

Efficacy of Duloxetine in Chronic Low Back Pain with a Neuropathic Component

A Randomized, Double-blind, Placebo-controlled Crossover Trial

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ABSTRACT

Background: Among patients with chronic low back pain (CLBP), approximately 37% show signs of a neuropathic pain component (radicular pain). Treatment of this condition remains challenging. Therefore, the current study aimed to investigate the efficacy of duloxetine in the treatment of CLBP patients with neuropathic leg pain.

Methods: The study was conducted as a prospective, randomized, placebo-controlled, double-blind crossover trial. CLBP with a visual analog scale (VAS) score greater than 5 and a neuropathic component that was assessed clinically and by the painDETECT questionnaire (score > 12) were required for inclusion. Patients were randomly assigned to either duloxetine or placebo for 4 weeks followed by a 2-week washout period before they crossed over to the alternate phase that lasted another 4 weeks. Duloxetine was titrated up to 120 mg/day. The primary outcome parameter was mean VAS score during the last week of treatment in each phase (VAS_{week4}).

Results: Of 41 patients, 21 patients completed both treatment phases. In the intention-to-treat analysis (n = 25), VAS_{week4} was significantly lower in the duloxetine phase compared with placebo (4.1 ± 2.9 vs. 6.0 ± 2.7 ; $P = 0.001$), corresponding to an average pain reduction of 32%. The painDETECT score at the end of each treatment phase was significantly lower in the duloxetine phase compared with placebo (17.7 ± 5.7 vs. 21.3 ± 3.6 points; $P = 0.0023$). Adverse events were distributed equally between the duloxetine (65%) and placebo phases (62%) ($P = 0.5$).

Conclusion: In this crossover study, duloxetine proved to be superior to placebo for the treatment of CLBP with a neuropathic leg pain. (ANESTHESIOLOGY 2016; 124:150-8)

LOW back pain is an extremely common condition with a reported lifetime prevalence of up to 84%.¹⁻³ Although chronic low back pain (CLBP) is less prevalent, it still affects up to 23% of the population of Western countries and constitutes a major public health issue.^{1,2} CLBP often presents as a mixture of nociceptive and neuropathic pain, and approximately 37% of CLBP patients suffer from predominantly neuropathic pain,⁴ which mainly presents as radicular leg pain.^{5,6} Radicular leg pain is defined as segmental pain that radiates below the knee.^{7,8} It is also referred to as projected pain, which is caused by damage or irritation of peripheral nerves or nerve roots. However, radicular pain may also be triggered by local inflammatory processes that are caused by disc degeneration, even without verifiable mechanical compression.^{5,9-13} To date, treatment of CLBP with a neuropathic component remains challenging,^{14,15} and no pharmacological intervention has as yet been shown to be efficacious in randomized placebo-controlled trials.¹⁶ Current treatment recommendations are extrapolated from trials

What We Already Know about This Topic

- Chronic low back pain with painful radicular symptoms is very common
- Little evidence exists demonstrating the efficacy of specific pharmacological treatments for radicular pain

What This Article Tells Us That Is New

- In this randomized, placebo-controlled crossover trial, patients with radicular symptoms experienced an average 32% reduction in pain after 4 weeks of treatment with duloxetine
- The overall adverse event rate was similar between placebo and duloxetine treatments

in diabetic neuropathy and postherpetic neuralgia, which may be inaccurate.

Duloxetine (Cymbalta®; Eli-Lilly, Austria) is a selective serotonin and norepinephrine reuptake inhibitor, which is effective in major depressive disorder,¹⁷⁻¹⁹ generalized anxiety disorder,²⁰ and fibromyalgia.²¹ Its efficacy and safety in

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the treatment of diabetic peripheral neuropathic pain was repeatedly demonstrated in large, randomized controlled trials.^{22–24}

A number of randomized controlled trials on the use of duloxetine in CLBP have been conducted,^{25–28} but the results of these trials are contradictory. In a large, placebo-controlled 13-week trial, duloxetine led to a statistically significant pain reduction between weeks 3 and 11. However, the significance was lost at week 13.²⁶ In another 13-week placebo-controlled trial of duloxetine in CLBP, a statistically significant pain reduction persisted throughout the study.²⁵ Importantly, in all the aforementioned randomized controlled trials, CLBP patients with a neuropathic pain component were explicitly excluded. Therefore, the aim of the current study was to investigate the efficacy of duloxetine in the treatment of CLBP patients with a neuropathic pain component (*i.e.*, radicular pain).

We hypothesized that duloxetine is superior to placebo for the treatment of CLBP with a neuropathic leg pain component.

Materials and Methods

This prospective, randomized, placebo-controlled, double-blind crossover study was conducted at the Outpatient Clinic of the Department of Special Anaesthesia and Pain Therapy at the Medical University of Vienna (Vienna, Austria). The protocol was approved by the local ethics committee (Ethics Committee of the Medical University Vienna, Vienna, Austria; Date of registration: December 2009; registration number: 657; and investigator: S.P.) and was registered at ClinicalTrials.gov (NCT01166048) by S.P., principal investigator, in May 2010. Recruitment was conducted from May 2010 to May 2013, and treatment was carried out from May 2010 to September 2013. All patients gave written informed consent before beginning study procedures. Patients were recruited at the Outpatient Clinic of the Department of Special Anaesthesia and Pain Therapy at the Medical University of Vienna and by advertisements in news print. Therefore, the majority of included patients did not receive prior analgesic medication and did not undergo specialized pain treatment before entering the study.

