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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is diacerein an alternative for the treatment of osteoarthritis?

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Abstract

INTRODUCTION: Among the possibilities for the management of osteoarthritis, different pharmacological alternatives have been proposed, being diacerein one of them due to its anti-inflammatory effect. However, diacerein clinical utility is not clear. METHODS: To answer this 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. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. RESULTS AND CONCLUSION: We concluded diacerein may lead to a slight reduction in pain and probably not improve functionality among patients with knee osteoarthritis and can frequently present diarrhea as an adverse effect

Problem

Osteoarthritis is a chronic joint disease of high prevalence, especially in older adults. Pain is one of the main symptoms and the major determinant of loss of function. Many patients remain symptomatic despite standard treatment. One of the therapeutic options that has been proposed is the use of diacerein, an anti-inflammatory with inhibitory activity on interleukin-1 beta. Diacerein would reduce IL-1 receptors levels, which would be involved in the destruction of articular cartilage through the inhibition of matrix protein synthesis and increased secretion of proteases in vitro. However, this drug is also associated with adverse effects, mainly diarrhea, so it is not clear if it is effective and if benefits are greater than risks.

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
- Diacerein may lead to a slight reduction in pain and it probably improve function in patients with osteoarthritis.
- Diacerein frequently produces diarrhea.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found five systematic reviews [1],[2],[3],[4],[5] which include nine primary studies [6],[7],[8],[9],[10],[11],[12],[13],[14] which answer the question of interest. All studies correspond to randomized controlled trials.
What types of patients were included*	Six trials included patients with osteoarthritis of the knee, [6],[10],[11],[12],[13],[14], two with hip osteoarthritis [7], [9] and one of the trials included hip or knee osteoarthritis [8]. The mean age range of patients included in the trials was 47 to 64 years. The average age of women included in the trials ranged from 55% to 83%.
What types of interventions were included*	All trials administered oral diacerein, seven of them 50 mg twice daily [6],[7],[8],[9],[10],[11],[12] and in two trials this data could not be obtained (the researchers did not specify the data [13],[14]). All trials compared diacerein against placebo.
What types of outcomes were measured	The systematic reviews grouped outcomes as follows: Pain, measured according to analogue visual scale of 0 to 100 mm Functionality, using the Lequesne questionnaire from 0 to 14 points Several adverse effects, in which onset of diarrhea is emphasized. None of the reviews mentioned the effect on severe diarrhea or liver tests abnormalities.

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

Summary of findings

The information on the effects of diacerein on osteoarthritis is based on nine randomized trials. Six trials measured the outcome pain [6],[7],[8],[9],[11],[12], four trials measured the outcome functionality [7],[8],[9],[12] and seven trials measured the occurrence of diarrhea [6],[7],[8],[9], [10],[11],[12]. The summary of findings is as follows:

- Diacerein may produce a slight decrease in pain in patients with osteoarthritis, but the certainty of the evidence is low.
- Diacerein probably not produce improvement in function in patients with osteoarthritis. The certainty of the evidence is moderate.
- Diacerein frequently produces diarrhea. The certainty of the evidence is high.

Diacerein for osteoarthritis				
Patients	Osteoarthritis			
Intervention	Diacerein			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT diacerein	**WITH diacerein**		
	Difference: patients per 1000			
Pain (visual analogue scale 0-100 mm)	52 mm	43.36 mm	--	⊕⊕◯◯[1,2] Low
	MD: 8.64 mm less (margin of error: 1.67 to 15.61 mm less)			
Functionality (Lequesne Index**)	9 points	8.71 points	--	⊕⊕⊕◯[1,2] Moderate
	MD: 0.29 points less (margin of error: 0.87 less to 0.28 more)			
Adverse effects: diarrhea	102 per 1000	358 per 1000	RR 3.51 (2.43 to 5.08)	⊕⊕⊕⊕[2] High
	Difference: 256 patients more per 1000 (Margin of error: from 146 to 416 more)			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITHOUT diacerein** is based on the risk in the control group of the trials. The risk **WITH diacerein** (and its margin of error) is calculated from relative effect (and its margin of error).

** Lequesne index: Goes from 0 to 14, being 14 extremely severe handicaps.

[1] The certainty of the evidence was downgraded for imprecision, since the confidence interval includes a non-clinically relevant effect.
[2] The certainty of the evidence was downgraded for inconsistency for the outcome pain. For functionality, it was not downgrade even though there is some inconsistency, since this factor would reinforce the conclusion.

