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Research Article

Comparative Efficacy of Pregabalin and Duloxetine in the Management of Diabetic Neuropathic Pain: A Randomized Controlled Study

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ABSTRACT

Objective: To assess and compare the efficacy, safety and patient-reported outcomes of pregabalin versus duloxetine in adults with painful diabetic peripheral neuropathy (DPN).

Methods: Prospective, Double blind, Double dummy, Parallel group, Randomized control trial was done in three tertiary care centers. Adults (30-70 years) with type 2 diabetes mellitus (T2DM) and confirmed painful DPN (Numerical Rating Scale [NRS]≥5)were randomized 1:1 to receive either pregabalin (150-300 mg/day) or duloxetine (60 mg/day) for 12 weeks. P value of < 0.05 was considered statistically significant.

Results: Both treatments resulted in significant decrease in pain from baseline ($p<0.001$). At weeks 2 and 4, pregabalin had a faster onset of action than duloxetine for pain ($p=0.003$ and 0.012, respectively), and SF-36 mental component scores ($p=0.008$ and $p=0.021$, respectively) at 12 weeks. There was a similar responder rate (pregabalin 68.3% and duloxetine 65.7%, $p=0.71$). The incidence of nausea and dry mouth was increased with duloxetine compared with pregabalin (all $p<0.05$), while dizziness and weight gain were increased with pregabalin compared with duloxetine.

Conclusion: Both Pregabalin and Duloxetine shown to be equally effective for the relief of DPN pain for 12 weeks, but they have different onset of action, patient-reported outcomes, and adverse effect profile. Choices of treatment should be individualized, taking into account symptom dominance and comorbid conditions, as well as tolerability.

Keywords: Diabetic Neuropathic Pain, Pregabalin, Duloxetine, Randomized Controlled Trial, Neuropathy Management, SNRI, Calcium Channel Modulator.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the common and crippling microvascular complications of diabetes mellitus affecting around 30-50% of people who have had type 2 diabetes for a long time. DPN presents with a wide clinical spectrum from silent nerve dysfunction to chronic, severely painful neuropathic syndromes, with a marked impact on mobility, sleep architecture, psychological well-being and quality of life. DPN can develop due to a variety of pathophysiological mechanisms that include chronic hyperglycemia-induced metabolic derangements including increased polyol pathway flux, advanced glycation end-product

accumulation, oxidative stress, mitochondrial dysfunction and microvascular ischemia. Such cascades eventually result in myelin degeneration, central and peripheral nociceptive signaling and aberrant myelination. Therefore, the control of painful DPN is far more than glycemic control and involves specific pharmacological modulation of pathological pain transmission[1,2].

Current 1st line therapeutic agents recommended by international guidelines are calcium channel alpha-2-delta ligands such as pregabalin and gabapentin, serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine), and tricyclic antidepressants (amitriptyline, nortriptyline). Of these, pregabalin and duloxetine have proved to be cornerstone treatments, with good evidence bases, good risk benefit ratios and specific regulatory approval for the treatment of DPN. Pregabalin is a gamma-aminobutyric acid (GABA) receptor that binds tightly to the alpha-2-delta subunit of voltage-gated calcium channels on presynaptic neurons, which blocks calcium influx and limits the release of excitatory neurotransmitters including glutamate, substance P and norepinephrine in the dorsal horn of the spinal cord. This is very effective in reducing central sensitization and hyper-excitability of neuropathic pain states. Pregabalin is consistently effective in lowering the intensity of pain [3,4] and improving sleep quality and functional outcomes, and the onset of action is usually seen after one week of treatment.

Duloxetine has been shown to inhibit reuptake of monoamines in descending pain modulatory pathways which arise from the brainstem and thereby enhance endogenous inhibitory mechanisms at the spinal level that inhibit the transmission of nociceptive impulses. But duloxetine's therapeutic effect is typically delayed, with peak analgesia effects taking two to four weeks to occur, and its tolerability profile is often restricted by gastrointestinal and autonomic side effects [5,6]. Both agents are commonly used and recommended as first line treatments; however, there is limited direct comparative information available and much of the data available comes from indirect network meta-analyses or older randomized trials with varying endpoints. A gap in evidence-based treatment of neuropathic pain is the lack of well-designed direct comparative trials that employ standardized patient reported outcome measures and comprehensive safety profiling, and that have been conducted recently [7,8]. A direct comparative randomized controlled trial is warranted because of the desire to provide the optimal prescribing strategy for each patient in the real world. Pregabalin is effective in treating pain, as is duloxetine, but the differences in their pharmacokinetics, actions, onset, and side effects mean that they are not all equally good. Modern guidelines focus on precision medicine management of neuropathic pain, but there is still not enough high-quality comparative evidence to support the algorithmic selection of the proper management [9,10].

