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REVIEW ARTICLE

WILEY BIPOLAR DISORDERS

Second-generation antipsychotic long-acting injections in bipolar disorder: Systematic review and meta-analysis

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Abstract

Background: Non-adherence is a significant problem in bipolar disorder. Second-generation antipsychotics (SGA) long-acting injections (LAIs) may improve adherence in bipolar disorder and may prevent relapses. However, the evidence is limited and conflicting.

Objective: The objective of this study was to evaluate efficacy and safety of SGA LAIs in bipolar disorder.

Method: Systematic review and meta-analysis of randomised controlled trials (RCTs) (≥6 months duration) investigating safety and efficacy of SGA LAIs for bipolar disorder. We searched Pubmed, Embase, CINAHL, Cochrane, PsycINFO, LiLACS, www.clinicaltrials.gov up to October 2016. We also contacted the manufacturers of SGA LAIs. Primary efficacy and safety outcomes were relapse rate and all-cause discontinuation respectively.

Results: Total of seven RCTs (n = 1192) were included. SGA LAIs show superiority over placebo for study-defined relapse rate (RR = 0.58, 95% CI = 0.49-0.68, $P < 0.00001$) and all-cause discontinuation (RR = 0.72, 95% CI = 0.64-0.82, $P < 0.00001$). However, no significant difference was found between SGA LAIs and oral active control for relapse rate (RR = 0.92, $P = 0.79$) and all-cause discontinuation (RR = 1.2, $P = 0.31$). In terms of secondary outcomes, SGA LAIs performed better than placebo in relapse to mania/hypomania, young mania rating scales (YMRS), clinical global impression-severity (CGI-S), montgomery-asberg depression rating scale (MADRS). There was no significant difference between SGA LAIs and oral active control regarding relapse to mania/hypomania, YMRS, CGI-S, extra-pyramidal side effects (EPSEs), weight gain. However, the active control performed better than SGA LAIs in relapse to depression, MADRS, and prolactin-related AEs.

Conclusions: Current evidence is very limited to support the use of SGA LAIs (compared to oral medication) in bipolar disorder. Further high-quality studies, particularly comparing SGA LAIs with active control, are warranted.

KEYWORDS
antipsychotic depots, antipsychotic long-acting injection, bipolar disorder, mental health, meta-analysis, second-generation antipsychotic

1 | INTRODUCTION

Treatment for bipolar disorder should aim to reduce relapses, prevent suicide, minimise resource utilisation and societal costs, and improve functioning.[1-3] However, about 40% of people with bipolar disorder do not adhere to their prescribed treatment. Non-adherence is associated with increased risk of relapse and suicide, unfavourable outcomes, and admission to hospital. The probability of hospitalisation is five times or higher in non-adherent patients compared to adherent patients with bipolar disorder.[4] Long-acting injections (LAIs, also known as depots) may improve adherence and thereby patient outcomes. Evidence from studies in people with schizophrenia suggests that antipsychotic LAIs reduce relapses, medication discontinuation rates, and admission to hospital compared to oral antipsychotics.[5-7] LAIs have some clear advantages including assurance of medication administration and the opportunity to intervene if patients stop treatment, and evidence from systematic review shows patients prefer LAIs to oral.[8] But LAIs could also cause embarrassment for some patient while being administered and could be stigmatising for patients.[9] Clinical experience and evidence suggest that the use of LAIs for bipolar disorder is not infrequent.[2,10,11] None of the SGA LAIs is licensed for bipolar disorder in the UK and the EU although risperidone LAI and more recently aripiprazole LAI have been approved in the US, Canada, and Australia for bipolar disorder. However, evidence base for efficacy is conflicting.[3,12-14] This meta-analysis of RCTs (≥6 months duration) sought to address whether there is sufficient evidence to recommend SGA LAIs in patients with bipolar disorder compared to placebo and active control. To our knowledge, this is the first meta-analysis focusing on SGA LAIs in bipolar disorder which included more than one SGA LAI: risperidone LAI (RLAI) and aripiprazole LAI (ALAI).

2 | METHOD

The study was registered with PROSPERO (international prospective register of systematic reviews) (CRD42015023948). The research protocol was based on PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, statement and published in BMJ Open.[15]

2.1 | Eligibility criteria

The study eligibility criteria were based on the PICOS framework; Participants, Interventions, Comparators, Outcomes, and Study design.

Any studies not meeting the following inclusion criteria were excluded:

- Participants: patients of any age or gender with bipolar disorder using any validated diagnostic system, for example, DSM-IV: 296 or ICD 10: F31.
- Interventions: SGA LAIs in bipolar disorder
- Comparators: placebo, other antipsychotics, mood stabiliser, or treatment as usual (TAU)
- Outcome measures:
  - Primary efficacy outcome—study-defined relapse rate
  - Primary safety outcome—all-cause discontinuation
  - Secondary outcomes included relapse to mania/hypomania, relapse to depression, changes in young mania rating scales, montgomery-asberg depression rating scale, clinical global impression-severity, discontinuation due to adverse effect, the proportion of patients experiencing extra-pyramidal side effects, weight gain, and prolactin-related adverse effects.
- Study design: RCTs with or without double blinding with a minimum duration of 6 months.

