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SYSTEMATIC REVIEW

Comparative Efficacy and Risk of Harms of Immediate- versus Extended-Release Second-Generation Antidepressants: A Systematic Review with Network Meta-Analysis

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Abstract

Background Major depressive disorder (MDD) has detrimental effects on an individual's personal life, leads to increased risk of comorbidities, and places an enormous economic burden on society. Several 'second-generation' antidepressants are available as both immediate-release (IR) and extended-release formulations. The advantage of extended-release formulations may be the potentially improved adherence and a lower risk of adverse events.

Objective We conducted a systematic review to assess the comparative efficacy, risk of harms, and patients' adherence of IR and extended-release antidepressants for the treatment of MDD.

Data Source English-language abstracts were retrieved from PubMed, EMBASE, the Cochrane Library, PsycINFO, and International Pharmaceutical Abstracts from 1980 to October 2012, as well as from reference lists of pertinent review articles and grey literature searches.

Eligibility Criteria We included head-to-head randomized controlled trials (RCTs) of at least 6 weeks' duration that compared an IR formulation with an extended-release formulation of the same antidepressant in adult patients with MDD. We also included placebo-controlled trials to conduct a network meta-analysis. To assess harms and adherence, in addition to RCTs, we searched for observational studies with $\geq$1,000 participants and a follow-up of $\geq$12 weeks.

Study Appraisal and Synthesis Methods We dually reviewed abstracts and full texts and assessed quality ratings. Lacking head-to-head evidence for many comparisons of interest, we conducted network meta-analyses using Bayesian methods. Our outcome measure of choice was response on the Hamilton Depression Rating Scale.

Results We located seven head-to-head trials and 94 placebo- and active-controlled trials for network meta-analysis. Overall, our analyses indicate that IR and extended-release formulations do not differ substantially with respect to efficacy and risk of harms. The evidence is mixed with respect to differences in adherence, indicating lower adherence for IR formulations.

Limitations The lack of head-to-head comparisons for many drugs compromises our conclusions. Network meta-analyses have methodological limitations that need to be taken into consideration when interpreting findings.

Conclusion Available evidence currently shows no clear differences between the two formulations and therefore we cannot recommend a first choice. However, if adherence or

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compliance with one medication is an issue, then clinicians and patients should consider the alternative medication. If adherence or costs are a problem with one formulation, consideration of the other formulation to provide an adequate treatment trial is reasonable.

Key Points

Overall, analyses indicate that immediate- and extended-release formulations do not differ substantially with respect to efficacy and risk of harms; regarding differences in adherence to treatment, the evidence is mixed.

While the evidence overall does not support clear differences between the two formulations at the group level, this does not mean that efficacy, harms, and adherence do not differ for a particular individual, therefore clinicians need to take a patient's individual situation regarding costs of treatment, adherence, and attitudes towards potential harms into consideration when choosing a treatment.

Strength of evidence of most of our findings was low, indicating that future studies might have a substantial impact on these findings.

1 Introduction

Major depressive disorder (MDD) will affect more than 16 % of adults in the US at some point during their lifetime [1]. In the EU, in any given year, about 7 % of the adult population suffers from MDD [2]. MDD not only has a detrimental effect on an individual's personal life with an increased risk of comorbidities and substantial role impairment [1] but also places an enormous economic burden on society. In the US, costs related to MDD are estimated at US$83 billion a year, with a workforce productivity loss of up to US$24 billion [3, 4].

Pharmacotherapy, especially with second-generation antidepressants (SGAs), is the primary choice of medical management of MDD [5]. SGAs include serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and other substances that selectively target neurotransmitters. Some of these medications (bupropion, fluoxetine, fluvoxamine, trazodone, paroxetine, and venlafaxine) are available as immediate-release (IR), and extended-release formulations. Companies use different terminology to differentiate their IR and extended-release formulations, such as extended-release (XR, XL), sustained-release (SR), or controlled release (CR) medications. In this manuscript, we use the term 'extended-release' for all of these formulations. While the extended-release formulations may differ across products, a common mechanism to achieve the extended-release of drugs is to embed the active ingredient in an insoluble substance and thus delay the drug release. A different technique is to use microsphere encapsulated formulations that prolong the duration of absorption.

No extended-release formulation of fluoxetine exists, but a weekly treatment regimen that is administered with an enteric-coated formulation is available. Because of the long elimination half-life of fluoxetine and its active metabolite norfluoxetine, we consider fluoxetine weekly an extended-release formulation in this article.

Table 1 summarizes dosing ranges and dosing forms of SGAs that are available as both IR and extended-release formulations.

The proposed clinical rationale for the prescription of extended-release formulations is the potentially improved adherence of patients to the prescribed drug regimens because of the less frequent administration. While some IR antidepressants must be taken two or three times per day, extended-release medications require an administration from once a day to once a week [6]. In addition, extended-release medications promise better tolerability because of reduced fluctuations of plasma drug concentrations with lower plasma peaks [7, 8]. Improved adherence, persistence, and tolerability could be crucial advancements for a drug class that is characterized by low response rates and a high risk of adverse events, with an average of 63 % of patients experiencing at least one adverse event during therapy [9]. Under the assumption of similar efficacy, supporters argue that advantages in adherence, persistence, and risk of harms are worth the additional costs that come with extended-release formulations [10, 11].

Critics argue that extended-release formulations are merely a marketing strategy of the pharmaceutical industry without any incremental benefits for patients but substantially higher costs [12].

The objective of this systematic review was to assess the comparative efficacy, risk of harms, and adherence of IR and extended-release antidepressants for the treatment of MDD in adults.

2 Materials and Methods

This systematic review is a partial update of a previous larger comparative effectiveness review on SGAs conducted for and funded by the US Agency for Healthcare Research and Quality (AHRQ) [13].

2.1 Data Sources

We searched PubMed, Embase, PsycINFO, the Cochrane Library, and International Pharmaceutical Abstracts from

Table 1 Second-generation antidepressants approved in the US that are available as IR or extended-release formulations

