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Efficacy and safety of second-generation antipsychotic long-acting injections (SGA LAIs) in maintenance treatment of bipolar disorder: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: Bipolar disorder requires long-term treatment but non-adherence is a common problem. Antipsychotic long-acting injections (LAIs) have been suggested to improve adherence but none are licensed in the UK for bipolar. However, the use of second-generation antipsychotics (SGA) LAIs in bipolar is not uncommon albeit there is a lack of systematic review in this area. This study aims to systematically review safety and efficacy of SGA LAIs in the maintenance treatment of bipolar disorder.

Methods and analysis: The protocol is based on Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and will include only randomised controlled trials comparing SGA LAIs in bipolar. PubMed, EMBASE, CINAHL, Cochrane Library (CENTRAL), PsychINFO, LiLACS, http://www.clinicaltrials.gov will be searched, with no language restriction, from 2000 to January 2016 as first SGA LAIs came to the market after 2000. Manufacturers of SGA LAIs will also be contacted. Primary efficacy outcome is relapse rate or delayed time to relapse or reduction in hospitalisation and primary safety outcomes are drop-out rates, all-cause discontinuation and discontinuation due to adverse events. Qualitative reporting of evidence will be based on 21 items listed on standards for reporting qualitative research (SRQR) focusing on study quality (assessed using the Jadad score, allocation concealment and data analysis), risk of bias and effect size. Publication bias will be assessed using funnel plots. If sufficient data are available meta-analysis will be performed with primary effect size as relative risk presented with 95% CI. Sensitivity analysis, conditional on number of studies and sample size, will be carried out on manic versus depressive symptoms and monotherapy versus adjunctive therapy.

Ethics and dissemination: Ethical approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication, conference presentation and the press.

Study registration number: PROSPERO CRD42015023948.

Strengths and limitations of this study

- This systematic review will search a comprehensive list of databases using well-defined search strategy; will contact manufacturers for any unpublished and/or ongoing trials.
- This study will clarify the position of second-generation antipsychotics (SGAs) long-acting injections (LAIs) in maintenance treatment of bipolar disorder.
- Qualitative evidence summary and meta-analysis will address some highly relevant clinical questions in bipolar disorder. Subgroup analyses will further enhance the applicability of the results from this study.
- This review is focused on as SGA LAIs since first generation antipsychotics are not considered preferred choice in maintenance treatment of bipolar disorder due to risk of induction of depression.
- Lack of data and significant heterogeneity may prevent meta-analysis.

BACKGROUND

The lifetime prevalence of bipolar I disorder is estimated at 1% of the adult population, and bipolar II disorder affects approximately 0.4% of adults.[1] Bipolar disorder, featuring mood and activity level disturbance, is a recurrent disorder; it usually requires long-term maintenance therapy to prevent future mood episodes—the primary goal of treatment.[2] Lithium remains the gold standard prophylactic treatment for bipolar disorder.[1] However, lithium may not be suitable for all patients due to a lack of response or adverse events, or patients may not accept lithium due to various reasons including monitoring requirement and/or side effects.[3] Thus, many patients require alternative prophylactic treatment for bipolar disorder. Many guidelines

including British Association of Psychopharmacology,[4] The World Federation of Societies of Biological Psychiatry (WFSBP),[5] Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD),[6] and National Institute for Health and Care Excellence (NICE)[1] from the UK recommend some second-generation antipsychotic (SGA, also known as atypical antipsychotics) as a long-term treatment option for bipolar disorder; and many oral SGAs are licensed in the UK for this indication.[7]

Non-adherence to the prescribed treatment is a major problem and common in bipolar disorder. Estimated frequency of non-adherence in bipolar range between 10% and 60% (median 40%).[8] Non-adherence increases the risk of relapse and suicide;[9] and increased risk of rehospitalisation.[8] LAIs, also known as depots have some clear advantages due to assurance that medication will be administered and the opportunity for healthcare professionals to step in immediately if patients stop treatment.[10] Evidence from studies in people with schizophrenia suggests antipsychotics LAIs reduce relapses, reduce medication discontinuation rates and improve outcomes compared to oral antipsychotics although some Cochrane reviews of various depots did not find any convincing difference.[10] However, these Cochrane reviews also included inpatient studies, short-term trials of just a few weeks duration[10] and mostly included only first-generation antipsychotic (FGA, also known as typical antipsychotics) LAIs. LAIs formulations have other pharmacological advantages: more predictable bioavailability since LAIs medications bypass gastrointestinal absorption and the effect of first-pass hepatic metabolism, more stable plasma levels compared to oral antipsychotics, sustained plasma levels of medication at therapeutic range.[8]

