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**ORIGINAL RESEARCH** **PAIN MANAGEMENT**

# Efficacy of amitriptyline and duloxetine in post-chikungunya neuropathic pain; a randomized, open-label, cross-over clinical trial

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## Abstract

**Background:** A significant number of chikungunya virus infected people develop neuropathic pain lasting for months to years. Patients with neuropathic pain are difficult to treat with conventional analgesics and frequently require antidepressant and anticonvulsant medications. The current study compared the efficacy of amitriptyline and duloxetine in the treatment of post-chikungunya neuropathic pain.

**Methodology:** In this randomized, cross-over, clinical trial, a total of forty patients were enrolled and randomly assigned to either amitriptyline or duloxetine for four weeks followed by a two-week washout period. Then the patients were crossed-over to the next phase which lasted for another four weeks. Amitriptyline was given in doses of 10, 25, and 50 mg and duloxetine was given in 20, 30, and 60 mg once daily at 8.00 PM respectively with optional dose up-titration. Pain relief was measured by VAS (visual analogue scale) after one, two, three, and four weeks in each phase as a primary outcome, and improvement of quality of life was assessed by SF-36 (short form-36) at the beginning and end of each phase as a secondary outcome.

**Results:** A total of twenty one patients completed both treatment phases out of forty patients. The reduction of pain intensity was significant in both amitriptyline and duloxetine groups compared with their baseline values ($p < 0.001$), with no significant difference between the groups ($p > 0.336$). The quality of life (SF-36) was significantly improved with both amitriptyline and duloxetine ($p < 0.001$) but the difference between the two treatments was not significant ($p > 0.324$). Regarding adverse events, dry mouth was significantly more common in the amitriptyline group than the duloxetine group ($p < 0.013$).

**Conclusion:** Amitriptyline and duloxetine can be used in the treatment of post-chikungunya neuropathic pain effectively, but duloxetine is preferred because of its less adverse effects.

**Trial registration:** The trial was approved by Institutional Review Board, Bangabandhu Sheikh Mujib Medical University dated January 19, 2020; Trial number: BSMMU/2020/712.

**Key words:** Chikungunya; Neuropathic pain; Quality of life; Amitriptyline; Duloxetine; DN4; SF-36

**Abbreviations:** VAS – Visual analogue scale, NSAIDs – Non-steroidal anti-inflammatory drugs, DMARD – Disease-modifying anti-rheumatic drugs, TCA – tricyclic antidepressants, NICE – National Institute for Health and Care Excellence, SNRI – Serotonin noradrenaline reuptake inhibitor

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# 1. Introduction

Chikungunya is a mosquito-borne illness caused by the chikungunya virus that belongs to the α-virus genus of the family Togaviridae.[1, 2] The disease is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes which are the main vectors of chikungunya in Asia and the Indian Ocean islands.[2] The name 'chikungunya' is derived from the Makonde (an ethnic group in southeast Tanzania and northern Mozambique) word meaning "that which bends up" about the stooped posture developed as a result of the arthritic symptoms of the disease. In Swahili, chikungunya means "the illness of the bended walker".[3] The first incidence of the chikungunya virus epidemic came into light in 1952 in East Africa followed by several epidemics in Asia. In the Indian sub-continent, the virus was first isolated at Kolkata in 1963. In 2008, the first recognized outbreak of Chikungunya in Bangladesh was identified in the northwest area of the country.[2] A massive outbreak of chikungunya disease occurred in 2017 in and around Dhaka city, the capital of Bangladesh, and over two million people were at risk of getting infected by the virus.[4] The disease may evolve in three phases which include acute or febrile (lasting up to 10 days), sub-acute (11-90 days), and chronic ( > 90 days). Approximately 50% of people who experience acute infection develop chronic joint pains that can last months to years.[5] On Reunion Island, it was reported that 80-93% of patients had the chronic disease after 3 months, 57% after 15 months, and 47% after 2 y of acute infection.[6] The joint pain in the different phases of Chikungunya disease causes important physical incapacity that significantly impacts the quality of life of the affected person.[5, 6]

In chikungunya infection, 19% of the patients had pain with neuropathic characteristics and about 53% of them had chronic pain, as compared to 6.9% and 5.1% in the general population.[7, 8] Neuropathic pain occurs as a result of disease or dysfunction of the somatosensory nervous system. Many patients with chikungunya virus infection did not respond to the usual analgesics prescribed because the nature of the chronic pain was not only nociceptive but also neuropathic.[5, 8, 9]

