MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
Medwave 2017 Sep-Oct; 17(8):e7064 doi: 10.5867/medwave.2017.08.7063

Is duloxetine an alternative in osteoarthritis treatment?

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Citation: Ananías J, Irarrázaval S. Is duloxetine an alternative in the treatment of osteoarthritis?. *Medwave* 2017 Sep-Oct; 17(8):e7063 doi: 10.5867/medwave.2017.08.7063
Submission date: 5/9/2017
Acceptance date: 11/10/2017
Publication date: 18/10/2017

Abstract

INTRODUCTION: Many osteoarthritis patients continue to present symptoms despite nonsurgical treatment. Duloxetine might be a viable alternative for such cases, but real clinical relevance remains unclear. METHODS: A literature review was conducted in Epistemonikos, the largest database for systematic reviews in health that compiles multiple sources, including MEDLINE, EMBASE, and Cochrane, among others. Relevant data were extracted, and information from the primary studies was reanalyzed. A subsequent meta-analysis was conducted, and summary of findings tables were constructed using the GRADE methodology. RESULTS AND CONCLUSIONS: Four systematic reviews including four randomized trials, were identified. In conclusion, while duloxetine slightly improves pain and functionality in osteoarthritis patients, its use is associated with frequent adverse side effects. Therefore, the benefit/risk balance appears unfavorable.

Problem

Osteoarthritis is a highly prevalent disease worldwide and a frequent cause for visits to both primary care and specialists. The persistence of pain despite nonsurgical treatment is one reason for such consults, and no clearly established alternatives exist for pain management.

Duloxetine has been used to treat various conditions with chronic pain, since it exerts central inhibitory effects, so it might be a therapeutic alternative for osteoarthritis with persistent pain after regular treatment. However, duloxetine is associated with adverse side effects, including fatigue, drowsiness, constipation, and high blood pressure.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Duloxetine leads to a slight decrease in pain and improvement in functionality in osteoarthritis, but is associated with frequent side effects.
- The benefit/risk ratio is probable not favorable.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews [1],[2],[3],[4]including four primary studies, reported in six references [5],[6],[7],[8],[9], [10]. All correspond to randomized controlled trials.
What types of patients were included*	Three trials focused on osteoarthritis of the knee [5],[6],[8] and one did not specify it [7]. Average WOMAC (The Western Ontario and McMaster Universities Osteoarthritis Index) ranged between 50 and 57 in three trials [5],[6],[8] and one did not report it [7]. Average age of the participants ranged between 61 and 69 years in the different trials. The proportion of women was between 16 and 77% in the different trials.
What types of interventions were included*	All of the trials used duloxetine in oral presentation. One trial used 60 mg/day as starting dose, which was increased to 120 mg/day at the seventh week in patients that reported a reduction in pain less than 30% [5]. One trial used 60 mg [6]. One trial used a flexible dosage between 60 and 120 mg per day, keeping a baseline treatment with NSAIDs at therapeutical dose [7]. One trial had two active arms, with 60 mg and 120 mg per day [8].** All trials allowed the use of concomitant analgesia. All trials compared against placebo.
What types of outcomes were measured	The outcomes, as classified in the identified systematic reviews, were as follows: effect on the intensity of pain (analyzed as a decrease or improvement); overall impression of the patient-reported improvement; sub-scale of physical functionality established by the Western Ontario and McMaster Universities Arthritis Index (WOMAC); and adverse side effects.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.
** This information was directly obtained from the primary studies.

Summary of Findings

The information on the effects of duloxetine was based on three randomized trials that included 1011 patients [5],[7],[8]. The remaining trials were not included in the meta-analysis as none of the identified systematic reviews extracted sufficient trial data. The three evaluated trials reported improvements in pain and functionality, and adverse side effects. The summary of findings is as follows:

- Duloxetine slightly decreases pain. The certainty of the evidence is high.
- Duloxetine slightly improves functionality in osteoarthritis. The certainty of the evidence is high.
- Duloxetine is associated with frequent side effects. The certainty of the evidence is high.

Duloxetine for osteoarthritis				
Patients	Individuals with osteoarthritis			
Intervention	Duloxetine			
Comparison	Placebo			
Outcomes	Absolute Effect***		Relative Effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT Duloxetine	WITH Duloxetine		
	Difference: patients in 1000			
Pain * (0 to 10 points)	3 points ****	2.12 points	--	⊕⊕⊕⊕ High
	MD: 0.88 less (Margin of Error: 0.65 to 1.11 less)			
Functionality ** (0 to 100 points)	18 points****	13.75 points	--	⊕⊕⊕⊕ High
	MD: 4.25 less (Margin of error: 5.82 to 2.68 less)			
Adverse side effects	73 per 1000	155 per 1000	RR 2.13 (1.43 to 3.17)	⊕⊕⊕⊕ High
	Difference: 82 patients more (Margin of error: 31 to 158 more)			

Margin of Error = 95% Confidence Interval.
RR: Relative Risk.
MD: Mean difference
GRADE: Grading of Evidence according to the GRADE *Working Group*.