Entry Criteria

Patients older than 18 yr and younger than 80 yr with chronic low back and leg pain (> 6-month duration) and visual analog scale (VAS) score greater than 5 cm on a 10-cm VAS scale were eligible for this trial. To establish the VAS score, patients marked the degree of their pain on a 10-cm paper scale, which was then measured by our research personnel. Patients were required to have local back pain with the main area not extending cranially beyond the border of lumbar vertebra 1 together with a radicular component, which was clinically described as burning, tingling pain, extending below the knee and traveling along the anatomic

distribution of a lumbar nerve root. The presence of the neuropathic component of pain was further verified by the painDETECT questionnaire before patients were eligible to enter the study. Patients were required to score greater than 12 in order to be included in the trial. In addition, clinical signs and symptoms of neuropathic pain, that is, radicular pain, were required for inclusion, which were evaluated by two independent experienced pain specialists not involved in the study.

All study subjects had to discontinue any concomitant medication that could interfere with their pain such as analgesic medication (nonopioids or opioids), antidepressants, and anticonvulsants before entering one of the treatment phases, except for analgesics defined as rescue medication in the protocol. Nonpharmacological pain-relieving procedures such as acupuncture or physical therapies were not allowed during the entire duration of the study.

Exclusion criteria were as follows: prior use of opioids classified by the World Health Organization as level III (*e.g.*, fentanyl, tapentadol, morphine, hydromorphone, buprenorphine, and oxycodone), mild depression present for more than 12 months (defined as ≥ 10 points in the Beck Depression Inventory), use of antidepressants or benzodiazepines 6 months before study entry, drug abuse, pregnancy, and severe coexisting diseases (such as severe heart failure, severe hypertension, glaucoma, convulsion, and kidney dysfunction).

Beck Depression Inventory

The Beck Depression Inventory is a 21-item questionnaire measuring the cognitive and somatic aspects of depressed mood. A score of 0 to 9 indicates minimal depression; 10 to 18, mild depression; 19 to 29, moderate depression; and 30 to 63, severe depression.²⁹ Patients scoring 10 points or greater at screening were excluded from the current study.

Intervention

After a 2-week screening period, patients were randomly assigned at a 1:1 ratio to one of the two treatment phases, commencing with either placebo or duloxetine and crossing to the next treatment phase after a 2-week washout period. Randomization was computer assisted and stratified according to age and sex. All study measures were carried out by blinded investigators and personnel. Blinding and randomization were performed by an independent study nurse. Both study physicians and patients were blinded. Appearance of study medication was identical in both treatment phases. Study drugs and placebo were packaged in blue opaque capsules, which were manufactured by the hospital pharmacy of the Medical University of Vienna, and administered according to the assignment code, which was held by an independent study nurse.

Each treatment phase of the crossover study lasted 4 weeks and was separated by a 2-week washout period. Patients were allowed to use the rescue medication up to 3,000 mg metamizole per day (Novalgine®; Aventis Pharma GmbH, Austria)

and/or 600 mg tramadol per day (Tramal®; Grünenthal, Austria). Patients kept a daily paper diary of their VAS score on a 10-cm VAS scale in the morning and evening as well as of their consumption of rescue medication. Duloxetine was titrated in a fixed scheme from 30 up to 60 mg in the first week and from 60 up to 120 mg in the second week of treatment. The stable dosage of 120 mg/day was then maintained for the last 2 weeks of treatment. If patients could not reach the maximum daily dosage of duloxetine, they were excluded from the study. Patients were instructed to take the study drug in the morning. All patients had weekly face-to-face study visits. These included monitoring of routine vital signs (electrocardiogram, blood pressure, and weight) and assessment of VAS score and adverse events. At the beginning and end of each treatment phase, a safety laboratory check, including electrolytes, creatinine, liver parameters (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase), and a complete blood count, was performed.

Primary Outcome Measure

The primary study endpoint was defined as the mean VAS score during the last week of each treatment period (VAS_{week4}). Pain scores were assessed twice daily by the patient. The resulting 14 single pain measurements during the last week were used to calculate the mean VAS_{week4}.

Secondary Outcome Measures

painDETECT Questionnaire. Signs and symptoms of low back and neuropathic leg pain were assessed by the pain-DETECT questionnaire.⁴ It is a validated screening tool specifically developed for the identification of a neuropathic component in CLBP patients, with a high sensitivity and specificity (80 and 83%) to neuropathic pain. Distribution and quality of pain perceived by the patient are obtained and rated on a 38-point scale. All study subjects were scored before entering the study and at the end of each treatment phase. Patients with a score of greater than 19 points are very likely to have a neuropathic component with their low back pain (> 90%), and in patients with a score from 12 to 18 points, a neuropathic component may be present. For the purposes of this study, a score of greater than 12 points together with the clinical symptoms of radicular pain, diagnosed by two independent experienced pain specialists not involved in the study, was required for inclusion.

