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Comparison of the effectiveness and safety between gabapentin and amitriptyline in pain improvement in peripheral diabetic neuropathy patients: a review

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ABSTRACT

Neuropathy pain is one chronic pain that is difficult to treat and has not had an ideal curative therapy, yet. Gabapentin and amitriptyline are widely used as diabetic neuropathy therapies. However, their effectiveness is still debatable and their side effect has been reported. Several factors affect the efficacy and morbidity of gabapentin and amitriptyline in diabetic neuropathy patients. Some treatment options for diabetic neuropathy are available in clinical setting, therefore evaluation the effectiveness of the treatment options is needed to choose the best treatment. This review article evaluated the effectiveness and safety between gabapentin and amitriptyline as pain relief in peripheral diabetic neuropathy (PDN) patients. It was a narrative review using electronic databases such as Science Direct, Scopus and PubMed. The results showed that effectiveness and safety of gabapentin is better than amitriptyline in relief pain on PDN.

ABSTRAK

Nyeri neuropati merupakan salah satu nyeri kronis yang sulit diobati dan belum tersedia terapi kuratif yang ideal. Gabapentin dan amitriptilin banyak digunakan sebagai terapi neuropati diabetik. Namun efektivitasnya masih diperdebatkan dan efek sampingnya telah dilaporkan. Beberapa faktor mempengaruhi efikasi dan morbiditas gabapentin dan amitriptilin pada pasien neuropati diabetik. Beberapa pilihan pengobatan untuk neuropati diabetik tersedia di klinik, oleh karena itu evaluasi efektivitas pilihan pengobatan diperlukan untuk memilih pengobatan terbaik. Artikel ulasan ini mengevaluasi efektivitas dan keamanan antara gabapentin dan amitriptilin sebagai pereda nyeri pada pasien neuropati diabetik perifer (NDP). Itu adalah tinjauan naratif menggunakan database elektronik seperti Science Direct, Scopus dan PubMed. Hasil penelitian menunjukkan efektivitas dan keamanan gabapentin lebih baik dibandingkan amitriptilin dalam meredakan nyeri pada NDP.

INTRODUCTION

The incidence of diabetes mellitus (DM) is increasing and becoming a challenge in the public health.[1] Diabetes mellitus care needs to be carried out on an ongoing basis so that blood glucose is controlled and avoid vascular complications.[2] Diabetic neuropathy is one of the most common vascular complications where the incidence can reach 60-70% compared to other

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complications.[3] Several therapeutic guidelines have been recommended to reduce diabetic neuropathy pain (DNP) such as anticonvulsants, antidepressants, opioids, and topical medications.[2,4]

The class of drugs that are often used as first line therapy in the treatment of peripheral diabetic neuropathy (PDN) are anticonvulsants and antidepressants.[5] However, the effectiveness as pain relief and the side effects are still debatable.[6] Chandra *et al.*[7] reported that gabapentin relieves pain more significantly than amitriptyline at 4, 8, and 12 wk in PDN with fewer more side effects. Sekar *et al.*[8] also reported that gabapentin is a better choice of therapy in PDN compared to amitriptyline. In contrast, Jaya *et al.*[9] reported that amitriptyline at dose of <25 mg/d relieves pain better than gabapentin at dose of 300 mg/d in geriatric patients with PDN. Liampas *et al.*[10] reported that gabapentin and amitriptyline have similar effectiveness in the treatment of painful diabetic polyneuropathy (DPN). While, Price *et al.*[11] reported that gabapentinoid and tricyclic antidepressant have similar effectiveness in DNP, however tricyclic antidepressants has a greater side effects than gabapentionid.

Several factors should be considered in the treatment of PDN included dose of administration, starting of the treatment, the order of drug administration, and others. These factors can affect pain efficacy and morbidity of diabetic neuropathy patients. The absence of ideal therapy and the available some treatment options for PDN, the need for comparison of such treatment options is urgently conducted to obtain the best option in the treatment of PDN.

This article review aimed to evaluate the effectiveness and safety of gabapentin compared to amitriptyline in PDN patients.

MATERIAL AND METHODS

Criteria of article

This literature review was conducted by tracing literature obtained from several databases such as, Science Direct, Scopus and PubMed. The inclusion criteria used were 1) articles published at least in 5 last year; 2) the drugs used were amitriptyline or gabapentin; 3) free full text original articles included from randomized controlled trial (RCT), and cohort studies. The exclusion criteria used were patients who were undergoing chemotherapy, pregnant and lactating women.

