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Pregabalin and amitriptyline as first-line drugs among patients with painful peripheral diabetic neuropathy: a systematic review and meta-analysis

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ABSTRACT. – OBJECTIVE: Painful peripheral diabetic neuropathy (PRDN) is a common disabling condition. Pregabalin and amitriptyline are commonly prescribed as the first-line for PPDN despite the contradicting recommendations. There is a need to inform the scientific community regarding first-line pain control among patients with PPDN. This meta-analysis assessed pregabalin and amitriptyline effects on PPDN.

PATIENTS AND METHODS: We searched PubMed, MEDLINE, Cochrane Library, EBSCO, and Google Scholar; the terms used were amitriptyline, pregabalin, painful diabetic neuropathy, antidepressant, gabapentinoids, quality of life, and adverse events. Boolean operators like AND, and OR were used. Six hundred and thirty-one studies were retrieved, and 37 full texts were screened. However, only six randomized controlled trials fulfilled the inclusion and exclusion criteria.

RESULTS: No significant statistical differences between amitriptyline and pregabalin regarding pain score and significant pain reduction (odd ratio, -0.82, 95% CI, -2.21-0.58, and odd ratio, 1.16, 95% CI, 0.76-1.76 respectively). Quality of life, total adverse events, and drug discontinuation were not different between the two drugs (odd ratio, 0.89, 95% CI, -2.11-3.89, odd ratio, 0.98, 95% CI, 0.52-1.85, and odd ratio, 0.51, 95% CI, 0.08-3.15, respectively).

CONCLUSIONS: No significant statistical differences between amitriptyline and pregabalin regarding their effects on pain and quality of life. The drugs showed similar total adverse events and drug withdrawal. Further larger real-world studies are needed.

Key Words:
Amitriptyline, Pregabalin, Pain control, Side effects, Drug discontinuation.

Introduction

Diabetic peripheral neuropathy (DPN) is the most common type of neuropathy; it affects nearly one-half of patients, depending on the duration of diabetes. Diabetic peripheral neuropathy is associated with high morbidity and mortality[1]. Diabetic peripheral neuropathy, in particular small-fire type, can increase the sensitivity to noxious stimuli and intractable pain. Therefore, patients suffering from DPN have disturbed sleep and poor quality of life[2]. Hyperglycemia and poor glycemic control are the major determinants of DPN, thus, improving glycemic control and addressing the components of the metabolic syndrome are essential[3]. Nearly one hundred million people suffer from painful diabetic peripheral neuropathy (25% of patients with diabetes), and the number is on the rise, mirroring the epidemic of type 2 diabetes[4], however, despite the high prevalence, there is underdiagnosis and treatment with a substantial burden on sleep, depression, financial instability, and poor quality of life[5]. The primary goal of painful DPN is to improve the overall function and not merely pain management. Quality of life, mood, and sleep are other important factors in the diabetes holistic care[6]. Pain, mood, sleep, and quality of life interaction are complex, each might exacerbate others with deleterious consequences. Importantly, complete pain resolution is achievable in only 30-50% of patients, and pain reduction is the main objective[7,8].

Many non-pharmacological interventions exist for the treatment of painful DPN, including lifestyle, dietary supplements, nerve stimulation, and acupuncture. However, the evidence is poor except for spinal cord stimulation[9].

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Most of the guidelines including the American Association of Clinical Endocrinology Clinical Practice, the American Diabetes Association, and American Academy of Neurology recommend gabapentinoids, including pregabalin and amitriptyline, as the first-line treatment for painful DPN[10-12], except for Diabetes Canada guidelines, which recommended pregabalin as the first suitable choice[13]. Compelling indications for various classes are, for example, serotonin and norepinephrine reuptake inhibitors among patients with depression and obesity and gabapentinoids among those with obesity, renal impairment, and hepatic failure[14].

To the best of our knowledge, face-to-face comparison between pregabalin and amitriptyline among patients with painful diabetic neuropathy is scarce. Therefore, we went ahead to compare pregabalin and amitriptyline regarding their effects on pain and quality of life and assessed the total adverse events of these two first-line therapies.

