact on the quality of life, increased risk of suicide, and a chronic and recurring course (Carvalho et al., 2020). The treatment of BD is based on both pharmacological (Yatham et al., 2018) and non-pharmacological approaches, such as psychotherapeutic (Lovas and Schuman-Olivier, 2018) and lifestyle interventions (Bauer et al., 2016). Nonetheless, the management of BD remains not entirely satisfactory (Carvalho et al., 2020; Ferrari et al., 2016). In terms of psychopharmacological treatments, only mood stabilizers, antipsychotics, and antidepressants have received regulatory approval for BD so far (Yatham et al., 2018; Geddes and Miklowitz, 2013). Notwithstanding research efforts on novel therapeutics for BD, their possible mechanisms of action, their effects, and their potential use in the different phases of the disease (Haggarty et al., 2021), few advances have been made in the last decades (Dean et al., 2018; Geddes and Miklowitz, 2013). However, growing evidence supports the involvement of different biological abnormalities in the complex pathophysiology of BD (Haggarty et al., 2021; Langan and McDonald, 2009), suggesting novel approaches to target additional pathways (Phillips and Kupfer, 2013). This is consistent with drug repurposing strategies, based on the identification of novel indications for drugs which have previously obtained regulatory approval or have been tested in clinical trials for other illnesses (Langedijk et al., 2015). Drug repurposing is considered a rapid, cost-effective, and reduced-risk

* Corresponding author.
E-mail address: d.cavaleri1@campus.unimib.it (D. Cavaleri).
[1] Joint first authors.

https://doi.org/10.1016/j.jpsychires.2021.09.018
Received 8 April 2021; Received in revised form 28 July 2021; Accepted 1 September 2021
Available online 3 September 2021

strategy for the development of new treatment options also for psychiatric disorders (Fava, 2018; Hemphill and Sampat, 2012). Several agents, all sustained by a plausible biological rationale, have been evaluated for BD in order to fill the relevant treatment gap (Kessing et al., 2019; Dean et al., 2018). A relatively recent narrative review has provided an update on new adjunctive treatment options for BD, including pharmacotherapy, nutraceuticals, and hormone therapy (Dean et al., 2018). Nonetheless, despite the large number of meta-analyses investigating such drugs for the treatment of BD mood episodes, to our knowledge no systematic work has previously summarized meta-analytic findings and assessed their quality. Hence, we performed a meta-review systematically reviewing and critically evaluating meta-analytic findings on efficacy, tolerability, and safety of repurposed drugs as adjunctive treatments for mania and bipolar depression. We aimed to provide a comprehensive, up-to-date guidance on the available evidence on these treatments and their potential role in clinical practice.

2. Material and methods

The current work was performed following standard recommendations for conducting overviews of reviews (Pollock et al., 2021). A protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) and was registered on January 1, 2021 (CRD42021223777).

2.1. Eligibility criteria

A 'repurposed drug' was defined as a compound which had previously obtained regulatory approval or had been tested in clinical trials for other diseases (Langedijk et al., 2015). We included meta-analyses of randomized controlled trials (RCTs) on adults suffering from BD during an acute mood episode (mania or depression) which compared a repurposed drug and placebo as adjunctive treatments. To be eligible, meta-analyses had to report measures of efficacy (i.e., response, remission, changes in symptom scores), tolerability (completion of treatment, dropout/discontinuation), and safety (side/adverse effects) outcomes after at least 3 weeks of treatment for manic episodes (Cipriani et al., 2011) and at least 4 weeks for depressive episodes (Cipriani et al., 2018).

In case of overlapping data from meta-analyses investigating identical drug and clinical outcomes, we selected the one including the largest number of RCTs or the most complete findings. In order to improve consistency and comparability of data, we excluded: i) meta-analyses on drugs belonging to classes already approved for the treatment of BD; ii) meta-analyses of monotherapy trials; iii) meta-analyses including studies other than RCTs; iv) non-systematic pooled analyses.

2.2. Search strategy and study selection

A systematic literature search for meta-analyses of RCTs was conducted on Ovid MEDLINE, Embase, APA PsycInfo, and the Allied and Complementary Medicine (AMED) electronic databases (via Ovid), as well as on the Cochrane Database of Systematic Reviews (CDSR), on March 2, 2021. No language restrictions were applied. The reference lists of the included studies and of relevant reviews (Firth et al., 2019; Dean et al., 2018) were also searched to identify possible additional studies. Gray literature, conference abstracts, and all publications not having undergone peer-review were excluded. The full search strategy is shown in **Supplement S1**. After a preliminary screening based on titles and abstracts, full texts were retrieved to evaluate eligibility. Articles were independently screened and read in full text by three authors (DC, BB, FM), and any potential disagreement was resolved by discussion with a fourth author (FB).

2.3. Critical appraisal of included meta-analyses

In order to evaluate the quality of reporting, we performed a critical appraisal of the included studies using 'A MeaSurement Tool to Assess systematic Reviews' Version 2 (AMSTAR 2) (Shea et al., 2017), whose 16 items are designed to methodologically assess systematic reviews. We considered four items as critical in our work: adherence to a previously established protocol (item 2); satisfactory assessment of the risk of bias in individual studies (item 9); use of appropriate methods to perform the meta-analysis (item 11); consideration of the risk of bias in primary studies when interpreting and discussing the results (item 13). Following standard recommendations (Shea et al., 2017), the overall confidence in the results of each meta-analysis was categorized as high (zero or one non-critical weaknesses), moderate (more than one non-critical weakness), low (one critical weakness), or critically low (more than one critical weakness). Five authors (FB, DC, BB, FM, IR) independently assessed the included studies applying AMSTAR 2, and disagreements were resolved by discussion.

2.4. Data extraction

Three authors (DC, BB, FM) independently extracted data and blindly cross-checked them for accuracy. A data extraction template was used to collect key information from the eligible studies, including: author(s) and year of publication; investigated repurposed agent(s); tested mood polarity (manic or depressive episode); number of included trials (k); total sample size (N) and number of subjects allocated to the index intervention and to placebo; tested doses; concomitant standard treatments; follow-up duration; main details needed to assess the quality of the included studies with AMSTAR 2; measures of the effects with their 95% confidence intervals (95%CIs), p-values, and heterogeneity measures (I^2 statistic values). In order to improve consistency and readability, we converted Odds Ratios (ORs) into Risk Ratios (RRs) for dichotomous outcomes and Mean Differences (MDs) into Standardized Mean Differences (SMDs) for continuous outcomes. Stata statistical software package release 16 was used (StataCorp, 2019).

2.5. Data synthesis and interpretation

We performed a narrative synthesis of efficacy (primary), tolerability, and safety (secondary) outcomes for each treatment. Statistical significance was set at $p < 0.05$ and the magnitude of the effect size was classified according to conventional cut-offs (Schünemann et al., 2021; Olivier and Bell, 2013; Rosenthal, 1996; Cohen, 1988).

Heterogeneity was assessed by considering the reported I^2 value, categorized as low (25%), moderate (50%), or high (75%) (Higgins et al., 2003).

2.6. Quality of evidence

We evaluated the quality of evidence from single meta-analyses following the GRADE approach (Schünemann et al., 2021; Guyatt et al., 2008). Accordingly, we assessed factors that may reduce the quality of evidence.