Strategy of article searching

A literature search was conducted in June 2023 using three electronic databases, namely Pubmed, Scopus and Science Direct. The search terms used are listed in TABLE 1. The selected literature is literature that meets the inclusion criteria that have been previously set and then a critical assessment is carried out.

Data extraction

This research was conducted in four stages, namely determining keywords, determining inclusion and exclusion criteria, selecting literature and analyzing results. Article search using keywords gets 1200 articles and after reviewing and identifying literature, articles that meet the criteria for 7 articles are obtained (FIGURE 1).

TABLE 1. Search term used to identify relevant literature

Database	Search term
PubMed (2017-2023)	((((diabetes mellitus[MeSH Terms]) OR (diabetic neuropathies[MeSH Terms])) AND (pain management[MeSH Terms])) AND (gabapentin[MeSH Terms])) OR (amitriptyline[MeSH Terms]) = 507 literatures
Scopus (2017-2023)	"neuropathies" AND "diabetic" OR "pain" AND "management" OR "analgesic" OR "drug" AND "therapy" AND "amitriptyline" AND "gabapentin" = 86 literatures
Science Direct (2017-2023)	"neuropathy diabetic" OR "complication" AND "pain management" OR "analgesic" AND "gabapentin" AND "amitriptyline" = 607 literatures

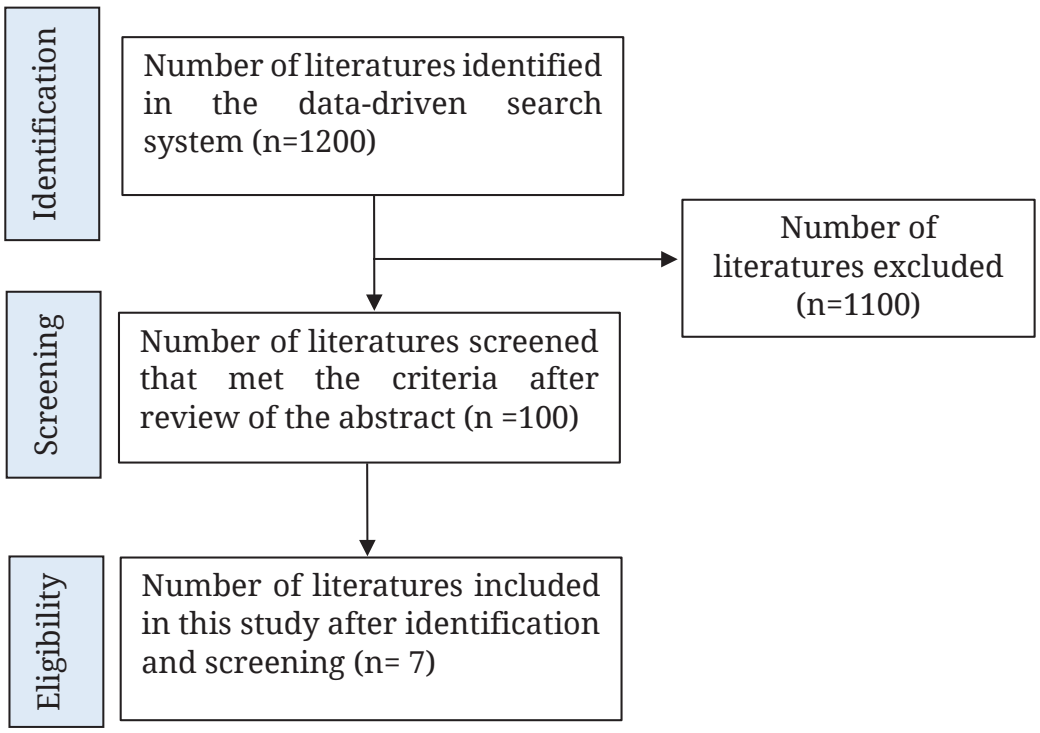

FIGURE 1. Literature selection flow

RESULTS

Among 1200 literatures identified from database, only 7 literatures were eligible to further evaluate. The characteristics of the literatures are presented in TABLE 2.

TABLE 2. Characteristics of the literatures.

