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The General and Comparative Efficacy and Safety of Duloxetine in Major Depressive Disorder

A Systematic Review and Meta-Analysis

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Abstract

Background: Second-generation antidepressants dominate the management of patients with major depressive disorder (MDD). Evidence on the general and comparative benefits and harms is still accruing.

Objective: To systematically review the general and comparative efficacy and safety of duloxetine for the treatment of acute-phase MDD in adults.

Data Sources: We conducted a search of MEDLINE, Embase, PsychLit, The Cochrane Library, and the International Pharmaceutical Abstracts from 1980 to July 2009, as well as manually searching reference lists of pertinent review articles and exploring the Center for Drug Evaluation and Research database to identify unpublished research.

Study Selection: For efficacy, randomized controlled trials (RCTs) comparing duloxetine with placebo or second-generation antidepressants were included. For safety, both experimental and observational studies were eligible.

Data Extraction: Abstracts and full-text articles were independently reviewed by two people, one investigator extracted relevant data, and a senior reviewer checked data for completeness and accuracy.

Results: We included 36 experimental and observational studies and, where sufficient data were available, meta-analyses of RCTs were conducted. Findings indicated that duloxetine is an effective treatment option for acute-phase MDD, with a tolerability profile similar to other second-generation antidepressants. No substantial differences in efficacy and safety appear to exist when duloxetine is compared with other second-generation antidepressants. Overall, about 40% of patients treated with duloxetine achieved remission. Compared with other

treatments, duloxetine had frequently higher rates of nausea, vomiting and dry mouth; however, these differences did not lead to higher discontinuation rates compared with selective serotonin reuptake inhibitors as a class. There is insufficient evidence to draw conclusions about rare but severe adverse events.
Conclusions: Current evidence does not warrant the choice of duloxetine over other second-generation antidepressants based on greater efficacy or safety for patients with acute-phase MDD with or without accompanying symptoms such as pain.

Background

Worldwide, major depressive disorder (MDD) is one of the most common reasons for disability, and the most prevalent Axis I disorder.[1] The estimated lifetime incidence of MDD in adults in the US is more than 18%.[2] In 2000, the economic burden of depressive disorders in the US was an estimated $83.1 billion, 30% of which was attributable to direct medical expenses.[3]

Clinically, most patients with MDD experience depressed moods and diminished interest in daily activities over a period of at least 2 weeks. Other symptoms may vary and include weight gain or loss, changes in sleep patterns, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate, or recurrent thoughts of death or suicidal ideation.[4]

Pharmacotherapy dominates the medical management of MDD. Current guidelines recommend the use of second-generation antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs) and other second-generation drugs with varying mechanisms, as first-line treatment of patients who meet the criteria for MDD.[5-7] While second-generation antidepressants can be effective, these medications do not work for all patients. Indeed, only about one-third of patients recover after aggressive treatment with a single second-generation antidepressant and, overall, less than 60% recover after two aggressive trials, suggesting a need for more treatment options.[8] Up-to-date information on the general and comparative benefits and harms of second-generation antidepressants is critical to informed decision making.

Duloxetine is a relatively new (2004) addition to the second-generation antidepressant group of medications. An SNRI, it is currently approved for the treatment of MDD, generalized anxiety disorder and fibromyalgia in the US, diabetic peripheral neuropathic pain in adults in the US and EU, and female urinary stress incontinence in the EU. This systematic review focuses on the benefits and risks of duloxetine for the treatment of acute-phase MDD. We also sought to determine whether efficacy, effectiveness and harms differ among subgroups of patients based on accompanying symptoms, age, sex or race/ethnicity. We also update the findings of an earlier report on second-generation antidepressants by the Agency for Healthcare Research and Quality (AHRQ).[9]

The following key questions are addressed:

- What is the general efficacy and safety of duloxetine for the treatment of patients with acute-phase MDD?
- What is the comparative efficacy and safety of duloxetine relative to other second-generation antidepressants for the treatment of patients with acute-phase MDD?
- Do any differences in efficacy and safety of duloxetine for the treatment of patients with acute-phase MDD in subgroups defined by age, sex, ethnicities or common co-morbidities exist?

Methods

Data Sources

A search of MEDLINE, Embase, PsychLit, Cochrane Library and International Pharmaceutical Abstracts from 1980 to July 2009 was conducted. Medical Subject Headings (MeSH)

were used as search terms when available, or key words were used when appropriate. In the original report,[9] we combined terms for depressive disorders with a list of 12 specific second-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone and venlafaxine) and their specific trade names. For this study, we confined results to literature identified for duloxetine using the following search terms: 'duloxetine' [substance name], 'cymbalta', 'depressive disorder' [MeSH], 'depressive disorder, major' [MeSH], 'adverse events', 'drug hypersensitivity' 'drug toxicity' and a variety of MeSH terms to delimit relevant study designs. Electronic searches were limited to 'adult 19 + years', 'human', and 'English language'. The detailed search strategy can be provided upon request.