Patients and Methods

This meta-analysis was conducted during August and September 2023 with extreme adherence to the PRISMA Guidelines. All articles published in the English language from inception up to September 2023 were eligible.

Inclusion Criteria

Randomized controlled trials comparing amitriptyline and pregabalin among patients with painful diabetic neuropathy were included in the study.

Exclusion Criteria

Prospective and retrospective cohorts, cross-sectional studies, case-control studies, editorials, expert opinions, and case reports were excluded. The search engine was limited to articles published in English.

Outcomes Measure

To compare the effects of amitriptyline and pregabalin, we evaluated pain reduction based on changes in baseline pain scores and the proportion of patients experiencing more than 50% pain reduction. Additionally, we assessed the impact on quality of life using a quality of life questionnaire and documented the total adverse effects.

Literature Search

The authors' manuscript independently searched PubMed, MEDLINE, Cochrane Library, EBSCO, and the first hundred articles in Google Scholar, the terms used were amitriptyline, pregabalin, painful diabetic neuropathy, antidepressant, gabapentinoids, quality of life, side effects, adverse events, and drug discontinuation. Boolean operators like AND, and OR were used. Six hundred and thirty-one studies were retrieved, and five hundred and twenty-three remained after duplication removal. Of them, 37 full texts were screened. However, only six randomized controlled trials were included in the final meta-analysis (Figure 1).

Data Extraction

A structured checklist was used to gather the author's name, country, year of publication, number of patients in amitriptyline and pregabalin arms, number of patients who experienced significant pain reduction, total adverse event in amitriptyline and pregabalin arms, and pain score reduction. Age, sex, study duration, doses of amitriptyline and pregabalin, and quality of life were recorded (Tables I, II, III).

Risk of Bias Assessment

The Cochrane Risk of Bias Assessment tool[15] assessed the quality of the included studies (see Table IV).

Statistical Analysis

RevMan version 5.4 (London, UK) was used to analyze the dichotomous and continuous data of seventeen cohorts from six randomized controlled trials. The fixed and random effects were used depending on heterogeneity. To test the effects of amitriptyline and pregabalin on pain reduction and total side effects. A p-value < 0.05 was considered significant.

Results

Included Studies

Seventeen cohorts from six randomized trials were included, four of them were from Asia[16-19] and two from Europe[2,20]. The study duration of the included studies ranged from 5 to 12 weeks and the participants were matched for age and sex. The dose for pregabalin ranged from 150 mg to 600 mg/day, while amitriptyline dose ranged from 25 mg to 125 mg daily.

Table I. Pain reduction and quality of life among patients on amitriptyline and pregabalin.

Author name	Country	Reduction of pain score (mean ± SD)		Reduction of pain score (no)		Quality of life	
		Amitriptyline	Pregabalin	Amitriptyline	Pregabalin	Amitriptyline	Pregabalin
Bansal et al 2009[16]	India	2.75±0.96/44	2.75±0.96/44	32/44	34/44	Not assessed	Not assessed
Boyle et al 2012[2]	UK	1.8±0.1/23	3.6±0.3/19	Not assessed	Not assessed	45.1±8.4/23	41.75±10.45/19
Chakrabarty et al 2019[17]	India	27.78±4.82/31	30.45±5.03/31	Not assessed	Not assessed	Not assessed	Not assessed
Daniel et al 2018[18]	India	23.15±4.43 /40	25.22±5.63/40/	37/40	36/40	Not assessed	Not assessed
Tesfaye et al 2022[19]	UK	2.9±2/100	2.5±2.2/104	38/100	36/104	36.05±12.75/100	36.05±12.75/104
Shabbir et al 2011[20]	Pakistan	Not assessed	Not assessed	55/70	64/70	Not assessed	Not assessed