The use of SGA LAIs in the maintenance treatment of bipolar disorder has ignited interest for improving adherence and reducing the risk of relapse.[8] Over the past 5 years two new SGA LAIs, aripiprazole and paliperidone, have been introduced in the UK. None of the SGA LAIs are currently licensed for bipolar disorder in the UK[7] albeit clinical experience suggests their uses for this indication are not infrequent. Recent (2011) mixed-treatment meta-analysis suggests that antipsychotics are more effective than mood stabilisers in the treatment of mania.[11] Some studies have found that risperidone LAI is effective for maintenance treatment in bipolar disorder[7 8] and CANMAT recommends risperidone LAI as one of the first-line treatment options in maintenance treatment of bipolar disorder.[6] Risperidone LAI is approved by US Food and Drug Administration for monotherapy or as an adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder.[12]

Despite these potential advantages of antipsychotic LAIs in the treatment of bipolar disorder there is a lack of any properly conducted systematic review. During a scoping search two literature reviews[8 9] conducted within past 5 years were identified. Literature reviews offer a useful overview of the subject; however they generally lack the rigour of systematic reviews. Systematic reviews of well-designed randomised controlled trials (RCTs) are considered gold standard and top of the evidence hierarchy in healthcare research.[13–15] A systematic review with a focused clinical question with clear specifications searches all relevant databases with predefined systematic search strategy and using prespecified eligibility criteria for studies to be included. A systematic review also provides the assessment of the quality of the studies included in the review aiming to avoid bias and therefore support evidence-based practice. With predefined protocol good systematic reviews provide robust evidence to support or change clinical practice.

Gigante *et al*[8] reviewed evidence of FGAs and SGA LAIs in bipolar disorder searching PubMed from 1950 to 2011 and published in English. This review included all types of studies from RCTs to retrospective chart reviews in their evidence synthesis. In terms of SGA LAIs only literatures pertaining to risperidone LAI were found. The level of evidence is limited due to small number (n=2) of large RCTs. No RCTs were found involving other SGA LAIs except risperidone. The authors 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. This is consistent with earlier literature review by Bond *et al*.[16]

Recently Samalin *et al*[9] carried out another 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. This review included RCTs, case series and did not include any specific inclusion/exclusion criteria; did not perform quality assessment; focused the search on PubMed and EMBASE; and no information sought from manufacturers. The authors carried out last search in April 2013 which gives us around 2½ years of potential extra literature, a good time frame to review evidence in this moving field. In addition, Samalin *et al* found studies only on risperidone LAI and this systematic review is expected to find studies related to other SGA as scoping exercise found some ongoing active studies of other SGA LAI.

Chou *et al*[17] authored an article titled "A Systemic Review and Experts' Consensus for Long-acting Injectable Antipsychotics in Bipolar Disorder". This was an expert consensus building study and good endeavour for consensus report on the topic but lacking any details on review process and methodology, a critical and essential aspect of any systematic reviews. In addition, Chou *et al* looked at both FGAs and SGAs and found studies pertaining to risperidone LAI only in terms of SGA LAIs.

This systematic review will:

- Include only RCTs comparing SGA LAIs with placebo or other antipsychotics or mood stabilisers or treatment as usual;

- Search many other relevant databases as listed in the methodology section;
- Contact manufacturers for further trials (both ongoing and unpublished trials);
- Quality assess all included studies;
- Investigate the risk of bias.

The protocol is registered with PROSPERO—http://www.crd.york.ac.uk/PROSPERO/—international prospective register of systematic reviews.

The result of this study will have an impact on clinical practice and prescribing decision either to support or discourage use of SGA LAIs in maintenance treatment of bipolar disorder. It is author's intention to publish the result of this study in a peer reviewed journal and to widely communicate with key clinical and academic stakeholders both nationally and internationally. The result from the study will close the evidence gap and thus inform healthcare professionals and patients of the evidence or lack of it in using SGA LAIs in bipolar disorder.

OBJECTIVE

To conduct systematic review and meta-analysis of RCTs evaluating efficacy and safety of SGA LAIs in maintenance treatment of bipolar disorder.

METHODOLOGY

The research protocol is based on Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[18] Specific Participants, Interventions, Comparators, Outcomes and Study design; detailed below will be used for study selection criteria:

1. Inclusion criteria:

Any studies not meeting following inclusion criteria will be excluded.