Generic name	US trade name[a]	Therapeutic classification	Dosage forms	Frequency	Average monthly cost[c]	IR or extended-release
Bupropion[b]	Wellbutrin®	Other	75, 100 mg tabs	Three times daily	$289, $357	IR
	Generic		75, 100 mg tabs	Three times daily	$64, $80	IR
	Wellbutrin SR®		100, 150, 200 mg SR tabs	Twice daily	$280, $294, $541	Extended-release
	Budeprion SR®		100, 150 mg SR tabs	Twice daily	$104, $99	Extended-release
	Generic SR®		100, 150, 200 mg SR tabs	Twice daily	$62, $65, $140	Extended-release
	Wellbutrin XL®		150, 300 mg XL tabs	Once or twice daily	$276, $406	Extended-release
	Budeprion XL		150, 300 mg XL tabs	Once daily	$158, $141	Extended-release
	Generic XL		150, 300 mg XL tabs	Once daily	$80, $81	Extended-release
	Aplenzin XL		174, 348, 522 mg XL tabs	Once daily	$339, $468, $1,053	Extended-release
Fluoxetine[b]	Prozac®	SSRI	10, 20, 40 mg caps	Once daily	$257, $260, $535	IR
	Generic		10, 20, 60 mg tabs; 10, 20, 40 mg caps; 20 mg/5 ml oral solution	Once daily	$49, $31, $94, $28, $31, $99, $80	IR
	Prozac Weekly®		90 mg caps	Once weekly	$199	Extended-release
	Generic weekly		90 mg caps	Once weekly	$145	Extended-release
Fluvoxamine[b]	Generic	SSRI	100 mg tabs	Once daily	$45	IR
	Luvox CR®		100, 150 mg continuous-delivery capsule	Once daily	$463, $417	Extended-release
	Generic CR		100, 150 mg continuous-delivery capsule	Once daily	$302, $316	Extended-release
Trazodone[b]	Desyrel®	Other	100, 150 mg tabs	Once daily	No cost data available	IR
	Generic		50, 100, 150, 300 mg tabs	Once daily	No cost data available	IR
	Oleptro (XR)		150–300 mg tabs	Once daily	No cost data available	Extended-release
Paroxetine[b]	Paxil®	SSRI	10, 20, 30, 40 mg tabs; 10 mg/5 ml oral suspension	Once daily	$144, $160, $171, $170, $151	IR
	Pexeva		10, 20, 30, 40 mg tabs	Once daily	$260, $253, $263, $331	IR
	Paxil CR®		12.5, 25, 37.5 mg CR tabs	Once daily	$153, $168, $177	Extended-release
	Generic		10, 20, 30, 40 mg tabs	Once daily	$21, $21, $38, $37	IR
	Generic SR		12.5, 25, 37.5 mg tabs	Once daily	$94, $103, $110	Extended-release

Table 1 continued

Generic name	US trade name[a]	Therapeutic classification	Dosage forms	Frequency	Average monthly cost[c]	IR or extended-release
Venlafaxine[b]	Generic		25, 37.5, 50, 75, 100 mg tabs	Twice daily	$89, $83, $93, $78, $99	IR
	Effexor XR®		37.5, 75, 150 mg XR caps	Once daily	$209, $223, $218	Extended-release
	Generic XR		37.5, 75, 150, 225 mg tabs; 37.5, 75, 150 mg caps	Once daily	$119, $108, $120, $270, $90, $100, $105	Extended-release

tabs tablets, *caps* capsules, *IR* immediate release, *SSRI* selective serotonin reuptake inhibitor

[a] CR, SR, XL, and XR are registered trademarks referring to controlled-, sustained-, or extended-release dosage forms, respectively

[b] Generic available for some dosage forms

[c] Prices reflect nationwide retail averages for May 2013, rounded to the nearest dollar; data provided by Symphony Health Solutions, presented in 'Consumer Report best buy drugs—using antidepressants to treat depression' [124]

1980 to October 2012, using Medical Subject Headings as search terms when available or keywords when appropriate. We combined terms for MDD with a list of 13 specific SGAs that (except for fluvoxamine) have been approved in the US for the treatment of MDD: bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine, and their specific trade names. We also included fluvoxamine in our search, because in the US it is often used off-label for the treatment of MDD. We limited electronic searches to 'adult 19+ years', 'human', and 'English language'. We also used semi-automatic manual searches of reference lists of pertinent review articles and letters to the editor employing the Scopus™ citation database (http://www.scopus.com) [14]. The search strategy is presented in the electronic supplementary material 1.

The AHRQ-funded Scientific Resource Center, which supports authors of AHRQ-commissioned evidence reports, searched the following sources for potentially relevant unpublished literature: the US FDA website; Health Canada; Authorized Medicines for the European Union; ClinicalTrial.gov; Current Controlled Trials; Clinical Study Results; World Health Organization Clinical Trials; Conference Papers Index; National Institutes of Health RePORTER; HSRProj; Hayes, Inc. Health Technology Assessment; and the New York Academy of Medicine's Grey Literature Index. The Center also invited pharmaceutical manufacturers to submit dossiers on completed research for each drug. We received dossiers from two firms (Astra Zeneca, London, UK; and Warner Chilcott, Dublin, Ireland).

2.2 Study Selection

Two authors independently reviewed abstracts and full-text articles. Studies available in abstract form only were excluded. We included head-to-head randomized controlled trials (RCTs) of at least 6 weeks' duration that compared an IR formulation with an extended-release formulation of the same drug to assess efficacy. Because head-to-head evidence was lacking for many comparisons, we also included placebo- and active-controlled trials for network meta-analyses. Outcomes of interest were all health outcomes (e.g. response, remission, quality of life). To assess harms and adherence, in addition to RCTs, we searched for observational studies with $\geq$1,000 participants and follow-up of $\geq$12 weeks.

If both reviewers agreed that the study did not meet eligibility criteria, we excluded it. Disagreements about inclusion or exclusion were solved by consensus or by involving a third reviewer.

2.3 Data Extraction and Quality Assessment

Trained reviewers abstracted data from each study and assessed the risk of bias (quality) of all included studies. To assess the risk of bias, we used predefined criteria (low, moderate, high risk of bias) based on those developed by the Cochrane Collaboration [15]. To assess the risk of bias of observational studies, we used criteria outlined by Deeks et al. [16]. A senior reviewer checked completeness of data abstraction and confirmed the assigned quality ratings.

2.4 Data Synthesis and Analyses

We a priori decided to perform a network meta-analysis in the event of the absence of direct comparisons. Lacking head-to-head evidence for many comparisons of interest, we conducted network meta-analyses of head-to-head, placebo- and active-controlled trials using Bayesian methods [17, 18] to compare the efficacy of IR versus extended-release formulations. Because of clinical heterogeneity and the fact that treatment effects of SGA are often smaller in elderly patients than in the general population, we did not include studies

conducted exclusively in elderly patients (65 years of age or older) in these analyses. Our outcome measure of choice was the rate of response (defined as a 50 % improvement of scores from baseline) on the Hamilton Depression Rating Scale (HAM-D). We used the methods developed and illustrated in the NICE Technical Support Document 2, which details the generalized linear modeling framework for network meta-analyses of RCTs [19]. We used a random effects logistic regression model that adjusted for correlations between multiple arms within each study. Study effect and treatment effect parameters were modeled by non-informative (flat) prior distributions that were normal (0.10000). For the heterogeneity of the random-effects model, we used a uniform prior distribution centered at zero with sufficiently large variance. The first 20,000 simulations were discarded to allow for model convergence, and then a further 100,000 simulations were used in estimating the posterior probabilities. Satisfactory convergence was verified by trace plots and inspection of the Gelman–Rubin statistic for monitored parameters. We also ran a sensitivity analysis, including studies rated as having a high risk of bias, to assess their impact on results. We recalculated response rates for each study using the number of all randomized patients as the denominator to reflect a true intention-to-treat (ITT) analysis. With this approach we attempted to correct variations in results of modified ITT analyses encountered in individual studies. The network meta-analyses were performed using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) methods. We calculated odds ratios (ORs) and 95 % credible intervals (CIs) for comparisons between IR and extended-release formulations. Because mechanisms of action and pharmacokinetics of extended-release formulations vary across drugs, meaningful comparisons are likely most valid within single drugs that have an IR and extended-release formulation.