We manually searched reference lists of pertinent review articles and letters to the editor, and used the Center for Drug Evaluation and Research database and ClinicalTrials.gov (up to February 2009) to identify unpublished research. The Scientific Resource Center of the Oregon Health and Science University invited pharmaceutical manufacturers to submit dossiers on completed research for each drug. With respect to duloxetine, a dossier was received from Eli Lilly and Company, the manufacturers of duloxetine.

Study Selection

Abstracts and relevant full-text articles were independently reviewed by two people. To assess efficacy or effectiveness regarding response, speed of onset, remission and quality of life, we included randomized controlled trials (RCTs) of at least 6 weeks' duration that compared duloxetine with placebo or another second-generation antidepressant. To assess harms (specific adverse events, rates of adverse events and discontinuation attributable to adverse events), data from observational studies with ≥100 participants and follow-up of ≥12 weeks were also examined. To assess differences of benefits and harms in subgroups and patients with accompanying symptoms, both head-to-head and placebo-controlled trials were reviewed. We included meta-analyses or pooled data analyses if we found them to be relevant for a question of interest and of good or fair methodological quality.[10] Table I summarizes the eligibility criteria.

Table I. Study eligibility criteria

Population
Adult in- and outpatients with acute-phase MDD
Intervention
Duloxetine
Control
Placebo or second-generation antidepressants
Study design
Efficacy: double-blinded RCTs
Safety: all experimental and observational designs
Minimum study duration: 6 weeks
Minimum sample size: none for experimental designs; n ≥ 100 for observational studies
Outcomes of interest
All health outcomes, e.g. response
Remission
Onset of action
Overall rate of adverse events
Discontinuation because of adverse events
Specific adverse events (e.g. gastrointestinal symptoms, weight gain, dizziness and others)
Severe adverse events (e.g. suicidality, hyponatraemia, sexual dysfunction and others)

MDD = major depressive disorder; **RCTs** = randomized controlled trials.

If both reviewers agreed that the study did not meet eligibility criteria, the study was excluded. We also excluded studies that met eligibility criteria but were reported only as an abstract.

Data Extraction and Quality Assessment

A structured, web-based data abstraction form (SRS 4.0, TrialStat Corp., Ottawa, ON, Canada) was used, onto which trained reviewers abstracted data from each study and assigned an initial quality rating. A senior reviewer read each abstracted article, evaluated completeness of data abstraction and confirmed the quality rating. Investigators resolved any disagreements by discussion and consensus or by consulting an independent party.

The internal validity (quality) of trials was assessed based on predefined criteria and applied ratings of good, fair or poor.[11,12] Primary elements of quality assessment for RCTs included

randomization and allocation concealment, similarity of compared groups at baseline, blinding, use of intention-to-treat analysis, and overall and differential loss to follow-up. To assess observational studies we used criteria involving a selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of follow-up, and statistical analysis.[13] Studies with a fatal flaw in one or more categories were rated 'poor' quality.

To identify effectiveness studies, a tool was used that distinguishes efficacy trials from effectiveness studies based on certain elements of study design.[14] Such studies have a higher applicability of results than efficacy trials because they enrol fewer selected study populations, employ assessment and treatment modalities that mimic clinical practice, and assess health outcomes along with adverse events.

Lacking clear definitions about equivalence of dosages among second-generation antidepressants in the published literature, we developed a roster of low, medium and high dosages for each drug based on the interquartile dosing range.[15] This roster, which does not indicate dosing equivalence, was used to detect gross inequalities in dosing that could affect comparative efficacy and effectiveness.

Data Synthesis

Because data on most outcomes of interest were insufficient to conduct meta-analyses, we synthesized the evidence on the majority of outcomes qualitatively. For harms, we were able to conduct meta-analyses of head-to-head trials on the relative risk (RR) of the comparative overall discontinuation rates, discontinuation rates due to adverse events and discontinuation rates due to lack of efficacy. However, because of limited data on individual second-generation antidepressants as active comparators, we assessed the comparative risk of duloxetine relative to SSRIs as a class, because SSRIs have similar efficacy and adverse event profiles.[16]

For each meta-analysis, we conducted a test of heterogeneity (I^2 index) and applied both random and fixed effects models. The results of the random effects models are reported in this study; however, the results from both models were very similar. Publication bias was assessed using funnel plots and Kendell's tests.

All statistical analyses used StatsDirect Statistical Software program, version 2.6.6 (StatsDirect Ltd, Cheshire, UK).

Results

Figure 1 depicts the search results and literature screening. We analysed data from 14 RCTs and 4 studies with observational design. In addition, we included 18 meta-analyses or pooled data analyses. None of the included studies could be considered an effectiveness trial with a high applicability to average primary-care populations. Details of study characteristics, quality ratings and main findings are described in the supplementary table (see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A19). Most studies (92%) were funded by Eli Lilly and Company, the makers of duloxetine.