Short-form-36 Health Survey. This patient-reported survey of health is commonly used for quality-of-life assessment. The following eight domains are routinely determined: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Each section is scored from 0 to 100, where 0 represents the lowest and 100 represents the highest level of health. From the results of the eight domains, two summary scores, the physical and mental composite scores (also with possible ranges between 0 and 100), are calculated. In the current trial, the German version

of the Short-form-36 Health Survey (SF-36), 2nd edition, was used.³⁰

Statistical Methods

After testing for normality by using Kolmogorov–Smirnov test, metric variables are described by medians and interquartile ranges or, where appropriate, by means and SDs. The reported mean daily dosage ranges of rescue medication, in each crossover phase, were calculated by averaging the total dosage consumed per phase by the number of days ($n = 28$) in each phase.

The treatment effect on the VAS score was estimated in a mixed model with the mean VAS score of the last 14 available values in each phase (VAS_{week4}) as dependent variable, phase and treatment as independent variables, and with the patients entering as the levels of a random factor. The presence of a carryover effect was investigated by testing for a significant interaction of treatment \times phase in a separate otherwise similar model. The effect of duloxetine on the painDETECT score, the mental composite score, and the physical composite score was analyzed analogously. The frequency of tramadol and metamizole intake was compared between the duloxetine and the placebo phases by using McNemar tests. Differences in VAS score according to treatment were analyzed by the modified intention-to-treat (ITT) principle by using data from all patients who entered both study phases and contributed at least 14 VAS measurements in the second study phase. Therefore, a minimum of 7 days in the second study phase was required for inclusion in the ITT analysis. Missing values of patients who discontinued the second phase were imputed by using the last available 14 VAS measurements.

All other analyses were based on the per-protocol (PP) population consisting of the patients who had completed both study phases. In a secondary analysis, the treatment effect on the VAS score was adjusted for the VAS baseline values. A responder analysis was conducted as another secondary analysis. “Response” was defined as a reduction in pain (VAS) by more than 50% from baseline. Response rates were compared by McNemar test. The sample size was first determined at 28 patients eligible for ITT analysis, based on a relevant mean difference of 1.5 points on the VAS scale, a power of 90%, and a two-sided significance level of 5%. Here, an estimate of the SD of the difference in outcome within patients was used. Therefore, according to the study protocol, the sample size was recalculated by a statistician after 14 patients had completed the second phase by making use of the current estimate of this SD, without unblinding treatment assignment. On the basis of ANOVA for crossover designs, a sample size of 22 patients eligible for ITT analysis was shown to be sufficient to detect a difference in VAS_{week4} of 1.5 points with a power of 90%. No α adjustments were made after reestimating the sample size. After the sample size recalculation, enrollment was stopped because it was predictable that a sufficient number of patients had already entered

for a number of at least 22 patients in the ITT population to be reached. However, treatment of the patients already enrolled into the study at this point was continued, which led to an ITT population consisting of a final 25 patients. All statistical analyses were performed with the Statistical Analysis System, version 9.3 (SAS Institute Inc., USA). The two-sided significance level was set at 5%.

Results

Study Population and Participant Flow

A total of 153 patients were screened by telephone and in person for eligibility by our research personnel. Forty-one patients were randomly assigned to this study. A total of seven patients dropped out before entering the first study phase: four withdrew their informed consent, one experienced an unacceptable increase in pain during washout of prior analgesic medication, one opted for an alternative pain treatment, and one was excluded due to intercurrent abuse of anabolic drugs. After randomization to the first phase ($n = 34$), 16 patients received duloxetine and 18 patients received placebo. In the first phase, two patients discontinued the study due to adverse events in the placebo group and five in the duloxetine group. One patient was lost in the washout period between the phases due to the wish to use an alternative treatment option. After randomization ($n = 26$) to the alternate phases (crossover), 11 patients received placebo and 15 patients received duloxetine. Of these, four

patients and one patient discontinued the study due to adverse events in the placebo and duloxetine phases, respectively. Summing up 26 patients entered both phases of the study, 21 patients completed both phases of the study. There was no statistically significant difference in dropout rates between the duloxetine ($n = 6$) and the placebo ($n = 6$) phases.

The trial was terminated after a sufficient number of patients eligible for ITT analysis was reached, as determined by the sample size recalculation. Participant flow through the trial and dropout including days are depicted in figure 1. Patient demographic data and baseline characteristics are shown in table 1.

Efficacy of Duloxetine

ITT Analysis. Patients who had completed one study phase and contributed at least 14 VAS values in the alternate phase were included in the ITT analysis ($n = 25$).

The mean VAS_{week4} was 6.0 ± 2.7 in the placebo phase and 4.1 ± 2.9 in the duloxetine phase. Mixed model analysis revealed that VAS_{week4} in the duloxetine phase was significantly lower (1.8 units; 95% CI, 0.8 to 2.8; $P = 0.001$) than VAS_{week4} in the placebo phase corresponding to an average pain reduction of 32% (fig. 2). If patients did not complete a phase, the last 14 available VAS values were used for calculation of VAS_{week4}.