3 Results

Overall, our searches identified 4,476 citations (see the PRISMA flow diagram, Fig. 1). We screened 1,532 full-text articles for eligibility; of these, seven studies directly compared IR with extended-release formulations of the same drug [20–26]. Two of these head-to-head studies were included in

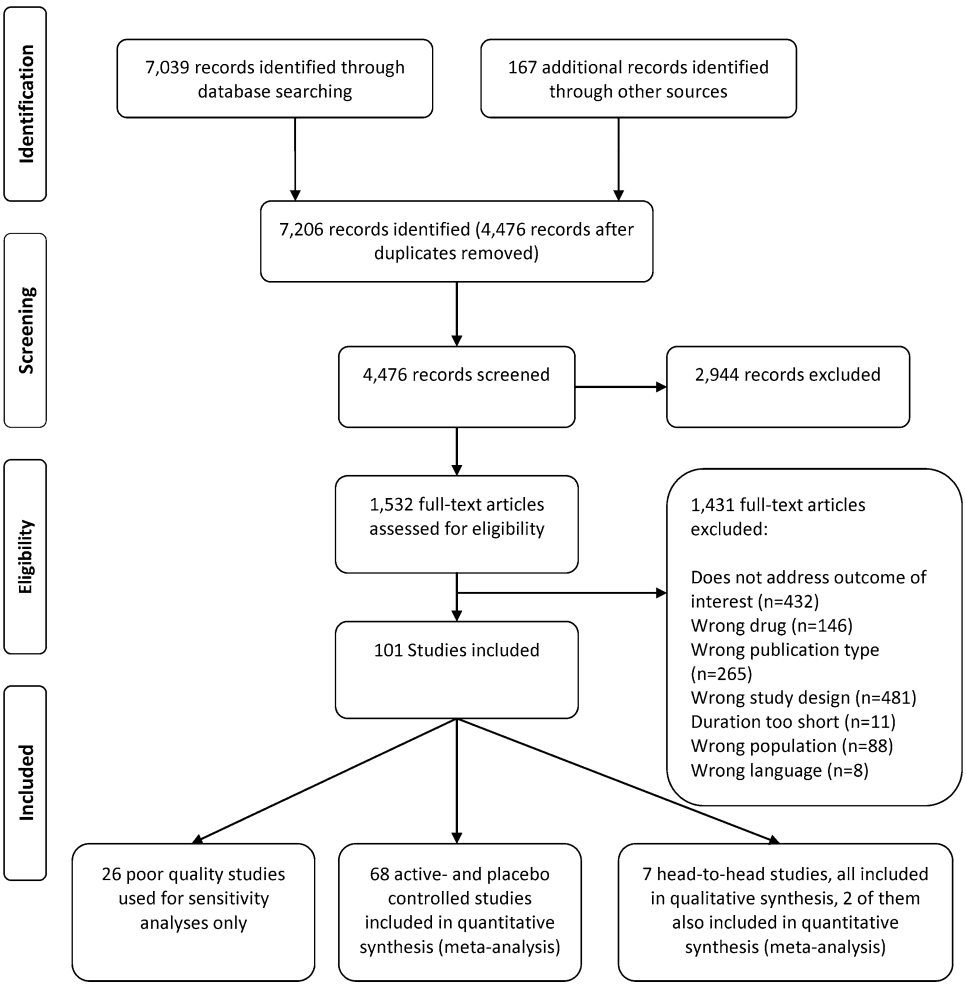
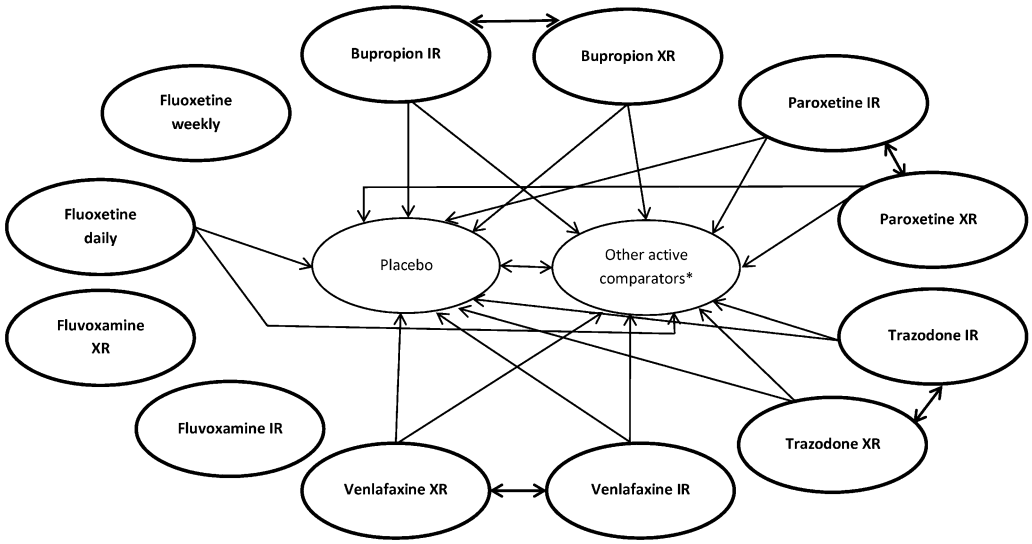


Fig. 1 PRISMA flow diagram (overview of evidence search and selection process)



*other active comparators: desvenlafaxine, duloxetine, nefazodone, sertraline, escitalopram, mirtazapine, citalopram, venlafaxine, trazodone, paroxetine, bupropion, fluoxetine, fluvoxamine

Fig. 2 Network of all included comparisons for the comparative efficacy network meta-analyses

the network meta-analyses on comparative response rates [23, 24]. In addition, we included 94 active- and placebo-controlled trials that reported response rates on HAM-D (see the network meta-analysis, Fig. 2) for network meta-analyses [27–94]. Of these, 26 were rated as high risk of bias trials and included for sensitivity analyses only [95–120].

We did not locate any eligible placebo- or active-controlled studies on fluvoxamine controlled release. All studies were funded by the pharmaceutical industry.

Table 2 summarizes study characteristics (e.g. study design, dosing) and the main findings of seven head-to-head trials comparing IR versus extended-release formulations with a total of 2,333 patients. This direct evidence is limited to comparisons of fluoxetine daily versus fluoxetine weekly [20, 21, 26], paroxetine IR versus paroxetine CR [22–24], and venlafaxine IR versus venlafaxine XR [25]. Only two head-to-head trials presented HAM-D response rates and could be included in the network meta-analyses [23, 24]. No direct evidence was available for trazodone IR/XR, fluvoxamine IR/CR, and bupropion IR/XL.