A. Participants: patients of any age or sex with bipolar disorder using any validated diagnostic system, for example, Diagnostic and Statistical Manual of Mental Disorders (DSM-V: 296) or the International Classification of Diseases (ICD 10: F31).
B. Interventions: SGA LAIs in bipolar disorder.
C. Comparators: placebo, other antipsychotics, mood stabiliser or treatment as usual.
D. Outcome measures:
   - Primary efficacy outcome—relapse rate or delayed time to relapse or reduction in hospitalisation
   - Primary safety outcome—drop-out rates or all-cause discontinuation or discontinuation due to adverse events
   - Secondary outcomes may include changes in BDRS (Bipolar Disorder Rating Scale) or YMRS (Young Mania Rating Scales), discontinuation due to hospitalisation and non-adherence (study defined), safety outcome of SGA LAIs for example, EPSEs and metabolic adverse effect—weight gain, hyperglycaemia, dyslipidaemia, hyperprolactinaemia.
E. Study design: RCTs with or without double blinding with minimum duration of 6 months. It is anticipated that most studies will be outpatient as non-adherence in inpatients is unlikely due to staff administration. Nonetheless this study will include both outpatients and inpatients as some units are long stay inpatient units in secure services or rehabilitation units and since sustained therapeutic plasma level has been suggested as a pharmacological advantage of LAIs in addition to improvement in adherence.

Data sources, search strategy and study selection

Missing any relevant and significant study may render the systematic review less credible. The following detailed search strategy will be employed to ensure all relevant studies are captured, independently analysed, verified and quality assessed.

A comprehensive, electronic search strategy will be used to identify relevant RCTs in humans where SGA LAIs are being assessed for efficacy and safety in bipolar disorder. There will be no language restrictions. Studies published between January 2000 and Jan 2016 will be searched since SGA LAIs came to the market only after 2000. The searches will be re-run just before the final analyses and any further eligible studies retrieved for inclusion.

Following databases will be searched: PubMed, EMBASE, CINAHL, Cochrane Library (CENTRAL), PsychINFO, LiLACS, http://www.clinicaltrials.gov. Any relevant studies mentioned in those identified studies will be searched manually, for example scoping the references listed. Manufacturers of SGA LAIs will be contacted for any ongoing or unpublished studies.

To capture all relevant studies the search strategy will consist of three domains: disease (bipolar disorder), treatment (SGA) and formulation (LAIs). Each domains will be searched using many terms (as listed below) with Boolean search operator "OR". The Boolean search operator "AND" will be used to connect these three domains.

A. Disease domain: bipolar*, mood disorder*, mania*, manic-depression*, hypomania*, AND
B. Treatment domain: antipsychotic*, neuroleptic*, psychotropic*, atypical*, second generation antipsychotic*, SGA*, aripiprazole, olanzapine, paliperidone, risperidone, ziprasidone AND
C. Formulation domain: depot*, long-acting injection*, LAI*, prolonged release injection*, sustained release injection*

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

Data collection, analysis and quality assessment

A list will be created for all identified studies from all the resources searched. Any other studies mentioned or referred to in these studies which seem relevant to the review will be manually searched. Titles of all the studies retrieved using the search strategy and those from additional sources will be screened for their relevance to