In the following sections, we discuss the general efficacy and safety of duloxetine based on placebo-controlled evidence, and subsequently assess differences in the efficacy and safety of duloxetine compared with other second-generation antidepressants. Finally, we examine the efficacy and safety of duloxetine in specific subgroups.

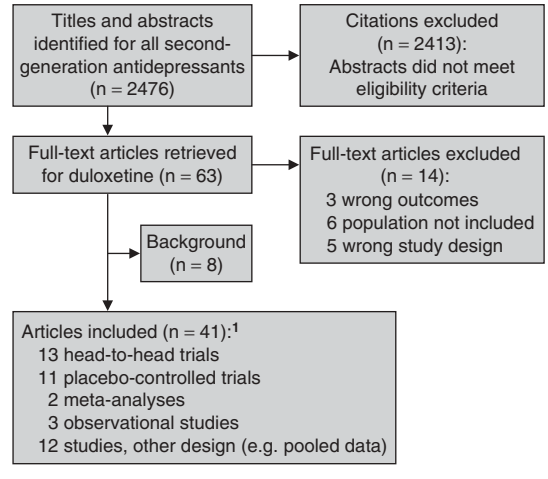

Fig. 1. Disposition of the literature search. **1** Numbers differ from those reported in the text because multiple articles were published on some studies.

General Efficacy of Duloxetine

The manufacturer of duloxetine submitted eight phase II and III RCTs[17-23] to the European Medicines Agency and the US FDA for regulatory approval of duloxetine for the treatment of MDD, representing 1099 patient-years of exposure.[24] Two of these studies have been published as pooled data only.[22] All studies enrolled adult outpatients with MDD and used fixed or flexible dosages between 40 mg/day and 120 mg/day over periods of 8–9 weeks.[25] Approximately two-thirds of patients were female. The FDA has recommended dosages up to 60 mg/day and notes that there is no evidence that doses >60 mg confer any additional benefit.[24]

In a meta-analysis of individual patient data (n = 1404) of studies with an active control arm, Thase et al.[25] examined the pooled remission rates (defined as an endpoint score of ≤7 on the 17-item Hamilton Depression Rating Scale [HAM-D17]) of duloxetine compared with placebo. Results presented significantly higher remission rates for duloxetine (40.3%) than for placebo (28.4%) across all dosages (odds ratio [OR] 1.70; 95% CI 1.34, 2.15). In a dose response analysis, the efficacy of duloxetine 40 mg/day was substantially smaller than that of higher dosages (60, 80 and 120 mg/day) and did not differ significantly from that of placebo (OR 1.25; 95% CI 0.78, 2.01). Treatment effects of duloxetine were largest in patients with severe depression.[26]

Two recent placebo- and active-controlled RCTs (three publications)[27-29] presented similar treatment effects as the meta-analysis by Thase et al.[25]

Risk for Harms of Duloxetine

The quality of reporting on the assessment of adverse events in duloxetine trials was suboptimal. In general, studies incorporated a mix of active and passive surveillance for adverse event assessment. Studies generally combined patient-reported adverse events with a clinical and laboratory examination. Some trials examined the occurrence of sexual dysfunction with targeted questionnaires.[19-21,28,30]

Determining whether assessment methods were unbiased and adequate was difficult. It remains unclear whether studies used objective scales such as the Utvalg Undersogelser Side Effect Scale (UKU-SERS)[31] or the adverse reaction terminology of the WHO. Short study durations and small sample sizes additionally limited the validity of adverse event assessment.

We have structured the following sections according to the FDA definitions of adverse events, distinguishing serious adverse events from other adverse drug reactions.[32]

Serious Adverse Events

The FDA defines 'serious adverse events' as any medical occurrences that result in death, are life threatening, require inpatient hospitalization, result in persistent or significant disability or incapacity, or are a congenital birth defect.[32] Serious adverse events that have been associated with second-generation antidepressants are suicidality, sexual dysfunction, seizures, serotonin syndrome, hyponatraemia and hepatotoxicity.[33] A long-term extension study of duloxetine estimated the rate of serious adverse events to be 1 event per 13 years of exposure.[34]

Suicidality

Like all second-generation antidepressants, duloxetine has an FDA 'black-box' warning about an increased risk of suicidality (i.e. self-harm, suicide attempts, completed suicides). The FDA derived the need for a warning from a class effect that became apparent in pooled analyses of data from all second-generation antidepressants[24] rather than data just from duloxetine trials. Sample sizes of duloxetine RCTs were generally too small to be able to detect statistically significant differences for the risk of suicidality between duloxetine and placebo. Even a pooled analysis of all duloxetine trials for MDD (n = 2996) did not detect a statistically significant difference although, numerically, the risk for all suicide attempts (fatal and non-fatal) was higher in those receiving duloxetine than those receiving placebo (8 vs 3 attempts; 0.016 vs 0.011 events per person-year of exposure).[35]