In the following sections we discuss the comparative efficacy, risk of harms, and adherence of IR versus extended-release formulations.

3.1 Comparative Efficacy of Immediate-Release (IR) versus Extended-Release Formulations

3.1.1 Fluoxetine Daily versus Fluoxetine Weekly

Two head-to-head trials reported on efficacy comparing fluoxetine daily with fluoxetine weekly. [20, 26] Both studies compared the efficacy of fluoxetine daily (20 mg/day) with fluoxetine weekly (60 and 90 mg/week) in patients with MDD who had responded to treatment and were randomly assigned to maintenance treatment.

One study randomized 501 patients to one of three treatment arms: fluoxetine daily (20 mg/day), fluoxetine weekly (90 mg/day), and placebo. Findings presented numerically higher relapse rates for patients switched to fluoxetine weekly (37 %) compared with those who stayed on fluoxetine daily (26 %) after 25 weeks of continuation treatment. However, the difference did not reach statistical significance. Both arms also showed similar changes in Clinical Global Impression–Severity (CGI–S; 1.0 vs. 0.9) and HAM-D (6.6 vs. 6.4) scores [20]. The other study enrolled 70 patients, lasted 7 weeks and did not find any statistically significant difference in their main outcome measures (changes in Montgomery–Åsberg Depression Rating Scale [MADRS] scores and on the Hopkins Symptom Checklist were not numerically reported) [26].

3.1.2 Paroxetine IR versus Paroxetine Controlled Release (CR)

We included two head-to-head trials and a pooled analysis of two identical RCTs comparing the efficacy of paroxetine IR and paroxetine CR in patients with MDD [22–24]. Overall, these studies enrolled almost 1,400 patients. Dosages are presented in Table 2. Study durations ranged from 8 to 12 weeks. In all three studies, patients treated with paroxetine IR or CR had similar response and remission rates. For example, in the pooled analysis of two identical RCTs, 49 % of patients treated with paroxetine IR

Table 2 Study characteristics of head-to-head trials comparing IR versus extended-release formulations of the same drug

Study	Design	N	Harms	Adherence	Response to HAM-D	Other efficacy outcomes (relapse, response, remission)	Quality rating per outcome
Fluoxetine daily versus fluoxetine weekly							
Burke and McArthur-Miller [26]	RCT Fluoxetine daily 20 mg/day Fluoxetine weekly 60 mg/week	70	NR	NR	NR	No statistically significant differences in main outcome measures (MADRS, Hopkins Symptom Checklist)	Efficacy: fair
Claxton et al. [21]	RCT (open-label), Fluoxetine 20 mg/day Fluoxetine 90 mg/week	109	NR	Higher adherence during maintenance treatment for fluoxetine weekly (85.9 %) than fluoxetine daily (79.4 %)	NR	NR	Adherence: fair
Schmidt et al. [20]	RCT, Fluoxetine 20 mg/day Fluoxetine 90 mg/week PL	501	Similar adverse events rates between fluoxetine daily and weekly	NR	NR	Relapse: fluoxetine daily 26 % vs. fluoxetine weekly 37 %, not statistically significant Changes on CGI-S: fluoxetine daily 0.9 vs. fluoxetine weekly 1.0 Changes on HAM-D: fluoxetine daily 6.4 vs. fluoxetine weekly 6.6	Efficacy: fair Harms: fair
Paroxetine IR versus paroxetine CR							
Golden et al. [24]	Pooled analysis of two identical RCTs Paroxetine IR 20–50 mg/day Paroxetine CR 25–62.5 mg/day PL	640	Higher rates of nausea with paroxetine IR than CR (23 % vs. 14 %; $p < 0.05$), no difference in other AE rates	NR	CR 53.3 %[a] IR 48.85 % PL 43.60 %	Remission on the HAM-D: CR 56 %, IR 53 %, PL 44 %	Efficacy: good Harms: fair
Higuchi et al. [23]	RCT Paroxetine CR 12.5–25 mg/day Paroxetine IR 10–20 mg/day PL	416	Similar adverse events rates for paroxetine IR and CR	NR	CR 61.5 %[a] IR 56.6 % PL 45.4 %	Response on CGI-I: CR 71 %, IR 75 %, PL 53 %	Efficacy: moderate Harms: moderate

Table 2 continued

Study	Design	N	Harms	Adherence	Response to HAM-D	Other efficacy outcomes (relapse, response, remission)	Quality rating per outcome
Rapaport et al. [22]	RCT Paroxetine IR 40 mg/day Paroxetine CR 50 mg/day PL	319	Similar adverse events rates for paroxetine IR and CR	Similar adherence rates between paroxetine IR and paroxetine CR IR 93.2 % vs. CR 96.3 %; p = NR	NR	Response on the CGI-I: CR 72 %, IR 65 %, PL 52 % Remission on HAM-D: CR 43 %, IR 44 %, PL 26 %	Efficacy: good Harms: fair Adherence: fair
Venlafaxine IR versus venlafaxine XR							
Cunningham [25]	RCT Venlafaxine IR 37.5–75 mg twice a day Venlafaxine XR 75–150 mg/day PL	278	Similar adverse events rates between venlafaxine IR and XR	NR	NR, only presented in a graph, no numbers	NR	Efficacy: fair Harms: fair

[a] Self-calculated as intention to treat

AE adverse event, *CR* controlled release, *CGI–I* Clinical Global Impression–Improvement, *CGI–S* CGI–Severity, *HAM-D* Hamilton Depression Rating Scale, *IR* immediate release, *MADRS* Montgomery–Åsberg Depression Rating Scale, *NR* not reported, *PL* placebo, *RCT* randomized controlled trial, *XR* extended-release

achieved response to treatment after 12 weeks compared with 53 % of patients taking paroxetine CR (self-calculated). Patients in both groups also exhibited similar remission rates (IR 53 % vs. CR 56 %) [24]. Likewise, in both RCTs patients had similar response rates on the HAM-D (IR 57 % vs. CR 62 %, self-calculated as ITT) and the CGI–Improvement (CGI–I) scale (IR 75 %; CR 71 %).

3.1.3 Venlafaxine IR versus Venlafaxine Extended-Release (XR)

One flexible-dose RCT compared the efficacy and safety of venlafaxine IR (37.5–75 mg twice a day) with venlafaxine XR (75–150 mg/day) and placebo in 278 patients with acute-phase MDD. After 12 weeks of treatment, statistically significantly more patients treated with venlafaxine XR responded to treatment (HAM-D, MADRS, and CGI) than patients taking venlafaxine IR (data not reported; $p < 0.05$) [25].

