

Quilici S, Chancellor J et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. BMC Neurology 2009;9:6.

Design: Indirect meta-analysis

PICOS:

- **Patients:** Diabetic neuropathy or diabetic peripheral neuropathic pain
- **Interventions:** Duloxetine (DLX) at doses of 60 mg qd or 60 mg bid
- **Comparison** intervention: Pregabalin (PGB) and gabapentin (GBP)
- **Outcomes:** 24-hour average pain severity, treatment response (defined as proportion of patients with a 50% reduction in pain), and patient global impression of improvement/change (PGI-I/C) on a 7 point scale from “very much improved” to “very much worse”
- **Studies:** Randomized, placebo-controlled, double-blind trials with a duration of 5-13 weeks or longer

Study search and selection:

- MEDLINE, EMBASE, and CENTRAL databases were searched without year or language limitations during January 2005
- Internal study reports of DLX were provided by Eli Lilly
- FDA and European Medicines Agency websites were searched for available reviews of PGB and GBP
- Studies could be parallel group or crossover trials, but crossover trials had to demonstrate sufficient washout period, stable disease, and randomization of the order of treatment
- All studies were required to show power calculations for their sample size

Results:

- For purposes of combining studies, pain severity scores were treated as continuous variables, with the mean change in severity from baseline to the end of the study used as the common effect estimate
- For discrete variables (treatment response and PGI-I/C) the treatment effect was estimated as the natural logarithm of the odds ratio
- Both fixed-effect and random-effects models were performed to test for and quantify study heterogeneity; the heterogeneity tests were non-significant, and all reported results were done using random-effects models
- Numbers needed to treat (NNT) were obtained for treatment response, and numbers needed to harm (NNH) were obtained for adverse effects
- Following the meta-analyses of each drug compared to placebo, indirect meta-analysis was done to compare DLX with PGB and DLX with GBP
- Indirect meta-analysis attempts to estimate a head-to-head comparison of drugs which have not been directly compared in a randomized trial; it uses placebo as a common comparison, and compares the treatment effect of each drug compared to placebo; for example, if drug A reduces pain severity by 4 points compared to placebo, and drug B reduces pain severity by only 2

points, indirect meta-analysis estimates that drug A is more effective than drug B by 2 points of pain severity

- For the comparison of DLX with GBP and PGB, non-inferiority tests were done, assuming that a difference of 2 points on an 11 point scale is the margin for non-inferiority
- All 3 drugs were superior to placebo in the individual drug meta-analyses
- The only outcome DLX and GBP had in common for purposes of indirect meta-analysis was the 24 hour pain severity score
- Three outcomes were available for comparison between DLX and PGB: 24 hour pain severity, pain response, and PGI-I/C
- The indirect meta-analysis comparing DLX with GBP yielded no significant differences in the 24 hour pain severity
- The indirect meta-analysis comparing DLX with PGB on 24 hour pain severity yielded a non-significant (0.248 point) advantage of DLX over PGB, and the upper bound of the confidence interval did not exceed 2 points
- The indirect meta-analysis comparing DLX with PGB on pain response yielded a difference of close to 0
- The indirect meta-analysis comparing DLX with PGB on PGI-I/C yielded a difference of 0.542 in favor of PGB; since this is expressed as log-odds, the estimate of the corresponding odds ratio for global improvement would be 1.72 in favor of PGB (confidence intervals between 1.02 and 2.88)
- For adverse effects, DLX produced less dizziness than PGB, and other tolerability comparisons (diarrhea, headache, premature discontinuation, and somnolence) were similar between the two drugs
- For adverse effects, there were no differences between DLX and GBP

Authors' conclusions:

- Duloxetine is comparably effective and tolerable when compared with the anticonvulsants pregabalin and gabapentin
- Duloxetine may offer a valuable additional treatment option for painful diabetic neuropathy

Comments:

- In addition to the effect measures mentioned above, the authors calculated NNT and NNH for treatment response; however, these cannot be calculated from the odds ratio alone, and require the response rates in the control groups, which involve data not presented in the article
- The authors appear to have followed accepted methods in carrying out indirect meta-analysis, performing meta-analyses of each drug with placebo, and using these results to compare duloxetine with each of the anticonvulsants
- It is very difficult to find the studies in Table 1 and Figure 2, since these are identified by a code (e.g., "DPN-131) whose key is not furnished; a request for clarification has been posted at the article website
- In addition, retrieval of the study data is complicated by the fact that the link to the European Medicines Agency (reference #14) is now out of date, and directs the user to the agency home page

- It is possible for indirect meta-analysis to produce a drug comparison which approximates a head-to-head comparison of the same drugs, but the results are uncertain and there may be discrepancies between indirect meta-analysis and later head-to-head trials of the drugs
- The discordance between the pain severity scores and the PPGI-I/C comparisons of duloxetine and pregabalin is not clearly explained, and suggests that the equivalence of the two drugs should be tested with a direct comparison

Assessment: Adequate for some evidence that duloxetine appears to be comparable to the anticonvulsants pregabalin and gabapentin for the treatment of neuropathic pain