Considering systematic reviews as the primary unit (Pollock et al., 2021), evidence quality was evaluated according to the following items:

- risk of bias, rating down when potential (one level) or crucial (two levels) limitations were likely to lower the confidence in the effect estimate;
- heterogeneity and inconsistency of results, rating down meta-analyses with an $I^2 > 50\%$;
- indirectness, rating down when populations, interventions, comparators (placebo), and outcomes were somehow (one level) or seriously (two levels) different from those of clinical interest;
- imprecision, rating down by one level for wide CIs when the difference in magnitude between the estimated effect size and the 95%CI boundaries was over one level of magnitude; by two levels for very wide CIs when the difference in magnitude between the effect size

and the 95%CI boundaries was over two levels of magnitude (Guyatt et al., 2011);
- publication bias, rating down when the literature search did not include ongoing studies and unpublished data or when funnel plots and Egger's test, if available, showed asymmetry.

We categorized significant meta-analytic findings according to the confidence that the effect estimate was correct. We thus considered effect estimates as of i) high, ii) moderate, iii) low, or iv) very low quality if they i) lied close, ii) were likely to be close but possibly substantially different, iii) might be substantially different, or iv) were likely to be substantially different from the true effect (Balshem et al., 2011). The quality was addressed independently by four authors (FB, DC, FM, IR) and any disagreement was resolved by discussion.

3. Results

3.1. Search results

Our systematic search generated 2,168 records via Ovid (446 from Ovid MEDLINE, 992 from Embase, 728 from APA PsycInfo, and 2 from AMED), reduced to 1,413 unique articles after deduplication, and 198 systematic reviews from the CDSR.

The screening of titles and abstracts identified 58 potentially eligible studies from Ovid and two from the CDSR, as well as three from the manual search of the reference lists of the included studies and two relevant reviews (Firth et al., 2019; Dean et al., 2018).

After a full-text review, nine out of 63 studies met the eligibility criteria and were included in this meta-review (Bahji et al., 2021; Kishi et al., 2021; Nery et al., 2020; Nunez et al., 2020; Palacios et al., 2019; Tundo et al., 2019; Bartoli et al., 2017a; McCloud et al., 2015; Mukai et al., 2014). Search and screening are described in **Supplement S1**. The list of the excluded articles (with related reasons) after full-text review is reported in **Supplement S2**. The study selection process is fully described in Fig. 1.

3.2. Study characteristics

The included studies were all in English and published between 2014 (Mukai et al., 2014) and 2021 (Bahji et al., 2021; Kishi et al., 2021). We identified 12 repurposed drugs from the nine included meta-analyses: four drugs, i.e., allopurinol (Bartoli et al., 2017a), melatonin and ramelteon (Kishi et al., 2021), and tamoxifen (Palacios et al., 2019) were investigated as adjunctive treatments for mania; eight drugs, i.e., acetylsalicylic acid (ASA) (Bahji et al., 2021), celecoxib (Bahji et al., 2021), N-acetylcysteine (NAC) (Bahji et al., 2021; Nery et al., 2020), pioglitazone (Bahji et al., 2021), memantine (Bahji et al., 2021; McCloud et al., 2015), modafinil/armodafinil (Nunez et al., 2020), pramipexole (Tundo et al., 2019), and inositol (Bahji et al., 2021; Mukai et al., 2014) were tested as add-on to standard therapy for bipolar depression. Sample sizes ranged from 41 subjects for inositol (Bahji et al., 2021; Mukai et al., 2014) to 1,587 for modafinil/armodafinil (Nunez et al., 2020).

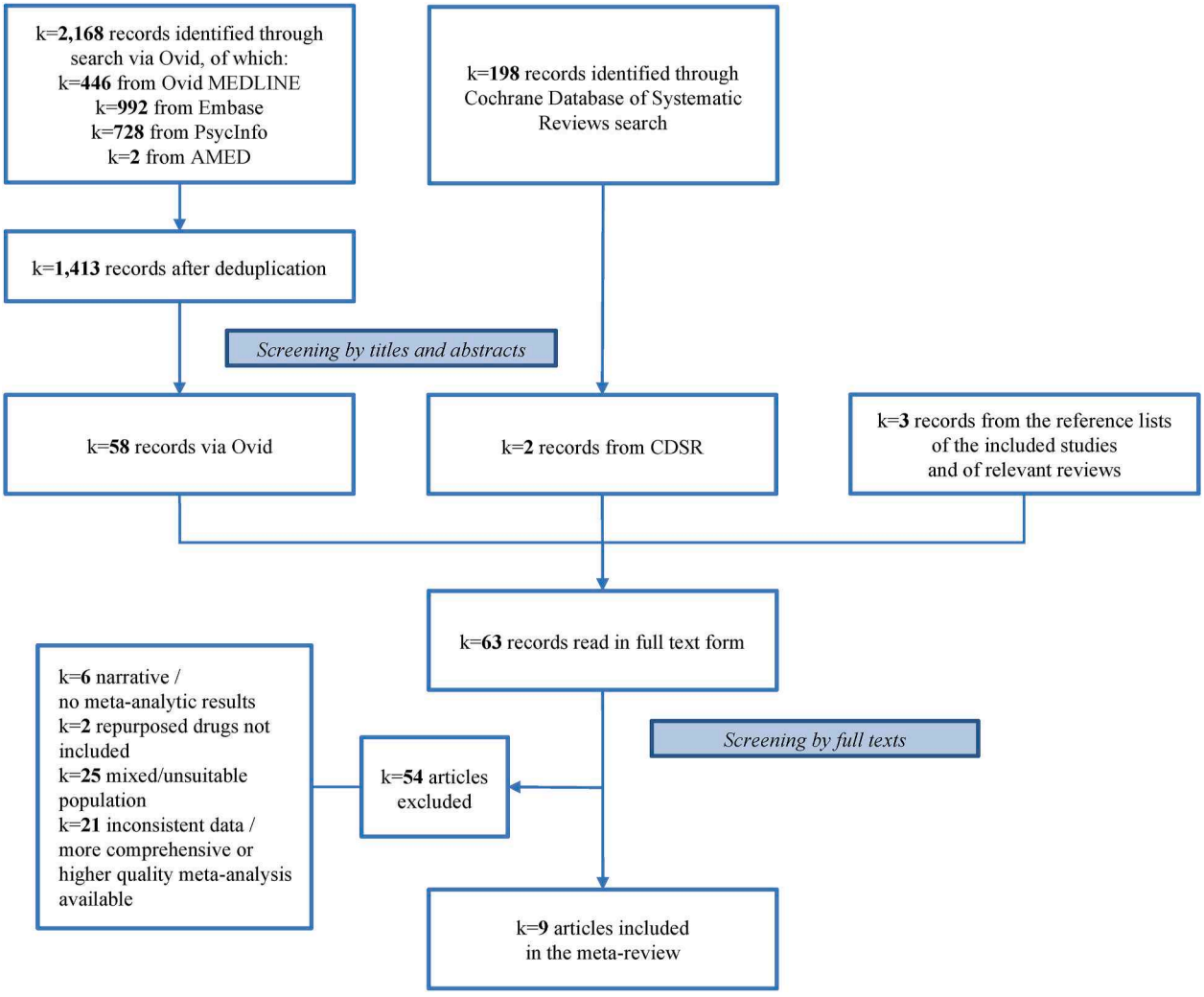

Fig. 1. Study selection process flow chart.

The characteristics of the included meta-analyses are displayed in Table 1.