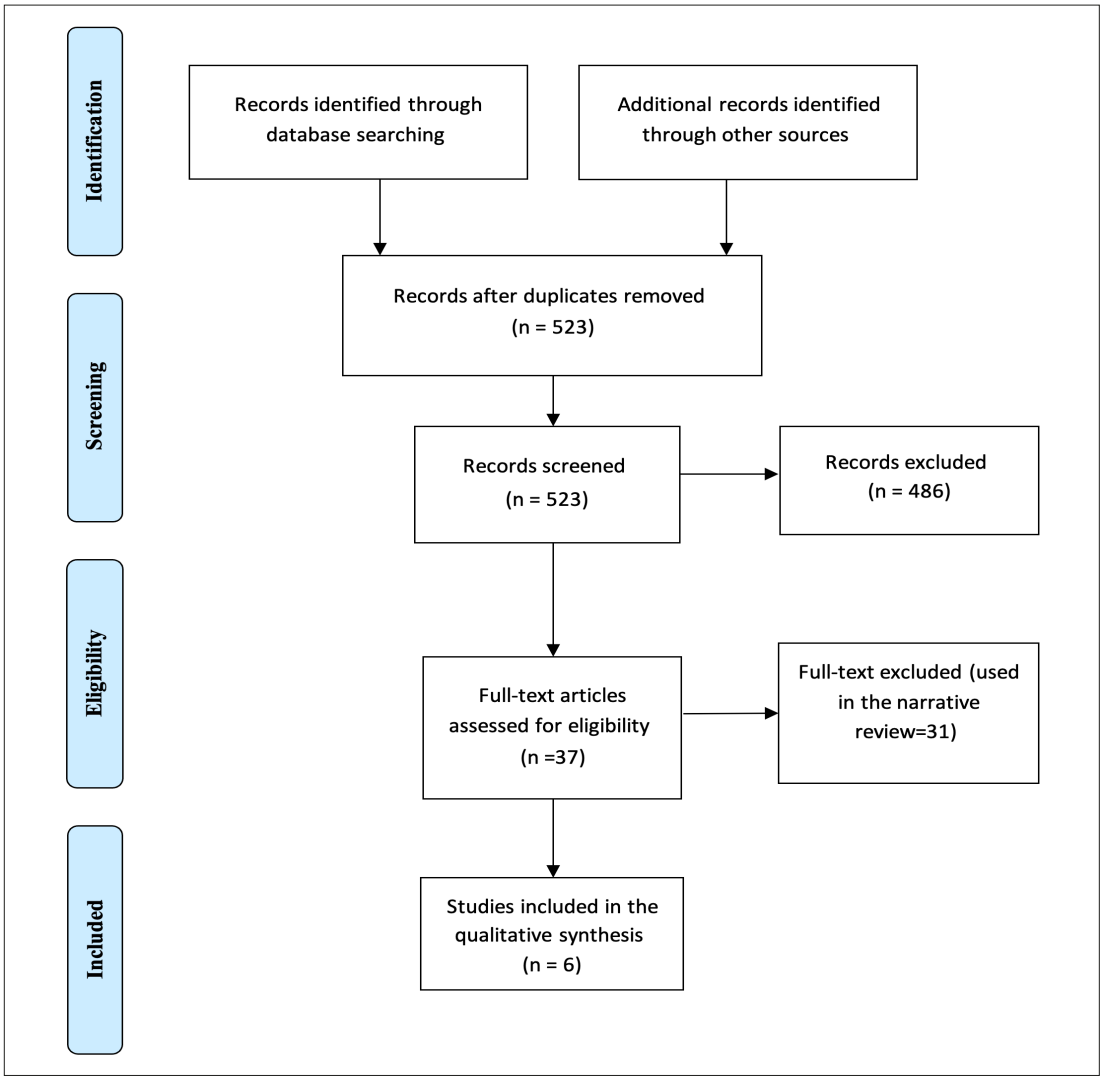

Figure 1. PRISMA flowchart of the selected studies.