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

- Although the aim of this summary was to evaluate all possible joints with osteoarthritis and its response to oral diacerein, most of trials focus on osteoarthritis of the knee and/or hip. Nevertheless, it is reasonable to extrapolate the conclusions to other joints.

About the outcomes included in this summary

- The chosen outcomes correspond to those critical for decision-making according to the opinion of the authors of this summary, which in general agree with those presented in the systematic reviews identified.

Balance between benefits and risks, and certainty of the evidence

- It would be an intervention that could have a small benefit, with low-moderate certainty of the evidence, and with frequent adverse effects. So, the risk/benefit balance is not in favor of its use.
- According to the results of this summary, there could be a benefit, but there is a substantial risk of adverse effects.
- It is important to note that the European Medicines Agency issued a statement recommending the suspension of the marketing of pharmaceutical products containing diacerein considering severe cases of diarrhea and hepatic impairment.

Resource considerations

- Because it is an intervention whose risk/benefit is not favorable, it is not appropriate to evaluate the balance between cost and benefit.
- Diacerein has a higher cost compared to the more commonly used treatment for osteoarthritis of the knee (e.g. acetaminophen and nonsteroidal anti-inflammatory drugs).

What would patients and their doctors think about this intervention

- Because diacerein is an intervention that could have a small benefit, but at the expense of frequent adverse effects, most patients and physicians are likely to avoid its use. This is reinforced by the fact that there are other alternative therapies, as well as the EMA's position on this product.

Differences between this summary and other sources

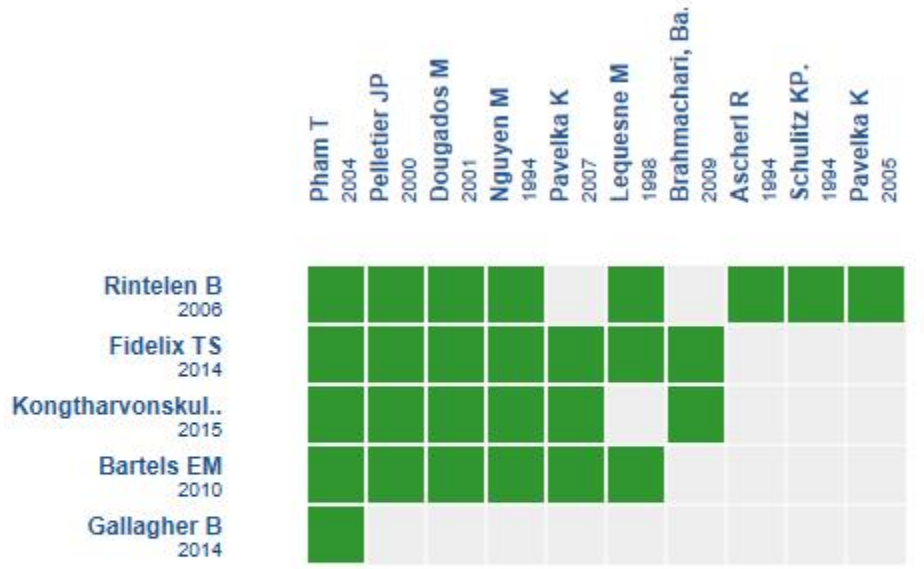
- The conclusions of this summary are consistent with the systematic reviews identified. The Cochrane review identified [3] concludes there is minimal benefit in reducing pain with the use of diacerein.
- There is agreement between this summary and the main guidelines. The Osteoarthritis Research Society International guideline [15] points out the improvement of pain is mild and the occurrence of diarrhea increases, so it does not recommend it. The American Academy of Orthopedic Surgeons guideline [16] does not recommend its use in patients with symptomatic knee osteoarthritis, which could be extrapolated to other joints.

Could this evidence change in the future?

- The likelihood that future research would change the conclusions of this summary is high because of the uncertainty of the evidence.
- There are at least two ongoing randomized trials evaluating the use of diacerein in osteoarthritis [17],[18] according to the International Clinical Trials Registry Platform of the World Health Organization, which could provide relevant information.

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:** Diacerein versus placebo or no treatment 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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