3.3. Critical appraisal of the included meta-analyses

According to AMSTAR 2, the included meta-analyses met between six (Palacios et al., 2019) and 15 (McCloud et al., 2015) criteria. Considering critical domains, confidence in the reporting was deemed high for two studies (Bartoli et al., 2017a; McCloud et al., 2015); moderate for one study (Kishi et al., 2021); low for four studies (Bahji et al., 2021; Nery et al., 2020; Nunez et al., 2020; Tundo et al., 2019); critically low for two studies (Palacios et al., 2019; Mukai et al., 2014).

The appraisal of the included meta-analyses according to AMSTAR 2 and the overall confidence in their results are displayed in Table 2. A detailed judgment for each AMSTAR 2 item is shown in **Supplement S3**.

3.4. Drugs repurposed for mania

Allopurinol. According to findings from five RCTs with follow-up periods ranging from 4 to 8 weeks, accounting for a total of 469 individuals, adjunctive allopurinol in manic and mixed-manic episodes showed higher efficacy than placebo in reducing Young Mania Rating Scale (YMRS) scores, with a small-to-moderate effect size (N = 433; SMD = −0.34, 95%CI: −0.60 to −0.09, p = 0.007) and low heterogeneity across studies (I^2 = 35%). No influence of allopurinol dosage (p = 0.50), follow-up duration (p = 0.41), and concurrent standard treatment (p = 0.59) was found. A subgroup analysis confirmed the efficacy of adjunctive allopurinol in pure manic episodes, with an effect of moderate size (k = 3; N = 230; SMD = −0.52, 95%CI: −0.78 to −0.25, p < 0.001). Clinical remission rates were higher for allopurinol than for placebo (k = 2; N = 177; RR = 1.51, 95%CI: 1.20 to 1.90, p < 0.001; I^2 = 0%). Data on discontinuation (RR = 0.91, 95%CI: 0.66 to 1.26, p = 0.58; I^2 = 0%) and side effects – i.e., asthenia (p = 0.78), diarrhoea (p = 0.75), dizziness (p = 0.73), headache (p = 0.41), and somnolence (p = 0.59) – did not show any difference between allopurinol and placebo, with low heterogeneity (Bartoli et al., 2017a).

Melatonin and ramelteon. A meta-analysis of three RCTs (N = 122) favoured add-on melatonin-receptor agonists, i.e., melatonin and ramelteon, over placebo, reporting significant differences in the improvement of YMRS scores (Kishi et al., 2021) at study endpoints (3–8 weeks). However, when these were standardized, no differences were estimated considering both melatonin and ramelteon (k = 3; N = 114; SMD = −0.56, 95%CI: −1.15 to 0.03, p = 0.07; I^2 = 55.7%) and melatonin only (k = 2; N = 95; SMD = −0.66, 95%CI: −1.48 to 0.16, p = 0.12; I^2 = 73.7%). All-cause discontinuation (k = 3; N = 122; RR = 0.95, 95%CI: 0.45 to 1.99, p = 0.88) and side effects (k = 2; N = 81) – i.e., sedation (p = 0.28), nausea/vomiting (p = 0.29), and headache (p = 0.48) – did not differ between the two groups, with no heterogeneity (I^2 = 0%) (Kishi et al., 2021).

Tamoxifen. In a meta-analysis of three RCTs (N = 82), tamoxifen in adjunct to lithium or valproate showed superiority to placebo on

Table 2
Critical appraisal according to AMSTAR 2 and overall confidence in the results of the review.

Author(s), year	Number of items rated positively (total)	Weaknesses detected in critical and non-critical items	Overall confidence in the results of the review
Bahji et al. (2021)	11	One critical flaw, more than one non-critical weakness	Low
Bartoli et al. (2017)	14.5	No critical flaws, one non-critical weakness	High
Kishi et al. (2021)	12.5	No critical flaws, more than one non-critical weakness	Moderate
McCloud et al. (2015)	15	No critical flaws, one non-critical weakness	High
Mukai et al. (2014)	10	More than one critical flaw	Critically low
Nery et al. (2020)	12.5	One critical flaw, more than one non-critical weakness	Low
Nunez et al. (2020)	10.5	One critical flaw, more than one non-critical weakness	Low
Palacios et al. (2019)	6	More than one critical flaw	Critically low
Tundo et al. (2019)	11	One critical flaw, more than one non-critical weakness	Low

Table 1
Characteristics of the included studies.

Author(s), year	Repurposed drug	Mood polarity	k	N total	N int	N PLB	Dose	Concomitant treatment	Follow-up duration (weeks)
Bahji et al. (2021)	Acetylsalicylic acid	Bipolar depression	2	68	24	44	162-1,000 mg/day	N/R	6–16
	Celecoxib		2	93	49	44	400 mg/day	N/R	6–8
	Inositol		2	41	21	20	5.7–19 g/day	N/R	6
	Memantine		2	261	129	132	5–20 mg/day	N/R	8–12
	N-acetylcysteine		4	240	118	122	1,000–3,000 mg/day	N/R	16–24
	Pioglitazone		2	82	40	42	15–45 mg/day	N/R	6–8
Bartoli et al. (2017a)	Allopurinol	Mania	5	469	236	233	300–600 mg/day	MS, AP	4–8
Kishi et al. (2021)	Melatonin	Mania	3	122	61	61	2–6 mg/day	MS, AP	3–8
	Ramelteon						8 mg/day		
McCloud et al. (2015)	Memantine	Bipolar depression	2	261	129	132	5–20 mg/day	LTR, Val, Flu	8–12
Mukai et al. (2014)	Inositol	Bipolar depression	2	41	21	20	5.7–19 g/day	Li, Val, CBZ, AD	6
Nery et al. (2020)	N-acetylcysteine	Bipolar depression	6	248	125	123	1,000–3,000 mg/day	MS, AP, AD	10–24
Nunez et al. (2020)	Modafinil/ Armodafinil	Bipolar depression	5	1,587	795	792	174.2 mg/day 150 mg/day	MS, AP	6–8
Palacios et al. (2019)	Tamoxifen	Mania	3	82	40	42	40–80 mg/day	Li, Val	4–6
Tundo et al. (2019)	Pramipexole	Bipolar depression	2	43	22	21	1–5 mg/day	MS, AD	6

k = number of included RCTs; N = number of participants; int = intervention; PLB = placebo.
AD = Antidepressants; AP = Antipsychotics; CBZ = Carbamazepine; Flu = Fluoxetine; Li = Lithium; LTR = Lamotrigine; MS = Mood Stabilizers; Val = Valproate.
N/R = not reported.

response rates (k = 2; N = 49; RR = 3.29, 95%CI: 1.27 to 8.52) and manic symptom score changes (k = 2; N = 49; SMD = −0.97, 95%CI: –1.57 to −0.36) after 4–6 weeks of treatment, with no heterogeneity between studies. Acceptability in terms of study completion was similar between tamoxifen and placebo groups (k = 3; N = 82, 81.7% females; RR = 1.02, 95%CI: 0.92 to 1.12; I^2 = 0%) (Palacios et al., 2019).

Measures of the effect for the main outcomes in mania are provided in Table 3.

3.5. Drugs repurposed for bipolar depression

Acetylsalicylic acid. A meta-analysis of two RCTs (N = 69) found no differences in terms of clinical response (RR = 1.91, 95%CI: 0.79 to 4.58), clinical remission (RR = 1.34, 95%CI: 0.46 to 3.86), and change in depression severity scores (SMD = −0.62, 95%CI: –2.16 to 0.92) among individuals with bipolar depression who received ASA as augmentation to standard treatment for 6–16 weeks. Dropout rates due to all causes were comparable between ASA and placebo groups (RR = 1.00, 95%CI: 0.41 to 2.47) (Bahji et al., 2021).