Researcher	Title	Methods (Design and location)	Parameter	Result
Chandra *et al.*[7]	Evaluation of efficacy of amitriptyline versus gabapentin in diabetic peripheral neuropathy	• Design: randomized open label • Location: Punjab, India	1. Population :100 patients • Amitriptyline (50 patients) • Gabapentin (50) patients 2. Sex: • Male (48 patients) • Female (52 patients) 3. Age: >18 y.o. 4. Efficacy scale: numeric pain rating scale (NPRS) 5. Duration of treatment:12 wk	• In amitriptyline group: 9 patients with full relief (100%) and 23 patients with 80-100 % relief. • In gabapentin group :12 patients with full relief (100%) and 29 patients with 80-100% relief. • Gabapentin has a more significant reduction in pain relief than amitriptyline at 4, 8 and 12 wk ($p<0.05$) on the NPRS scale with fewer side effects.
Sekar *et al.*[8]	Comparative study of safety and efficacy of gabapentin versus amitriptyline in patients with painful diabetic peripheral neuropathy: a randomized open label parallel group study	• Design: randomized open label parallel group study • Location: Sri Muthukumaran Medical College Hospital, India	1. Population: 100 patients • Amitriptyline (48 patients; 2 patients discontinued) • Gabapentin (48 patients; 2 patients discontinued) 2. Age: 18 to 75 y.o.; HbA1c: 6-10%; and diabetic neuropathy from 1 mo - 5 yr 3. Efficacy scale: visual analog scale (VAS) and sleep interference scale 4. Safety scale: descriptive analysis 5. Duration of treatment: 12 wk	• Gabapentin showed better improvement than on the percentage change in mean pain score (56% in gabapentin vs. 44% in amitriptyline). • Gabapentin has better improvement neuropathy pain compared to amitriptyline after 12 wk ($p=0.024$). • Side effects of gabapentin were appetite and somnolence, while amitriptyline were increased micturition and dizziness. • Gabapentin is safer than amitriptyline for painful diabetic neuropathy.
Jaya *et al.*[9]	Effectivity comparison of amitriptyline versus gabapentin as neurophatic pain therapy in elderly with type II diabetes mellitus	• Design: prospective cohort prospective • Location: Sanglah General Hospital Center, Denpasar, Bali, Indonesia	1. Population: 70 (patients) • Amitriptyline (35 patients) • Gabapentin (35 patients) 2. Sex: • Male (45 patients) • Female (25 patients) 3. Age: >60 y.o. 4. Efficacy scale: visual analog scale (VAS), numeric pain rating scale (NPRS) or verbal rating scale (VRS). 5. Duration of treatment: 4 wk	• Amitriptyline (<25mg/day) showed better improvement in neuropathic pain than the gabapentin (<300mg/day), with a percentage reduction in pain intensity >2 units of 66.75% and 21%, respectively.

TABLE 2. Characteristics of the literatures (cont.)

Researcher	Title	Methods (Design and location)	Parameter	Result
Jetli *et al.*[12]	A comparative study on efficacy and safety for management of neuropathic pain with gabapentin, pregabalin and amitriptyline	• Design: original research article • Location: India	1. Population: 270 patients • Gabapentin (90 patients) • Pregabalin (90 patients) • Amitriptyline (patients) 2. Sex: • Male (122 patients) • Female (88 patients) 3. Age: >18 y.o. 4. Efficacy scale: numeric pain rating scale (NPRS) 5. Safety scale: descriptive analysis 6. Duration of treatment: 4 wk	• All patients experienced significant improvement in neuropathy pain after 4 wk (p=0.001). • The most common side effect was dizziness in pregabalin (23.3%) followed by gabapentin (12.22%) and amitriptyline (4.44%) (p=0.041). • Sedation also occurred significantly more in the pregabalin (31.1%) compared to the other drugs (p=0.036).
Kaur *et al.*[13]	Comparative analysis of efficacy and safety of gabapentin vs amitriptyline in patients of peripheral neuropathic pain in case of diabetes mellitus	• Design: original research article • Location: Rajindra Hospital, India	1. Population: 60 (patients) • Amitriptyline (30 patients) • Gabapentin (30 patients) 2. Sex: • Male (31 patients) • Female (29 patients) 3. Age: 18-65 y.o. 4. Efficacy scale: Michigan neuropathy screening instrument (MNSI) 5. Safety scale: descriptive analysis 6. Duration of treatment: 4 mo	• Gabapentin and amitriptyline are effective in improving diabetic neuropathy pain. • The MNSI after 4 weeks was 5.83±1.06 in gabapentin and 6.27±1.01 in amitriptyline (p=0.087). • The side effects such as dizziness (46.66%), somnolence (43.33%), and dry mouth (23.30%) was higher in the amitriptyline. • Overall, the incidence of side effects was considered mild and well tolerated.
Shaikh *et al.*[14]	Comparative study of efficacy and safety of gabapentin and amitriptyline in treatment of neuropathic pain associated with chronic lumbar radiculopathy. An open label, prospective randomized clinical study	• Design: Original research article • Location: Aurangabad Hospital, India	1. Population: 150 patients • Amitriptyline (75 patients) • Gabapentin (75 patients) 2. Sex: • Male (97 patients) • Female (53 patients) 3. Age: 18-65 y.o. 4. Efficacy scale: numeric pain rating scale (NPRS) 5. Safety scale: descriptive analysis 6. Duration of treatment: 12 wk	• Gabapentin has better efficacy than amitriptyline in pain relief. • The reduction in NPRS at 12 wk was 4.38 (52.96%) in gabapentin and 2.39 (29.76%) in amitriptyline (p=0.002). • Side effects were more common in the amitriptyline included sedation (16%) and dry mouth (92%) (p=0.003)