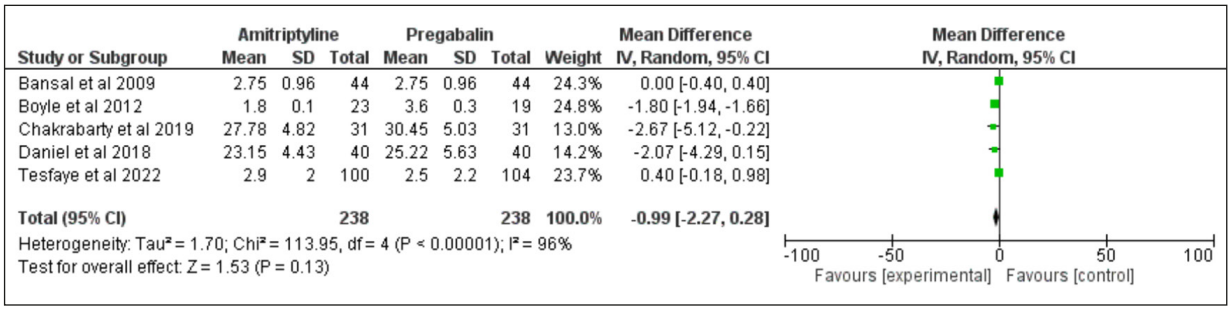

Figure 2. Change from baseline pain score among patients with painful diabetes neuropathy and receiving amitriptyline or pregabalin (forest plot).

Table II. Total adverse events and treatment discontinuation among patients with painful diabetes neuropathy and receiving amitriptyline or pregabalin.

Author name	Country	Amitriptyline	Pregabalin	Amitriptyline	Pregabalin
Bansal et al 2009[16]	India	3/44	2/44	Not observed	Not observed
Boyle et al 2012[2]	UK	1/23	6/19	6/27	1/28
Chakrabarty et al 2019[17]	India	5/31	3/31	11/42	3/34
Daniel et al 2018[18]	India	4/40	2/40	Not observed	Not observed
Tesfaye et al 2022[19]	UK	8/100	7/104	5/107	11/104

Pain Score Reduction

In the present meta-analysis, five cohorts assessed the improvement in pain score among patients with painful diabetic neuropathy (576 patients included) with no significant statistical difference between amitriptyline and pregabalin (odd ratio: -0.99, 95% CI: -2.27-0.28, *p*-value for overall effect: 0.13, and Chi-square: 113.95). A significant heterogeneity was found (I^2 for heterogeneity: 96% and *p*-value for heterogeneity: < 0.001; Figures 2 and 3). No significant statistical difference was found after removing Boyle et al[2] to reduce heterogeneity (odd ratio: -0.31, 95% CI: -1.14-0.51, *p*-value for overall effect: 0.46, and the heterogeneity was 69%; Figure 4).

Significant (> 50%) Pain Reduction

No significant difference was evident between amitriptyline and pregabalin regarding the number of patients (512 patients from four cohorts) who had significant pain reduction (> 50%) (odd ratio: 1.16, 95% CI: 0.76-1.76, *p*-value for overall effect: 0.49,

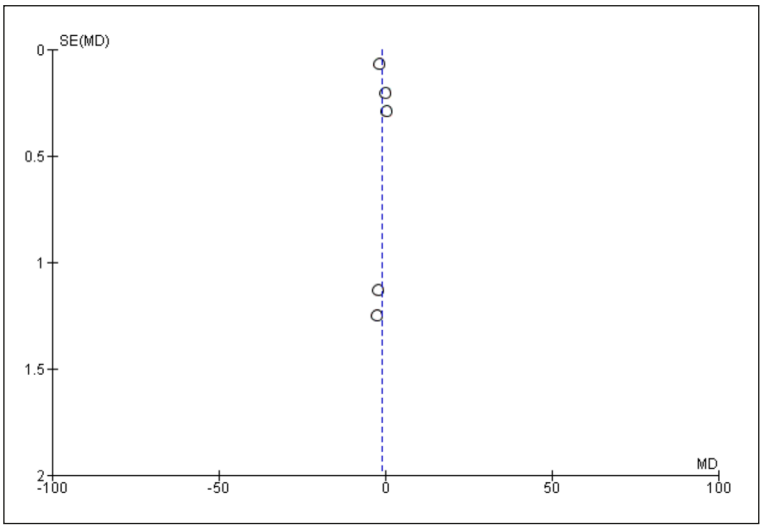

Figure 3. Change from baseline pain score among patients with painful diabetes neuropathy and receiving amitriptyline or pregabalin (Funnel Plot).

Table III. Age, sex, study duration, and doses of amitriptyline and pregabalin.

