The Efficacy of Duloxetine, Non-steroidal Anti-inflammatory Drugs, and Opioids in Osteoarthritis: A Meta-analysis

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ABSTRACT

OBJECTIVES: There is a lack of comparative evidence evaluating the efficacy of oral osteoarthritis treatments beyond the duration of short-term trials. This meta-analysis was conducted to assess the efficacy of duloxetine vs. other oral treatments recommended after the use of acetaminophen for osteoarthritis, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.

METHODS: Search strategy: A systematic literature review was performed in PUBMED, EMBASE, MEDLINE In Process, Cochrane Library, and ClinicalTrials.gov through the end of August 2010. Randomized controlled trials (RCTs) of duloxetine and all NSAIDs and opioids that used the duration of treatment was twelve weeks or longer, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score was available, and they were published in English. Data extraction and analysis: The WOMAC baseline and change from baseline total scores were collected and standardized. Twelve additional study characteristics were collected and study quality was assessed. Frequentist and Bayesian meta-analysis were performed using the DerSimonian-Laird and Bucher methods. Bayesian analyses with and without study-level covariates were performed using noninformative priors.

RESULTS: A search of the literature identified 24 studies which met inclusion criteria. Our analysis found no statistically significant difference between the efficacy of duloxetine and the other treatments.

CONCLUSIONS: This analysis suggests that the efficacy of duloxetine in osteoarthritis, as measured by the WOMAC total score at 12 weeks or longer, is similar to competitor drugs.

BACKGROUND

Osteoarthritis treatment guidelines have recommended acetaminophen for first-line use, with NSAIDs and opioids as second and third line of treatment. However, recent publications have expressed concern about the long-term safety and efficacy of NSAIDs and opioids. Some studies have gone further and recommended against their long-term use. Recently published meta-analyses suggest that currently available oral treatments have only limited efficacy in the treatment of patients with osteoarthritis. Earlier meta-analyses have primarily focused on pain and have not assessed broader functioning. They have predominantly investigated single substance classes, included both short and long-term trials, and sometimes encompassed both OA and other chronic pain indications.

We conducted a meta-analysis to assess the efficacy of duloxetine versus other commonly used post-first-line OA treatments, including NSAIDs and opioids.

METHODS

The literature search was conducted to identify all published RCTs for osteoarthritis evaluating symptomatic efficacy of NSAIDs, duloxetine, and opioids. The literature search was performed in PUBMED, EMBASE, MEDLINE In Process, & Other Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov. RCTs and pooled studies included were of OA treatment with duloxetine, or with NSAIDs or opioids. All included arms were of at least twelve weeks duration and published in English. Articles were analyzed if they evaluated clinical efficacy using WOMAC total scores.

For the frequentist meta-analysis random effects models using the DerSimonian-Laird method were employed to estimate the overall mean of the population of all possible studies. Estimated treatment effects compared to placebo and compared to duloxetine were calculated with their 95% confidence intervals using the Fisher method of indirect comparison. Random effects Bayesian network meta-analyses were performed using the burn-in and normal distributions with very large variances for all other parameters including treatment effect and covariate effect.

Figure 1. Forest Plot by Baseline WOMAC Showing Difference in Change from Baseline.

Of the initial 72 articles identified, 44 were selected for data extraction. Twenty-four studies with 30 active treatment arms contained sufficient information to be included in the meta-analysis. The duration of nearly all studies was 12 to 24 weeks although nearly all arms were included.

In the frequentist analysis all active treatments were found to statistically improve the WOMAC total score compared to placebo. In the indirect comparison vs. duloxetine using the other method all 95% confidence intervals encompassed zero, indicating that the differences between duloxetine and other treatment were not statistically significant.

Results from the Bayesian analysis were similar to the frequentist methods, as all 95% credible intervals of the difference between duloxetine and any active treatment include zero. In addition, the probability of duloxetine being superior to a treatment ranged from 25% with ibuprofen to 78% with tramadol.