Celecoxib. A meta-analysis of two RCTs (N = 93) found that subjects with bipolar depression treated with adjunctive celecoxib were more likely to achieve clinical remission (RR = 3.30, 95%CI: 1.40 to 7.80) after 6–8 weeks. Nonetheless, such positive effect was not confirmed for response rates (RR = 1.53, 95%CI: 0.92 to 2.52) and changes in depression severity scores (SMD = −0.42, 95%CI: –1.98 to 1.15). There were no significant differences in all-cause dropout rates (RR = 0.64, 95%CI: 0.30 to 1.34) (Bahji et al., 2021).

N-acetylcysteine. Meta-analytic data showed that adjunctive NAC was more effective than placebo in improving depression scores up to 24 weeks of treatment (k = 6; N = 248; SMD = −0.45, 95%CI: –0.84 to −0.06), with a moderate statistical heterogeneity (I^2 = 49%) (Nery et al., 2020), but had no effects on clinical response (k = 4; N = 240; RR = 0.84, 95%CI: 0.51 to 1.38) and remission (k = 4; N = 240; RR = 0.87, 95%CI: 0.49 to 1.56) (Bahji et al., 2021). Dropout rates were similar (k = 4; N = 240; RR = 1.00, 95%CI: 0.70 to 1.42) (Bahji et al., 2021).

Pioglitazone. A meta-analysis of two RCTs (N = 82) showed no differences in clinical response (RR = 1.02, 95%CI: 0.58 to 1.79), remission (RR = 1.00, 95%CI: 0.27 to 3.80), changes in depression severity scores (SMD = 0.95, 95%CI: –0.64 to 2.53), and dropouts (RR = 1.29, 95%CI: 0.50 to 3.30) between add-on pioglitazone and placebo after 6–8 weeks of treatment (Bahji et al., 2021).

Memantine. Meta-analytic data based on two RCTs (N = 261) did not show differences between memantine and placebo in terms of response rates (RR = 1.34, 95%CI: 0.82 to 2.17, p = 0.24; I^2 = 26.2%), remission rates (RR = 1.42, 95%CI: 0.79 to 2.54, p = 0.24; I^2 = 27.2%) (McCloud et al., 2015), and change in depressive symptom scores (SMD = −0.19, 95%CI: –1.74 to 1.35) (Bahji et al., 2021) at study endpoints (8–12 weeks). Acceptability did not significantly differ in total dropouts (RR = 0.84, 95%CI: 0.58 to 1.21, p = 0.34; I^2 = 0%) and in discontinuation for lack of efficacy (RR = 0.62, 95%CI: 0.20 to 1.97, p = 0.42; I^2 = 0%) (McCloud et al., 2015).

Modafinil/armodafinil. A meta-analysis of five RCTs with follow-ups of 6–8 weeks (N = 1,587) verified that modafinil (k = 1) and armodafinil (k = 4) were superior to placebo with regard to response (RR = 1.18, 95%CI: 1.01 to 1.37, p = 0.03; I^2 = 34%) and remission rates (RR = 1.38, 95%CI: 1.10 to 1.73, p = 0.005; I^2 = 18%), as well as to depressive symptom scores (SMD = −0.18, 95%CI: –0.28 to −0.08, p < 0.001; I^2 = 2.4%), at study endpoints. No differences in overall discontinuation (RR = 1.08, 95%CI: 0.89 to 1.30, p = 0.45; I^2 = 0%) were found, although modafinil/armodafinil entailed an increased risk of gastrointestinal disorders (RR = 1.41, 95%CI: 1.09 to 1.84, p = 0.01; I^2 = 0%), nausea (RR = 1.72, 95%CI: 1.09 to 2.73, p = 0.02; I^2 = 0%), and dry mouth (k = 3; N = 1,109; RR = 2.18, 95%CI: 1.11 to 4.29, p = 0.02; I^2 = 0%) (Nunez et al., 2020).

Pramipexole. A meta-analysis (k = 2; N = 43) showed that pramipexole was largely superior to placebo in inducing clinical response (RR = 4.12, 95%CI: 1.40 to 12.15, p = 0.01) and depressive symptoms reduction (SMD = −1.16, 95%CI: –1.82 to −0.51, p < 0.001), but not clinical remission (RR = 2.85, 95%CI: 0.64 to 12.81, p = 0.17), after 6 weeks of treatment, with no statistical heterogeneity. No differences in all-cause dropouts were detected (RR = 1.56, 95%CI: 0.21 to 11.64, p = 0.66; I^2 = 0%) (Tundo et al., 2019).

Inositol. Meta-analytic data based on two RCTs (N = 42) did not find add-on inositol to be more effective than placebo on response rates (RR = 1.59, 95%CI: 0.89 to 2.86) (Mukai et al., 2014), remission rates (RR = 1.31, 95%CI: 0.51 to 3.39) (Bahji et al., 2021), and change in depressive symptom scores (SMD = 0.11, 95%CI: –0.52 to 0.75, p = 0.72; I^2 = 0%) at 6 weeks (Mukai et al., 2014). No differences in dropouts due to any cause were estimated (RR = 0.82, 95%CI: 0.35 to 1.93) (Bahji et al., 2021).

Measures of the effect for the main outcomes in bipolar depression are provided in Table 4.

Table 3
Measures of effects and grading of evidence for repurposed drugs as adjunctive treatments for mania.

Repurposed drug	Author(s), year	k	N	ES [95%CI]	Grading of the evidence
Clinical response – RRs					
Tamoxifen	Palacios et al. (2019)	2	49	3.29† [1.27 to 8.52]	**VERY LOW** ⊕x̂x̂x̂
Clinical remission – RRs					
Allopurinol	Bartoli et al. (2017a)	2	177	1.51*** [1.20 to 1.90]	**LOW** ⊕⊕x̂x̂
Changes in symptom scores – SMDs					
Allopurinol (manic/mixed)	Bartoli et al. (2017a)	5	433	−0.34** [–0.60 to −0.09]	**LOW** ⊕⊕x̂x̂
Allopurinol (pure manic)	Bartoli et al. (2017a)	3	230	−0.52*** [–0.78 to −0.25]	**LOW** ⊕⊕x̂x̂
Melatonin, Ramelteon	Kishi et al. (2021)	3	114	−0.56 [−1.15 to 0.03]	N/A
Melatonin	Kishi et al. (2021)	2	95	−0.66 [−1.48 to 0.16]	N/A
Tamoxifen	Palacios et al. (2019)	2	49	−0.97† [–1.57 to −0.36]	**VERY LOW** ⊕x̂x̂x̂
Acceptability (all-cause discontinuation) – RRs					
Allopurinol	Bartoli et al. (2017a)	5	469	0.91 [0.66 to 1.26]	N/A
Melatonin, Ramelteon	Kishi et al. (2021)	3	122	0.95 [0.45 to 1.99]	N/A
Tamoxifen	Palacios et al. (2019)	3	82	1.02 [0.92 to 1.12]	N/A

*p < 0.05; **p < 0.01; ***p < 0.001; †p-value not reported.
95%CI = 95% Confidence Interval; ES = Effect Size; k = number of included RCTs; N = number of included subjects; N/A = Not Applicable; RRs = Risk Ratios; SMDs = Standardized Mean Differences.

Table 4
Measures of effects and grading of evidence for repurposed drugs as adjunctive treatments for bipolar depression.

