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## RESEARCH ARTICLE

# EFFECTIVITY COMPARISON OF AMITRIPTYLINE VERSUS GABAPENTIN AS NEUROPHATIC PAIN THERAPY IN ELDERLY WITH TYPE II DIABETES MELLITUS

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**ABSTRACT**

**Background:** Neuropathy in diabetes mellitus is a disorder that occurs in the peripheral nervous system. The incidence of diabetic neuropathy was found more prevalent in elderly (44%) compared to adult (24%). Amitriptyline and Gabapentin are widely used on treatment of neuropathic pain. There were variations in the results of the studies that have been done related to effectiveness between both drugs, causes the need further research, especially on geriatrics.
**Objective:** The aim of this study was to compare the effectiveness of Amitriptyline versus Gabapentin for diabetic neuropathic pain in geriatric.
**Methods:** A prospective cohort study involving 70 elderly were observed during 4 weeks. The outcome targets were neuropathy pain scale reduction (≥ 2 unit). Non-parametric Wilcoxon, Mann Whitney U, and Chi-Square test were used to analyze the outcome.
**Result:** The whole subjects who got Amitriptyline or Gabapentin decreased pain scale ≥ 2 units compared to baseline. Comparison head to head at low doses, Amitriptyline showed reduce pain intensity greater than Gabapentin ($p < 0.05$), while on therapeutic doses show there was no difference in efficacy between two drugs ($p > 0.05$).
**Conclusion:** Amitriptyline was found better in reducing diabetic neuropathic pain intensity compared to Gabapentin.



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## INTRODUCTION

Neuropathy in diabetes mellitus is a disorder that occurs in the peripheral nervous system. These disorders arise due to damage small blood vessels (microvascular) due to blood glucose levels are high. (Dyck *et al*., 2009; Fink and Oaklander, 2005; Javed *et al*., 2015) Neuropathy in patients with diabetes, is a complication with the greatest incidence, which is 60-70% compared to other diabetic complications. The incidence of diabetic neuropathy was found more prevalent in elderly (44%) compared to adult (24%). (Lavery *et al*., 2004; Onge and Miller, 2008) Amitriptyline and Gabapentin are widely used on treatment of neuropathic pain. There were many variation effectivity research result between both drug as first line neurophatic pain, cause need further reaserch with hope the results can be used as a reference, especially in the local health authority to determine the best therapy of diabetic neuropathic pain on geriatrics. (Jefferies, 2010; Lacy *et al*., 2012)

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## MATERIALS AND METHODS

### Subjects

The population of this study were all patients age group ≥ 60 years with painful diabetic neuropathy who have a pain score at least 2 of Visual Analog Scale (VAS), Numeric Rating Scale (NRS), or Verbal Rating Scale (VRS). Patients were undergoing outpatient in polyclinic nervous, endocrine, and interna at Sanglah General Hospital Center in Denpasar-Bali, who received Amitriptyline or Gabapentin therapy. Samples are part of the population that met the inclusion criteria and there are no samples are included in the exclusion criteria. The inclusion criteria were defined: men and women aged ≥ 60 years, patients with diabetes mellitus type 2 with blood sugar levels under control, patients with a diagnosis of painful diabetic neuropathy, patients who obtain pain therapy of diabetic neuropathy such as Amitriptyline or Gabapentin for the first time or who have history of both drugs and therapy has been stopped at least 5 half-lives (t½) elimination of these drugs. The exclusion criteria were defined: patients were not willing to participate in the study; patients with a history of heart disease, kidney failure, and impaired liver function;

patient contraindications or allergy to Amitriptyline or Gabapentin. Sampling was carried out after obtaining the approval of research ethics committee. Ethical clearance number was 185 / UN.14.2 / R & D / 2015 as well as delivery to the patient's informed consent. Patients will be involved in this study if they have understood and signed the informed consent that has been prepared by the researcher. This study used a non-experimental analytical methods, that is prospective cohort, where the study subjects were divided into two groups according to treatment obtained by the patients.