Sexual Dysfunction

Sexual dysfunction (i.e. lack of sexual desire, pleasure, arousal and orgasm) is a common

adverse event among patients taking second-generation antidepressants.[33] Estimates from large observational studies indicate that up to 60% of patients receiving second-generation antidepressants experience some form of drug-induced sexual dysfunction.[36] The assessment quality of sexual dysfunction in duloxetine trials was mixed. Some studies relied on spontaneous reporting by patients, while others employed targeted questionnaires, such as the Arizona Sexual Experience Scale (ASEX) or the Changes in Sexual Functioning Questionnaire (CSFQ) to determine the incidence of sexual dysfunction. The exact estimate of the duloxetine-attributable risk for sexual dysfunction is difficult to assess because sexual dysfunction is a common symptom of MDD. Approximately 60% of patients met the criteria for sexual dysfunction at baseline.[37] Among patients considered normal at baseline, 46% developed sexual dysfunction during the course of treatment with duloxetine; among patients considered dysfunctional at baseline, 35% achieved normal sexual functioning during acute-phase duloxetine treatment.[37]

Serotonin Syndrome

Duloxetine bears the risk of causing a potentially life-threatening increase of the neurotransmitter serotonin, a condition termed serotonin syndrome. Symptoms of serotonin syndrome include hallucinations, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting and diarrhoea. The risk for serotonin syndrome is particularly pronounced if duloxetine is combined with other serotonergic drugs such as monoamine oxidase inhibitors or triptans, a medication commonly used to treat migraines. In June 2006 the FDA issued an alert that all SNRIs, including duloxetine, have an increased risk for serotonin syndrome when combined with triptans.[38]

Other Serious Adverse Events

Based on data from trials, the magnitude of risks for other serious adverse events remains unclear. The FDA warns against hepatotoxicity, orthostatic hypotension and syncope, activation of mania and hypomania, seizures and hyponatraemia in the prescription information of duloxetine.[24] No large observational studies that would provide more reliable evidence on such rare but potentially life-threatening adverse events have been published.

General Tolerability

Nausea, dry mouth, constipation, insomnia, dizziness, fatigue, diarrhoea and somnolence were commonly reported adverse events during acute-phase treatment. During continuation-phase treatment, the most frequently reported adverse events were headache and viral infections.[37] Table II summarizes the frequencies of the most commonly reported adverse events, based on studies submitted to the FDA.[39]

Overall, up to 80% of patients in duloxetine trials experienced at least one adverse event during the course of the study. Most adverse events were mild and tolerable for patients (e.g. dry mouth, headache). Others, however, led to discontinuation of treatment. Based on pooled data of studies submitted to regulatory agencies, 9.7% of patients discontinued duloxetine treatment because of adverse effects (compared with 4.2% receiving placebo).[37] Nausea was the adverse event most commonly associated with the discontinuation of duloxetine treatment. Other common adverse events resulting in discontinuation were somnolence, dizziness, fatigue and insomnia.[37] During a long-term (mean duration 305 days), open-label,

Table II. Average frequencies of common adverse events of duloxetine compared with placebo[39]

Adverse event	Percentage of patients reporting the event	
	duloxetine (n = 1139)	placebo (n = 777)
Nausea	20	7
Dry mouth	15	6
Constipation	11	4
Insomnia	11	6
Dizziness	9	5
Diarrhoea	8	6
Appetite decreased	8	2
Somnolence	7	3
Sweating increased	6	2
Vomiting	5	3

extension phase of a clinical trial, approximately 12% of patients discontinued treatment because of adverse events.[40]

Gastrointestinal Adverse Events

Nausea was the most frequently reported adverse event during acute-phase duloxetine treatment in RCTs. Almost 20% of patients receiving duloxetine experienced nausea, mostly in the beginning of the course of treatment. The mean time to onset of nausea was 1 day and median duration was 7 days.[37] Constipation (11%) and diarrhoea (8%) were also two gastrointestinal adverse events that occurred statistically significantly more frequently with duloxetine than with placebo (4% and 5%, respectively; $p < 0.01$).[37]

Changes in Weight

A pooled analysis of efficacy trials reported that the mean change of bodyweight over a period of 8–9 weeks was –0.46 kg in patients receiving duloxetine, compared with +0.23 kg in those receiving placebo ($p < 0.001$).[37] During the 34-week extension phase, this trend reverted, resulting in a weight gain in patients treated with duloxetine (0.8 kg for duloxetine 80 mg, 1.0 kg for duloxetine 120 mg). An open-label, uncontrolled trial reported a mean weight gain of 2.4 kg for patients taking duloxetine for 52 weeks.[34]

Cardiovascular Adverse Events

In a meta-analysis of 42 placebo-controlled trials of duloxetine ($n = 8504$) for the treatment of various indications, no statistically significant differences in blood pressure, heart rate or ECG changes could be detected.[41] These results are consistent with findings from a pooled data analyses that focused on MDD trials only.[42]

Other Adverse Events

Event rates for other potentially relevant adverse effects such as urinary retention or bleeding disorders were too low to draw any firm conclusions about increased risks associated with duloxetine. Furthermore, we could not find any evidence on the risk of withdrawal syndrome, another potentially relevant adverse event of second-generation antidepressants.

