| **Critique author** | **Ed Whitney** |
|---|---|

| **Bibliographic Data** | |
|---|---|
| Authors | Tesfaye S, Wilhelm S, et al. |
| Title | Duloxetine and pregabalin: High-dose monotherapy or their combination? The ‘‘COMBO-DN study’’ – a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain |
| PMID | 23732189 |
| Citation | Pain 2013;154:2616-2625 |
| Other information if relevant | |

| **Methods** | |
|---|---|
| Aim of study | In patients with neuropathic pain due to diabetes who do not respond to several weeks of treatment with a standard dose of pregabalin or duloxetine, to compare the effectiveness of a *strategy* of high dose monotherapy with pregabalin or duloxetine versus a *strategy* of a combination of standard doses of each drug |
| Design | Randomized clinical trial |

| **Participants** | |
|---|---|
| Population from which participants are drawn | Patients with neuropathic pain from type 1 or type 2 diabetes mellitus who had not previously been treated with either duloxetine or pregabalin |
| Setting (location and type of facility) | Multinational study in 10 European countries, Turkey, Australia, Canada, Mexico, and South Korea from February 2010 until November 2011 |
| Age | 61.7 |
| Sex | 448 men, 356 women |

| | |
|---|---|
| Total number of participants for whom outcome data were reported | 804 |
| Inclusion criteria | Age over 18, not taking medication for neuropathic pain from diabetes, (or who completed a 2 week washout period), bilateral neuropathic pain beginning in the feet in a relatively symmetric fashion, lasting at least three months, confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument, stable glycemic control with HbA1c <=12 |
| Exclusion criteria | Any suicidal risk as judged by the investigator, or a score of >=2 on Beck Depression Inventory item 9 |
| Other information if relevant | Randomization was into one of four groups, but for purposes of comparing high-dose monotherapy versus combination therapy, they can be clustered into two intervention groups as outlined below |

**Intervention Groups**

| **Group 1** | |
|---|---|
| Group name | "High dose monotherapy strategy" |
| Number in group | 399 (197 on pregabalin and 202 on duloxetine) |
| Description of intervention | - A screening and washout period of 2 weeks preceded an initial therapy period lasting 7 weeks<br>- The initial therapy period had the patients on a standard dose of the test drugs: 300 mg for pregabalin and 60 mg for duloxetine<br>- Patients whose average pain score in the previous 24 hours decreased by 30% or better were considered "responders" and did not continue to the second phase of the study, which is where the "nonresponders" were treated by increasing the dose of the drug they had been taking in the first phase<br>- The 7 week initial treatment phase was followed by a one week titration period in which the dose of pregabalin was increased to 450 mg and the dose of duloxetine was increased to 90 mg<br>- That titration period was followed by a 7 week test period which was the focus of the study analysis: the dose of pregabalin was increased to 600 mg and the dose of pregabalin was increased to 120 mg<br>- The 7 week test period was followed by a two week tapering period; duloxetine was decreased to 60 mg and then to 30 mg, while pregabalin was decreased to 300 mg and then to 150 mg |
| Duration of treatment period | 20 weeks to complete all phases of the study |

| | |
|---|---|
| Co-interventions if reported | |
| Additional information if relevant | This group was designed to test the strategy of increasing the dose of either drug when the initial response to a standard dose of the drug did not provide adequate relief, which is why the main comparison of interest was of patients who did not experience at least 30% relief after the starting dose had been attempted |

| **Group 2** | |
|---|---|
| Group name | "Combination drug strategy" |
| Number in group | 405 (204 who started with standard dose pregabalin and then were tried on a combination of standard dose pregabalin + standard dose duloxetine, and 201 who started with duloxetine and then tried the drug combination |
| Description of intervention | The approach for Group 2 was similar to group 1: a trial of monotherapy on a standard dose of each drug:<br>- A screening and washout period of 2 weeks preceded an initial therapy period lasting 7 weeks<br>- The initial therapy period had the patients on a standard dose of the test drugs: 300 mg for pregabalin and 60 mg for duloxetine<br>- Patients whose average pain score in the previous 24 hours decreased by 30% or better were considered "responders" and did not continue to the second phase of the study, which is where the "nonresponders" were treated by increasing the dose of the drug they had been taking in the first phase<br>- However, the "nonresponders" were treated with the same drug they had been taking, but then took a standard dose of the drug they had not been taking, so that both groups were taking 60 mg of duloxetine and 300 mg of pregabalin for the 7 week main test phase of the trial<br>- The 7 week main test phase was followed by a 2 week taper phase during which the doses of the drugs was reduced by half to 150 mg pregabalin and 30 mg of duloxetine |
| Duration of treatment period | 20 weeks to complete all phases of the study |
| Co-interventions if reported | |
| Additional information if relevant | |