TABLE 2. Characteristics of the literatures (cont.)

Researcher	Title	Methods (Design and location)	Parameter	Result
Alharbi *et al.*[15]	Comparative study to evaluate efficacy and safety for management of neuropathic pain with gabapentin, pregabalin and amitriptyline	• Design: original article • Location: Saudi Arabia	1. Population: 270 patients • Gabapentin (90 patients) • Pregabalin (90 patients) • Amitriptyline (90 patients) 2. Sex: • Male (122 patients) • Female (88 patients) 3. Age: >18 y.o. 4. Efficacy scale: numeric pain rating scale (NPRS) 5. Safety scale: report by patients or observed by the clinician during study was reported using ADR reporting form 6. Duration of treatment: 8 wk	• Gabapentin, pregabalin, and amitriptyline had similar efficacy in reducing neuropathy pain. • The mean reduction was 4.73, 4.33, and 3.48, respectively. • Side effects were more common in the pregabalin group included dizziness 21 patients (23.3%) (p=0.041) and sedation 28 patients (31.1%) (p=0.036) compared to the other drugs.

DISCUSSION

The first step in DNP management is intensive glycemic control to prevent neuropathy progression. Sometimes pain relief drugs are added to patients with DNP to alleviate the painful symptoms.[2] The pain relief drugs can be categorized into two groups i.e. drugs with moderate activity if they can relieve pain around 30-50% and drugs with good activity if they can relieve pain >50%.[16] Several pain relief drugs are commonly used for patients with DNP included anticonvulsants, antidepressants, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids.[2,4] Nonsteroidal anti-inflammatory drugs is generally less effective in the treatment of DPN, whereas opioids are not recommended as a primary treatment due to the potential side effects included physical dependence, drug tolerance and respiratory depression.[5]

Some therapeutic guidelines included the European Federation of Neurological Societies 2010 (EFNS 2010), American Academy of Neurology 2011 (AAN 2011), and the National Institute for Health and Care Excellence 2013 (NICE 2013) recommended anticonvulsants (gabapentin and pregabalin) and antidepressants (amitriptyline) as first-line therapy for DNP.[12,17,18] Pregabalin and gabapentin are often used for DNP patients.[19] The mechanism of action of gabapentin through calcium channel α2-δ ligands which results in decreased release of the neurotransmitters noradrenaline and glutamate.[13] Gabapentin has an analgesic effect, namely GABA analogs that work selectively on the α2δ subunit of VGCC. Gabapentin inhibits the entry of calcium ions into nerve cells leading to a decrease in neurotransmitter release that affects post-synoptic activity and a decrease in hyperexcitability. In addition, activation of GABAb receptors modulates the presynaptic NMDA receptors leading to disruption of the

release of neurotransmitters such as glutamate, aspartate, substance P, and calcitonin gene-related peptide (CGRP).[19]

Amitriptyline, a tricyclic antidepressant, has been recommended in some guidelines as first- or second-line therapy for DNP patients.[2,4] Amitriptyline has low bioavailability due to first-pass metabolism in the liver.[9] However, its oral absorption and lipophilic properties allow amitriptyline to be widely distributed until the central nervous system (CNS).[13] The effectiveness of amitriptyline in pain relief occurs in the inhibition of serotonin and norepinephrine reuptake in the hospital, increasing the number of both neurotransmitters that play a role in pain modulation (pain inhibition system). Amitriptyline is also associated with NMDA receptors and the activity of ion channels causes the analgesic effect of amitriptyline in diabetic neuropathy patients.[20]

Seven studies that compared the efficacy and safety of gabapentin and amitriptyline for pain relief in DNP were conducted. Six randomized control trials reported gabapentin to be superior to amitriptyline for pain relief in DNP, and only one cohort study reported the opposite results. The characteristics examined in this review are sex and age. Five literatures reported that the incidence of DNP is more prevalent in male patients.[9,12–15] Only one study that includes detailed inclusion criteria included HbA1c values, duration of diabetes, and onset of diabetic neuropathy pain.[8]