Comparative Efficacy

Only a few head-to-head trials directly compared the efficacy and safety of duloxetine with other second-generation antidepressants. Comparisons are limited to duloxetine with escitalopram,[29,43,44] fluoxetine,[20] paroxetine[21,23,45] and venlafaxine.[46] To date, the largest attempt to determine the comparative efficacy of second-generation antidepressants has been a meta-analysis by Gartlehner et al.[16] who employed adjusted indirect comparisons based on placebo-controlled and head-to-head trials to achieve estimates of the comparative efficacy. Results indicate similar efficacy of duloxetine compared with other second-generation antidepressants. Figure 2 depicts comparisons of duloxetine response rates (more than 50% improvement on the HAM-D) with those of other second-generation antidepressants.

Given the lack of head-to-head evidence for most comparisons, this study provides the best available evidence on the efficacy of duloxetine compared with other second-generation antidepressants. Unfortunately, the indirect statistical methods necessary resulted in wide confidence intervals that encompass clinically significant differences for some of the comparisons. Reassuringly, pooled analyses of individual patient data of head-to-head studies (all funded by the manufacturer of duloxetine) reported consistent findings.[25,47,48] Pooled results showed similar remission rates of duloxetine compared with fluoxetine and paroxetine as a class (40.3% vs 38.3%; OR = 1.09; 95% CI 0.86, 1.38).[25] Statistically significant findings between duloxetine and SSRIs in certain HAM-D17 items, such as psychomotor retardation, hypochondriasis and others that have been highlighted in one of these studies,[48] must be interpreted cautiously because testing multiple items can lead to chance findings.

In the following sections we summarize findings of head-to head trials of duloxetine. In general, results are consistent with findings of the meta-analysis[16] reported above.

Duloxetine Compared with Escitalopram

Three fixed-dose studies with fair methodological quality compared duloxetine (60 mg/day) with

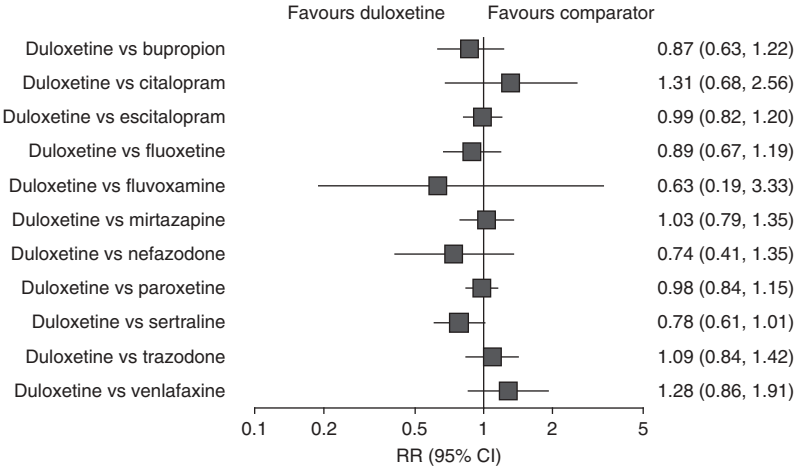

Fig. 2. Relative risk (RR) of response with duloxetine compared with other second-generation antidepressants.[9]

escitalopram (10–20 mg/day).[29,43,44] Overall, no substantial differences in efficacy could be detected. The study with the longest follow-up reported similar response (73% compared with 77%) and remission (70% compared with 73%) rates after 24 weeks between duloxetine and escitalopram, respectively.[29] In addition, no differences in efficacy could be detected on the Hamilton Rating Scale for Anxiety (HAM-A) and Clinical Global Impression-Improvement Scale (CGI-I) after 24 weeks.

Duloxetine Compared with Fluoxetine

Only one fair quality trial compared duloxetine with fluoxetine.[20] This 8-week RCT assigned 173 patients to duloxetine (40–120 mg/day), fluoxetine (20 mg/day) or placebo. Overall loss to follow-up was 35%. Results revealed no statistically significant differences between duloxetine and fluoxetine, respectively, in response (49% vs 45%) and remission (43% vs 30%) rates. However, the fixed-dose design for fluoxetine but not for duloxetine reduces the validity of this direct comparison.

Duloxetine Compared with Paroxetine

Two fair[23,45] and one poor[21] fixed-dose trials assessed the comparative efficacy of duloxetine (40–120 mg/day) and paroxetine (20 mg/day). All three trials were funded by the manufacturers of duloxetine. In all three trials, efficacy outcomes were similar among duloxetine and paroxetine regimens. In the largest study, 60% of patients receiving duloxetine achieved response and 49% achieved remission compared with 65% and 50%, respectively, of patients receiving paroxetine.[45] Important to note is that these trials compared a low to medium dose of paroxetine (20 mg) to high doses (80 and 120 mg) of duloxetine. Both duloxetine dosages exceed the FDA approved dosing range (i.e. 40–60 mg/day) Because of these dosing disparities, we did not attempt meta-analyses of these trials.