MATERIALS AND METHODS

This study was carried out as a prospective, randomized, double blind, double dummy, parallel group, clinical trial at Ibn-e-Siena hospital and research institute, Multan. Pakistan. The length of the trial was 18 months for recruitment, 12 weeks for the interventional period, and 2 weeks for the post-treatment safety monitoring. Patients were screened for inclusion in the study if they were adults (30-70 years) with confirmed type 2 diabetes mellitus for at least 5 years. The Toronto Consensus criteria was used to define painful DPN, which was defined as both clinical evidence (symmetrical distal sensory loss and lack of ankle reflexes) and electrodiagnostic proof (electroneurographic evidence of axonal polyneuropathy). Participants eligible for the study had a baseline pain intensity score ≥5 on an 11-point Numerical Rating Scale (NRS) that lasted for ≥ 3 months. Patients needed to have a stable blood glucose level (HbA1c ≤9.0%) and diabetes medication regimen for at least 8 weeks before screening. Exclusion criteria included moderate to severe renal impairment (eGFR <30 mL/min/1.73m²), moderate to severe hepatic dysfunction, uncontrolled hypertension (systolic >160

mmHg), history of substance use disorder within the last 2 years, use of other neuropathic pain drugs or antidepressants within the previous 4 weeks, non-diabetic neuropathies, pregnancy or breastfeeding, and known hypersensitivity to pregabalin or duloxetine. Randomization and Blinding Eligible participants were randomized in a 1:1 ratio using a computer-generated block randomization sequence (block size 4) stratified by baseline HbA1c < 7.5% vs. ≥7.5% and baseline NRS 5–7 vs. 8–10). Randomization was done in a central manner by using a web-based random allocation system, which ensured allocation concealment. Allocation of treatment was kept blinded to patients and investigators during the trial. Unblinding was done only in instances of severe adverse events that demanded immediate clinical intervention. Intervention Protocol Pregabalin was initiated at 75mg once daily for 3 days, stepped up to 75mg twice daily by week 1 and up to 150mg twice daily (300mg daily) by week 2 if tolerated and pain persisted. Duloxetine was started at 30 mg/day for 1 week to help minimize gastrointestinal side effects, followed by an increase to 60 mg/day for the next 11 weeks. All medications were administered in divided doses if applicable and dose reduction was allowed if an adverse event was intolerable, but no more than 50% before considering discontinuation. The use of rescue analgesics (acetaminophen ≤2 g/day) was allowed and recorded, but not included in the main analysis, as it was regarded as a covariate. Primary Endpoint Mean NRS pain score change from baseline to week 12. Secondary endpoints were: (1) the change of Brief Pain Inventory (BPI) interference score (which measures the impact of pain on functioning); (2) the change of Pittsburgh Sleep Quality Index (PSQI) total score; (3) the change of SF-36 Health Survey physical and mental component summaries; (4) treatment adherence measured by the percentage of pills counted and by compliance with an electronic diary; (5) incidence of adverse events, severity of adverse events, and changes in laboratory parameters; and (6) responder rate, defined as a ≥50% reduction in NRS from baseline. Assessments for all measures were in baseline and at weeks 2, 4, 8 and 12. With a standard deviation of 2.0, alpha of 0.05, and a power of 80%, a sample size of at least 94 patients per group was needed. With an expected 15% drop out, 220 participants were expected with 110 in each arm. For improving the statistical robustness, 240 patients were randomized. Data analysis: The analyses were conducted using intention-to-treat (ITT) approach with missing values handled by multiple imputation. Between-group comparisons of the primary endpoint were performed using analysis of covariance (ANCOVA) with baseline NRS, baseline HbA1c and site as covariates. Linear mixed-effects models (LMMs) with random intercepts were used to model longitudinal pain trajectories. Chi-square or Fisher's exact test was used for the analysis of categorical variables. Safety data were reported descriptively and comparisons of AEs between groups were made using logistic regression. A $p<0.05$ was defined as statistically significant.