2.2 | Data sources, search strategy, and study selection

The following search strategy was employed to ensure all relevant studies assessing SGA LAIs in bipolar disorder were captured, data independently extracted, analysed, verified, and quality assessed. Pubmed, Embase, CINAHL, Cochrane Library, PsycINFO, LiLACS, and www.clinicaltrials.gov were searched for studies published between January 2000 and October 2016 since SGA LAIs only came to the market after 2000. There were no language restrictions. Any relevant studies mentioned in those identified studies were searched manually, for example, by scoping the references listed. Manufacturers of SGA LAIs were contacted for any ongoing or unpublished studies. The initial search was carried out in April 2016 and was rerun in October 2016 which resulted in 30 more studies being identified.

The search strategy consisted of the following three domains:

a Disease: bipolar*, mood disorder*, mania*, manic-depression*, hypomania*, AND
b Treatment: antipsychotic*, neuroleptic*, psychotropic*, atypical*, second generation antipsychotic*, SGA*, aripiprazole, olanzapine, paliperidone, risperidone, AND
c Formulation: depot*, long-acting inject*, LAI*, prolonged release inject*, sustained release inject*

The process of identifying, screening of studies, and inclusion or exclusion of those studies is shown in the PRISMA flow diagram below (see Figure 1).

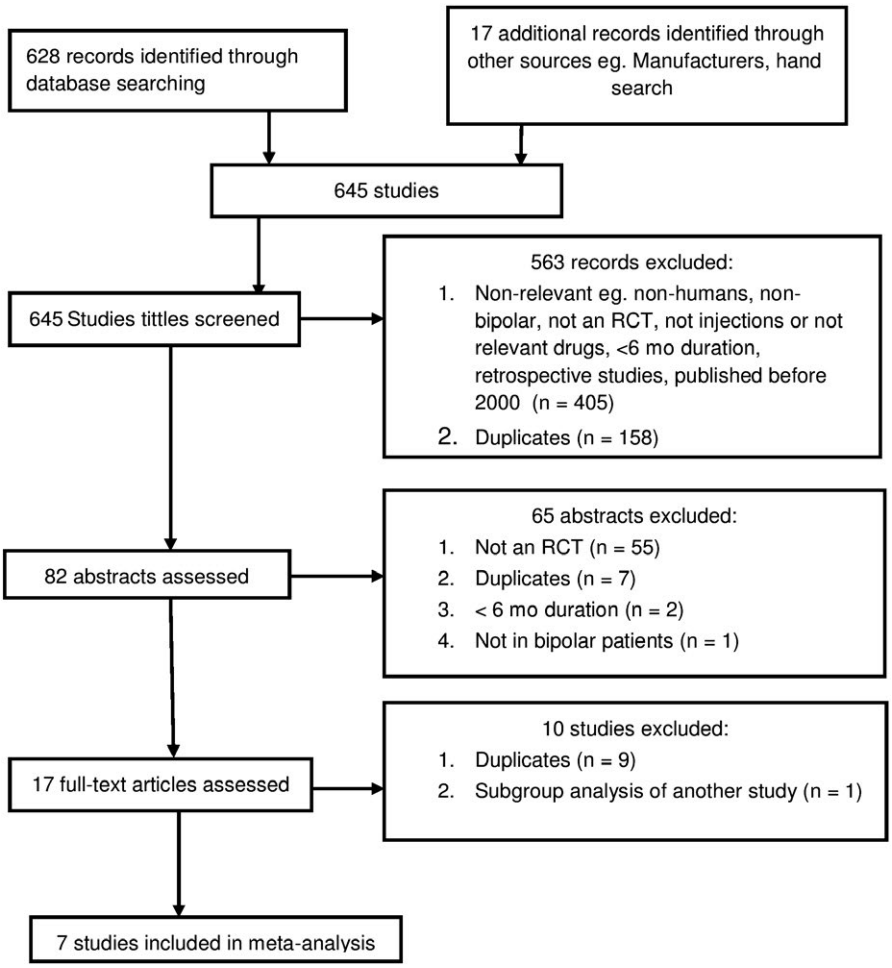

FIGURE 1 PRISMA flow diagram of studies

2.3 | Screening, data extraction, and analysis

ARP screened titles of all retrieved studies. During title screening, we excluded only definitely non-relevant studies, that is, studies that were not in human, not in bipolar patients, not an RCT, did not involve SGA LAIs, studies published before 2000, retrospective studies, studies of less than 6 months' duration or duplicates. If there was any doubt, the studies were included in stage 2 abstract screening. Abstracts of remaining studies were screened against prespecified criteria as per published protocol[15] by ARP and JW independently. ARP and JW screened full article of remaining studies. Any discrepancies were resolved through further discussion or via third reviewer IM.

The data extraction form was adopted from EPOC (Effective Practice and Organisation of Care) resources for review authors and CONSORT (Consolidated Standards of Reporting Trials) 2010 checklist. All quantitative data (both primary and secondary outcome measures) for meta-analysis were extracted by two reviewers (ARP and FS) independently. The remaining data were extracted by ARP and JW independently.