Duloxetine Compared with Venlafaxine

The only evidence available is a pooled analysis of two identical RCTs comparing duloxetine (60–120 mg/day) with venlafaxine extended release (XR; 150–225 mg/day) over a period of 12 weeks.[46] No differences in the majority of efficacy measures could be detected at study endpoint. Overall, 71% of patients receiving duloxetine achieved remission compared with 67% of patients receiving venlafaxine XR.

Comparative Harms

Evidence on the comparative harms is limited to the seven head-to-head trials described above.[20,21,23,29,43-45] Overall, adverse event profiles were similar among duloxetine and comparison drugs. Differences in frequencies of

specific adverse events must be viewed cautiously because chance findings can play a large role in small studies. A pattern that emerged in trials comparing duloxetine with escitalopram was that duloxetine consistently led to higher rates of nausea and dry mouth than escitalopram.

A pooled analysis of data assessing differences in nausea between duloxetine and fluoxetine or paroxetine did not find any substantial differences between medications.[49]

Sexual Dysfunction

The three RCTs comparing duloxetine with escitalopram presented similar risks for sexual dysfunction and other serious adverse events.[43,44,50] By contrast, a pooled analysis (n = 1566) of four RCTs comparing duloxetine with paroxetine (all funded by the manufacturer of duloxetine) reported significantly lower rates of treatment-emergent sexual dysfunction for patients treated with duloxetine (28.8% vs 46.6%; p = 0.007).[51]

Discontinuation Rates

Discontinuation rates due to adverse events can be viewed as a crude measure for tolerability.[52,53] For clinical trials, such discontinuation rates should be interpreted in the context of overall loss to follow up (i.e. the number of persons who were randomly assigned but did not reach the endpoint of the study) because the quality of adverse event assessment differs greatly among studies. Meta-analyses of data from efficacy trials were conducted to assess differences in the overall rates of discontinuation, discontinuation rates due to adverse events and discontinuation rates because of lack of efficacy of duloxetine compared with some SSRIs (escitalopram, fluoxetine and paroxetine) as a class. In our pooled estimates, the only statistically significant difference was a higher discontinuation rate because of adverse events for patients taking duloxetine than for patients taking SSRIs (8.1% vs 5.3%; RR 1.58; 95% CI 1.15, 2.17 [figure 3a]). The corresponding number-needed-to-harm is 29 (95% CI 16, 139). In other words, for every 29 patients treated with duloxetine rather than with other SSRIs for acute-phase MDD, one additional patient will discontinue treatment because of adverse events. Overall discontinuation rates (26.2% vs 22.2%; RR 1.20; 95% CI 0.98, 1.47 [figure 3b]) and discontinuation rates due to lack of efficacy (3.2% vs 2.4%; RR 0.88; 95% CI 0.46, 1.67 [figure 3c]) were similar between duloxetine and SSRIs.

General and Comparative Efficacy and Harms in Subgroups

Overall, the available evidence on the efficacy and safety of duloxetine in subgroups was sparse and fraught with methodological limitations. Most studies were underpowered to detect differences in outcomes, particularly with respect to co-morbid conditions and demographic subgroups.

Patients with Accompanying Symptoms

MDD is frequently associated with accompanying symptoms such as anxiety, insomnia, melancholia, pain or psychomotor changes. For most of these concurrent symptoms, we found no evidence relating to duloxetine. However, an exception was pain as a concurrent symptom of depression. In a well conducted, publicly-funded meta-analysis, Krebs et al.[54] compared the efficacy of duloxetine and paroxetine on pain as an accompanying symptom in patients with depression. Pooled results on the visual analogue scale suggested no evidence of differential efficacy between duloxetine and paroxetine in the treatment of pain accompanying depression (weighted mean difference [WMD] −0.8 mm; 95% CI −3.8, 2.3). For both drugs, pooled pain score outcomes were superior to placebo (WMD for duloxetine vs placebo 5.2 mm; 95% CI 2.7, 7.7; WMD for paroxetine vs placebo 5.8 mm; 95% CI 2.2, 9.4). However, because of the small magnitude, the clinical significance of this finding remains unclear.