RESULTS

Of those, 228 patients (95.0%) followed the 12 week study protocol, 114 patients per treatment arm. Of the 12 participants who discontinued treatment prematurely, 6 experienced adverse events (4 on pregabalin, 2 on duloxetine), 3 were lost to follow-up, 2 had protocol deviations and 1 for personal reasons.

Both agents achieved clinically meaningful pain reduction from baseline, however, pregabalin achieved a statistically significantly greater degree of pain reduction at weeks 2 and 4 ($p<0.05$) and a more rapid onset of analgesic effect.

Table 1: Mean Change in Numerical Rating Scale (NRS) Pain Score over Time

Timepoint	Pregabalin (n=114) MeanΔNRS(±SD)	Duloxetine (n=114) MeanΔNRS (±SD)	p-value

Week 2	-2.1± 0.8	-1.3± 0.9	0.003
Week 4	-3.2± 0.7	-2.4± 0.8	0.012
Week 8	-3.6± 0.6	-3.3± 0.7	0.084
Week 12	-3.8± 0.5	-3.6± 0.6	0.041

Duloxetine produced statistically significant greater improvement in pain interference (BPI), sleep quality (PSQI) and mental health-related quality of life (SF-36 MCS) than pregabalin after 12 weeks (all $p<0.05$).

Table 2: secondary Patient-Reported Outcomes at Week 12

Parameter	Pregabalin (Mean±SD)	Duloxetine (Mean± SD)	p-value
BPI Interference Score	3.1± 1.2	2.6± 1.1	0.009
PSQI Total Score	8.4± 2.3	6.2± 2.1	0.008
SF-36 Mental Component	44.2± 6.8	48.7± 5.9	0.021
SF-36 Physical Component	41.5± 7.1	43.2± 6.9	0.134

There was no statistically significant difference between the responder rates for ≥30% pain reduction and ≥50% ($p>0.05$) which indicates that there is similar clinical efficacy overall.

Table 3: The Rates of Responders and Adherence to Treatment

Outcome	Pregabalin (%)	Duloxetine (%)	p-value
≥50% NRS Reduction (Responder)	68.3	65.7	0.712
≥30% NRS Reduction	84.2	81.6	0.604
Pill Count Adherence (≥80%)	89.5	91.2	0.643
Diary Compliance (≥80%)	87.7	90.4	0.488

The adverse event profiles were different to a large extent between treatment arms, due to their different modes of action. All the central nervous system related events and metabolic effects (weight gain) were more frequent with Pregabalin and statistically significant ($p<0.05$).

Table 4: Adverse Event Profile by System Organ Class (SOC)

Adverse Event	Pregabalin (%)	Duloxetine (%)	p-value
Dizziness	28.9	9.6	<0.001
Somnolence	22.4	11.4	0.024
Weight Gain(≥2kg)	19.3	5.3	0.003
Nausea	10.5	31.6	<0.001
Dry Mouth	8.8	26.3	<0.001
Constipation	6.1	14.0	0.041

There were no changes of clinical relevance in metabolic and hepatic parameters in either group. Compared to pregabalin, however, duloxetine was found to have a statistically significant effect on increasing SBP ($p=0.018$).

Table 5: Laboratory and Metabolic Parameters Change from Baseline to Week 12

Parameter	Pregabalin (MeanΔ)	Duloxetine (MeanΔ)	p-value
HbA1c (%)	-0.1± 0.3	-0.2± 0.4	0.112
Fasting Glucose (mg/dL)	+2.4± 18.1	-1.6± 16.8	0.098
ALT (U/L)	+4.2± 12.3	+6.8± 14.1	0.154
Creatinine (mg/dL)	+0.02± 0.11	+0.01± 0.09	0.431
Blood Pressure (mmHg) Systolic	+1.2± 8.4	+4.6± 9.2	0.018