| **Primary outcome** | |
|---|---|
| Outcome name and criteria for definition | - Primary outcome was the average pain score during the previous 24 hours, measured on a scale of 0 to 10, and evaluated based on a 30%, 50%, or a 2 point reduction in pain |
| Time points measured and/or reported | - Baseline, at the end of the first 7 week test period, and at the end of the second 7 week test period |
| Differences between groups | - The comparison at the end of the first 7 week test period had a different purpose from that at the end of the second 7 week test period<br>- The comparison at the end of the first test period served two purposes: to determine how many participants were "responders" to monotherapy so that they were excluded from going on to the second test period, and to compare the effectiveness of pregabalin monotherapy vs. duloxetine monotherapy<br>- After the first test period, 40.9% of duloxetine patients and 28.8% of pregabalin patients had responded with a 30% or better reduction in average pain, and did not proceed to the second test period<br>- The "non-responders" did proceed to the second phase of the trial, where the two treatment strategies were compared: high dose monotherapy(n=170) versus combination therapy (n=169)<br>- In this second test period, the two strategies were comparably effective: the combination therapy group had a mean pain reduction of 2.35 points and the high-dose monotherapy group had a mean pain reduction of 2.16 points<br>- The combination group enjoyed a numerically superior but statistically non-significant advantage over the monotherapy group on the proportion of patients with a 50% pain reduction: this occurred in 52.1% of the combination group and in 39.3% of the monotherapy group<br>Within the monotherapy group, where 39.3% had a 50% pain reduction, the two drugs were not equally effective: this happened in 49% of the group taking 600 mg of pregabalin versus 28.4% of the group taking 120 mg duloxetine |
| Additional information if relevant | - The early comparison between the 60 mg duloxetine versus 300 mg of pregabalin, in which duloxetine outperformed pregabalin, was exploratory in nature<br>- In the second phase of the trial, monotherapy with 600 mg pregabalin outperformed 120 mg of duloxetine; this was also exploratory in nature, and may have been observed because more of the pregabalin than duloxetine patients entered the second phase of the trial |

| **Secondary outcomes** | |
|---|---|
| Outcome name and criteria for definition | Treatment-emergent adverse effects (TEAE) |
| Time points measured | At the end of the first test period and again at the end of the second test period |
| Differences between groups | - TEAE occurred more often in the first test period (>10% of patients) than in the second (3% of patients), but there were no significant differences between comparison groups during either period<br>- In the first test period of standard dose monotherapy, dizziness was reported in 7.2% of duloxetine patients versus 15.1% of pregabalin patients; other TEAE were somnolence (10% duloxetine vs 10.9% pregabalin) and nausea (14.2% duloxetine vs 6.5% pregabalin) |
| Additional information if relevant | During both periods, changes inHbA1c were minimal |

| **Conclusions** | |
|---|---|
| Key conclusions of study authors | - This is the first multicenter trial to address the question: "In diabetic neuropathy patients who have not had satisfactory analgesic responses to duloxetine or pregabalin, is it better to increase the dose of the drug they are taking or is it better to try a combination of the two drugs?"<br>- Although the two strategies did not have statistically significant differences between them, the numerical differences consistently favored combination therapy over higher dose monotherapy<br>- Safety and tolerability were not negatively affected when the two drugs were combined over when the dose of each was increased<br>- In patients with neuropathic pain due to diabetes who have not responded to monotherapy with either duloxetine or pregabalin, it is reasonable to try a combination of both drugs rather than to increase the dose of either drug |

| **Risk of bias assessment** | | |
|---|---|---|
| Domain | Risk of bias<br>Low High Unclear | Comments |

| | | |
|---|---|---|
| Random sequence generation *(selection bias)* | | Low |
| Allocation concealment *(selection bias)* | | Low |
| Blinding of participants and personnel *(performance bias)* | | Low (blinding was maintained through all treatment periods by using over-encapsulated capsules of both test drugs and matching placebo, such that the timing and number of capsules was kept constant throughout the entire trial) |
| Blinding of outcome assessment *(detection bias)* | | Low |
| Incomplete outcome data *(attrition bias)* | | Low |
| Selective outcome reporting? *(reporting bias)* | | Low (trial was registered at clinicaltrials.gov) |
| Other bias | | |

| **Sponsorship if reported** | | |
|---|---|---|
| Study funding sources if reported | Eli Lilly (maker of Cymbalta, the brand name of duloxetine) | |
| Possible conflicts of interest for study authors | Several authors are employed by Eli Lilly and also own stock in Eli Lilly and other pharmaceutical manufacturers, and the first author also owns stock in Pfizer (maker of Lyrica, the brand name of pregabalin) | |
| Notes: Reporting of conflict of interest section appears to be transparent, and shows financial interests by most authors in both drug companies whose drugs were tested during the trial | | |

**Comments by DOWC staff**

- Although the design of the study is complex and difficult to summarize easily, the study is also well-designed to deliver an unbiased answer to an important and commonly encountered clinical question when patients are not doing well on monotherapy with commonly used drugs for neuropathic pain: whether to increase the dose or whether to maintain the dose and add a second drug
- While statistically significant differences between strategies were not reported, the response rates were reasonably good in the second phase of the trial: a 50% pain reduction was observed in just over half of the combination patients and in just under 40% of the high-dose monotherapy patients
- The initial, standard dose monotherapy phase of the trial, used a 30% pain reduction as a success criterion to exclude responders from the second phase of the trial, but in the second phase a 50% pain reduction was reported as a criterion on which to compare treatment groups
- The instrument used to compare outcomes, the Brief Pain Inventory Modified Short Form, includes items for overall physical function such as walking and normal work, but only one item, average pain in the past 24 hours, was reported as an outcome measure for purposes of treatment comparisons
- Control of bias was well-designed and executed: the encapsulation of all drugs was done in order to maintain all patients on a constant number and timing of capsules throughout the study
- The drugs were made by different companies, but the authors had financial interests in both companies

| **Assessment by DOWC staff** | |
|---|---|
| Overall assessment as suitability of evidence for the guideline<br>x☐ High quality<br>☐ Adequate<br>☐ Inadequate | High quality RCT supporting good evidence that in patients with painful diabetic neuropathy who have not had good responses to monotherapy with 60 mg of duloxetine or 300 mg of pregabalin, a clinically important benefit can be achieved by either of two strategies: doubling the dose of either drug, or combining both drugs at the same dose. It is likely that the strategy of combining the two drugs at doses of 60 and 300 mg respectively is more beneficial overall |
| If inadequate, main reasons for recommending that the article not be cited as evidence | |

| **Additional references if relevant** |
|---|
| - |