The mean reduction of VAS from baseline to last week of each treatment phase was 2.7 ± 2.5 in the duloxetine

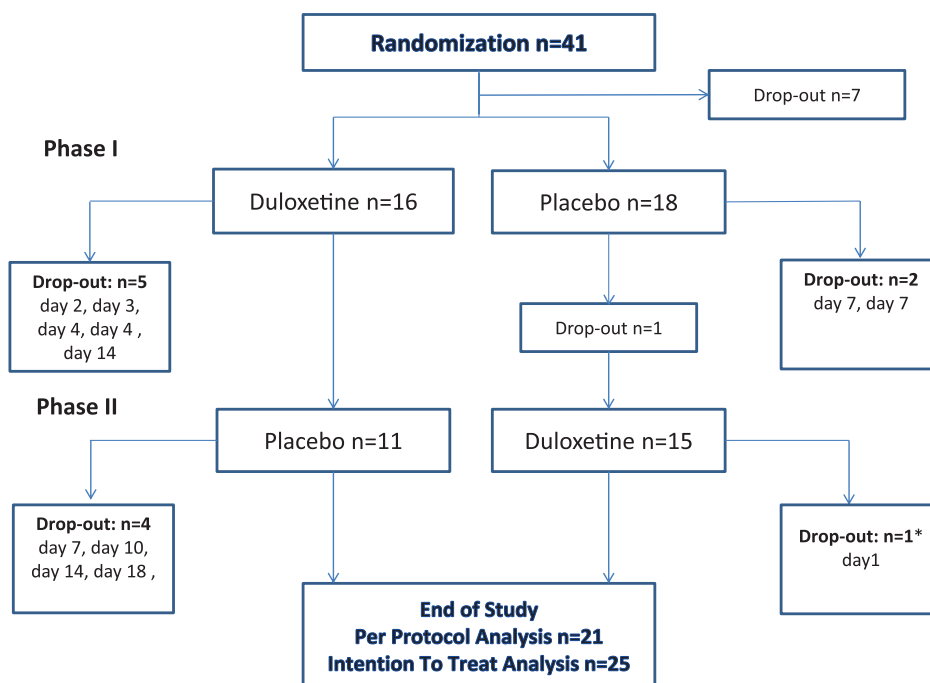


Fig. 1. Flow diagram of patient progress through the trial. In order to be included in the modified intention-to-treat analysis, patients had to complete the first study phase as well as a minimum of 7 days in the second study phase. Numbered days denote the study days on which the patients dropped from the study. Twenty-five patients entered the modified intention-to-treat analysis and 21 patients entered the per-protocol analysis. *Patient did not meet the criteria for inclusion into the intention-to-treat-analysis (number of study days in phase II = 1).

Table 1. Demographic Data and Baseline Characteristics of the Patients (n = 41)

Age, yr	57.9 ± 13.4
Sex, female	21 (51.0)
Weight, kg	80.5 ± 18.3
painDETECT score	20.0 ± 3.1
Duration of CLBP since onset, months	18 (6–70)
NSAID use	12 (29.2)
WHO level II opioid use	3 (7.3)
Pain (VAS) at baseline	6.8 ± 1.5
Pain (VAS) at end of washout	5.8 ± 2.5
SF-36	
Physical Component Summary	28.4 ± 8.7
Mental Component Summary	48.9 ± 11.4

Data are depicted as mean ± SD, median and (IQR), or n (percentages) as appropriate. painDETECT cutoff value for inclusion > 12, higher scores indicate presence of more neuropathic pain symptoms. Score ranges from 0 to 38.

CLBP = chronic low back pain; IQR = interquartile range; NSAID = non-steroidal antiinflammatory drug; SF-36 = Short-Form-36 Health Survey, questionnaire used for quality-of-life assessment. Score ranges from 0 to 100. Higher scores indicate better physical or mental health; VAS = visual analog scale ranging from 0 to 10 (higher scores indicate more pain); WHO level II = opioid classified as level II according to the World Health Organization analgesic ladder (e.g., tramadol).

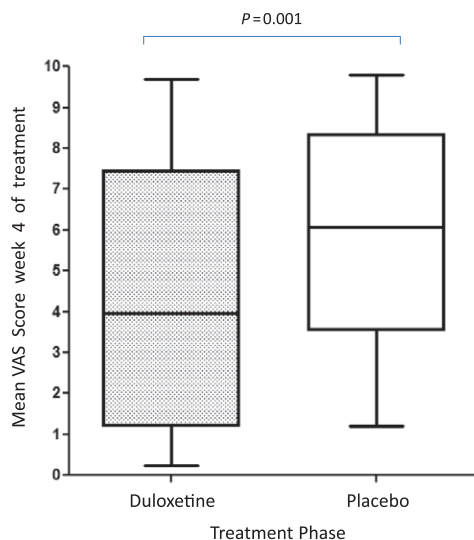


Fig. 2. Mean pain intensity at week 4 of each treatment phase (primary endpoint) in the intention-to-treat population (n = 25). Pain intensity quantified on a 10-cm visual analog scale (VAS) during the last week of each treatment phase, assessed twice daily by the patient (range: 0–10). Higher scores indicate higher pain intensity. x-axis: treatment phase; y-axis mean VAS score during week 4 of treatment. Whiskers: minimum and maximum values; line: mean. Mean VAS score during week 4 of treatment was significantly lower in the duloxetine phase than in the placebo phase ($P = 0.001$).

phase compared with 0.5 ± 1.6 points in the placebo phase ($P = 0.002$). Although the mean VAS score at baseline differed between study phases 1 and 2 (6.8 ± 1.5 and 5.8 ± 2.5 , respectively; $P = 0.045$), there was no statistically significant carryover effect. The treatment effect was found to be 0.4 points higher in the second phase than in the first phase ($P = 0.854$).