2.4 | Meta-analytic method and quality assessment

The RevMan 5 computer program was used for undertaking the meta-analysis. Primary efficacy and safety outcome measure were presented as RISK Ratio (RR). Statistical significance was set at 0.05 with *P*-value <0.05 considered statistically significant. The estimated effect size and mean difference for continuously distributed outcomes were presented with 95% Confidence Interval (CI). The analysis was based on intention-to-treat (ie, all randomly allocated patients were accounted for the analysis of outcomes) where the data were available. Study heterogeneity was measured using I^2 statistics with values of 50% or higher reflecting considerable heterogeneity. Statistical heterogeneity across studies was tested using Chi-square or Q test. We employed random effect model in this meta-analysis. Where only standard error (SE) was given but lacked standard deviation (SD), we calculated SD using the formula, SD = square root of (n) * SE.

3 | RESULTS

A total of 645 studies were found. The result from each stage of screening is shown in Prisma flow diagram (See Figure 1).

3.1 | Summary of included studies

Table 1 below presents summary of studies included in the meta-analysis. All studies included 18- to 70-year-old male and female patients. (See Supporting information Table S2 for more detailed summary).

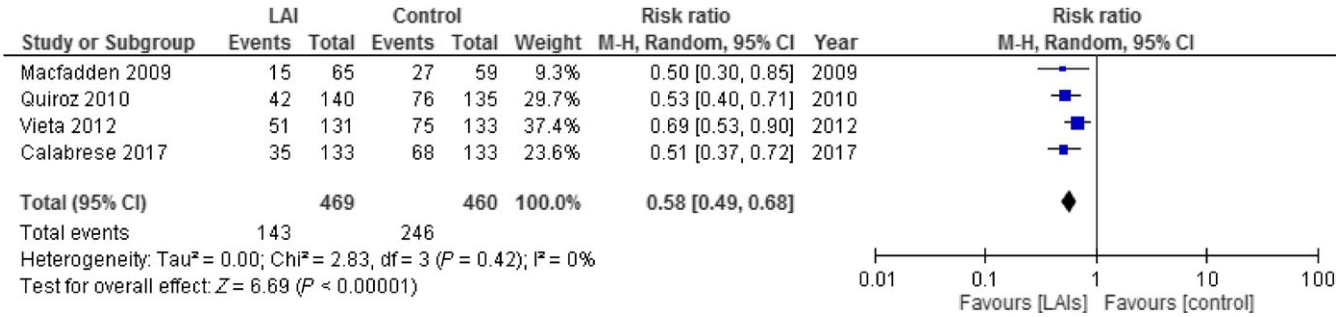

FIGURE 2 Study-defined relapse rate (placebo-controlled studies only) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Summary of studies included in meta-analysis

Study (Ref)	Study design	No. of Participants	No. completed study
Calabrese et al[16]	12 months, RCT, DB, PC	133 ALAI vs 133 Placebo	64 ALAI vs 38 Placebo
Bobo et al[17]	12 months, RCT, OL, AC	20 RLAI + TAU vs 25 TAU Alone	16 RLAI + TAU vs 19 TAU Alone
Chengappa et al[18]	12 months, Pilot, RCT, OL, AC	21 RLAI + TAU vs 18 Oral Antipsychotic + TAU	14 RLAI + TAU vs 9 Oral Antipsychotic + TAU
Macfadden et al[19]	12 months, RCT, DB, PC	65 RLAI + TAU vs 59 Placebo + TAU	39 RLAI + TAU vs 25 Placebo + TAU
Quiroz et al[21]	24 months, RCT, DB, PC	140 RLAI vs 135 Placebo	72 RLAI vs 31 Placebo
Vieta et al[20]	18 months, RCT, DB, DD PC/AC	131 RLAI vs 133 Placebo vs 130 Oral Olanzapine	53 RLAI vs 38 Placebo vs 77 Olanzapine
Yatham et al[3]	6 months, Pilot, RCT, OL, AC	23 RLAI vs 26 Oral Antipsychotics	12 RLAI vs 17 Oral Antipsychotics

AC, active control; ALAI, aripiprazole LAI; CGI-S, clinical global impression-severity; DB, double blind; DD, double dummy; OL, open label; PC, placebo control; RLAI, risperidone LAI; TAU, treatment as usual.

3.2 | Primary Outcomes

The meta-analysis included seven RCTs (n = 1192), of which three were open label[3,17,18] and four were double blind.[16,19-21] Six of the RCTs[3,17-21] involved the use of risperidone LAI and one aripiprazole LAI.[16]

For the meta-analysis, studies were categorised into placebo controlled[16,19-21] (n = 4 RCTs) and active controlled[3,17,18,20] (n = 4 RCTs). Since study by Vieta et al[20] contained three arms (risperidone LAI vs placebo vs oral olanzapine), this study appeared in both categories. Risperidone LAI vs placebo (Vieta, 2012) was put under placebo-controlled category while risperidone LAI vs oral olanzapine (Vieta, 2012 A) under active controlled.

a Study-defined relapse rate (placebo-controlled studies only): Pooled data from four placebo-controlled studies favour SGA LAIs for study-defined relapse rate as shown in Figure 2 with statistically significant difference between the two groups.