Repurposed drug	Author(s), year	k	N	ES [95%CI]	Grading of the evidence
Clinical response – RRs					
Acetylsalicylic acid	Bahji et al. (2021)	2	68	1.91 [0.79 to 4.58]	N/A
Celecoxib	Bahji et al. (2021)	2	93	1.53 [0.92 to 2.52]	N/A
N-acetylcysteine	Bahji et al. (2021)	4	240	0.84 [0.51 to 1.38]	N/A
Pioglitazone	Bahji et al. (2021)	2	81	1.02 [0.58 to 1.79]	N/A
Memantine	McCloud et al. (2015)	2	261	1.34 [0.82 to 2.17]	N/A
Modafinil/Armodafinil	Nunez et al. (2020)	5	1,587	1.18 [1.01 to 1.37]	**LOW** ⊕⊕x̂x̂
Pramipexole	Tundo et al. (2019)	2	43	4.12* [1.40 to 12.15]	**LOW** ⊕⊕x̂x̂
Inositol	Mukai et al. (2014)	2	41	1.59 [0.89 to 2.86]	N/A
Clinical remission – RRs					
Acetylsalicylic acid	Bahji et al. (2021)	2	68	1.34 [0.46 to 3.86]	N/A
Celecoxib	Bahji et al. (2021)	2	93	3.30† [1.40 to 7.80]	**LOW** ⊕⊕x̂x̂
N-acetylcysteine	Bahji et al. (2021)	4	240	0.87 [0.49 to 1.56]	N/A
Pioglitazone	Bahji et al. (2021)	2	81	1.00 [0.27 to 3.80]	N/A
Memantine	McCloud et al. (2015)	2	261	1.42 [0.79 to 2.54]	N/A
Modafinil/Armodafinil	Nunez et al. (2020)	5	1,587	1.38** [1.10 to 1.73]	**LOW** ⊕⊕x̂x̂
Pramipexole	Tundo et al. (2019)	2	43	2.85 [0.64 to 12.81]	N/A
Inositol	Bahji et al. (2021)	2	41	1.31 [0.51 to 3.39]	N/A
Changes in symptom scores – SMDs					
Acetylsalicylic acid	Bahji et al. (2021)	2	68	−0.62 [–2.16 to 0.92]	N/A
Celecoxib	Bahji et al. (2021)	2	93	−0.42 [–1.98 to 1.15]	N/A
N-acetylcysteine	Nery et al. (2020)	6	248	−0.45† [–0.84 to −0.06]	**LOW** ⊕⊕x̂x̂
Pioglitazone	Bahji et al. (2021)	2	81	0.95 [–0.64 to 2.53]	N/A
Memantine	Bahji et al. (2021)	2	261	−0.19 [–1.74 to 1.35]	N/A
Modafinil/Armodafinil	Nunez et al. (2020)	5	1,587	−0.18*** [–0.28 to −0.08]	**LOW** ⊕⊕x̂x̂
Pramipexole	Tundo et al. (2019)	2	43	−1.16 [–1.82 to −0.51]	**LOW** ⊕⊕x̂x̂
Inositol	Mukai et al. (2014)	2	41	0.11 [–0.52 to 0.75]	N/A
Acceptability (all-cause discontinuation) – RRs					
Acetylsalicylic acid	Bahji et al. (2021)	2	68	1.00 [0.41 to 2.47]	N/A
Celecoxib	Bahji et al. (2021)	2	93	0.64 [0.30 to 1.34]	N/A
N-acetylcysteine	Bahji et al. (2021)	4	240	1.00 [0.70 to 1.42]	N/A
Pioglitazone	Bahji et al. (2021)	2	82	1.29 [0.50 to 3.30]	N/A
Memantine	McCloud et al. (2015)	2	261	0.84 [0.58 to 1.21]	N/A
Modafinil/Armodafinil	Nunez et al. (2020)	5	1,587	1.08 [0.89 to 1.30]	N/A
Pramipexole	Tundo et al. (2019)	2	43	1.56 [0.21 to 11.64]	N/A
Inositol	Bahji et al. (2021)	2	41	0.82 [0.35 to 1.93]	N/A

*p < 0.05; **p < 0.01; ***p < 0.001; †p-value not reported.
95%CI = 95% Confidence Interval; ES = Effect Size; k = number of included RCTs; N = number of included subjects; N/A = Not Applicable; RRs = Risk Ratios; SMDs = Standardized Mean Differences.

All outcomes of interest available from the included meta-analyses, with their effect estimates, are reported in **Supplement S4**.

3.6. Grading of the evidence

According to the GRADE assessment, no body of evidence could be deemed of high or moderate quality. With regard to drugs repurposed for mania, evidence of efficacy should be considered as of low quality for allopurinol and of very low quality for tamoxifen, mainly due to high or unclear risk of bias of the included RCTs, imprecision of the estimates, and uncertainty of publication bias. For similar reasons, all evidence concerning drugs repurposed for bipolar depression was graded as of low quality. The overall assessment of the quality of evidence for add-on drugs tested for mania and bipolar depression is displayed in Tables 3 and 4, respectively. A detailed report of the GRADE assessment is shown in **Supplements S5** and **S6**.

4. Discussion

In this meta-review, based on nine eligible studies, we appraised, synthesized, and graded the available evidence from meta-analyses of RCTs examining the efficacy, tolerability, and safety of 12 drugs repurposed as adjunctive treatments of acute mood episodes (mania and depression) in BD. Our work enabled to summarize a large number of findings and to make a careful judgment on repurposed drugs, based on a balanced evaluation of the effect sizes, the quality of evidence, and the clinical relevance of considered outcomes (Balshem et al., 2011).

Meta-analytic data on drugs repurposed for mania indicated allopurinol and tamoxifen as possibly effective and safe adjunctive therapeutic options. Allopurinol, a xanthine oxidase inhibitor that may act increasing adenosine levels, was found to have significant effects on both manic symptoms reduction and clinical remission (Bartoli et al., 2017a). Its efficacy was not influenced by dosage, follow-up duration, or concurrent standard treatment. Notwithstanding the low quality of evidence and the small-to-moderate magnitude of the efficacy outcomes, this finding appears promising in terms of possible clinical applicability, especially in pure manic episodes. This, along with the abnormalities of the purinergic system that have been demonstrated to contribute to the pathophysiology of BD (Bartoli et al, 2016, 2017b), should encourage further clinical studies, with larger samples and longer follow-ups. Likewise, the anti-cancer drug tamoxifen in adjunct to standard treatment with lithium or valproate showed superiority to placebo in terms of response to treatment and reduction in manic symptoms, with large effects (Palacios et al., 2019). Although the mechanisms of action of

tamoxifen are not entirely elucidated, this result seems to support the hypothesis that protein kinase C might represent a biochemical target for the treatment of BD (Armani et al., 2014). Tamoxifen has been suggested as a treatment option for acute mania in recent guidelines (Yatham et al., 2018). However, findings on tamoxifen efficacy should be interpreted with caution in terms of clinical recommendations since, notwithstanding the large effect sizes, they are based on evidence of very low quality and on critically poor reporting according to AMSTAR 2. Conversely, evidence did not support the use of melatonin-receptor agonists as adjunctive treatments for mania, although the small sample size did not allow us to rule out their beneficial effect (Kishi et al., 2021).