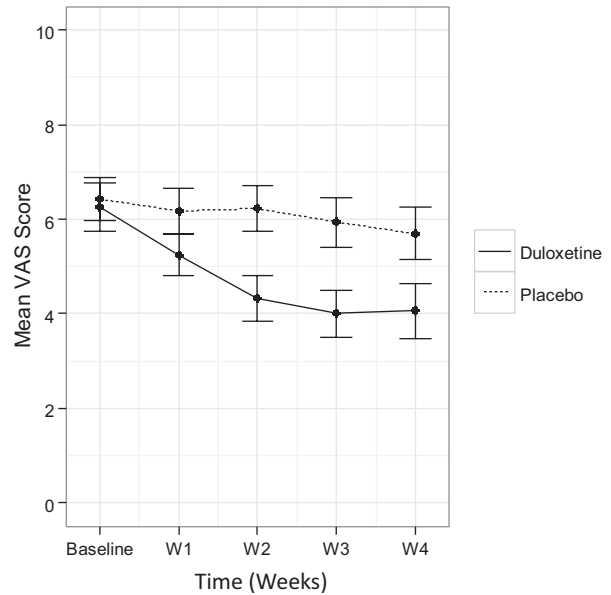


Fig. 3. Average weekly pain intensity in each treatment phase in the intention-to-treat population (n = 25). Average weekly pain intensity quantified by mean visual analog scale (VAS) during each study week (range: 0–10). Calculated from pain scores, assessed twice daily by the patient. Higher scores indicate higher pain intensity. Intention-to-treat population includes all patients who finished the first study phase and completed a minimum of 7 days in the second study phase. x-axis: time in weeks (W1–W4); y-axis: mean weekly VAS score ± SEM. Solid line = duloxetine phase; broken line = placebo phase.

Figure 3 shows the time course of mean VAS score from week 1 to week 4 in the duloxetine phase compared with the placebo phase in the ITT population.

A responder analysis was performed for patients in the ITT population. Response was defined as a reduction in pain (VAS) by more than 50% from baseline. Treatment by duloxetine led to higher response rates than placebo (10 responses [40%] under duloxetine and 2 responses [8%] under placebo; $P = 0.037$).

PP Analysis. Patients who had completed both phases were included in the PP analysis (n = 21). Mean VAS score in the last week of each treatment phase VAS_{week4} was significantly lower in the duloxetine phase (3.7 ± 2.9) compared with the placebo phase (5.7 ± 2.5), corresponding to an average pain reduction of 35%. Mixed model analysis revealed that in the last week of treatment, the mean VAS score was on average 1.7 units (95% CI, 0.4 to 3.0) lower in the duloxetine phase than in the placebo phase ($P = 0.013$).

Mirroring the VAS score, the painDETECT score at the end of each treatment phase was lower in the duloxetine phase (17.7 ± 5.7 points) compared with the placebo phase (21.3 ± 3.6 points) ($P = 0.002$) (fig. 4). This can be considered a clinically significant effect.

The mental component summary (mental composite score) of the SF-36 questionnaire performed at the end of

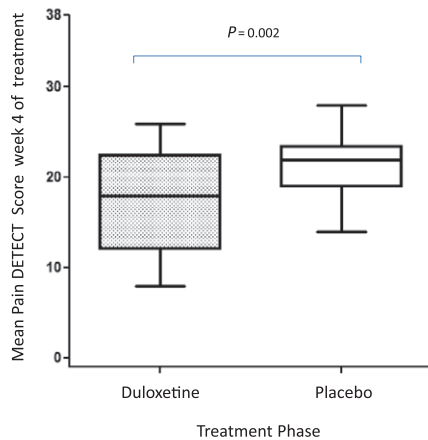


Fig. 4. Mean painDETECT score at week 4 of each treatment phase (secondary endpoint) in the per-protocol population ($n = 21$). Higher painDETECT scores indicate presence of more symptoms of neuropathic pain. Score ranges from 0 to 38. *Whiskers:* minimum and maximum value; *line:* mean. x-axis: treatment phase; y-axis: mean painDETECT score in week 4 of treatment. painDETECT score was significantly lower in week 4 of the duloxetine phase than in the placebo phase ($P = 0.002$).

each treatment phase was higher in the duloxetine phase (50.0 ± 11.6) compared with the placebo phase (46.5 ± 12.5) ($P = 0.022$).

Similarly, the physical component summary (physical composite score) in the SF-36 questionnaire performed at the end of each treatment phase was higher in the duloxetine phase (36.0 ± 10.9) compared with the placebo phase (31.3 ± 9.3) ($P = 0.007$).

Residual Effects

No statistically significant carryover effects were observed between the treatment phases for any of these outcomes ($P = 0.854$ for the VAS score in the ITT analysis; $P = 0.581$, $P = 0.137$, $P = 0.657$, and $P = 0.740$ for the VAS score, the painDETECT score, the mental composite score, and the physical composite score in the PP analysis, respectively).