b Primary safety outcome: All-cause discontinuation (placebo-controlled studies only). All-cause discontinuation was significantly less in SGA LAIs group compared to placebo group as shown in Figure 3 below.

c Primary efficacy outcome: Study-defined relapse rate (active-controlled studies only). Active-controlled studies evaluated various oral antipsychotics or TAU against risperidone LAI. There was no statistically significant difference between SGA LAIs and active control as shown in Figure 4 below. However, there was significant heterogeneity. Heterogeneity reduced to 0% when a study by Vieta et al[20] was removed. This led to a significant difference, that is, SGA LAIs performing better than active control (RR = 0.7, 95% CI = 0.53 - 0.94, $P = 0.02$), but this would have removed a high quality, highest weighted study with two third of participants. Thus, the study by Vieta et al was retained in the analysis.

d All-cause discontinuation (Active-controlled studies only). All-cause discontinuation was not significantly different between SGA LAIs group and active control group as shown in Figure 5 below.

3.3 | Sensitivity and subgroup analysis

We conducted sensitivity analysis excluding low-quality studies (ie, Jadad score <4) for study-defined relapse rate. Active control outperformed SGA LAI (n = 261, RR = 1.63, 95% CI = 1.12-2.37, $P = 0.01$, I^2 = NA) in terms of study-defined relapse rate but included only one RCT.[20] All the placebo-controlled studies were of high quality and SGA LAIs performed better than placebo as shown in Figure 2.

We also performed the following analyses by subgroup of RCTs—adjunctive vs monotherapy, double blind vs open label, rapid cycling

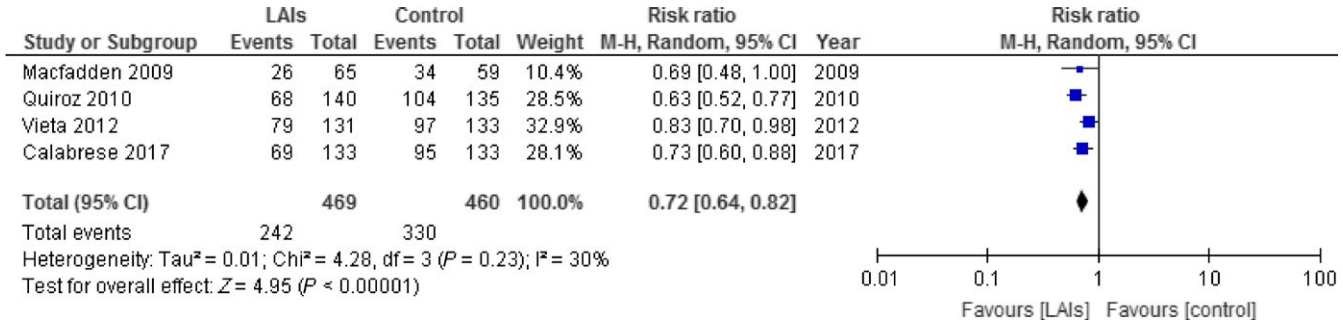

FIGURE 3 All-cause discontinuation (placebo-controlled studies only) [Colour figure can be viewed at wileyonlinelibrary.com]

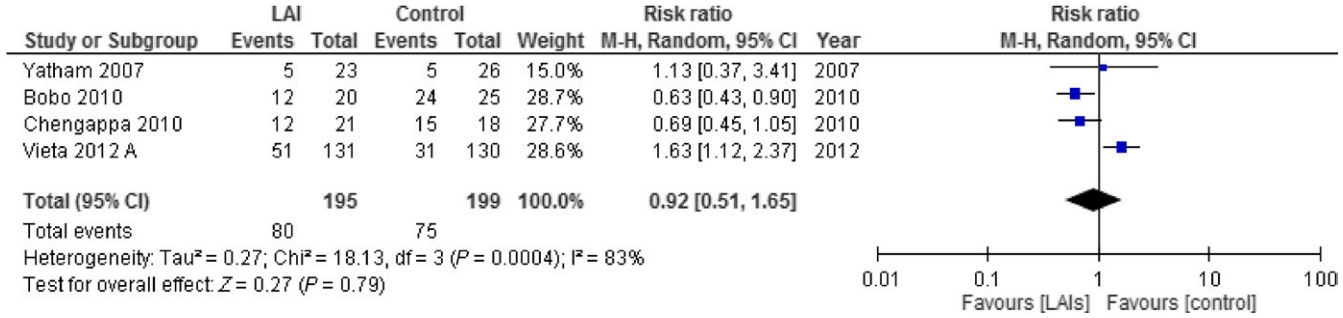

FIGURE 4 Study-defined Relapse rate (active-controlled studies only) [Colour figure can be viewed at wileyonlinelibrary.com]