Visually, an association was indicated between baseline and change from baseline scores, with a higher baseline score associated with a larger negative (improved) change from baseline (Figure 1). An association between the baseline and change from baseline scores was confirmed with an R² of 0.615, indicating much of the observed improvement in symptoms was associated with a higher baseline level of symptoms, thus it was important to correct for this bias. Bayesian meta-regression models including study-level covariates were used to evaluate the extent to which covariates accounted for heterogeneity of treatment effects. The model including the baseline score also yielded a substantially smaller SD. Therefore the model including the baseline score was preferred. In figure 1 there is one tramadol trial that seems to be an outlier.

Table 1. Indirect comparison

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of studies</th>
<th>Change from baseline</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>12</td>
<td>0.60</td>
<td>-0.07</td>
<td>[-0.64, 0.50]</td>
<td>0.40</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>12</td>
<td>0.60</td>
<td>0.07</td>
<td>[0.00, 0.14]</td>
<td>0.007</td>
</tr>
<tr>
<td>Naproxen</td>
<td>12</td>
<td>0.60</td>
<td>0.07</td>
<td>[0.00, 0.14]</td>
<td>0.007</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>12</td>
<td>0.60</td>
<td>0.07</td>
<td>[0.00, 0.14]</td>
<td>0.007</td>
</tr>
<tr>
<td>Tramadol</td>
<td>12</td>
<td>0.60</td>
<td>0.07</td>
<td>[0.00, 0.14]</td>
<td>0.007</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>12</td>
<td>0.60</td>
<td>0.07</td>
<td>[0.00, 0.14]</td>
<td>0.007</td>
</tr>
</tbody>
</table>

REFERENCES

1. Zhang W, Zhang W, Tubach Nüesch E. Indirect vs. Duloxetine: Change from baseline vs. placebo, mean

2. 95% CI

3. Bayesian methods assumed the same covariate effect for all active treatment arms. A uniform distribution for covariate effects across all active arms was assumed.

4. Of study WOMAC scores. When forest plots suggested a possible relationship both the meta analysis and forest plots included were of OA treatment with duloxetine, or with NSAIDs or opioids. All included arms were of at least twelve weeks duration and published in English. Articles were analyzed if they evaluated clinical efficacy using WOMAC total scores.

5. For the frequentist meta-analysis random effects models using the DerSimonian-Laird method were employed to estimate the overall mean of the population of all possible studies.

6. Estimated treatment effects compared to placebo and compared to duloxetine were calculated with their 95% confidence intervals using the Fisher method of indirect comparison. Random effects Bayesian network meta-analyses were performed using the burn-in and normal distributions with very large variances for all other parameters including treatment effect and covariate effect.

7. Heterogeneity was assessed by visually inspecting 12 forest plots for the magnitude and variance of study WOMAC scores. When forest plots suggested a possible relationship both frequentist and Bayesian meta-regression were conducted to account for heterogeneity of treatment effect.

8. Bayesian methods assumed the same covariate effect for all active treatments. A uniform distribution was used for covariate variances and normal distributions with very large variance for all other parameters including treatment effect and covariate effect.

9. A large proportion of results indicates that the compared treatment in women (better) than duloxetine.

10. In the Random effects model, there were no significant differences in the meta-analysis. The duration of nearly all studies was 12 to 24 weeks although nearly all arms were included.

11. In the frequentist analysis all active treatments were found to statistically improve the WOMAC total score compared to placebo.

12. In the indirect comparison vs. duloxetine using the other method all 95% confidence intervals encompassed zero, indicating that the differences between duloxetine and other treatment were not statistically significant.

13. Results from the Bayesian analysis were similar to the frequentist methods, as all 95% credible intervals of the difference between duloxetine and any active treatment include zero. In addition, the probability of duloxetine being superior to a treatment ranged from 25% with ibuprofen to 78% with tramadol.

14. Visually, an association was indicated between baseline and change from baseline scores, with a higher baseline score associated with a larger negative (improved) change from baseline. An association between the baseline and change from baseline scores was confirmed with an R² of 0.615, indicating much of the observed improvement in symptoms was associated with a higher baseline level of symptoms, thus it was important to correct for this bias.

15. Bayesian meta-regression models including study-level covariates were used to evaluate the extent to which covariates accounted for heterogeneity of treatment effects. The model including the baseline score also yielded a substantially smaller SD. Therefore the model including the baseline score was preferred. In figure 1 there is one tramadol trial that seems to be an outlier.