3.1.4 Network Meta-Analyses

Because of the dearth of studies directly comparing IR with extended-release formulations, we conducted network meta-analyses including placebo- or active-controlled RCTs of IR and extended-release formulations. Results of the network meta-analyses indicate that, overall, treatment effects are similar between IR and extended-release formulations (see network meta-analysis, Fig. 3), which confirms most of the findings from RCTs directly comparing IR and extended-released formulations. However, an exception is the results from the RCT that reported a greater efficacy of venlafaxine XR compared with venlafaxine IR. This finding could not be confirmed when a larger (albeit indirect) body of evidence was taken into consideration (OR 1.02; 95 % CI 0.64–1.54). Other comparisons of the network meta-analyses are limited to bupropion IR versus bupropion XR (OR 0.78; 95 % CI 0.32–1.60), paroxetine IR versus paroxetine CR (OR 1.09; 95 % CI 0.70–1.62), and trazodone IR versus trazodone XR (OR 2.34; 95 % CI 0.69–5.88).

Sensitivity analyses including high risk of bias studies in the network meta-analysis model rendered similar findings. We did not find sufficient evidence on response to treatment for fluoxetine and fluvoxamine to add them into the network meta-analysis model.

3.2 Comparative Risk of Harms of IR versus Extended-Release Formulations

Five head-to-head studies provided evidence on the comparative risk of harms (see study characteristics, Table 2) and will be discussed qualitatively [20, 22–25].

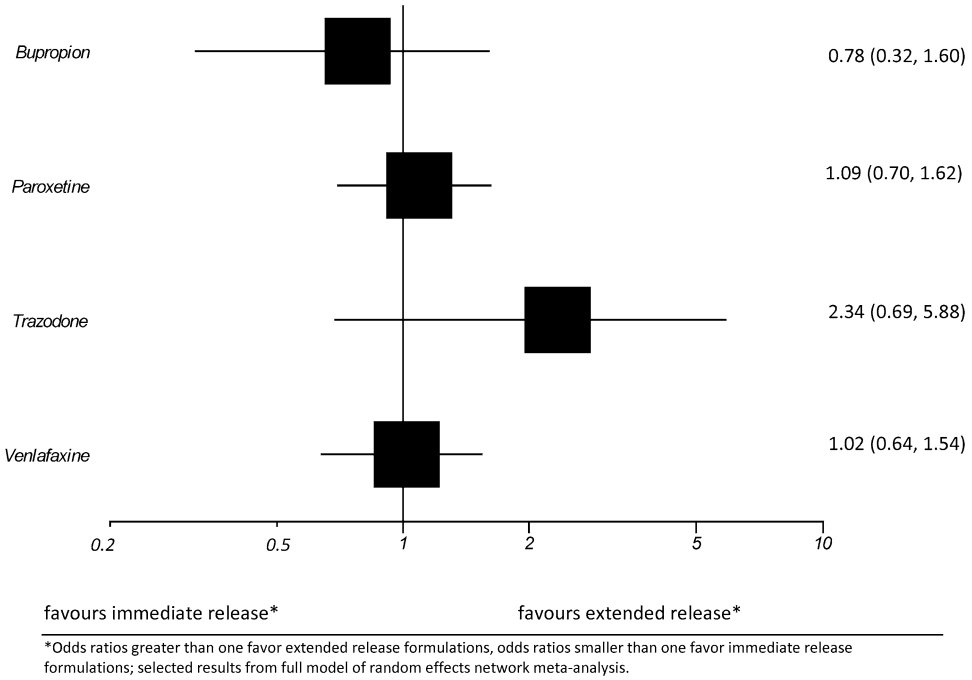


Fig. 3 Results of network meta-analysis: odds ratios of response rates comparing immediate- versus extended-release formulations

3.2.1 Fluoxetine Daily versus Fluoxetine Weekly

One RCT compared harms between daily and weekly fluoxetine regimens [20]. The acute treatment period lasted 7 weeks and was open label. Responders were randomized to double-blinded maintenance treatment with fluoxetine (20 mg/day), or fluoxetine weekly (90 mg/week). Rates for most adverse events were similar for patients in both treatment groups during 25 weeks of follow-up. The two adverse events 'nervousness' and 'thinking abnormal' occurred significantly more often in the 90 mg/week group than in the 20 mg/day group ($p = 0.025$ and 0.004, respectively).

3.2.2 Paroxetine IR versus Paroxetine CR

Two double-blinded RCTs [22, 23] and a pooled analysis of two identical RCTs [24] determined the comparative harms between paroxetine IR and paroxetine CR. Adverse event rates were comparable for the IR and the extended-release formulation of paroxetine, except for nausea, which occurred significantly more frequently in patients treated with paroxetine IR than CR during the first weeks of treatment (23 vs. 14 %; $p < 0.05$) [24].

3.2.3 Venlafaxine IR versus Venlafaxine XR

One flexible-dose RCT compared the safety of venlafaxine IR (mean daily dose 115–125 mg) with venlafaxine XR (mean daily dose 124–140 mg) and placebo in 278 patients with acute-phase MDD. During 12 weeks of treatment, there was no significant difference in adverse event rates between the groups [25].

We could not find any evidence that compared the risk of harms in IR and extended-release formulations of bupropion, fluvoxamine, and trazodone.

3.3 Adherence: Results of Head-to-Head Trials

We identified two RCTs that assessed the comparative adherence of IR and extended-release formulations (see study characteristics, Table 2) [21, 22].

3.3.1 Fluoxetine Daily versus Fluoxetine Weekly

The open-label RCT described above, comparing fluoxetine daily (20 mg/day) and fluoxetine weekly (90 mg/week) during maintenance treatment reported statistically significantly lower adherence rates in patients taking fluoxetine daily than weekly (79.4 vs. 85.9 %; $p < 0.01$) during 3 months of follow-up [21].

3.3.2 Paroxetine IR versus Paroxetine CR

In the study comparing paroxetine IR with paroxetine CR, adherence rates were similar for both treatment groups during the 12-week study period (93.2 vs. 96.3 %; $p =$ not reported) [22].

We could not find any studies assessing adherence between IR and extended-release formulations of fluvoxamine, trazodone, and venlafaxine.

4 Discussion

To our knowledge, this systematic review is the first to compare the efficacy, risk of harms and adherence of IR versus extended-release formulations of SGA. Overall, for the treatment of acute phase MDD, our analyses indicate that IR and extended-release formulations do not differ substantially with respect to efficacy and risk of harms. Differences in efficacy based on one RCT comparing venlafaxine XR with venlafaxine IR [25] could not be confirmed with network meta-analyses and might be a chance finding. We could not find any head-to-head trials comparing IR- versus extended-release formulations of bupropion and trazodone. However, network meta-analyses indicate similar treatment effects for patients with acute-phase MDD. One RCT reported numerically higher relapse rates for patients receiving maintenance treatment with fluoxetine weekly than fluoxetine daily. However, this finding is based on a single RCT and has to be interpreted cautiously.