Two recent RCTs not included in the meta-analysis described above, reported similar treatment effects of duloxetine compared with placebo for alleviating pain associated with depression.[55,56]

Subgroups Based on Age

The only study directly comparing differences in efficacy due to age was a pooled analysis of two

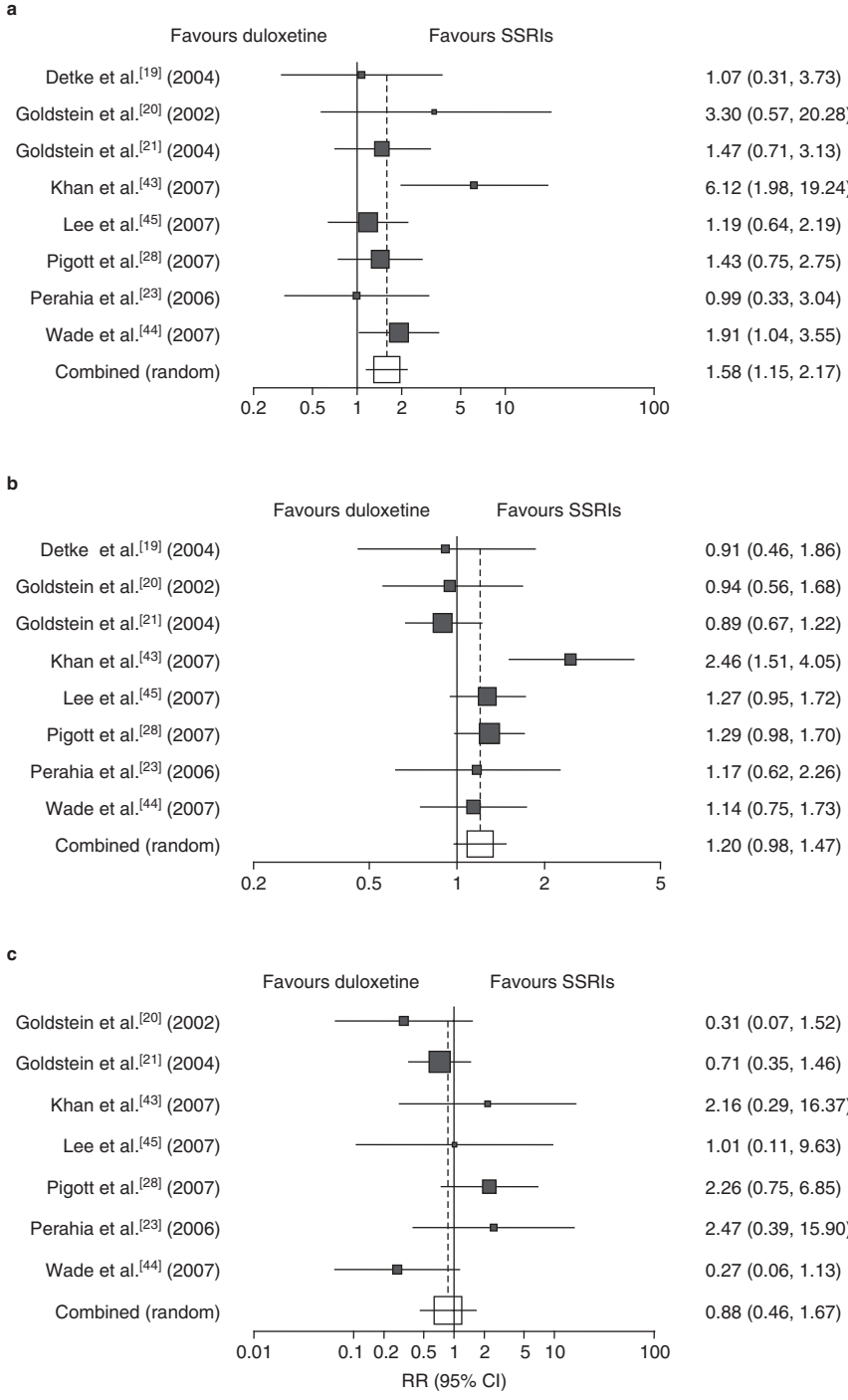

Fig. 3. Relative risk (RR) of discontinuation of duloxetine vs selective serotonin reuptake inhibitors [SSRIs] (**a**) due to adverse events; (**b**) RR of overall discontinuation; and (**c**) due to lack of efficacy.

RCTs.[57] This study indicated similar efficacy of duloxetine in women aged 40–55 years compared with those younger than 40 years or older than 55 years.

A good quality RCT, however, provides indirect evidence that differences in efficacy might exist between younger and older patients.[56,58,59] This study assessed the efficacy and safety of duloxetine (40–120 mg/day) in elderly patients with MDD (median age 72 years). Overall, duloxetine was statistically significantly more efficacious than placebo. Remission rates were 27.4% for patients receiving duloxetine compared with 14.7% for patients receiving placebo. The magnitude of this treatment effect, however, was substantially smaller than results reported for younger patients in other studies. For example, in a pooled analysis of efficacy trials, 40.3% of patients receiving duloxetine achieved remission.[25] Interestingly, even remission rates under placebo treatment were substantially higher in this younger population (28.4%).