Author name	Age, sex	Amitriptyline dose	Pregabalin dose	Duration of therapy
Bansal et al 2009[16]	matched	50 mg/day	300 mg/day	5 weeks
Boyle et al 2012[2]	Matched	75 mg/day	300 mg/day	6 weeks
Chakrabarty et al 2019[17]	Matched	25 mg/day	150 mg/day	12 weeks
Daniel et al 2018[18]	Matched	125 mg/day	300 mg/day	6 weeks
Tesfaye et al 2022[19]	Matched	75 mg/day	600 mg/day	16 weeks
Shabbir et al 2011[20]	Matched	75 mg/day	300 mg/day	6 weeks

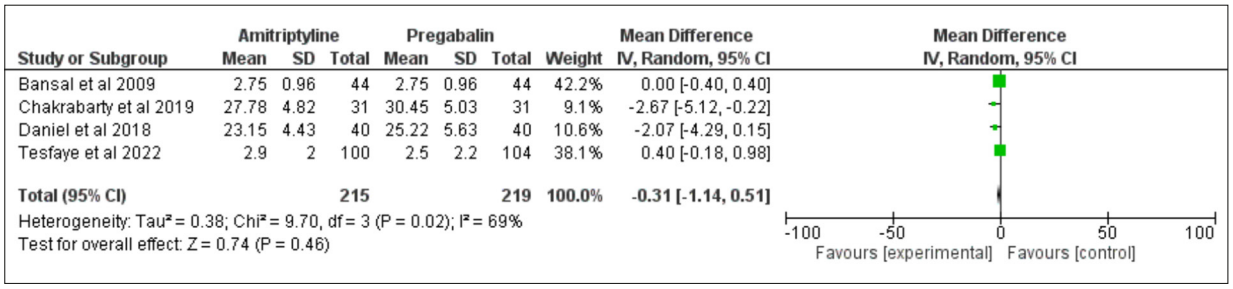

Figure 4. Change from baseline pain score among patients with painful diabetes neuropathy and receiving amitriptyline or pregabalin following the sensitivity analysis and removing the study with highest heterogeneity.

and Chi-square: 4.56). No significant heterogeneity was observed (I^2 for heterogeneity: 34% and *p*-value for heterogeneity: 0.21; Figure 5).

Effects on Patient's Quality of Life

No difference was found between the two drugs regarding the effects on patients' quality of life (only two cohorts with 246 patients included).

The Total Adverse Events

The total adverse events were not different among patients who took amitriptyline or pregabalin (472 patients from five cohorts; odd ratio: 0.98, 95% CI: 0.52-1.85, *p*-value for overall effect: 0.96, and Chi-square: 5.67). No significant heterogeneity was observed (I^2 for heterogeneity: 29% and *p*-value for heterogeneity: 0.23; Figure 6).

Treatment Discontinuation Due to Adverse Events

No significant difference was observed regarding treatment discontinuation (odd ratio: 0.51, 95% CI: 0.08-3.15, *p*-value for overall effect: 0.47, and Chi-square: 8.98). A significant heterogeneity was observed (I^2 for heterogeneity: 78% and *p*-value for heterogeneity: 0.01; Figure 7).

Table IV. Cochrane risk of bias of the included randomized controlled trial.

Author	Selection bias[1]	Selection bias[2]	Performance bias	Attrition bias	Detection bias	Reporting bias	Overall bias
Bansal et al 2009[16]	low	Low	Low	Low	Some concern	High	Some concern
Boyle et al 2012[2]	Low	Low	Low	Low	Some concern	Low	Low
Chakrabarty et al 2019[17]	Low	Some concern	high	Low	High	low	Some concerns
Daniel et al 2018[18]	Low	Low	Low	Some concern	High	Some concern	Some concern
Tesfaye et al 2022[19]	Low	Low	Low	Low	Low	Low	Low
Shabbir et al 2011[20]	Low	Low	Low	Low	Some concern	Low	Low
Bansal et al 2009[16]	Some concern	Some concern	Low	Low	Some concern	Low	Some concern