**Clinical Assesment**

Basic characteristics such as demographics, Body Mass Index (BMI), risk factors, lipid profile (total cholesterol, HDL, LDL, TG), the use of drug therapy with other diagnoses (antihypertension, antidyslipidemia, and neuroprotector therapy), polypharmacy and compliance recorded as a basic characteristic. The methods of data collection is done by direct measurement technique in which researchers take measurements and recording of subjects with diabetic neuropathic pain. The data collection of Amitriptyline and Gabapentin effectiveness performed by asking the patient to fill the VAS, NRS, or VRS before it is treated as a baseline and 4 weeks after treatment with Amitriptyline and Gabapentin as an end point measurement. (EMEA 2007) The sampling technique used is non-probability consecutive sampling where researchers will take all subjects who were diagnosed with diabetic neuropathy in accordance with the inclusion and exclusion criteria, up to the minimum number of subjects met. By using the formula robustness analysis in a cohort study, the minimum sample to be observed to represent the population in each group was 35 patients.

**Clinical Outcomes**

The observed therapeutic effectiveness outcomes were reduction in diabetic neuropathy pain intensity at least 30-50% or reduction at least two units on VAS, NRS, or VRS as compared to baseline and comparison head to head between two drugs. (EMEA 2007)

**Statistical Analysis**

Statistical analysiswere performed to test the baseline characteristic and outcomes study.

1. Baseline Characteristic Analysis

Analysis of baseline characteristics comparison conducted by the Mann-Whitney U and Chi-Square test for abnormally distributed and Tow Independent Sample Pair T-Test for normally distributed data.

2. Therapeutic Effectiveness Analysis

Effectiveness between two drugs were analyzed by Wilcoxon Sign Rank Test for dependent sample and Maan Whitney U for independent sample.

## RESULTS

Ninety one subjects were collected during 4 month period. There were 52 patients placed on Amitriptyline group and 39 patients in the Gabapentin group. Twenty-one subjects were dropped out during the observation period, eventually 70 subjects were observed until the final stages, which consisted of 35 patients in the group of Amitriptyline and 35 patients in the Gabapentin group.