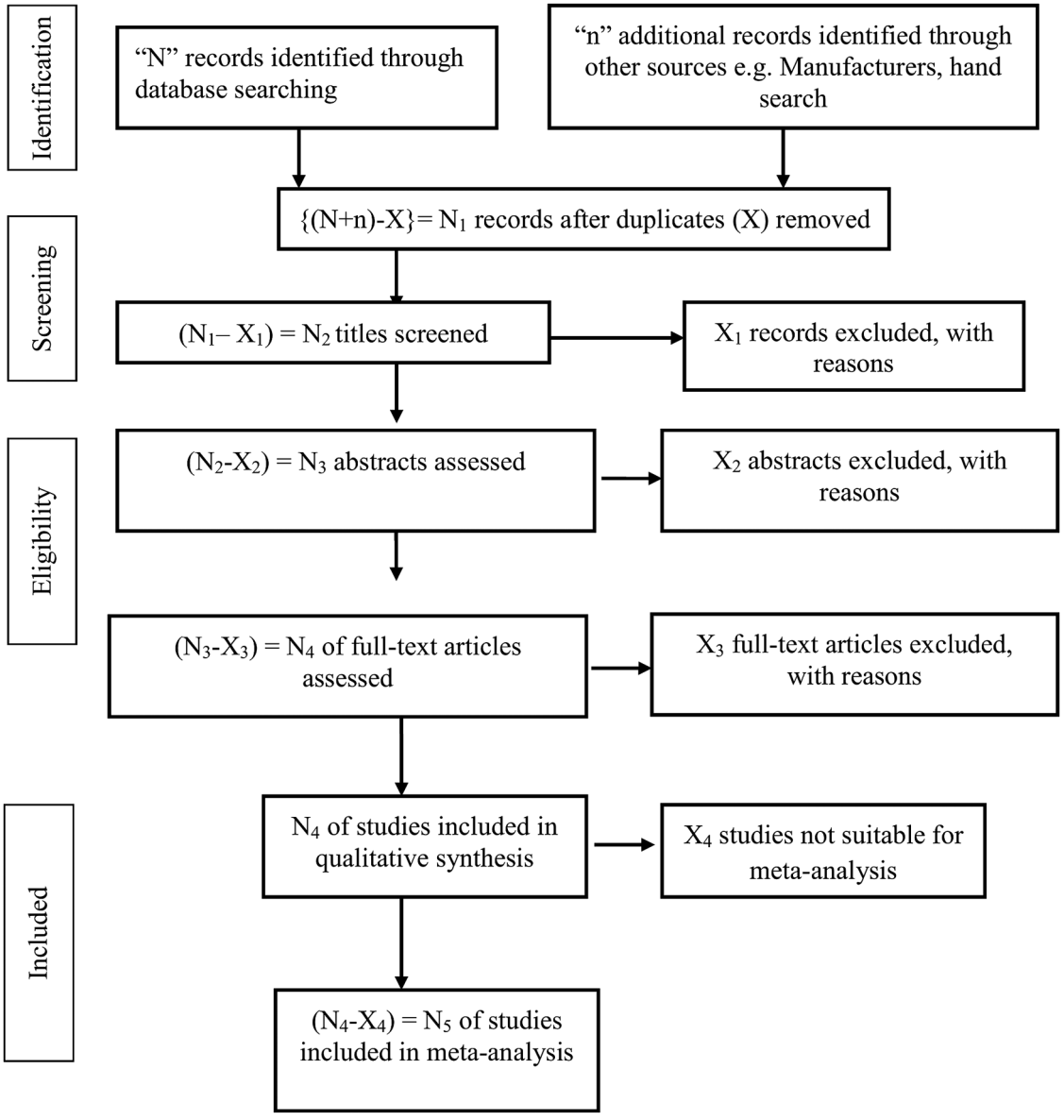

Figure 1 PRISMA flow diagram of identification, screening, eligibility and inclusion studies.

the review. Definite non-relevant studies will be excluded while relevant, ambiguous or unclear studies will be included for screening abstract.

All the articles will be screened for its title to check their relevance by lead author (AP) and second reviewer (JW). Abstracts of the remaining studies, after discarding definite irrelevant studies, will be screened by the lead author (AP) and second reviewer (JW) to identify studies that potentially meet the inclusion criteria outlined above. The second reviewer (JW) will review titles and abstract independently and list studies to be included and those to exclude. Any disagreement between two reviewers over the eligibility of particular studies will be resolved through further discussion and/or with third reviewer (IM) involvement.

A standardised, prepiloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study design; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement; information for assessment of the risk of bias. The lead reviewer (AP) will extract the data and any ambiguity/questions will be discussed with second (JW) and/or third (IM) reviewer. Missing data will be requested from study authors and/or manufacturers.

Study quality will be assessed using Cochrane collaboration's risk of bias tool and publication bias by visual inspection of funnel plots.[19]

Narrative qualitative evidence synthesis will be provided on aggregate level on study outcome for their primary and secondary outcome. Qualitative reporting of evidence will be based on 21 items listed on standards for reporting qualitative research (SRQR).[20] Total

number of patients in the study, study quality, risk of bias and effect size will be detailed on qualitative evidence summary.

Meta-analysis

It is authors' intention to undertake quantitative meta-analysis. If study data and sample size are sufficient meta-analysis will be performed. Statistical significance will be set at 0.05 with p value <0.05 considered statistically significant. The primary effect size will be relative risk presented with 95% CI. The analysis will be based on intention-to-treat where data available. Study heterogeneity will be measured using I^2-statistic considering values of 50% or higher to reflect considerable heterogeneity which will be investigated.

Sensitivity analysis

If sufficient number of studies (eg at least one RCT on each side of the parameter) and sample size are available, sensitivity analysis will be carried out on manic versus depressive symptoms and monotherapy versus adjunctive therapy or different antipsychotic.

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Competing interests AP received conference travel expenses from Janssen. IM has received speaker honoraria from Astellas Pharmaceuticals. JW received grants from Lundbeck, personal fees from Shire outside the submitted work.

Ethics approval This systematic review does not require ethical approval as data used here are not individual or private and there will be no primary data collection.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Most data for this study would come from public domain although some may come from unpublished studies, manufacturers or study authors. Corresponding author would make the sources of the data available to requester.

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