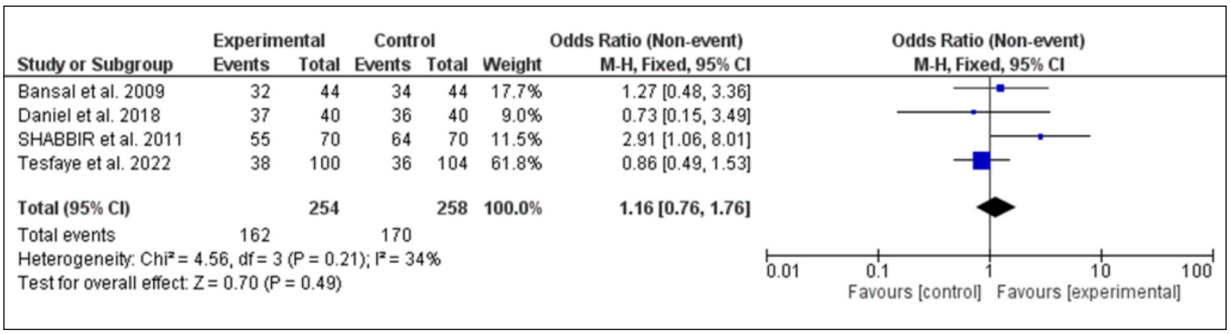

Figure 5. Significant pain reduction among patients with painful diabetes neuropathy and receiving amitriptyline or pregabalin.

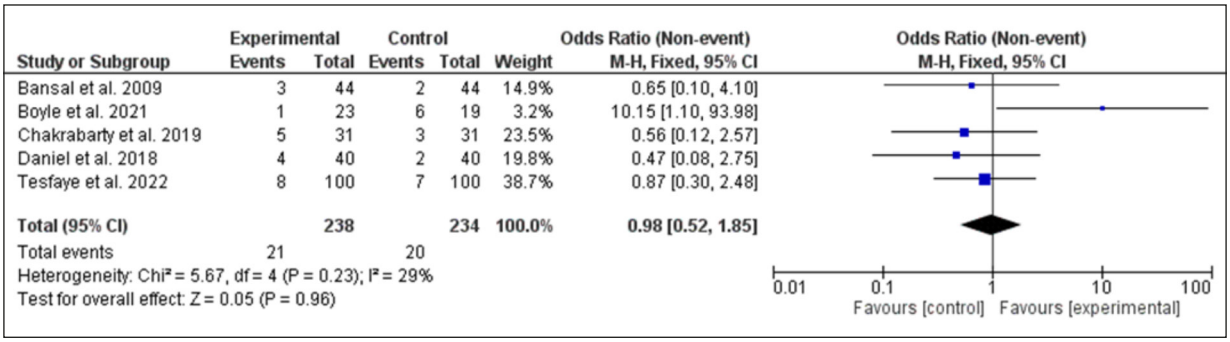

Figure 6. Total adverse events among patients with painful diabetes neuropathy and receiving amitriptyline or pregabalin.

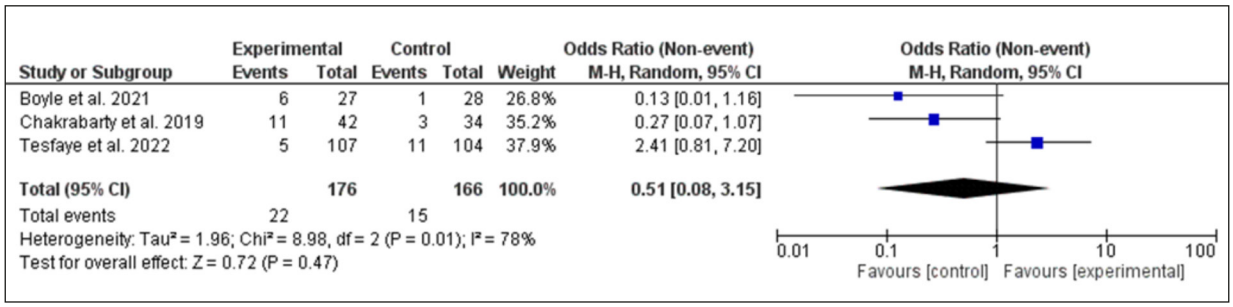

Figure 7. Treatment discontinuation among patients with painful diabetes neuropathy and receiving amitriptyline or pregabalin.