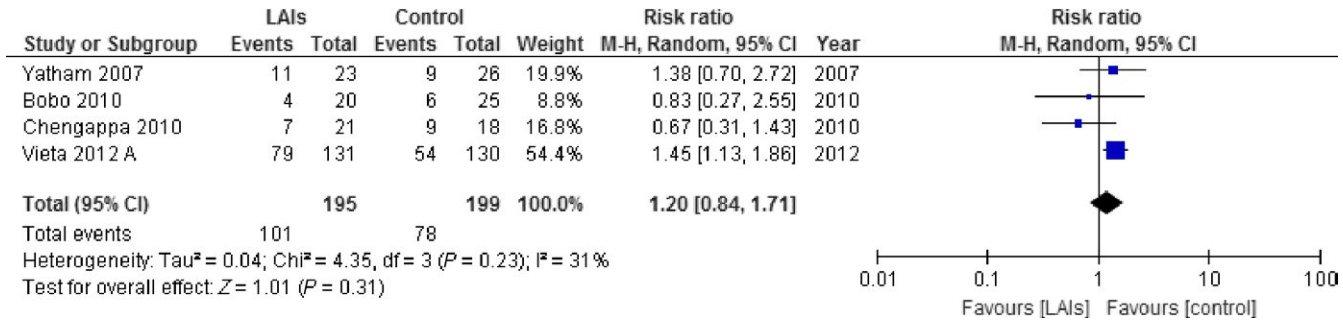

FIGURE 5 All-cause discontinuation (active-controlled studies only) [Colour figure can be viewed at wileyonlinelibrary.com]

vs non-rapid cycling—for study-defined relapse rates in placebo-controlled and active-controlled studies.

Placebo-controlled studies show SGA LAIs better than placebo both as an adjunctive (RR = 0.5, 95% CI = 0.3-0.85, $P = 0.01$) and as monotherapy (RR = 0.58, 95% CI = 0.49-0.69, $P < 0.00001$). However, active control performed better than SGA LAIs as monotherapy (RR = 1.63, 95% CI = 1.12-2.37, $P = 0.01$) and SGA LAIs performed better as an adjunctive (RR = 0.70, 95% CI = 0.53-0.94, $P = 0.02$).

Double-blind studies show a statistically significant improvement of SGA LAIs over placebo (RR = 0.58, 95% CI = 0.49-0.68, $P < 0.00001$), but active control performed better than SGA LAIs (RR = 1.63, 95% CI = 1.12-2.37, $P = 0.01$). Three open-label studies[3,17,18] show SGA LAIs performing better than active control (n = 133, RR = 0.70, 95% CI = 0.53-0.94, $P = 0.02$).

Studies in patients with rapid cycling bipolar disorder show statistically significant improvement with SGA LAIs compared to placebo (n = 1RCT) and active control (n = 1RCT). In nonrapid cycling studies, SGA LAI were superior to placebo (RR = 0.58, 95% CI = 0.49-0.69, $P < 0.00001$) but not active control (RR = 1.29, 95% CI = 0.97-1.29, $P = 0.08$).

3.4 | Secondary outcome measures

Secondary outcome measures were analysed similar to the primary outcome by dividing all RCTs into two groups: placebo controlled (PC) and active controlled (AC). The results from meta-analysis for secondary outcome measures are presented below in Table 2.

It is worth highlighting that SGA LAIs performed better than placebo only in relapse to mania/hypomania, YMRS, CGI-S, MADRS. There was no significant difference between SGA LAIs and oral active control regarding relapse to mania/hypomania, YMRS, CGI-S, EPSEs, weight gain. However, the active control performed better than SGA LAIs in relapse to depression, MADRS, and prolactin-related AEs. These are

TABLE 2 Meta-analysis result for secondary outcome measures

Outcome	No. of RCTs	No. of Patients	Effect size	95% CI	I^2	*P*-value
PC: Relapse to mania/ hypomania	4	929	RR = 0.39	0.30 to 0.51	0%	<0.00001
AC: Relapse to mania/ hypomania	2	300	RR = 0.83	0.29 to 2.36	80%	0.72
PC: Relapse to depression	4	929	RR = 1.07	0.79 to 1.45	0%	0.67
AC: Relapse to depression	2	300	RR = 1.83	1.05 to 3.19	0%	0.03
PC: YMRS	4	922	MD = −5.05	−6.27 to −3.84	0%	<0.00001
AC: YMRS	4	394	MD = −0.04	−1.41 to 1.33	0%	0.96
PC: MADRS	3	656	MD = −1.55	−2.86 to −0.25	0%	0.02
AC: MADRS	3	345	MD = 2.2	0.52 to 3.88	0%	0.01
PC: CGI-S	3	656	MD = −0.77	−1.01 to −0.53	0%	<0.00001
AC: CGI-S	4	394	MD = 0.05	−0.39 to 0.49	59%	0.82
PC: Discontinuation due to AEs	4	929	RR = 2.89	1.03 to 8.09	0%	0.04
AC: Discontinuation due to AEs	4	403	RR = 1.63	0.6 to 4.45	0%	0.34
PC: EPSEs	3	693	RR = 1.69	1.16 to 2.45	0%	0.006
AC: EPSEs	2	84	RR = 1.06	0.43 to 2.65	0%	0.9
PC: Weight gain	4	960	RR = 2.32	1.33 to 4.06	40%	0.003
AC: Weight gain	3	347	RR = 0.86	0.59 to 1.26	0%	0.44
PC: Prolactin related AEs	3	694	RR = 3.43	1.13 to 10.39	37%	0.03
AC: Prolactin related AEs	3	347	RR = 5.75	2.03 to 16.29	0%	0.0010

AEs, adverse effects; RR, risk ratio; MD, mean difference.