**Table 1. Subjects Baseline Characteristics**

| Baseline Characteristics | Amitriptyline Group (n = 35) | Gabapentin Group (n = 35) | p Value | Analysis |
|---|---|---|---|---|
| Age (Year) | 62.11 ± 3.47 | 63.46 ± 4.90 | 0.709 | MWU |
| Gender | | | | |
| •Male [n (%)] | 23 (65.71%) | 22 (62.86%) | 0.803 | Chi-S |
| •Female (P) [n (%)] | 12 (34.29%) | 13 (37.14%) | | |
| BMI (Kg/m$^2$) | 26.73 ± 3.71 | 26.15 ± 2.96 | 0.469 | T-Test |
| High (cm) | 164 ± 6.67 | 162 ± 6.86 | 0.118 | UMW |
| Weight (Kg) | 72 ± 10.69 | 68 ± 8.92 | 0.128 | T-Test |
| Risk Factor | | | | |
| 1. Smoking [n (%)] | 7 (20%) | 10 (28.57%) | 0.403 | Chi-S |
| 2. Hypertension [n (%)] | 18 (51.43%) | 24 (68.57%) | 0.143 | Chi-S |
| •SBP (mmHg) | 135 ± 20.10 | 133 ± 16.72 | 0.845 | MWU |
| •DBP (mmHg) | 86 ± 9.00 | 83 ± 10.36 | 0.412 | MWU |
| 3. Dyslipidemia [n (%)] | 20 (57.14%) | 21 (60%) | 0.808 | Chi-S |
| •Total Cholesterol (mg/dL) | 163.83 ± 55.20 | 165.37 ± 46.97 | 0.810 | MWU |
| •LDL (mg/dL) | 96.20 ± 35.14 | 88.91 ± 29.92 | 0.385 | MWU |
| •HDL (mg/dL) | 42.91 ± 14.48 | 43.26 ± 12.81 | 0.604 | MWU |
| •TG (mg/dL) | 151.29 ± 95.17 | 147.31 ± 71.72 | 0.729 | MWU |
| Duration of Diabetes Mellitus (Year) | 7.46 ± 4.02 | 8.74 ± 3.80 | 0.079 | MWU |
| Another Therapy | | | | |
| 1. Neuroprotector [n (%)] | 25 (71.43%) | 30 (71.43%) | 0.145 | Chi-S |
| •B complex Vitamin | 10 (28.57%) | 12 (34.28%) | | |
| •Mecobalamin | 15 (42.86%) | 18 (51.43%) | | |
| 2. Antihypertension Drug [n (%)] | 18 (51.43%) | 24 (68.57%) | 0.143 | Chi-S |
| 3. Antidiabetic Drug [n (%)] | 35 (100%) | 35 (100%) | 1.000 | Chi-S |
| 4. Antidyslipidemia Drug [n (%)] | 20 (57.14%) | 21 (60%) | 0.808 | Chi-S |
| Baseline Pain Score | 3.37 ± 1.06 | 3.14 ± 1.00 | 0.376 | MWU |
| Compliance (%) | 90.67 ± 6.95 | 91.95 ± 5.83 | 0.332 | MWU |
| Polypharmacy (amount of drug) | 4.69 ± 1.32 | 5.14 ± 1.09 | 0.110 | MWU |

Glossary of terms: MWU = Mann Whitney U; T-Test = Tow Independent Sample T-Test Pair ; Chi-S = Chi-Square Analysis; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure ; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; TG = Triglyserid; B-Complex : Contains Vitamin B1, B6, and B12; Mecobalamin = Vitamin B12.

**Table 2. Amitriptyline and Gabapentin Effectiveness as Therapy**

| Reduction in Pain Intensity (Unit) | Amitriptyline Group (n = 35) [n (%)] | p Value of Amitriptyline Group Compare to Baseline | Gabapentin Group (n = 35) [n (%)] | p Value of Gabapentin Group Compare to Baseline |
|---|---|---|---|---|
| 4 | 3 (8.57%) | p = 0.0000 | 1 (2.86%) | p = 0.0000 |
| 3 | 19 (54.29%) | Sig. | 12 (34.29%) | Sig. |
| 2 | 13 (37.14%) | | 22 (62.86%) | |

n = Number of Subjects; Sig = Significant ($p < 0.05$)

**Table 3. Results Comparison of Amitriptyline and Gabapentin at Sub Therapeutic Doses**

| The Research Group | Reduction in Pain Intensity [n (%)] | | p Value |
|---|---|---|---|
| | > 2 (Unit) | 2 (Unit) | |
| Amitriptyline Group (< 25 mg/day) (n = 6) | 4 (66.7%) | 2 (33.3%) | 0.037 Sig. |
| Gabapentin Group (< 300 mg/day) (n=19) | 4 (21%) | 15 (79%) | |

n = Number of Subjects ; Sig = Significant ($p < 0.05$)

**Table 4. Results Comparison of Amitriptyline and Gabapentin at Usual Doses**

| The Research Group | Reduction in Pain Intensity [n (%)] | | p Value |
|---|---|---|---|
| | > 2 (Unit) | 2 (Unit) | |
| Amitriptyline Group (25 mg/day) (n= 29) | 18 (62%) | 11 (38%) | 0.703 NS |
| Gabapentin Group (< 300 mg/day) (n=16) | 9 (56.3%) | 7 (43.8%) | |

n = Number of Subjects ; NS = Not Significant ($p > 0.05$)