Discussion

In the present meta-analysis, no significant difference was evident between pregabalin and amitriptyline regarding their effects on pain reduction, odd ratio: -0.99, 95% CI: -2.27-0.28. In addition, no significant statistical difference was found after removing Boyle et al[2] to reduce heterogeneity (odd ratio: -0.31, 95% CI: -1.14-0.51). The significant (> 50%) pain reduction was not different between the two drugs (odd ratio, 1.16, 95% CI: 0.76-1.76), and the total adverse events were not different between pregabalin and amitriptyline (odd ratio: 0.98, 95% CI: 0.52-1.85). Previous evidence[21] showed that pregabalin is the effective first-line drug for painful diabetic neuropathy. However, some of the patients did not tolerate high doses, in addition, small doses therapeutic effect might be insufficient. Patients treated with pregabalin showed a significant improvement in the quality of life. Although the quality of life was improved more among patients with greater pain relief, pain relief or improved sleep alone cannot explain the effects[22]. Studies[23,24] on amitriptyline

showed better short-term pain relief than placebo, with some meta-analyses stating that its effects might be overestimated. Importantly, there is a lack of comparative efficacy between different classes. This is the first meta-analysis to compare pregabalin and amitriptyline. Our results showed no differences regarding pain control, quality of life, and total adverse events. The above results imply that looking for individual side effects and patients' profiles might help select one drug over the other. Dizziness, xerostomia, and somnolence are common with amitriptyline, while burning sensation and peripheral edema are commoners with pregabalin[20]. Pregabalin was effective in pain reduction when higher doses were prescribed (300-600 mg/day) with no difference from placebo in intermediate doses (150-300). Patients with sleep disturbances benefited more from pregabalin[25-27]. While the drug increases weight, it has an unwanted effect on both patients with diabetes and the general population[28]. Regarding the effects on blood glucose, pregabalin showed a significant increase, while a drop in nocturnal blood glucose was observed with amitriptyline[2]. Pregabalin showed a higher percentage of dropout compared to amitriptyline[2,17].

Combination vs. High-Dose Monotherapy

Combining the two drugs at low doses improved tolerability, however, efficacy showed contradicting results. Chakrabarty et al[17] showed similar efficacy, while Tesfaye et al[19] showed a superiority of the combination.

Cost

Pregabalin is more expensive than amitriptyline; therefore, amitriptyline and combination at low doses are more convenient in a low-economic subset of patients[17,19].

Strength and Limitations

This is the first meta-analysis to compare two commonly used first-choice drugs for painful diabetic neuropathy; the comparison is broad and involves various endpoints. The choice between pregabalin and amitriptyline for treating painful diabetic neuropathy is conflicting. The American Academy of Neurology, and WHO recommended pregabalin and amitryptiline as first choice drugs. On the other hand, the French recommendations listed pregabalin as the second choice[29-31]. This meta-analysis showed no difference between pregabalin and amitriptyline; therefore, our data could be used for future recommendations. Other factors that affect pain perception, like mood swings and sleep, are essential and should be considered when choosing pregabalin or amitryptiline. The study was limited by the small size of the included trials, which were of short duration.

Conclusions

No differences were evident between pregabalin and amitriptyline regarding the effects on pain reduction, quality of life, total adverse events, and treatment discontinuation. Pregabalin and amitriptyline were similar regarding pain reduction, effect on quality of life, and side effects. Combination therapy is a good option to reduce cost and drug side effects. Amitriptyline is cheaper and is, therefore, a better choice for low-income populations.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Not applicable due to the type of study.

Ethics Approval

Not applicable due to the type of study.

Acknowledgments

The authors would like to acknowledge the Saudi Digital Library for free data access.

Availability of Data and Materials

The data of the current study are available from the corresponding author upon request.

Authors' Contributions

Both authors contributed equally to literature search, data analysis, and manuscript drafting. Both authors revised and approved the manuscript before submission.

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