TABLE 3 Quality assessment of studies included in meta-analysis

Questions	Calabrese[16]	Bobo [17]	Chengappa [18]	Macfadden[19]	Quiroz [21]	Vieta [20]	Yatham [3]
1. Was the study described as randomised? Yes = 1, No = 0	1	1	1	1	1	1	1
2. Was the method used to generate the sequence of randomisation described and appropriate? Yes = 1, No = 0	1	1	0	1	1	1	1
3. Was the study described as double blind? Yes = 1, No = 0	1	0	0	1	1	1	0
4. Was the method of double blinding described and appropriate? Yes = 1, No = 0	1	0	0	1	1	1	0
5. Was there a description of withdrawals and dropouts? Yes = 1, No = 0	1	1	1	1	0	0	1
6. Deduct one point if the method used to generate the sequence of randomisation was described and it was inappropriate. Described but inappropriate = −1, Described and appropriate = 0	0	0	0	0	0	0	0
7. Deduct one point if the study was described as double blind, but the method of blinding was inappropriate. Described but inappropriate = −1, Described and appropriate = 0	0	0	0	0	0	0	0
Total Jadad Score	**5**	**3**	**2**	**5**	**4**	**5**	**3**

interesting findings as most guidelines recommend treatment according to the spectrum of the disorder, that is, manic phase, depressive episodes, or maintenance treatment.

3.5 | Quality Assessment of Studies

Study quality was assessed by AP and JW independently using the Jadad Scale (See Table 3). The Jadad scale is a commonly used scale for quality assessment of randomised controlled trials. It is a five-point scale with seven questions with a higher score meaning higher quality.

No attrition or reporting bias was noted within individual RCTs. Publication bias was investigated using funnel plot, see Figure 6.

4 | DISCUSSION

4.1 | Primary outcome measures

Our systematic review and meta-analysis found that on primary outcome measures, that is, study-defined relapse rate and all-cause discontinuation, SGA LAIs performed better than placebo but not when compared with oral active control.

It is worth noting that three[3,17,18] of four active-controlled studies are open label, two[3,18] of them are pilot studies and the number of patients in active control studies is less than half that of placebo-controlled studies. However, the active-controlled study by Vieta et al[20] was of high quality (Jadad score = 5) with a larger sample size (n = 260), in which SGA LAI was less effective than oral olanzapine (RR 1.63, 95% CI = 1.12 to 2.37). Study by Vieta et al[20] contained three arms: risperidone LAI, placebo, oral olanzapine, and used double dummy, that is, placebo LAI was given to patient assigned to oral olanzapine group and placebo oral was given to patients assigned to risperidone LAI and placebo LAI group.

It is also argued that participants in the RCTs are more likely to adhere to their oral medication owing to extra care and monitoring they receive during studies compared to real-world patients. This may have favoured the active control group and can be a limitation of RCT

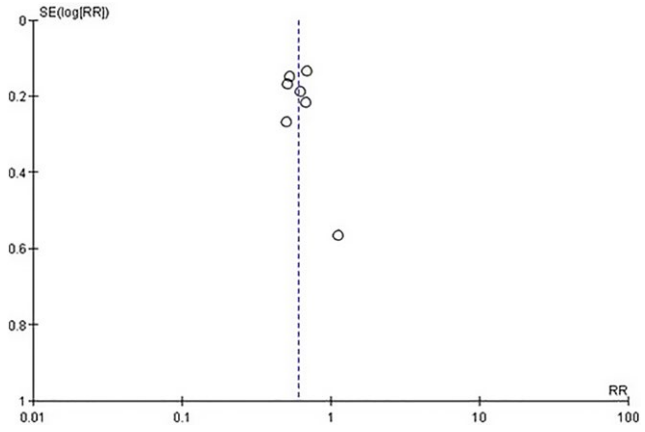

FIGURE 6 Funnel plot of all active- and placebo-controlled studies [Colour figure can be viewed at wileyonlinelibrary.com]

comparing SGA LAIs with oral active control. This limitation could be overcome by designing double-blind RCTs with double dummy, that is, giving LAI placebo for oral active control group and giving oral placebo for SGA LAI group as in the case of the study by Vieta et al.[20] Such design would make the study scientifically more robust but would also add significant logistical burden to the RCT. It could also be argued that extra care and monitoring received by two groups (SGA LAIs and oral active control group) are unlikely to be huge, and thus, their effect on adherence is likely to be minimal.

4.2 | Secondary outcome measures

With regard to the secondary outcome measures of relapse to mania, YMRS, and CGI-S, SGA LAIs group performed only better than placebo. There was no significant difference between SGA LAIs group and active control group for relapse to mania, YMRS, and CGI-S. Active control group performed better than SGA LAI group regarding relapse to depression and MADRS. This finding indicates that SGA LAIs are not a better option for patients with depression dominant bipolar disorder and suggest that the benefits of SGA LAIs are mainly in the prevention of mania, similar to previous findings.[13,14,22]

In terms of discontinuation due to adverse effects, EPSEs, and weight gain, placebo was safer than SGA LAIs, but there was no significant difference between SGA LAIs and active control. Both placebo and active control were better than SGA LAIs for prolactin-related adverse effects.