Our analyses indicate that IR and extended-release formulations also have similar risks of harms. Adverse event rates were comparable for the IR and the extended-release formulation of paroxetine, fluoxetine, and venlafaxine. However, one exception was nausea. It occurred significantly more frequently in patients treated with paroxetine IR than CR during the first weeks of treatment [24]. Although, even if group rates do not differ, it could be possible that different people get particular side effects. However, the strength of evidence is low, indicating that future studies might have a substantial impact on these findings.

With respect to adherence, the main marketing argument to use extended-release formulations, the evidence is mixed. Adherence to fluoxetine weekly was significantly better than to fluoxetine daily. However, the absolute difference of 6.6 % points over a time period of 3 months was small. Comparing paroxetine IR versus CR showed no difference in adherence, maybe because both paroxetine formulations had to be taken daily. One factor influencing adherence regimens is frequency of dosing. Medications requiring less frequent dosing are associated with better adherence than those requiring more frequent dosing [121, 122]. Also, a retrospective cohort study that compared data from patients taking bupropion SR with patients with a prescription for bupropion XL demonstrated a difference between once- and twice-daily dosing regimens. Bupropion SR was administered twice daily, bupropion XL once daily. Analyses showed that patients with a prescription for the SR formulation were significantly less likely to fill a future prescription than were patients with a prescription for bupropion XL [123]. Although both formulations are considered extended-release in our article and therefore not included in this review, the study demonstrates a better adherence for the daily formulation compared with the twice-daily formulation.

Our study has several limitations. First, evidence directly comparing IR with extended-release formulations was limited to seven studies. We did not find any direct evidence on fluvoxamine IR and XR for any of our outcomes of interest. Due to the lack of head-to-head trials, we performed indirect comparisons of IR and XR formulations employing network meta-analyses. However, any indirect comparison has methodological limitations, most notably the assumption that prognostic factors for a specific outcome are similar across study populations in the network. Therefore, findings have to be interpreted carefully. Nevertheless, indirect comparisons are an important analytic tool if head-to-head evidence is missing. Second, the strength of evidence of most of our findings was low, indicating a substantial uncertainty in the estimate of effect. It is likely that future studies might substantially alter these estimates. This uncertainty is also indicated by wide CIs for some comparisons which encompass differences between drugs that would be clinically important. Finally, any systematic review is susceptible to publication bias. Despite extensive searches of the grey literature, we have no way to be sure that we have detected all important unpublished studies.

5 Conclusions

Evidence addressing the comparative efficacy, risk of harms, and adherence of IR and extended-release formulations of antidepressant medications is limited and should be interpreted cautiously. While the evidence overall does not support clear differences between the two formulations at the group level, these findings do not mean that efficacy, harms, and adherence do not differ for a particular individual. Clinical strategy should still aim to provide a medication trial of adequate dose and duration. If adherence or compliance is a problem with one formulation, consideration of the other formulation to provide an adequate trial is reasonable. If out-of-pocket costs play a role for the choice of a medication, our findings indicate that IR formulations, which are more readily available as generic medications, do not differ substantially with respect to adherence or risk of adverse events than extended-release formulations.

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References

1. Kessler RC, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005;62(6):593–602.
2. Wittchen HU, Jacobi F. Size and burden of mental disorders in Europe: a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol. 2005;15(4):357–76.
3. Wu E, et al. Comparison of treatment persistence, hospital utilization and costs among major depressive disorder geriatric patients treated with escitalopram versus other SSRI/SNRI antidepressants. Curr Med Res Opin. 2008;24(10):2805–13.
4. Birnbaum HG, Ben-Hamadi R, Greenberg PE, Hsieh M, Tang J, Reygrobellet C. Determinants of direct cost differences among US employees with major depressive disorders using antidepressants. Pharmacoeconomics. 2009;27:507–17.
5. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. Arch Gen Psychiatry. 2009;66(8):848–56.
6. DeVane CL. Immediate-release versus controlled-release formulations: pharmacokinetics of newer antidepressants in relation to nausea. J Clin Psychiatry. 2003;64(Suppl 18):14–9.
7. Kondo T, et al. Altered pharmacokinetics and metabolism of valproate after replacement of conventional valproate with the slow-release formulation in epileptic patients. Pharmacol Toxicol. 2002;90(3):135–8.
8. Kennedy SH, et al. Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. J Clin Psychiatry. 2002;63(3):181–6.
9. Gartlehner G, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011;155(11):772–85.
10. Sussman N. Venlafaxine XR therapy for major depression and anxiety disorders: the clinical implications that its advantages pose. Postgrad Med. 1999;106(6 Suppl):31–6.
11. Keene MS, et al. Adherence to paroxetine CR compared with paroxetine IR in a Medicare-eligible population with anxiety disorders. Am J Manag Care. 2005;11(12 Suppl):S362–9.
12. Huskamp HA. Prices, profits, and innovation: examining criticisms of new psychotropic drugs' value. Health Aff (Millwood). 2006;25(3):635–46.
13. Gartlehner G, et al. Second-generation antidepressants in the pharmacologic treatment of adult depression: an update of the 2007 comparative effectiveness review. Report no. 12-EHC012-EF. Rockville: Agency for Healthcare Research and Quality; Dec 2011.
14. Chapman A, Morgan LC, Gartlehner G. Semi-automating the manual literature search for systematic reviews increases efficiency. Health Inf Libr J. 2009;27(1):22–7.
15. Higgins JPT, Altman DG, Sterne J. Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
16. Deeks JJ, et al. Evaluating non-randomised intervention studies. Health Technol Assess, 2003;7(27):iii–x, 1–173.
17. Jansen JP, et al. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value Health. 2008;11(5):956–64.
18. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004;23(20):3105–24.
19. Dias S, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Mak. 2013;33(5):607–17.
20. Schmidt ME, et al. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. J Clin Psychiatry. 2000;61(11):851–7.
21. Claxton A, et al. Patient compliance to a new enteric-coated weekly formulation of fluoxetine during continuation treatment of major depressive disorder. J Clin Psychiatry. 2000;61(12):928–32.
22. Rapaport MH, et al. Efficacy of controlled-release paroxetine in the treatment of late-life depression. J Clin Psychiatry. 2003;64(9):1065–74.
23. Higuchi T, et al. Paroxetine controlled-release formulation in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled study in Japan and Korea. Psychiatry Clin Neurosci. 2011;65(7):655–63.
24. Golden RN, et al. Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. J Clin Psychiatry. 2002;63(7):577–84.
25. Cunningham LA. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Venlafaxine XR 208 Study Group. Ann Clin Psychiatry. 1997;9(3):157–64.
26. Burke WJ, McArthur-Miller DA. Exploring treatment alternatives: weekly dosing of fluoxetine for the continuation phase of major depressive disorder. J Clin Psychiatry. 2001;62(Suppl 22):38–42.
27. Feiger A, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry. 1996;57(Suppl 2):53–62.
28. Feiger AD, et al. A placebo-controlled study evaluating the efficacy and safety of flexible-dose desvenlafaxine treatment in outpatients with major depressive disorder. CNS Spectr. 2009;14(1):41–50.
29. Boyer P, et al. Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial. Int Clin Psychopharmacol. 2008;23(5):243–53.
30. Liebowitz MR, Yeung PP, Entsuah R. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. J Clin Psychiatry. 2007;68(11):1663–72.
31. Septien-Velez L, et al. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. Int Clin Psychopharmacol. 2007; 22(6):338–47.