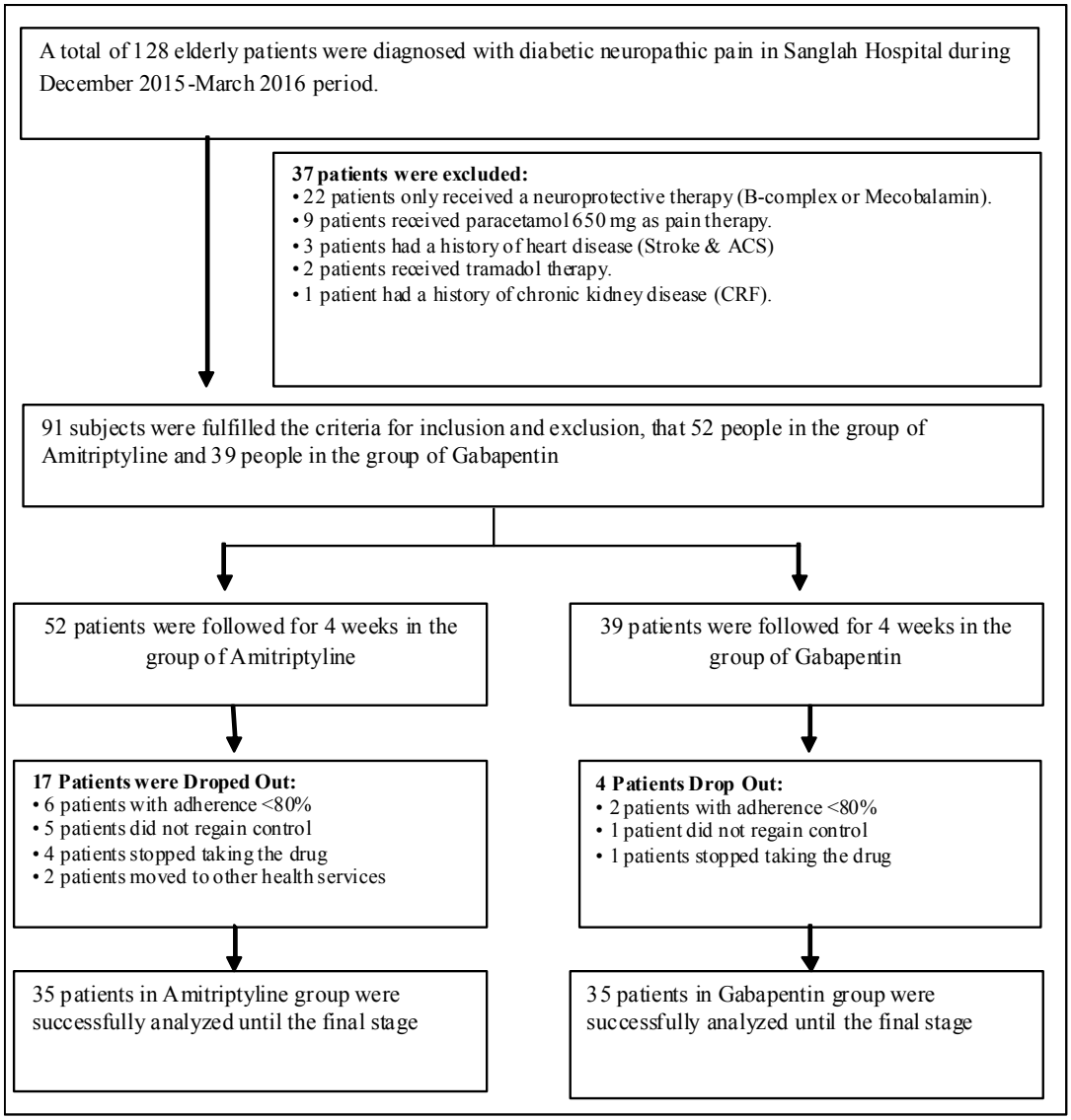


**Figure 1. Flow Chart of Subjects Selection**

**Subjects Characteristics**

The demographic characteristics of subjects in this study were determined by age, gender, body mass index, the risk factors, another therapeutic drugs, baseline pain score, adherence, and polypharmacy. The demographic characteristics of patients were found not significantly different between both groups ($p > 0.05$). The characteristics of patients are shown in Table 1.