DISCUSSION

The current randomized controlled trial provides up-to-date, head-to-head comparison of the efficacy, safety and patient-centered outcomes of the use of pregabalin versus duloxetine in the treatment of painful diabetic peripheral neuropathy. Both agents were clinically effective in reducing pain over a 12-week period and had similar responder rates and high levels of treatment adherence. The more rapid onset of action for pregabalin is observed in line with its mechanism of action acting on the presynaptic voltage gated calcium channel, which quickly regulates the release of excitatory neurotransmitters in the dorsal horn. There are clinical implications of these temporal differences: pregabalin may be a better choice when immediate symptom relief is desired; duloxetine may be more suited for patients with comorbid mood disorders or sleep difficulties [11,12]. In our secondary end point analyses, duloxetine was more effective in improving sleep quality as well as reducing pain interference and mental health-related quality of life. These conclusions are mechanistically plausible, because serotonergic and noradrenergic enhancement can modulate nociceptive transmission, and can also affect the stability of circadian rhythms and circuits related to emotional processing. The findings of the Pittsburgh Sleep Quality Index for improvement with duloxetine are consistent with more recent meta-analyses that show that SNRIs are particularly beneficial in patients with neuropathic pain who have depressive symptoms or insomnia [13,14]. On the other hand, the relatively narrow spectrum of activity of pregabalin means that it might be best suited in patients whose chief complaint is pain from isolated neuropathic pain rather than those with prominent affective or sleep architecture-altering symptoms. The increased incidence of nausea, dry mouth and moderate elevation of systolic blood pressure is consistent with the anticholinergic and noradrenergic effects of duloxetine and is a reason for caution in patients at risk of gastrointestinal sensitivity, glaucoma and cardiovascular disease [15,16].

Our study, however, builds on literature by using a very well controlled double-dummy design, validated instruments that have been standardized, and a comprehensive longitudinal analysis that includes an assessment of both the analgesic trajectory and comprehensive patient-reported outcomes. Many previous studies used variable doses or open-label designs or had short follow-up times, which may have masked meaningful differences. In addition, multiple imputations for missing data and intention-to-treat analysis increases the validity of our findings [17,18]. There are several assets to this investigation. A multicenter design increases generalizability and stratification of randomizations allow for balancing for important prognostic factors. The double-dummy method is an effective method to ensure blind integrity and reduces performance and detection bias. Multidimensional assessment of the impact of treatment includes comprehensive outcome measures that measure pain intensity, functional interference, sleep, quality of life, and laboratory parameters. The 12 week treatment period did not measure long-term efficacy, tolerance or late onset adverse

events. Dose titration followed a standardized protocol which might not mimic flexible dosing in real life conditions, possibly underestimating the potential benefits of higher doses of pregabalin and/or slower titration of duloxetine in some populations. Longer-term follow-up studies to assess long-lasting efficacy, combination therapy and biomarker-based patient selection should be the focus of future research. Mechanism-based treatment allocation will be possible in the future, thanks to the new applications of neuroimaging and quantitative sensory testing in predicting drug response, which will replace the current "trial and error" methods[19,20,21,22].

These findings reinforce a clinical strategy of symptom-driven and/or comorbidity-informed prescribing. Patients who have significant sleep disturbance, comorbid depression or who prefer once daily dosing may be suitable for duloxetine starting, whereas patients who require prompt pain relief, have substantial pain interference without depression or who are well-tolerant of CNS depressants may be more appropriate for pregabalin. Shared decision-making, therapeutic optimization and adverse effects monitoring are still core elements in managing diabetic neuropathic pain.

CONCLUSION

Overall results of the 12-week treatment suggest that Pregabalin and duloxetine are equally effective in providing pain relief for diabetic neuropathic pain, with similar responder rates and high rates of treatment adherence. Pregabalin, however, has faster analgesic efficacy, and duloxetine results in better improvement in sleep quality, pain interference and mental health-related quality of life. The adverse event profiles are also very different, with higher rates of dizziness and weight gain reported with pregabalin, and nausea, dry mouth and mild increases in systolic blood pressure reported more frequently with duloxetine. Treatment choice must be tailored to the symptom dominance, their risk tolerance, their comorbidities, and their pharmacokinetics.

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