32. Brannan SK, et al. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. J Psychiatr Res. 2005;39(1):43–53.
33. Detke MJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res. 2002;36(6):383–90.
34. Detke MJ, et al. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry. 2002;63(4):308–15.
35. Detke MJ, et al. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Neuropsychopharmacol. 2004;14(6):457–70.
36. Wernicke JF, et al. Low-dose fluoxetine therapy for depression. Psychopharmacol Bull. 1988;24(1):183–8.
37. Lydiard RB, et al. Fluvoxamine, imipramine, and placebo in the treatment of depressed outpatients: effects on depression. Psychopharmacol Bull. 1989;25(1):68–70.
38. Cohn CK, et al. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. J Clin Psychiatry. 1996;57(Suppl 2):15–8.
39. Fontaine R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry. 1994;55(6):234–41.
40. Rickels K, et al. A placebo-controlled, double-blind, clinical trial of paroxetine in depressed outpatients. Acta Psychiatr Scand Suppl. 1989;350:117–23.
41. Reimherr FW, et al. Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression. J Clin Psychiatry. 1990;51(Suppl B):18–27.
42. Lydiard RB, et al. A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. J Clin Psychiatry. 1997;58(11):484–91.
43. Hypericum Depression Trial Study Group. Effect of hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. JAMA. 2002;287(14):1807–14.
44. Olie J, Gunn K, Katz E. A double-blind placebo-controlled multicentre study of sertraline in the acute and continuation treatment of major depression. Eur Psychiatry. 1997;12(1):34–41.
45. Blumenthal JA, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom Med. 2007;69(7):587–96.
46. Thase ME. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. The Venlafaxine XR 209 Study Group. J Clin Psychiatry. 1997;58(9):393–8.
47. Wade A, Gembert K, Florea I. A comparative study of the efficacy of acute and continuation treatment with escitalopram versus duloxetine in patients with major depressive disorder. Curr Med Res Opin. 2007;23(7):1605–14.
48. Khan A, et al. Double-blind comparison of escitalopram and duloxetine in the acute treatment of major depressive disorder. Clin Drug Investig. 2007;27(7):481–92.
49. Lee P, et al. Once-daily duloxetine 60 mg in the treatment of major depressive disorder: multicenter, double-blind, randomized, paroxetine-controlled, non-inferiority trial in China, Korea, Taiwan and Brazil. Psychiatry Clin Neurosci. 2007;61(3):295–307.
50. Feighner JP, et al. Double-blind comparison of bupropion and fluoxetine in depressed outpatients. J Clin Psychiatry. 1991;52(8):329–35.
51. Mao PX, et al. Escitalopram in major depressive disorder: a multicenter, randomized, double-blind, fixed-dose, parallel trial in a Chinese population. Depress Anxiety. 2008;25(1):46–54.
52. Hong CJ, et al. A double-blind, randomized, group-comparative study of the tolerability and efficacy of 6 weeks' treatment with mirtazapine or fluoxetine in depressed Chinese patients. J Clin Psychiatry. 2003;64(8):921–6.
53. Rush AJ, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biol Psychiatry. 1998;44(1):3–14.
54. Gagiano C. A double blind comparison of paroxetine and fluoxetine in patients with major depression. Br J Clin Res. 1993;4:145–52.
55. De Wilde J, et al. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. Acta Psychiatr Scand. 1993;87(2):141–5.
56. Chouinard G, et al. A Canadian multicenter, double-blind study of paroxetine and fluoxetine in major depressive disorder. J Affect Disord. 1999;54(1–2):39–48.
57. Sechter D, et al. A double-blind comparison of sertraline and fluoxetine in the treatment of major depressive episode in outpatients. Eur Psychiatry. 1999;14(1):41–8.
58. Bennie EH, Mullin JM, Martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. J Clin Psychiatry. 1995;56(6):229–37.
59. Dierick M, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry. 1996;20(1):57–71.
60. Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. J Clin Psychiatry. 1998;59(7):352–7.
61. Alves C, Cachola I, Brandao J. Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. Prim Care Psychiatry. 1999;5(2):52–63.
62. Tzanakaki M, et al. Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia. Int Clin Psychopharmacol. 2000;15(1):29–34.
63. De Nayer A, et al. Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. Int J Neuropsychopharmacol. 2002;5(2):115–20.
64. Tylee A, et al. A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice. Prim Care Psychiatry. 1997;3(1):51–8.
65. Haffmans PM, Timmerman L, Hoogduin CA. Efficacy and tolerability of citalopram in comparison with fluvoxamine in depressed outpatients: a double-blind, multicentre study. The LUCIFER Group. Int Clin Psychopharmacol. 1996;11(3):157–64.
66. Hicks JA, et al. Randomised controlled study of sleep after nefazodone or paroxetine treatment in out-patients with depression. Br J Psychiatry. 2002;180:528–35.
67. Benkert O, Szegedi A, Kohnen R. Mirtazapine compared with paroxetine in major depression. J Clin Psychiatry. 2000;61(9):656–63.
68. Rush AJ, et al. Response in relation to baseline anxiety levels in major depressive disorder treated with bupropion sustained release or sertraline. Neuropsychopharmacology. 2001;25(1):131–8.
69. Munizza C, et al. A comparative, randomized, double-blind study of trazodone prolonged-release and sertraline in the treatment of major depressive disorder. Curr Med Res Opin. 2006;22(9):1703–13.
70. Weisler RH, et al. Comparison of bupropion and trazodone for the treatment of major depression. J Clin Psychopharmacol. 1994;14(3):170–9.
71. van Moffaert M, et al. Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. Int Clin Psychopharmacol. 1995; 10(1):3–9.

