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

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Summary

Background Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalised criteria. We excluded quasi-randomised trials and trials that were incomplete or included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness. We extracted data following a predefined hierarchy. In network meta-analysis, we used group-level data. We assessed the studies' risk of bias in accordance to the Cochrane Handbook for Systematic Reviews of Interventions, and certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework. Primary outcomes were efficacy (response rate) and acceptability (treatment discontinuations due to any cause). We estimated summary odds ratios (ORs) using pairwise and network meta-analysis with random effects. This study is registered with PROSPERO, number CRD42012002291.

Findings We identified 28 552 citations and of these included 522 trials comprising 116 477 participants. In terms of efficacy, all antidepressants were more effective than placebo, with ORs ranging between 2·13 (95% credible interval [CrI] 1·89–2·41) for amitriptyline and 1·37 (1·16–1·63) for reboxetine. For acceptability, only agomelatine (OR 0·84, 95% CrI 0·72–0·97) and fluoxetine (0·88, 0·80–0·96) were associated with fewer dropouts than placebo, whereas clomipramine was worse than placebo (1·30, 1·01–1·68). When all trials were considered, differences in ORs between antidepressants ranged from 1·15 to 1·55 for efficacy and from 0·64 to 0·83 for acceptability, with wide CrIs on most of the comparative analyses. In head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs 1·19–1·96), whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious drugs (0·51–0·84). For acceptability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants (range of ORs 0·43–0·77), whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine had the highest dropout rates (1·30–2·32). 46 (9%) of 522 trials were rated as high risk of bias, 380 (73%) trials as moderate, and 96 (18%) as low; and the certainty of evidence was moderate to very low.

Interpretation All antidepressants were more efficacious than placebo in adults with major depressive disorder. Smaller differences between active drugs were found when placebo-controlled trials were included in the analysis, whereas there was more variability in efficacy and acceptability in head-to-head trials. These results should serve evidence-based practice and inform patients, physicians, guideline developers, and policy makers on the relative merits of the different antidepressants.

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Research in context

Evidence before this study

Antidepressants are routinely used worldwide for the treatment of major depressive disorder, which is one of the most important global health challenges; however, in the scientific literature, there remains considerable debate about both their effectiveness as a group, and the potential differences in effectiveness and tolerability between individual drugs. With the marketing of new antidepressants and increasing numbers of trials published every year, an updated systematic review and network meta-analysis was required to synthesise the evidence in this important clinical area.

Added value of this study

This network meta-analysis represents a major update and extension of our previous study, which addressed 12 antidepressants with data for head-to-head comparisons only, and provides the best currently available evidence base to guide the choice about pharmacological treatment for adults with acute major depressive disorder. We now include a more comprehensive list of 21 antidepressants and placebo, consider three new clinical outcome measures and many potential effect modifiers, and use the most advanced statistical methodology for network meta-analysis to date.

Implications of all the available evidence

Our findings should inform clinical guidelines and assist the shared decision making process between patients, carers, and clinicians in routine practice on selecting the most appropriate antidepressant for adults with acute major depressive disorder. Future research should seek to extend network meta-analysis to combine aggregate and individual-patient data from trials in a so-called individual-patient data network meta-analysis. This analysis will allow the prediction of personalised clinical outcomes, such as early response or specific side-effects, and the estimate of comparative efficacy at multiple timepoints.

Introduction

Psychiatric disorders account for 22·8% of the global burden of diseases.[1] The leading cause of this disability is depression, which has substantially increased since 1990, largely driven by population growth and ageing.[2] With an estimated 350 million people affected globally, the economic burden of depressive disorders in the USA alone has been estimated to be more than US$210 billion, with approximately 45% attributable to direct costs, 5% to suicide-related costs, and 50% to workplace costs.[3] This trend poses a substantial challenge for health systems in both developed and developing countries, with the need to treat patients, optimise resources, and improve overall health care in mental health.

Grouped into various classes of drugs with slightly different mechanisms of action, antidepressants are widely used treatments for major depressive disorder, which are available worldwide. However, there is a long-lasting debate and concern about their efficacy and effectiveness, because short-term benefits are, on average, modest; and because long-term balance of benefits and harms is often understudied.[4] Therefore, innovation in psychopharmacology is of crucial importance, but the identification of new molecular targets is difficult, primarily because of the paucity of knowledge about how antidepressants work.[5] In routine practice, clinicians have a wide choice of individual drugs and they need good evidence to make the best choice for each individual patient. Network meta-analyses of existing datasets make it possible to estimate comparative efficacy, summarise and interpret the wider picture of the evidence base, and to understand the relative merits of the multiple interventions.[6] Therefore, in this study, we aimed to do a systematic review and network meta-analysis to inform clinical practice by comparing different antidepressants for the acute treatment of adults with unipolar major depressive disorder.

Methods

Search strategy and selection criteria

We did a systematic review and network meta-analysis. We searched the Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, AMED, the UK National Research Register, and PSYNDEX from the date of their inception to Jan 8, 2016, with no language restrictions. We used the search terms "depress*" OR "dysthymi*" OR "adjustment disorder*" OR "mood disorder*" OR "affective disorder" OR "affective symptoms" combined with a list of all included antidepressants.

We included double-blind, randomised controlled trials (RCTs) comparing antidepressants with placebo or another active antidepressant as oral monotherapy for the acute treatment of adults (≥18 years old and of both sexes) with a primary diagnosis of major depressive disorder according to standard operationalised diagnostic criteria (Feighner criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, and ICD-10). We considered only double-blind trials because we included placebo in the network meta-analysis, and because this study design increases methodological rigour by minimising performance and ascertainment biases.[7] Additionally, we included all second-generation antidepressants approved by the regulatory agencies in the USA, Europe, or Japan: agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone, and vortioxetine. To inform clinical practice