A randomized controlled trial was conducted by Shaikh *et al.*[14] to evaluate the efficacy and safety of gabapentin compared to amitriptyline in the treatment of DNP. One hundred and fifty DNP patients over 18 y.o. equally divided into 2 groups, group A (gabapentin 300mg/d) and group B (amitriptyline 10mg/) for 12 wk. Pain was measured by NPRS at 0, 6 and 12 wk. The results showed that gabapentin [NPRS=4.38 (52.96%)] is more effective than amitriptyline [NPRS=2.39 (29.7%)] after 12-wk treatment of DNP (p=0.002).

Chandra *et al.*[7] also reported that gabapentin is better in relieving pain associated with DNP at 4-wk (p=0.0025), 8-wk (p=0.0109), and 12-wk (p=0.0412) of treatment. Sekar *et al.*[8] also evaluated the efficacy of amitriptyline compared to gabapentin in patients with DNP using VAS. The VAS value after gabapentin treatment (56.42%) was significantly higher than after amitriptyline treatment (44.10%) (p<0.05). Kaur *et al.*[13] also reported the efficacy and safety of gabapentin and amitriptyline using the MNSI. The results showed that the mean difference in MNSI before and after gabapentin treatment [3.37 ± 0.09 (58%)] is significantly higher than after amitriptyline treatment [3.07 ± 0.11 (48.96%)] (p<0.001). These four studies demonstrated that gabapentin is more effective and safer than amitriptyline in DNP patients.

Several studies reported the different results as above mentioned. Alharbi[15] evaluated the efficacy and safety of gabapentin, pregabalin and amitriptyline in DNP patients. A total 270 patients were divided into 3 groups, namely group A received gabapentin 300mg, group B received pregabalin 75mg and group C received amitriptyline 10mg. Pain measurement using NPRS/VAS after 4 wk treatment. The results showed that gabapentin, pregabalin and amitriptyline have equivalent efficacy in relieving pain of DNP patients with a percentage reduction ratio of 4.73, 4.33. and 3.48, respectively. Jaya and Herawati[9] also investigated the efficacy of gabapentin (dose of <300mg) and amitriptyline (dose of <25mg) after 4 wk treatment in geriatric patients (>70 y.o.) with DNP using VAS/NPRS to measure pain. The results showed that the amitriptyline provided better pain relief than gabapentin after 4 wk administration (p=0.037). The management of DNP in geriatric patients requires attention due to several issues included the presence of comorbidities,

polypharmacy, and the increase of side effects. It is recommended to initiate therapy at the lowest dose and adjust the maximum tolerated dose.[2]

The higher incidence of amitriptyline side effects compared to gabapentin may be caused by its pharmacokinetic and pharmacodynamic profiles. Amitriptyline is well absorbed after oral administration with low bioavailability (30-60%) due to high first-pass metabolism. Amitriptyline is a highly lipophilic compound that is widely distributed throughout the body and extensively bound to tissue and plasma proteins. The volume of the distribution of amitriptyline is high (17.1 ± 2.4 L/kg) and also its protein binding is high (91-97%). It is primarily metabolized by the liver to be active metabolites included nortriptyline, didesmethyl-amitriptyline, 10-hydroxy-amitriptyline, and amitriptyline n-oxide with a half-life of 10 to 28 hr. Amitriptyline is primarily excreted by the kidney.[21,22] With its pharmacokinetics profile characterized by high protein binding, active metabolites produced, and long half-life, amitriptyline causes more common side effects than gabapentin.

The common side effects of gabapentin are dizziness (19%), drowsiness (14%) and walking disorders (14%). These side effects can affect on daily activities of patients, patients education concerning the side effects of amitriptyline and its impact is needed.[11] The occurrence of these side effects is due to the reduced release of excitatory neurotransmitters, namely glutamate and noradrenaline. The decrease in glutamate leads to decreased activation of alpha-amino-3-hydroxy-5- methyl-4- isoxazole propionic acid (AMPA) receptors in the brain whereas noradrenaline functions to regulate the pituitary gland secretion and regulate alertness levels. A decrease in noradrenaline in the brain causes a decrease in the level of alertness such as drowsiness or dizziness.[7]

CONCLUSION

The effectiveness and safety of gabapentin are better than amitriptyline in relief pain on DNP. However, both gabapentin and amitriptyline can be used as therapeutic options on the DNP. Pharmacokinetics and pharmacodynamics profiles of amitriptyline are associated with its common side effects.

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