As regards drugs repurposed for bipolar depression, mixed findings could be derived from meta-analyses. First, the rationale on the use of stimulants and stimulant-like drugs – acting on dopaminergic, noradrenergic, and serotoninergic neurotransmission (Corp et al., 2014; Connolly and Thase, 2011) – seems supported by meta-analytic evidence. We found racemic modafinil and its (R)-enantiomer armodafinil to be more effective than placebo on all three efficacy outcomes examined, with only minor side effects. However, the magnitude of the effects was small and both the quality of evidence and the overall confidence in the results of the meta-analysis could not be judged more than low (Nunez et al., 2020), limiting the clinical relevance of these findings. Further, adjunctive treatment with pramipexole was superior to placebo in inducing response to treatment and reducing symptoms of bipolar depression, without safety concerns (Tundo et al., 2019). However, both the body of evidence and the review report were of low quality, limiting its actual relevance in clinical practice. Consistently, at present pramipexole is recommended only as a possible third-line option for the treatment of bipolar depression (Yatham et al., 2018). Additional studies yielding more precise estimates could better define its role in the treatment of bipolar depression. In sum, currently available evidence does not enable to warrant specific recommendations about add-on stimulant drugs. Nonetheless, given the absence of clearly effective treatments for depressive episodes in BD and the enduring controversies about the use of traditional antidepressants in this condition (Gitlin, 2018), their utilization in the clinical management of BD may represent a feasible augmentation strategy.

Second, in light of the possible role of inflammation in the pathogenesis of BD (Bartoli et al., 2020a; Misiak et al., 2020; Langan and McDonald, 2009), several agents with anti-inflammatory properties have been suggested for the treatment of bipolar depression. Meta-analytic evidence showed that adjunctive celecoxib performed better than placebo in terms of remission, while add-on NAC was more effective than placebo in reducing depression scales scores, with no safety issues (Bahji et al., 2021; Nery et al., 2020). However, the magnitude of the effects was only small-to-moderate and both evidence quality and overall confidence in the results of the reviews were low. Moreover, no positive effects were detected for other outcomes, severely limiting their possible clinical utility. Additionally, data did not suggest any efficacy of ASA and pioglitazone (Bahji et al., 2021). Thus, notwithstanding the biological rationale, the clinical perspectives of anti-inflammatory agents in the treatment of bipolar depression remain uncertain.

Third, evidence does not support the clinical utility of memantine and inositol as add-on treatments for bipolar depression (Bahji et al., 2021; McCloud et al., 2015; Mukai et al., 2014). In particular, NMDA receptor antagonist memantine was not superior to placebo, despite the possible involvement of the glutamatergic system in the pathophysiology of BD (Bartoli et al., 2020b; Sanacora et al., 2008). Other glutamate receptor modulators have been evaluated as add-ons for bipolar depression, including single-dose intravenous ketamine, but conclusions about its extremely rapid antidepressant effect are limited by the small sample sizes and the short follow-ups of relevant studies (McCloud et al., 2015). Current evidence is thus insufficient to support the clinical use of glutamatergic agents for the treatment of bipolar depression. Similarly, no effects were estimated for second messenger precursor inositol, notwithstanding its link to serotonin, dopamine, and glutamate receptors (Mukai et al., 2014).

As a whole, our study provides a comprehensive overview about drugs repurposed as adjunctive treatments for acute mood episodes in BD. Benefiting from a study design acknowledged as the highest level of evidence synthesis methods (Fusar-Poli and Radua, 2018), we were able to examine a vast amount of meta-analytic data and to explore a broad range of treatment options with the aim of providing up-to-date evidence to clinicians and regulatory decision makers.

Nonetheless, the findings of this meta-review should be interpreted with caution considering some limitations. First, several factors downgraded the quality of evidence, not allowing to draw strong conclusions about many of the investigated drugs. Second, the overall confidence in the results of the meta-analyses could be deemed moderate-to-high only for three of the included studies, primarily because some of them did not adequately assess or discuss the risk of bias of the original RCTs. Third, the included studies provided data only on short-term follow-ups, precluding clear information on long-term efficacy and side effects. Moreover, the nature of our synthesis did not allow direct comparisons between the different interventions addressed, since meta-reviews, by definition, are limited by methodological variability across the included meta-analyses (Pollock et al., 2021; Ioannidis, 2009). In addition, our study design did not allow to consider data – even if available or retrievable – appropriate to derive the number needed to treat/harm for relevant outcomes, precluding a deeper interpretation of the possible clinical utility of single repurposed drugs. Finally, as existing meta-analyses did not consider all the possible treatment options, recent, single RCTs are not covered by our meta-review. Other agents have been repurposed as possible adjunctive treatments for BD, including cytidine (Yoon et al., 2009), levothyroxine (Stamm et al., 2014), and minocycline (Husain et al., 2020; Savitz et al., 2018) for bipolar depression, as well as medroxyprogesterone (Kulkarni et al., 2014) and rivastigmine (Keshavrzi et al., 2019) for mania.

In sum, since standard treatments for mania and bipolar depression remain not entirely satisfactory, the analysis of novel therapeutic strategies stands as a major issue to enhance the management of BD (Carvalho et al., 2020; McIntyre et al., 2020; Ferrari et al., 2016). The lack of evidence of high and moderate quality does not allow making reliable recommendations for the use of repurposed drugs in clinical practice. However, some of them have shown promising results and deserve further research, with adequate study designs, larger samples, and direct comparisons between drugs.

Role of the funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Francesco Bartoli: Conceptualization, Methodology, Investigation, Writing – original draft, Project administration. **Daniele Cavaleri:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Bianca Bachi:** Investigation, Data curation, Writing – review & editing, Visualization. **Federico Moretti:** Investigation, Data curation, Writing – review & editing, Visualization. **Ilaria Riboldi:** Investigation, Writing – review & editing. **Cristina Crocamo:** Software, Formal analysis, Resources, Writing – review & editing. **Giuseppe Carrà:** Writing – review & editing, Supervision.

Declaration of competing interest

None.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.09.018.

References

Armani, F., Andersen, M.L., Galduróz, J.C., 2014. Tamoxifen use for the management of mania: a review of current preclinical evidence. Psychopharmacology (Berlin) 231 (4), 639–649. https://doi.org/10.1007/s00213-013-3397-x.

Bahji, A., Ermacora, D., Stephenson, C., Hawken, E.R., Vazquez, G., 2021. Comparative efficacy and tolerability of adjunctive pharmacotherapies for acute bipolar depression: a systematic review and network meta-analysis. Can. J. Psychiatr. 66 (3), 274–288. https://doi.org/10.1177/0706743720970857.

Balshem, H., Helfand, M., Schünemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., Vist, G. E., Falck-Ytter, Y., Meerpohl, J., Norris, S., Guyatt, G.H., 2011. GRADE guidelines: 3. Rating the quality of evidence. J. Clin. Epidemiol. 64 (4), 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015.

Bartoli, F., Misiak, B., Crocamo, C., Carrà, G., 2020a. Glial and neuronal markers in bipolar disorder: a meta-analysis testing S100B and NSE peripheral blood levels. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 101, 109922. https://doi.org/10.1016/j.pnpbp.2020.109922.

Bartoli, F., Misiak, B., Callovini, T., Cavaleri, D., Cioni, R.M., Crocamo, C., Savitz, J.B., Carrà, G., 2020b. The kynurenine pathway in bipolar disorder: a meta-analysis on the peripheral blood levels of tryptophan and related metabolites. Mol. Psychiatr. https://doi.org/10.1038/s41380-020-00913-1, 10.1038/s41380-020-00913-1 (published online ahead of print 2020 Oct 19).

Bartoli, F., Crocamo, C., Clerici, M., Carrà, G., 2017a. Allopurinol as add-on treatment for mania symptoms in bipolar disorder: systematic review and meta-analysis of randomised controlled trials. Br. J. Psychiatry 210 (1), 10–15. https://doi.org/10.1192/bjp.bp.115.180281.