4.3 | Strengths and limitations of the study

Systematic review and meta-analysis of randomised controlled trials provide the highest level of evidence to key stakeholders. Registration of the study with PROSPERO, publication of the study protocol in the BMJ Open, extensive and broad database search as well as enquiry with manufacturers, finding new data unavailable in the previous study are some of the key strengths of this meta-analysis. The study followed the standard guideline for systematic reviews and meta-analysis including those of PRISMA statement, CONSORT checklist, and Cochrane Handbook.

The primary outcomes of the included studies were wide and the definitions of the primary outcome varied among the studies although our primary outcomes were included in those studies. This is often an issue when undertaking a meta-analysis where data are combined which is nonidentical but which is clinically reasonable to combine. In addition, this is more likely to represent the real-world scenarios and day-to-day clinical practice. It is also worth noting that the patients in the selected studies were mix of rapid cycling, mixed episodes, and varied severity. This makes our findings difficult to generalise to all patients with bipolar disorder without taking into patient-specific diagnosis, polarity, and severity of the disorder into account. This is often the challenge in RCTs which generally includes highly selective population making it difficult to generalise the evidence.

Cochrane does not recommend the use of scales for quality or risk assessment. However, the Jadad scale is well known, simple, and

easy to use. It contains important elements that have empirically been shown to correlate with the risk of bias,[23] and thus, Jadad scale was used to quality assess included RCTs.

The use of a funnel plot to assess the risk of bias is generally used if 10 or more studies are included in the meta-analysis. However, we have presented a funnel plot for visual inspection. Notwithstanding the small number of studies (n = 7), visual inspection of the funnel plot (Figure 6) does not suggest publication bias. However, it is worth emphasising that drug manufacturers funded all the studies included in this meta-analysis with varying degree of influence in the study design, conduct, analysis, reporting, and publication.

4.4 | Comparison to other studies

Details of literature reviews of FGA and SGA LAIs in bipolar disorder are described by Prajapati et al[15] highlighting the differences between this study and previous reviews. Gigante et al[13] and Bond et al[22] reviewed evidence of FGAs and SGA LAIs in bipolar disorder and concluded that FGA LAI should not be a first choice due to risk of induction of depression, but suggested risperidone LAI is effective in bipolar. Samalin et al[14] carried out review of SGA LAIs in bipolar disorder and concluded that risperidone LAI may be considered for maintenance treatment of bipolar disorder but more evidence is required. While these literature reviews provide a useful overview of the subject, they generally lack the scientific rigour of systematic reviews.[15] Recently, Chou et al[24] authored an article titled "A Systemic Review and Experts' Consensus for Long-acting Injectable Antipsychotics in Bipolar Disorder." This was an expert consensus; details on review process and methodology were not reported. In addition, all aforementioned studies included only one SGA LAIs, namely, risperidone LAI, and none included meta-analysis.

As far as we are aware, this is the first meta-analysis focusing on SGA LAIs in bipolar disorder that included more than one SGA LAI. The only other meta-analysis on this topic was by Kishi et al[25] and there are significant differences between the two meta-analyses in terms of included studies, methodology, and some results. Our meta-analysis includes studies of risperidone LAI and aripiprazole LAI whereas Kishi et al included only risperidone LAI. This is important because aripiprazole is also one of the recommended treatment options for bipolar disorder and aripiprazole LAI has recently been licensed for bipolar disorder in the US, Canada, and Australia.

Unlike Kishi et al,[25] we did not include first-generation antipsychotics (FGAs) LAIs in our meta-analysis because they are not considered the preferred choice in bipolar disorder due to the risk of induction of depression.[13,22] Another reason to exclude FGA LAIs is that patients with bipolar disorder may be more at risk of EPSEs, for example, when treated with high potency dopamine antagonists like haloperidol.[26] Accordingly, successful treatment of bipolar disorder without extrapyramidal symptoms is an important practical clinical objective.

Another major difference between the two studies was the result of relapse to depression and MADRS. Kishi et al show no statistically significant difference between LAIs and active control (RR = 1.25, 95% CI = 0.6-2.59, $P = 0.55$) whereas this meta-analysis favours active control for this outcome (RR = 1.83, 95% CI = 1.05-3.19, $P = 0.03$). Similarly, MADRS was not significantly different between LAIs and active control in Kishi et al (WMD = 1.27, 95% CI = 0.59-3.12, $P = 0.18$) whereas this study favours active control (MD = 2.2, 95% CI = 0.52-3.88, $P = 0.01$). This is likely to be due to another significant difference between the two meta-analyses: we have four studies in each group (placebo controlled and active controlled) compared to two placebo-controlled and five active-controlled studies in Kishi et al.[25] This was due to two reasons: inclusion of FGA LAIs in previous meta-analysis and the allocation of the RCT by Macfadden[19] as an active-controlled study by Kishi et al. The study by Macfadden[19] contained two arms risperidone LAI + TAU vs Placebo + TAU and the study was itself titled "…placebo controlled…" in their publication. Thus, we put this study by Macfadden[19] et al under placebo-controlled group. In addition, by putting RCT by Macfadden[19] into an active control group, Kishi et al may have diluted the positive effect of active control in reducing relapse to depression.