**Effectivity comparison between amitriptyline versus gabapentin**

The results of measuring the effectiveness between Amitriptyline Vs Gabapentin for the treatment of diabetic neuropathic pain in geriatrics, showed that both drugs can reduce pain scale score ≥ 2 units compare to baseline with the p value < 0.05 (Table 2). The drugs administration doses in this study were varied, so that the necessary test head to head between Amitriptyline and Gabapentin at sub therapeutic doses (low dose) and the usual dose (therapeutic dose). Low dose group Amitriptyline is < 25 mg / day whereas Gabapentin < 300 mg / day. Amitriptyline usual dose is 25 mg / day whereas Gabapentin is 300 mg / day. Comparisons head to head between two drugs are shown in Table 3 and Table 4.

## DISCUSSION

The therapeutic dose recommended guidelines in the treatment of diabetic neuropathic pain for Amitriptyline was started at a dose of 10-25 mg / day followed by a maintenance dose of 25-100 mg / day, whereas Gabapentin begins with a dose of 100-300 mg / day followed by a maintenance dose of 300- 1200 mg / day according to the severity of pain experienced by the patient. (Moulin *et al*., 2014; Aslam *et al*., 2014; Attal *et al*., 2010; Bansal *et al*., 2006) In this study Amitriptyline and Gabapentin proved effective in reducing diabetic neuropathic pain significantly compared with baseline ($p < 0.05$). Comparison head to head at the usual dose between two drugs showed there was no difference effectivity ($p > 0.05$) with the value of Number Need to Treat (NNT) is 18. Comparison on sub therapeutic doses showed a different results, which Amitriptyline can reduce pain intensity significantly greater ($p < 0.05$) when compared Gabapentin with NNT values equal to 3. The results obtained in this study are in accordance with a systematic study and meta-analysis showed that the Amitriptyline had NNT value better than Gabapentin, where the value of NNT Amitriptyline is in the interval 1.3-1.5, while NNT for Gabapentin were in the interval from 5.8 to 6.6. (Javed *et al*., 2015; Moulin *et al*., 2014; Backonja *et al*., 1998) Amitriptyline was allegedly working reduce pain intensity by modulating the transmission of serotonin and norepinephrine (NE), which will impact on the activity of inhibiting the reuptake of serotonin (5-HT) and norepinephrine by presynaptic receptor. Increased concentrations of these neurotransmitters in the synaptic cleft cause a decrease in the number of adrenaline receptor beta which will have an impact on pain reduction. (Singh *et al*., 2011) Gabapentin is known as an anticonvulsant drug classes also have an activity that can reduce pain intensity through a mechanism similar to Amitriptyline. Gabapentin works by inhibiting the hyperactivity especially with blocks Si-Na or prevention of central sensitization and increased inhibition which would result in a decrease in pain intensity. (Singh *et al*., 2011; Brownlee, 2005)

**Conclusion**

Amitriptyline was found relatively better in reducing diabetic neuropathic pain intensity compared to Gabapentin.

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**Author Contribution**

All authors contributed in the manuscript, based on their contribution as: study proposal in general (Krisna Adi Jaya [KAJ] and Fauna Herawati [FH]), study design (KAJ, FH), statistical analysis (KAJ, FH), study running (KAJ, FH), manuscript writing (KAJ, FH). We confirmed that all authors have read and agreed to the content of this manuscript.

**Conflict of Interest**

This paper was written independently. All authors disclose no financial or personal relationships with other people or organizations that could inappropriately influence the work.

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