72. Kasper S, et al. A comparative, randomised, double-blind study of trazodone prolonged-release and paroxetine in the treatment of patients with major depressive disorder. Curr Med Res Opin. 2005;21(8):1139–46.
73. Bielski RJ, Ventura D, Chang CC. A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. J Clin Psychiatry. 2004;65(9):1190–6.
74. Sir A, et al. Randomized trial of sertraline versus venlafaxine XR in major depression: efficacy and discontinuation symptoms. J Clin Psychiatry. 2005;66(10):1312–20.
75. Shelton RC, et al. A randomized, double-blind, active-control study of sertraline versus venlafaxine XR in major depressive disorder. J Clin Psychiatry. 2006;67(11):1674–81.
76. Boulenger JP, et al. A comparative study of the efficacy of long-term treatment with escitalopram and paroxetine in severely depressed patients. Curr Med Res Opin. 2006;22(7):1331–41.
77. Ventura D, et al. Escitalopram versus sertraline in the treatment of major depressive disorder: a randomized clinical trial. Curr Med Res Opin. 2007;23(2):245–50.
78. Perahia DG, et al. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. Eur Psychiatry. 2006;21(6):367–78.
79. Tourian KA, et al. Desvenlafaxine 50 and 100 mg/d in the treatment of major depressive disorder: an 8-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial and a post hoc pooled analysis of three studies. Clin Ther. 2009;31:1405–23.
80. Nierenberg AA, et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. Curr Med Res Opin. 2007;23(2):401–16.
81. Goldstein DJ, et al. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. J Clin Psychiatry. 2002;63(3):225–31.
82. Coleman CC, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. Ann Clin Psychiatry. 1999;11(4):205–15.
83. Croft H, et al. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. Clin Ther. 1999;21(4):643–58.
84. Coleman CC, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained release and fluoxetine. Clin Ther. 2001;23(7):1040–58.
85. Fava M, et al. A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression. Ann Clin Psychiatry. 1998;10(4):145–50.
86. Rudolph RL, Feiger AD. A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affect Disord. 1999;56(2–3):171–81.
87. Nemeroff CB, Thase ME. A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. J Psychiatric Res. 2007;41(3):351–9.
88. Fava M, et al. Acute efficacy of fluoxetine versus sertraline and paroxetine in major depressive disorder including effects of baseline insomnia. J Clin Psychopharmacol. 2002;22(2):137–47.
89. Ou JJ, et al. Efficacy and safety of escitalopram versus citalopram in major depressive disorder: a 6-week, multicenter, randomized, double-blind, flexible-dose study. Psychopharmacology. 2011; 213(2–3):639–46.
90. Barber JP, et al. Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. J Clin Psychiatry. 2012;73(1):66–73.
91. Dunlop BW, et al. Symptomatic and functional improvement in employed depressed patients: a double-blind clinical trial of desvenlafaxine versus placebo. J Clin Psychopharmacol. 2011;31(5):569–76.
92. Alvarez E, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol. 2012;15(5):589–600.
93. Oakes TM, et al. Assessment of depressive symptoms and functional outcomes in patients with major depressive disorder treated with duloxetine versus placebo: primary outcomes from two trials conducted under the same protocol. Hum Psychopharmacol. 2012;27(1):47–56.
94. Mehtonen OP, et al. Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. Venlafaxine 631 Study Group. J Clin Psychiatry. 2000;61(2):95–100.
95. Fabre LF, Putman HP 3rd. A fixed-dose clinical trial of fluoxetine in outpatients with major depression. J Clin Psychiatry. 1987;48(10):406–8.
96. Elliott AJ, et al. Randomized, placebo-controlled trial of paroxetine versus imipramine in depressed HIV-positive outpatients. Am J Psychiatry. 1998;155(3):367–72.
97. Fabre L, et al. Fluvoxamine versus imipramine and placebo: a double-blind comparison in depressed patients. Int Clin Psychopharmacol. 1996;11(2):119–27.
98. Feighner JP, Boyer WF. Paroxetine in the treatment of depression: a comparison with imipramine and placebo. J Clin Psychiatry. 1992;53(Suppl):44–7.
99. Feighner J, et al. A double-blind, placebo-controlled trial of nefazodone in the treatment of patients hospitalized for major depression. J Clin Psychiatry. 1998;59(5):246–53.
100. Smith WT, Glaudin V. A placebo-controlled trial of paroxetine in the treatment of major depression. J Clin Psychiatry. 1992;53(Suppl):36–9.
101. Muijen M, et al. A comparative clinical trial of fluoxetine, mianserin and placebo in depressed outpatients. Acta Psychiatr Scand. 1988;78(3):384–90.
102. Smith WT, et al. Mirtazapine vs. amitriptyline vs. placebo in the treatment of major depressive disorder. Psychopharmacol Bull. 1990;26(2):191–6.
103. Wernicke J, et al. Fixed-dose fluoxetine therapy for depression. Psychopharmacol Bull. 1987;23(1):164.
104. Rudolph RL, et al. A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. J Clin Psychiatry. 1998;59(3):116–22.
105. Rickels K, et al. The efficacy and safety of paroxetine compared with placebo in outpatients with major depression. J Clin Psychiatry. 1992;53(Suppl):30–2.
106. Rickels K, et al. Nefazodone and imipramine in major depression: a placebo-controlled trial. Br J Psychiatry. 1994;164(6):802–5.
107. Roy-Byrne PP, et al. Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2000;20(2):129–36.
108. McGrath PJ, et al. A placebo-controlled study of fluoxetine versus imipramine in the acute treatment of atypical depression. Am J Psychiatry. 2000;157(3):344–50.
109. Hegerl U, et al. Effects of pharmacotherapy and psychotherapy in depressed primary-care patients: a randomized, controlled trial including a patients' choice arm. Int J Neuropsychopharmacol. 2010;13(1):31–44.
110. Soares CN, et al. Desvenlafaxine and escitalopram for the treatment of postmenopausal women with major depressive disorder. Menopause. 2010;17(4):700–11.
111. Beasley CM Jr, et al. Fluoxetine versus trazodone: efficacy and activating-sedating effects. J Clin Psychiatry. 1991;52(7):294–9.
112. Silverstone PH, Ravindran A. Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with

depression and anxiety. Venlafaxine XR 360 Study Group. J Clin Psychiatry. 1999;60(1):22–8.
113. Lapierre YD, et al. Treatment of major affective disorder with fluvoxamine. J Clin Psychiatry. 1987;48(2):65–8.
114. Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. Pharmacopsychiatry. 2006;39:66–75.
115. Goldstein DJ, et al. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol. 2004;24(4):389–99.
116. Claghorn JL. The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients. J Clin Psychiatry. 1992;53(Suppl):33–5.
117. Corrigan MH, et al. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety. 2000;11(2):58–65.
118. Clerc GE, Ruimy P, Verdeau-Palles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. The Venlafaxine French Inpatient Study Group. Int Clin Psychopharmacol. 1994;9(3):139–43.
119. Gulseren L, et al. Comparison of fluoxetine and paroxetine in type II diabetes mellitus patients. Arch Med Res. 2005;36(2):159–65.
120. Wade A, et al. A randomized, double-blind, 24-week study comparing the efficacy and tolerability of mirtazapine and paroxetine in depressed patients in primary care. Int Clin Psychopharmacol. 2003;18(3):133–41.
121. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med. 1990;150(9):1881–4.
122. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23(8):1296–310.
123. Stang P, Young S, Hogue S. Better patient persistence with once-daily bupropion compared with twice-daily bupropion. Am J Ther. 2007;14(1):20–4.
124. Consumer Reports Best Buy Drugs™. Using antidepressants to treat depression. 2013. Available from: http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/Antidepressants_update.pdf. Accessed 9 Apr 2014.