Another difference between the two meta-analyses was the completeness of the search. In addition to databases searched by Kishi et al (Medline, Cochrane Library, PsycINFO, Clinicaltrials.gov), we also searched LiLACS (to cover literature from Latin America and the Caribbean which may not have been covered elsewhere), EMBASE, and CINAHL (to cover allied health professional literature). Furthermore, we also contacted manufacturers of SGA LAIs for further published or unpublished studies which were lacking in the previous meta-analysis.

Both meta-analyses show that placebo and active control were better than LAI regarding prolactin-related adverse effects. However, the risk ratio of prolactin-related adverse events in this meta-analysis is twice that was in Kishi et al (RR = 5.75 in this meta-analysis vs 2.66 in Kishi et al) in active control studies. This is even more interesting as active control studies in Kishi et al contained a study comparing FGA LAI (namely flupentixol decanoate) which is known to cause more prolactin-related adverse effect than SGA LAIs in general. This difference between the two meta-analyses is again likely to be due to the inclusion of study by Macfadden et al[19] into active control group by Kishi et al.

Another significant difference between the two meta-analyses is in their conclusion. The main conclusion from Kishi et al was that "Long-acting injectable antipsychotics appear beneficial for relapse prevention in patients with rapid cycling." Although we found a similar result in our subgroup analysis, this was not the main question or the primary objective of the published meta-analysis. In addition, to base concluding remarks on two RCTs of seven is difficult to justify; more so when a number of patients to draw conclusion was less than one-fifth of the total. It is also worth noting that one of those two RCTs was active control and one was a placebo control. So combining the result makes it difficult to interpret and goes against their primary analytical design, that is, analysis by separating studies into a placebo controlled from active controlled. We conclude that currently there is limited evidence to support SGA LAIs in bipolar disorder, when compared with oral active control.

4.5 | Future research

Further studies, particularly high-quality active-controlled studies, are warranted for conclusive evidence. There are four SGA LAIs

(aripiprazole LAI, olanzapine LAI, paliperidone LAI, and risperidone LAI) on the market, but only studies involving risperidone LAI and aripiprazole LAI were found. Further research on SGA LAIs, preferably comparing with active control and in a more pragmatic, real-world setting, will add significant evidence base in this area. Data on aripiprazole LAI are limited due to there being only a single RCT and lack of any active control studies. Further research comparing aripiprazole LAI with active control is warranted. Research on paliperidone LAIs and olanzapine LAI also merits consideration. However, olanzapine LAI has some significant logistical issues due to the post injection syndrome and thus requiring patients to be observed for 3-hour post injection. This may be a significant barrier to prescribing as well as any future research.

4.6 | Cost and policy implication

Future research would benefit from incorporating cost-effectiveness analysis. It is often argued that LAIs reduce relapse and thus reduce healthcare cost; however, this meta-analysis shows no significant difference in study-defined relapse rate when SGA LAIs are compared with active control. The cost of SGA LAIs is significantly more than the oral equivalent, for example, in the UK, risperidone LAI 50 mg costs around £3700 per patient per year compared to less than £20 for oral risperidone. Similarly, oral aripiprazole 30 mg per day costs around £48 per patient per year compared to approx. £2640 for aripiprazole LAI. Although drug price structure is different in the US and Australia and price can vary widely, risperidone LAI (50 mg fortnightly/per patient per year) cost roughly around US $23000 (≈£17500) in the US and Aus $5500 (≈£3100) in Australia and aripiprazole LAI (400 mg monthly/per patient per year) costing roughly around US $26000 (≈£19800) in the US and Aus $4500 (≈£2500) in Australia. Equivalent oral dose is available at a fraction of the cost. The results from this meta-analysis fail to support the use of SGA LAIs instead of oral antipsychotics on health economic grounds and further research is required to provide the evidence for policymakers. The significantly higher cost of SGA LAIs will have policy implications. Thus, it is prudent that further research looking into SGA LAIs use in bipolar disorder, particularly comparing with oral active control is conducted to provide evidence-based recommendations to policymakers. In general, when patency of a drug expires the price of that drug drops significantly due to the availability of generic drug. However, despite patency for risperidone LAI expiring in 2014, no generic formulation has become available. This is likely to be due to the complexity in formulation technology and cost involved in manufacturing. But if and when generic SGA LAIs become available, the cost is likely to drop significantly.

5 | CONCLUSION

Preventing relapse in bipolar disorder is a primary concern for patients and healthcare professionals alike. SGA LAIs may have a role in bipolar patients with known adherence problems with oral medication. However, this meta-analysis suggests that SGA LAIs is better only compared to placebo and not active control. Considering the significant cost pressure and other issues which come with prescribing SGA LAIs, further high-quality active control studies are required to guide clinical practice.

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ETHICAL APPROVAL

This systematic review did not require ethical approval as data used here are not individual or private and there was no primary data collection.

DISCLOSURE

No conflict of interest related to this study. ARP received conference expenses from Janssen, research honoraria from Accession. IM has received speaker honoraria from Astellas Pharmaceuticals. JW received grants from Lundbeck and personal fees from Shire.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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