Discontinuation rates because of adverse events in elderly patients were identical to those in efficacy trials with younger populations (9.7%).[37] However, this finding was not consistent with results from two other studies, which indicated substantially higher discontinuation rates due to adverse events in elderly populations.[60,61] A subgroup analysis of an open-label, 52-week duloxetine trial on patients older than 65 years reported that 26.7% of patients discontinued treatment because of adverse events.[61] Similarly, pooled data of six RCTs on patients older than 55 years showed that 21% discontinued treatment because of adverse events.[60]

Subgroups Based on Co-Morbid Conditions

An analysis of data of the duloxetine RCT conducted in elderly patients[56] examined the impact of co-morbidity on efficacy and tolerability outcomes.[62] In this study, 75% of patients had at least one co-morbidity, mostly arthritis, vascular disease and diabetes. Overall, results indicated no significant treatment by co-morbidity interactions for response, remission, quality of life or tolerability.[62]

Subgroups Based on Ethnicity

Two pooled analyses of seven placebo-controlled duloxetine trials assessed the efficacy and tolerability of duloxetine in Hispanic[63] and African American patients[64] compared with Caucasian patients. The first analysis included 1342 Caucasian and 120 Hispanic patients and found no difference in efficacy outcomes between Hispanics and Caucasians.[63] There were no significant differences between groups in discontinuation rates due to adverse events or in the types or occurrence of specific adverse events. The second analysis of 1300 Caucasians and 123 African Americans also found no evidence for a differential effect of duloxetine in African American and Caucasian patients in efficacy or safety outcomes.[64]

Subgroups Based on Sex

A pooled data analysis of four placebo-controlled duloxetine trials assessed safety and tolerability of duloxetine for the treatment of MDD in 560 men and 1062 women.[65] This analysis revealed no clinically meaningful differential sex effects for efficacy or safety. Withdrawals due to adverse events were similar between men and women.

Discussion

In this systematic review of data from 36 studies, qualitative and quantitative analyses confirmed the general efficacy and safety of duloxetine for the treatment of MDD. Existing evidence indicates that no substantial differences in efficacy between duloxetine and other second-generation antidepressants appear to exist. Although the evidence does not conclusively establish equivalence, results suggesting similar efficacy between duloxetine and SSRIs were generally consistent across studies. Furthermore, adverse event profiles between duloxetine and compared drugs were also similar, although some differences in the frequencies of specific adverse events exist.

Recently, a meta-analysis employing indirect comparisons was published, indicating better

efficacy-harm profiles of sertraline and escitalopram over other second-generation antidepressants.[66] This study has led to a substantial debate about the validity of rankings of antidepressants. It employed a statistical technique called mixed treatment comparisons, which is a legitimate approach given the lack of head-to-head data. However, results have to be interpreted very cautiously because they are based on multiple assumptions and fraught with uncertainties.[67] Therefore, this study will most likely not change current treatment recommendations.

Although the dual uptake inhibition of duloxetine has been hypothesized to confer analgesic effects,[68] the existing evidence does not indicate any clinically meaningful differences compared with paroxetine in depressed patients with accompanying pain. No evidence of differential efficacy between duloxetine and paroxetine were apparent in the treatment of pain accompanying depression. Moreover, differences in pain reduction of duloxetine compared with placebo were small in magnitude and unclear in clinical significance. Data are insufficient or unavailable to form any conclusions about comparisons with other SSRIs.

Across all efficacy trials, about 60% of patients treated with duloxetine for acute-phase depression did not achieve remission, the primary goal of depression treatment. Interestingly, indirect evidence indicates that the efficacy of duloxetine in older patients is lower than in younger patients and that discontinuation rates due to adverse events are substantially higher in older than in younger patients. Currently, evidence is insufficient to identify patient factors that determine response or non-response to an individual drug. Overall, our findings indicate that more than one-half of patients treated with duloxetine for acute-phase depression will require a second-line treatment, which is generally a similar proportion as for other second-generation antidepressants.[16]

Our study has two main limitations. First, all of the studies were efficacy trials conducted in highly selected populations. The applicability of their results to the average patient with acute MDD might be limited. The amount of evidence available was particularly minimal for subgroups such as patients with co-morbidities, who represent a large group of patients in real-world practice.

Second, publication bias is an issue for all systematic reviews. Selective availability of studies with positive results can seriously bias conclusions of systematic reviews, particularly when the focus is on placebo-controlled trials that are generally conducted for regulatory approval by the manufacturer of a specific drug.[69] More than 90% of the studies included in this study have been funded by Eli Lilly and Company, the manufacturers of duloxetine.

How do our findings – that duloxetine has similar efficacy and safety to other second-generation antidepressants – inform practicing clinicians? Given the low remission rates of all antidepressive treatments and the difficulty in predicting what medication will be both efficacious and well tolerated, duloxetine is another option in the group of antidepressive medications. However, current evidence does not warrant the choice of duloxetine over any other second-generation antidepressant for patients with acute-phase MDD.

Conclusions

Duloxetine is yet another treatment option for patients with acute-phase MDD. The existing evidence indicates that the comparative efficacy and safety of duloxetine is similar to other second-generation antidepressants. Furthermore, the current evidence does not support the choice of duloxetine over other second-generation antidepressants for the treatment of depressed patients with accompanying symptoms such as pain.

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