Bartoli, F., Crocamo, C., Dakanalis, A., Brosio, E., Miotto, A., Capuzzi, E., Clerici, M., Carrà, G., 2017b. Purinergic system dysfunctions in subjects with bipolar disorder: a comparative cross-sectional study. Compr. Psychiatr. 73, 1–6. https://doi.org/10.1016/j.comppsych.2016.09.011.

Bartoli, F., Crocamo, C., Mazza, M.G., Clerici, M., Carrà, G., 2016. Uric acid levels in subjects with bipolar disorder: a comparative meta-analysis. J. Psychiatr. Res. 81, 133–139. https://doi.org/10.1016/j.jpsychires.2016.07.007.

Bauer, I.E., Gálvez, J.F., Hamilton, J.E., Balanzá-Martínez, V., Zunta-Soares, G.B., Soares, J.C., Meyer, T.D., 2016. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: a systematic review. J. Psychiatr. Res. 74, 1–7. https://doi.org/10.1016/j.jpsychires.2015.12.006.

Carvalho, A.F., Firth, J., Vieta, E., 2020. Bipolar disorder. N. Engl. J. Med. 383 (1), 58–66. https://doi.org/10.1056/NEJMra1906193.

Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J.P.A., Geddes, J.R., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 391 (10128), 1357–1366. https://doi.org/10.1016/S0140-6736(17)32802-7.

Cipriani, A., Barbui, C., Salanti, G., Rendell, J., Brown, R., Stockton, S., Purgato, M., Spineli, L.M., Goodwin, G.M., Geddes, J.R., 2011. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 378 (9799), 1306–1315. https://doi.org/10.1016/S0140-6736(11)60873-8.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Lawrence Erlbaum Associates, Hillsdale, NJ, USA.

Connolly, K.R., Thase, M.E., 2011. If at first you don't succeed: a review of the evidence for antidepressant augmentation, combination and switching strategies. Drugs 71 (1), 43–64. https://doi.org/10.2165/11587620-000000000-00000.

Corp, S.A., Gitlin, M.J., Altshuler, L.L., 2014. A review of the use of stimulants and stimulant alternatives in treating bipolar depression and major depressive disorder. J. Clin. Psychiatr. 75 (9), 1010–1018. https://doi.org/10.4088/JCP.13r08851.

Dean, O.M., Gliddon, E., Van Rheenen, T.E., Giorlando, F., Davidson, S.K., Kaur, M., Ngo, T.T., Williams, L.J., 2018. An update on adjunctive treatment options for bipolar disorder. Bipolar Disord. 20 (2), 87–96. https://doi.org/10.1111/bdi.12601.

Fava, M., 2018. The promise and challenges of drug repurposing in psychiatry. World Psychiatr. 17 (1), 28–29. https://doi.org/10.1002/wps.20481.

Ferrari, A.J., Stockings, E., Khoo, J.P., Erskine, H.E., Degenhardt, L., Vos, T., Whiteford, H.A., 2016. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. Bipolar Disord. 18 (5), 440–450. https://doi.org/10.1111/bdi.12423.

Firth, J., Teasdale, S.B., Allott, K., Siskind, D., Marx, W., Cotter, J., Veronese, N., Schuch, F., Smith, L., Solmi, M., Carvalho, A.F., Vancampfort, D., Berk, M., Stubbs, B., Sarris, J., 2019. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. World Psychiatr. 18 (3), 308–324. https://doi.org/10.1002/wps.20672.

Fusar-Poli, P., Radua, J., 2018. Ten simple rules for conducting umbrella reviews. Evid. Base Ment. Health 21 (3), 95–100. https://doi.org/10.1136/ebmental-2018-300014.

Geddes, J.R., Miklowitz, D.J., 2013. Treatment of bipolar disorder. Lancet 381 (9878), 1672–1682. https://doi.org/10.1016/S0140-6736(13)60857-0.

Gitlin, M.J., 2018. Antidepressants in bipolar depression: an enduring controversy. Int. J. Bipolar Disord. 6 (1), 25. https://doi.org/10.1186/s40345-018-0133-9.

Guyatt, G.H., Oxman, A.D., Kunz, R., Brozek, J., Alonso-Coello, P., Rind, D., Devereaux, P.J., Montori, V.M., Freyschuss, B., Vist, G., Jaeschke, R., Williams Jr., J. W., Murad, M.H., Sinclair, D., Falck-Ytter, Y., Meerpohl, J., Whittington, C., Thorlund, K., Andrews, J., Schünemann, H.J., 2011. GRADE guidelines 6. Rating the quality of evidence–imprecision. J. Clin. Epidemiol. 64 (12), 1283–1293. https://doi.org/10.1016/j.jclinepi.2011.01.012.

Guyatt, G.H., Oxman, A.D., Vist, G.E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H.J., GRADE Working Group, 2008. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336 (7650), 924–926. https://doi.org/10.1136/bmj.39489.470347.AD.

Haggarty, S.J., Karmacharya, R., Perlis, R.H., 2021. Advances toward precision medicine for bipolar disorder: mechanisms & molecules. Mol. Psychiatr. 26 (1), 168–185. https://doi.org/10.1038/s41380-020-0831-4.

Hemphill, C.S., Sampat, B.N., 2012. Evergreening, patent challenges, and effective market life in pharmaceuticals. J. Health Econ. 31 (2), 327–339. https://doi.org/10.1016/j.jhealeco.2012.01.004.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557.

Husain, M.I., Chaudhry, I.B., Khoso, A.B., Husain, M.O., Hodsoll, J., Ansari, M.A., Naqvi, H.A., Minhas, F.A., Carvalho, A.F., Meyer, J.H., Deakin, B., Mulsant, B.H., Husain, N., Young, A.H., 2020. Minocycline and celecoxib as adjunctive treatments for bipolar depression: a multicentre, factorial design randomised controlled trial. Lancet Psychiatr. 7 (6), 515–527. https://doi.org/10.1016/S2215-0366(20)30138-3.

Ioannidis, J.P., 2009. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ (Can. Med. Assoc. J.) 181 (8), 488–493. https://doi.org/10.1503/cmaj.081086.

Keshavrzi, A., Rezaei, H., Haghighi, M., Jahangard, L., 2019. Effect of rivastigmine (acetyl cholinesterase inhibitor) versus placebo on manic episodes in patients with bipolar disorders: results from a double blind, randomized, placebo-controlled clinical trial. Neuropsychobiology 78 (4), 200–208. https://doi.org/10.1159/000501210.

Kessing, L.V., Rytgaard, H.C., Gerds, T.A., Berk, M., Ekstrøm, C.T., Andersen, P.K., 2019. New drug candidates for bipolar disorder-A nation-wide population-based study. Bipolar Disord. 21 (5), 410–418. https://doi.org/10.1111/bdi.12772.

Kishi, T., Nishiyama, H., Kimura, Y., Sadaka, T., Terada, A., Tatsumi, Y., Wakahara, M., Iwata, N., 2021. Melatonin receptor agonists for bipolar mania: a systematic review and meta-analyses of double-blind randomized placebo-controlled trials. Bipolar Disord. https://doi.org/10.1111/bdi.13064, 10.1111/bdi.13064 (published online ahead of print 2021 Feb 24).