Rescue Medication

In the current trial, rescue medication was consumed by a total of 17 patients. Seven patients in the placebo phase (mean daily dosage range between 1.7 and 513.0 mg) and five patients in the duloxetine phase (mean daily dosage range between 5.4 and 570.6 mg) used tramadol. Metamizole was consumed by nine patients in the placebo phase (mean daily dosage range between 17.9 and 2,464.3 mg) and eight patients in the duloxetine phase (mean daily dosage range between 26.8 and 3,000.0 mg).

No statistically significant differences between the frequencies of tramadol and metamizole use were observed between the treatment phases ($P < 0.05$).

Table 2. Incidence of Frequent Adverse Events in the Duloxetine and Placebo Phase

Adverse Events	Duloxetine Phase, n = 31 (%)	Placebo Phase, n = 29 (%)
Dry mouth*	11 (35)	1 (3)
Sweating	11 (35)	8 (28)
Fatigue	8 (26)	2 (7)
Nausea	6 (19)	1 (3)
Constipation	6 (19)	2 (7)
Loss of appetite†	6 (19)	0
Dizziness	5 (16)	3 (10)
Diarrhea	2 (6)	4 (14)
Insomnia	2 (6)	4 (14)
Increased pain	0	4 (14)

Incidence of frequent adverse events during the two study phases is given as percentages. Statistically significant differences in frequencies of adverse events between treatment phases:

* $P = 0.025$, † $P = 0.05$.

Safety Laboratory

All parameters assessed remained within the normal range throughout the study in all patients. No safety signals were observed in the duloxetine phase.

Adverse Events

Side effects were common in both the placebo and the duloxetine phases. Twenty patients (65%) experienced at least one side effect in the duloxetine phase and 18 patients (62%) at least one side effect in the placebo phase ($P = 0.5$). Table 2 lists the 10 most frequent side effects reported in each phase. There were no statistically significant differences in frequencies of these side effects between the two phases, with the exception of dry mouth and loss of appetite, which were significantly more common in the duloxetine phase ($P = 0.025$ and $P = 0.05$, respectively).

Discussion

The current trial demonstrates that duloxetine is efficacious in the treatment of CLBP with a clear radicular neuropathic component.

The primary outcome parameter VAS_{week4} was significantly lower in the duloxetine phase compared with the placebo phase in both the ITT and the PP analyses. Moreover, the difference in VAS score was pronounced (-1.8 in the ITT population; -1.7 in the PP population) and can be considered clinically significant. Although the threshold for an “important improvement” in the individual patient is usually set at a reduction of 20 mm on the VAS scale, it is recognized that group differences between placebo and study medication tend to be smaller.³¹ Eight trials of pregabalin or duloxetine *versus* placebo in painful diabetic polyneuropathy reported group differences from baseline between 0.9 and 1.5 points on 0- to 10-point pain intensity scales.³² These results are well compatible with the group differences reported in this study.

A mean reduction of 2.7 in weekly average pain from baseline in the individual patient was found in the fourth week of the duloxetine phase, which exceeds the 2-point reduction suggested as “clinically important” in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations.³² A 2-point reduction in VAS score has also been identified as a cutoff value for patient reports of being “much improved.”³¹

The mean painDETECT score was 4.2 units lower at the end of the duloxetine phase than at the end of the placebo phase. Although the painDETECT questionnaire is not validated for the assessment of neuropathic pain over time, a change of mean painDETECT score from a “positive” to an “unclear” neuropathic component was observed. This can be considered a relevant finding because it clearly shows that not only pain intensity but also neuropathic signs and symptoms were significantly improved by treatment with duloxetine.

The presence of a neuropathic component in CLBP is associated with higher pain intensity,⁴ a lower quality of life,³³ and higher healthcare costs⁵ compared with CLBP without neuropathic pain component. Therefore, the finding that duloxetine can target precisely this pain component is important.

As randomized, double-blind, placebo-controlled trials on the efficacy of antineuropathic medication in CLBP with a neuropathic component are sparse,^{16,34} interpretation of these results by comparison with other treatment options is challenging.

A crossover, randomized controlled trial of morphine, nortriptyline, or their combination *versus* placebo in patients with chronic lumbar root pain did not find a statistically significant difference between placebo and verum agents in the primary outcome parameter, which was average leg pain during the maintenance phase.²⁹

Atkinson *et al.*³⁵ failed to find a difference between paroxetine, maprotiline, and placebo in a very small sample of patients with lumbar radiculopathy.

A randomized controlled trial on topiramate in chronic lumbar radicular pain found a 19% decrease in mean leg pain during maintenance phase, which was not clinically relevant compared with placebo. The authors concluded that topiramate cannot be recommended in chronic lumbar radicular pain due to an insufficient therapeutic ratio in view of frequent side effects and dropouts.³⁶

Cohen *et al.*³⁷ performed a large comparative efficacy study on gabapentin *versus* steroid injections in lumbosacral radicular pain. No significant differences in the primary outcome parameter leg pain (on a 0 to 10 numeric rating scale) were observed between the two treatments at 1 month after injection. The mean change from baseline was reported as -2.2 and -1.7 for steroid injections and gabapentin, respectively.