*Pain: Evaluated on a numerical Likert-based scale ranging from 0 to 10 points (0 = no pain, 10 = worst pain imaginable).
**WOMAC Questionnaire: Consisted of 24 questions in which patients evaluated how much pain, stiffness, or difficulty they had when performing each of the tasks presented in the questionnaire. The possible responses were: none, little, some, a lot, and impossible to perform. These responses were respectively scored 0, 1, 2, 3, and 4 points. The range of final scores was from 0 to 96 points, with higher scores indicating worse functionality.

***The risks WITHOUT Duloxetine were based on risks of the control groups in the studies. The risk WITH Duloxetine (and the respective margin of error) was calculated from the relative effect (and respective margin of error). The adverse side effects included nausea, fatigue, constipation, hyperhidrosis, dizziness, diarrhea, insomnia, and dry mouth.
****The average of the study with the greatest weight in the meta-analysis was used [7].

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯

Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- While the intention of this summary was to include osteoarthritis in general, considering all of the possible affected joints, the trials that were found focused specifically on osteoarthritis of the knee. However, in the absence of direct evidence for other joints, it appears reasonable to extrapolate the conclusions of this summary.

About the outcomes included in this summary

- The outcomes included in this summary are those we consider critical for making adequate clinical decisions. Furthermore, we conducted a search of the Core Outcome Measures in Effectiveness Trials (COMET) Initiative, finding one relevant article [11] that indicated, through a consensus, the following as the most relevant outcomes: joint pain, functionality, quality of life in relation to health, work situation, mortality, reoperation, hospital readmission, and overall satisfaction with the results of the treatment.

Balance between benefits and risks, and certainty of the evidence

- While the observed benefits on pain and functionality were statistically significant, the magnitude of the effect was below the minimally important difference reported in the literature [12].
- Considering there are substantial side effects, the balance between benefits and harms is probably unfavorable.

Resource considerations

- Although duloxetine is widely available in most countries, the cost is usually high. Taking into account the reported small or irrelevant benefits, the increase in side effects, and the cost, the balance between cost and benefit is clearly unfavorable.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary, most patients and attending clinicians should lean against the use of this intervention.
- However, without clearly effective therapeutic alternatives, variations could exist in the clinical decisions made by individual patients.
- Recommendations against the use of this intervention in the main clinical guidelines should minimize variability in the decisions made by physicians.

Differences between this summary and other sources

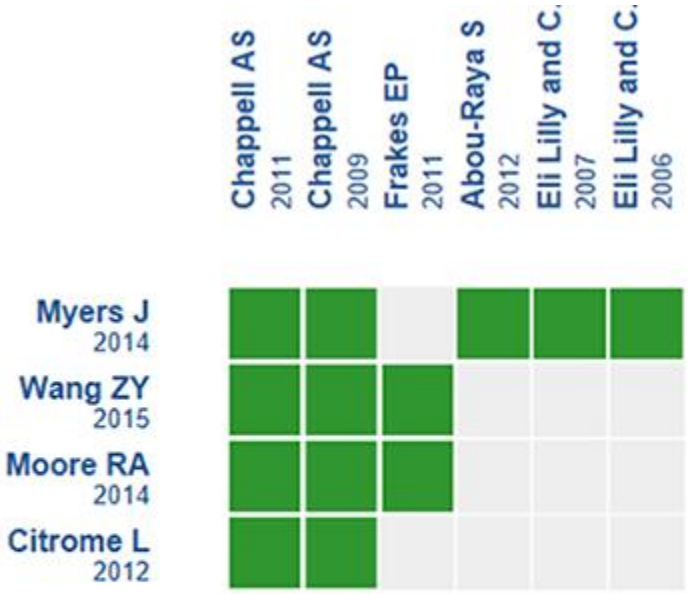
- The reviews included in this summary differ among one another. One review [1]concluded there are no differences between duloxetine and other second-line oral treatments. Two reviews [2],[3] reported duloxetine would be better than placebo at reducing pain and improving functionality, with the adverse side effects considered acceptable for treating osteoarthritis pain. Finally, another review [4] determined the effect of duloxetine in pain management is conservative and that the generated effect is likely influenced by the clinical-practice experience of the professional recommending treatment (the authors base this conclusion on the abnormal effect distribution, i.e., few patients had an average response and the average was not an appropriate descriptor).
- The conclusions of this summary partially disagree with the main international guidelines for osteoarthritis: the Osteoarthritis Research Society International (OARSI) [13] indicates duloxetine would be useful as treatment for osteoarthritis of the knee in patients without comorbidities and in patients presenting osteoarthritis in multiple joints. The American Academy of Orthopaedic Surgeons (AAOS) [14] does not mention the use of duloxetine for osteoarthritis.

Could this evidence change in the future?

- The probability is low that the conclusions of this summary change with future trials, due to the high certainty of the existing evidence.
- At least one published trial exists that was not included in the identified systematic reviews [15]. Future reviews incorporating this trial could provide new information.
- We did not identify any ongoing trial in the International Clinical Trials Registry Platform of the World Health Organization.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Duloxetine for osteoarthritis

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

Potential conflicts of interest
The authors do not have relevant interests to declare.

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