Kulkarni, J., Berk, M., Wang, W., Mu, L., Scarr, E., Van Rheenen, T.E., Worsley, R., Gurvich, C., Gavrilidis, E., de Castella, A., Fitzgerald, P., Davis, S.R., 2014. A four week randomised control trial of adjunctive medroxyprogesterone and tamoxifen in women with mania. Psychoneuroendocrinology 43, 52–61. https://doi.org/10.1016/j.psyneuen.2014.02.004.

Langan, C., McDonald, C., 2009. Neurobiological trait abnormalities in bipolar disorder. Mol. Psychiatr. 14 (9), 833–846. https://doi.org/10.1038/mp.2009.39.

Langedijk, J., Mantel-Teeuwisse, A.K., Slijkerman, D.S., Schutjens, M.H., 2015. Drug repositioning and repurposing: terminology and definitions in literature. Drug Discov. Today 20 (8), 1027–1034. https://doi.org/10.1016/j.drudis.2015.05.001.

Lovas, D.A., Schuman-Olivier, Z., 2018. Mindfulness-based cognitive therapy for bipolar disorder: a systematic review. J. Affect. Disord. 240, 247–261. https://doi.org/10.1016/j.jad.2018.06.017.

McCloud, T.L., Caddy, C., Jochim, J., Rendell, J.M., Diamond, P.R., Shuttleworth, C., Brett, D., Amit, B.H., McShane, R., Hamadi, L., Hawton, K., Cipriani, A., 2015. Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. Cochrane Database Syst. Rev. 9, CD011611. https://doi.org/10.1002/14651858.CD011611.pub2.

McIntyre, R.S., Berk, M., Brietzke, E., Goldstein, B.I., López-Jaramillo, C., Kessing, L.V., Malhi, G.S., Nierenberg, A.A., Rosenblat, J.D., Majeed, A., Vieta, E., Vinberg, M., Young, A.H., Mansur, R.B., 2020. Bipolar disorders. Lancet 396 (10265), 1841–1856. https://doi.org/10.1016/S0140-6736(20)31544-0.

Misiak, B., Bartoli, F., Carrà, G., Małecka, M., Samochowiec, J., Jarosz, K., Banik, A., Stańczykiewicz, B., 2020. Chemokine alterations in bipolar disorder: a systematic review and meta-analysis. Brain Behav. Immun. 88, 870–877. https://doi.org/10.1016/j.bbi.2020.04.013.

Mukai, T., Kishi, T., Matsuda, Y., Iwata, N., 2014. A meta-analysis of inositol for depression and anxiety disorders. Hum. Psychopharmacol. 29 (1), 55–63. https://doi.org/10.1002/hup.2369.

Nery, F.G., Li, W., DelBello, M.P., Welge, J.A., 2020. N-acetylcysteine as an adjunctive treatment for bipolar depression: a systematic review and meta-analysis of randomized controlled trials. Bipolar Disord. https://doi.org/10.1111/bdi.13039, 10.1111/bdi.13039 (published online ahead of print 2020 Dec 22).

Nunez, N.A., Singh, B., Romo-Nava, F., Joseph, B., Veldic, M., Cuellar-Barboza, A., Cabello Arreola, A., Vande Voort, J.L., Croarkin, P., Moore, K.M., Biernacka, J., McElroy, S.L., Frye, M.A., 2020. Efficacy and tolerability of adjunctive modafinil/armodafinil in bipolar depression: a meta-analysis of randomized controlled trials. Bipolar Disord. 22 (2), 109–120. https://doi.org/10.1111/bdi.12859.

Olivier, J., Bell, M.L., 2013. Effect sizes for 2×2 contingency tables. PloS One 8 (3), e58777. https://doi.org/10.1371/journal.pone.0058777.

Palacios, J., Yildiz, A., Young, A.H., Taylor, M.J., 2019. Tamoxifen for bipolar disorder: systematic review and meta-analysis. J. Psychopharmacol. 33 (2), 177–184. https://doi.org/10.1177/0269881118822167.

Phillips, M.L., Kupfer, D.J., 2013. Bipolar disorder diagnosis: challenges and future directions. Lancet 381 (9878), 1663–1671. https://doi.org/10.1016/S0140-6736(13)60989-7.

Pollock, M., Fernandes, R.M., Becker, L.A., Pieper, D., Hartling, L., 2021. Chapter V: overviews of reviews. In: Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane. Available from: www.training.cochrane.org/handbook.

Rosenthal, J.A., 1996. Qualitative descriptors of strength of association and effect size. J. Soc. Serv. Res. 21 (4), 37–59. https://doi.org/10.1300/J079v21n04_02.

Sanacora, G., Zarate, C.A., Krystal, J.H., Manji, H.K., 2008. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat. Rev. Drug Discov. 7 (5), 426–437. https://doi.org/10.1038/nrd2462.

Savitz, J.B., Teague, T.K., Misaki, M., Macaluso, M., Wurfel, B.E., Meyer, M., Drevets, D., Yates, W., Gleason, O., Drevets, W.C., Preskorn, S.H., 2018. Treatment of bipolar depression with minocycline and/or aspirin: an adaptive, 2×2 double-blind, randomized, placebo-controlled, phase IIA clinical trial. Transl. Psychiatry 8 (1), 27. https://doi.org/10.1038/s41398-017-0073-7.

Schünemann, H.J., Higgins, J.P.T., Vist, G.E., Glasziou, P., Akl, E.A., Skoetz, N., Guyatt, G.H., 2021. Chapter 14: completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane. Available from: www.training.cochrane.org/handbook.

Shea, B.J., Reeves, B.C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E., Henry, D.A., 2017. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 358, j4008. https://doi.org/10.1136/bmj.j4008.

Stamm, T.J., Lewitzka, U., Sauer, C., Pilhatsch, M., Smolka, M.N., Koeberle, U., Adli, M., Ricken, R., Scherk, H., Frye, M.A., Juckel, G., Assion, H.J., Gitlin, M., Whybrow, P.C., Bauer, M., 2014. Supraphysiologic doses of levothyroxine as adjunctive therapy in bipolar depression: a randomized, double-blind, placebo-controlled study. J. Clin. Psychiatr. 75 (2), 162–168. https://doi.org/10.4088/JCP.12m08305.

StataCorp, 2019. Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX, USA.

Tundo, A., de Filippis, R., De Crescenzo, F., 2019. Pramipexole in the treatment of unipolar and bipolar depression. A systematic review and meta-analysis. Acta Psychiatr. Scand. 140 (2), 116–125. https://doi.org/10.1111/acps.13055.

Yatham, L.N., Kennedy, S.H., Parikh, S.V., Schaffer, A., Bond, D.J., Frey, B.N., Sharma, V., Goldstein, B.I., Rej, S., Beaulieu, S., Alda, M., MacQueen, G., Milev, R.V., Ravindran, A., O'Donovan, C., McIntosh, D., Lam, R.W., Vazquez, G., Kapczinski, F., McIntyre, R.S., Kozicky, J., Kanba, S., Lafer, B., Suppes, T., Calabrese, J.R., Vieta, E., Malhi, G., Post, R.M., Berk, M., 2018. Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disord. 20 (2), 97–170. https://doi.org/10.1111/bdi.12609.

Yoon, S.J., Lyoo, I.K., Haws, C., Kim, T.S., Cohen, B.M., Renshaw, P.F., 2009. Decreased glutamate/glutamine levels may mediate cytidine's efficacy in treating bipolar depression: a longitudinal proton magnetic resonance spectroscopy study. Neuropsychopharmacology 34 (7), 1810–1818. https://doi.org/10.1038/npp.2009.2.