A 2-week, randomized controlled trial of minocycline in lumbar radicular neuropathic pain with amitriptyline as

a comparator showed a reduction of pain intensity on the numeric rating scale of 1.47 and 1.41, respectively, compared with placebo. Although statistically significant, the authors rated these reductions as too small in effect size to be clinically meaningful. Furthermore, no statistically significant difference in Douleur Neuropathique 4 score between the minocycline, amitriptyline, and placebo arm was shown.³⁸

An open-label, phase 3b study evaluated the effectiveness and tolerability of tapentadol in patients with CLBP with or without neuropathic component. Tapentadol prolonged release treatment was associated with statistically significant improvements in neuropathic pain symptoms, with decreases in the number of pain attacks and the duration of spontaneous pain in the last 24 h in patients with low back pain with a neuropathic pain component (painDETECT unclear or positive score at baseline or screening)³⁹

However, these results are difficult to put into context with the current study, as quoted change in pain intensity included an open-label treatment phase and the study was not placebo controlled.

Three large trials of duloxetine in CLBP explicitly excluded patients with a neuropathic pain component.^{25,26,28} In one of these trials,²⁶ a greater reduction of weekly average pain (-2.2 on the numeric rating scale) was observed in the duloxetine 120 mg arm compared with the placebo arm. However, the statistically significant effect was lost by week 13 due to increased placebo response.

We observed a larger reduction of weekly average pain at week 4 (-2.7) compared with the aforementioned studies.^{25,28} This may be due to the exclusion of patients who had a strong neuropathic component to their CLBP in these studies. In a large trial of duloxetine in diabetic peripheral neuropathic pain, Wernicke *et al.*²⁴ reported a very similar magnitude of weekly average pain reduction at 60 mg of duloxetine two times per day (-2.84 on the 11-point Likert scale).

The limitations of the current study are clear and include small sample size and short duration of each treatment phase. Due to the relatively short duration of the study treatment phases, we cannot rule out that the statistically significant effect might be lost at a later time point.²⁶ We did not directly assess the effectiveness of blinding in this study, but the even distribution of adverse events between the crossover phases ($P = 0.5$) can be considered an indirect indicator of successful blinding. Randomized controlled trials investigating CLBP of predominantly neuropathic nature^{29,36,38} also had small sample sizes comparable to that of this study. Although a neuropathic component is very common in CLBP, patients who display predominantly neuropathic symptoms are less abundant, which makes recruitment for such studies cumbersome. Khoromi *et al.*²⁹ were only able to screen 5% of patients who responded to their study advertisement, as most patients did not report predominant neuropathic symptoms. In our study, only 27% of patients who applied could be included. As in the

study by Khoromi *et al.*, the main reason for exclusion was the absence of predominantly neuropathic pain (70%).

Although we did not require proof of radiculopathy by either magnetic resonance imaging or electrodiagnostic studies, we are confident to have reliably identified patients with clear symptoms of neuropathic pain by the combination of clinical assessment and painDETECT questionnaire. The observed reduction in pain intensity as well as in painDETECT scores strongly suggests a therapeutic effect of duloxetine in this type of neuropathic pain.

The results of our study can only be applied to the patient group actually assessed (*i.e.*, patients with a verified radicular pain). Therefore, we cannot exclude that patients suffering from pain with a less well-defined neuropathic component may not benefit from duloxetine to the same extent.

Conclusion

This study reveals that duloxetine can be considered an effective option for the treatment of CLBP with radicular pain. However, for assessment of long-term efficacy, further trials with larger sample sizes and longer treatment durations are needed.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: sibylle.pramhas@meduniwien.ac.at. Raw data available at: sibylle.pramhas@meduniwien.ac.at.

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References

- Andersson GB: Epidemiological features of chronic low-back pain. *Lancet* 1999; 354:581–5
- Balagué F, Mannion AF, Pellisé F, Cedraschi C: Non-specific low back pain. *Lancet* 2012; 379:482–91
- Deyo RA, Weinstein JN: Low back pain. *N Engl J Med* 2001; 344:363–70
- Freyenhagen R, Baron R, Gockel U, Tölle TR: painDETECT: A new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006; 22:1911–20
- Schmidt CO, Schweikert B, Wenig CM, Schmidt U, Gockel U, Freynhagen R, Tölle TR, Baron R, Kohlmann T: Modelling the prevalence and cost of back pain with neuropathic components in the general population. *Eur J Pain* 2009; 13:1030–5
- Tarulli AW, Raynor EM: Lumbosacral radiculopathy. *Neurol Clin* 2007; 25:387–405
- Bruegger A: On vertebral, radicular and pseudoradicular syndromes. On the differential diagnosis of rheumatological and neurological diseases. I. Vertebral syndromes. *Doc Geigy Acta Rheumatol* 1960; 18:1–139
- Sutter M: An attempt to define radicular and pseudoradicular syndromes (author's transl). *Schweiz Rundsch Med Prax* 1974; 63:842–5
- Freyenhagen R, Rolke R, Baron R, Tölle TR, Rutjes AK, Schu S, Treede RD: Pseudoradicular and radicular low-back pain—A disease continuum rather than different entities? Answers from quantitative sensory testing. *Pain* 2008; 135:65–74
- Kaki AM, El-Yaski AZ, Youseif E: Identifying neuropathic pain among patients with chronic low-back pain: Use of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale. *Reg Anesth Pain Med* 2005; 30:422–8
- Bennett MI, Attal N, Backonja MM, Baron R, Bouhassira D, Freynhagen R, Scholz J, Tölle TR, Wittchen HU, Jensen TS: Using screening tools to identify neuropathic pain. *Pain* 2007; 127:199–203
- Freyenhagen R, Baron R: The evaluation of neuropathic components in low back pain. *Curr Pain Headache Rep* 2009; 13:185–90
- Baron R, Martin-Mola E, Müller M, Dubois C, Falke D, Steigerwald I: Effectiveness and safety of tapentadol prolonged release (PR) *versus* a combination of tapentadol PR and pregabalin for the management of severe, chronic low back pain with a neuropathic component: A randomized, double-blind, phase 3b study. *Pain Pract* 2015; 15:455–70
- Cohen SP, Argoff CE, Carragee EJ: Management of low back pain. *BMJ* 2008; 337:a2718
- Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, Owens DK: Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel: Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147:478–91
- Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS: Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007; 132:237–51
- Nemeroff CB, Schatzberg AF, Goldstein DJ, Detke MJ, Mallinckrodt C, Lu Y, Tran PV: Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull* 2002; 36:106–32
- Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA: Duloxetine, 60 mg once daily, for major depressive disorder: A randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002; 63:308–15
- Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA: Duloxetine 60 mg once daily dosing *versus* placebo in the acute treatment of major depression. *J Psychiatr Res* 2002; 36:383–90
- Allgulander C, Hartford J, Russell J, Ball S, Erickson J, Raskin J, Rynn M: Pharmacotherapy of generalized anxiety disorder:

- Results of duloxetine treatment from a pooled analysis of three clinical trials. *Curr Med Res Opin* 2007; 23:1245–52
21. Sultan A, Gaskell H, Derry S, Moore RA: Duloxetine for painful diabetic neuropathy and fibromyalgia pain: Systematic review of randomised trials. *BMC Neurol* 2008; 8:29
 22. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S: Duloxetine *vs.* placebo in patients with painful diabetic neuropathy. *Pain* 2005; 116:109–18
 23. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, Wernicke JF: A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med* 2005; 6:346–56
 24. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, Raskin J: A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology* 2006; 67:1411–20
 25. Skljarevski V, Desai D, Liu-Seifert H, Zhang Q, Chappell AS, Detke MJ, Iyengar S, Atkinson JH, Backonja M: Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine (Phila Pa 1976)* 2010; 35:E578–85
 26. Skljarevski V, Ossanna M, Liu-Seifert H, Zhang Q, Chappell A, Iyengar S, Detke M, Backonja M: A double-blind, randomized trial of duloxetine *versus* placebo in the management of chronic low back pain. *Eur J Neurol* 2009; 16:1041–8
 27. Skljarevski V, Zhang S, Chappell AS, Walker DJ, Murray I, Backonja M: Maintenance of effect of duloxetine in patients with chronic low back pain: A 41-week uncontrolled, dose-blinded study. *Pain Med* 2010; 11:648–57
 28. Skljarevski V, Zhang S, Desai D, Alaka KJ, Palacios S, Miazgowski T, Patrick K: Duloxetine *versus* placebo in patients with chronic low back pain: A 12-week, fixed-dose, randomized, double-blind trial. *J Pain* 2010; 11:1282–90
 29. Khoromi S, Cui L, Nackers L, Max MB: Morphine, nortriptyline and their combination *vs.* placebo in patients with chronic lumbar root pain. *Pain* 2007; 130:66–75
 30. McHorney CA, Ware JE Jr, Raczek AE: The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; 31:247–63
 31. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; 94:149–58
 32. Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P, Farrar JT, Hertz S, Raja SN, Rappaport BA, Rauschkolb C, Sampaio C: Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2009; 146:238–44
 33. O'Connor AB: Neuropathic pain: Quality-of-life impact, costs and cost effectiveness of therapy. *Pharmacoeconomics* 2009; 27:95–112
 34. Morlion B: Pharmacotherapy of low back pain: Targeting nociceptive and neuropathic pain components. *Curr Med Res Opin* 2011; 27:11–33
 35. Atkinson JH, Slater MA, Wahlgren DR, Williams RA, Zisook S, Pruitt SD, Epping-Jordan JE, Patterson TL, Grant I, Abramson I, Garfin SR: Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity. *Pain* 1999; 83:137–45
 36. Khoromi S, Patsalides A, Parada S, Salehi V, Meegan JM, Max MB: Topiramate in chronic lumbar radicular pain. *J Pain* 2005; 6:829–36
 37. Cohen SP, Hanling S, Bicket MC, White RL, Veizi E, Kurihara C, Zhao Z, Hayek S, Guthmiller KB, Griffith SR, Gordin V, White MA, Vorobeychik Y, Pasquina PF: Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: Multicenter randomized double blind comparative efficacy study. *BMJ* 2015; 350:h1748
 38. Vanelderen P, Van Zundert J, Kozicz T, Puylaert M, De Vooght P, Mestrum R, Heylen R, Roubos E, Vissers K: Effect of minocycline on lumbar radicular neuropathic pain: A randomized, placebo-controlled, double-blind clinical trial with amitriptyline as a comparator. *ANESTHESIOLOGY* 2015; 122:399–406
 39. Steigerwald I, Müller M, Davies A, Samper D, Sabatowski R, Baron R, Rozenberg S, Szczepanska-Szerej A, Gatti A, Kress HG: Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: Results of an open-label, phase 3b study. *Curr Med Res Opin* 2012; 28:911–36