There are few studies or guidelines in the literature regarding the approach to pain treatment in chikungunya disease. The common medicines used include dipyrone, paracetamol, non-steroidal anti-inflammatory drugs (NSAID), corticosteroids, and opioids. The use of disease-modifying anti-rheumatic drugs (DMARD) like methotrexate, chloroquine, and sulfasalazine have also been reported in patients with chronic pain.[2, 10, 11] Paracetamol alone or with tramadol may be used in addition to tricyclic antidepressants and anticonvulsants.[5, 8, 10, 12, 13]

Among tricyclic antidepressants (TCAs), amitriptyline is clinically the most studied and prescribed medicine. Titration to higher doses is limited due to unwanted effects and the most worrisome side effect is sudden death supposedly related to cardiac arrhythmia[14] On the other hand, the selective serotonin noradrenaline reuptake inhibitor (SNRI), duloxetine has been reported to be safe and effective in painful diabetic peripheral neuropathy with a relatively low rate of adverse events.[13-17] It may interact with tramadol, causing serotonin syndrome, although this risk seems to be low in clinical practice[14, 18, 19] It is a good choice for neuropathic pain treatment in patients with coexisting depression, anxiety, fibromyalgia, or chronic musculoskeletal pain.[20, 21] Both amitriptyline and duloxetine are being used in neuropathic pain, but their head to head comparison in post-chikungunya neuropathic pain is so far not available. Thus, a comparison between the effects of amitriptyline and duloxetine in the treatment of post-chikungunya neuropathic pain would help physicians to decide on the treatment of neuropathic pain in patients with chikungunya.

This study compared the efficacy of amitriptyline and duloxetine in the treatment of post-chikungunya neuropathic pain.

# 2. Methodology

The study was conducted at the Pain Medicine Outpatient Unit and Specialized Pain OPD (Kosaka Pain Clinic), Department of Anaesthesia, Analgesia & Intensive Care Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from November 2019 – October 2020.

Patients aging 18 to 60 y of either sex with a history of positive chikungunya IgG and/or IgM, DN4 score ≥ 4, and VAS score ≥ 4, were included in the study. The exclusion criteria were as follows: patients having diabetic polyneuropathy, spinal cord injury, stroke, cancer pain, persistent postsurgical pain, lumbar or cervical radiculopathies, pregnant patient, patients with psychiatric disease and receiving antipsychotic drugs, and patients with severe renal, hepatic, or cardiac disease.

Formal approval was obtained from the Institutional Review Board (IRB) of our institution and informed written consent from each patient. The demographic characteristics of all subjects were recorded. Those who exposed to medications for neuropathic pain regardless of dose and duration were considered after a two-week washout period.

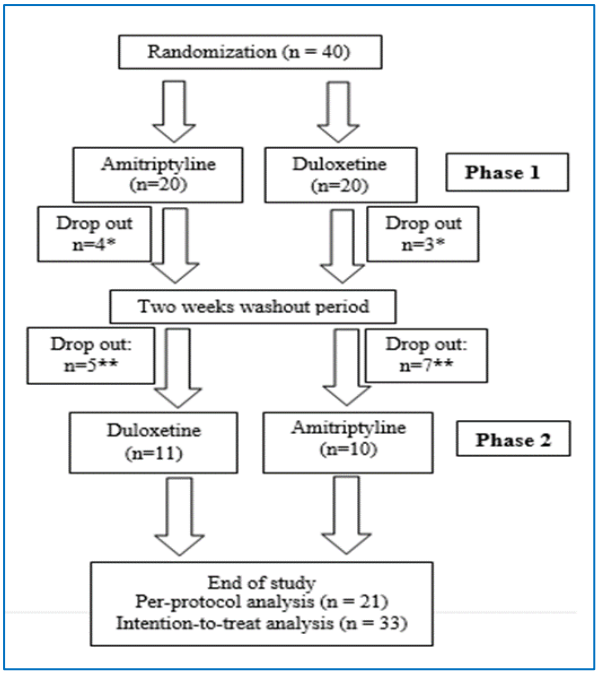


**Figure 1: CONSORT patient flow diagram (* Number of patients dropped in phase–I; ** Number of patients dropped before entering phase–II)**

The patients were randomly assigned to either amitriptyline (10, 25, or 50 mg) or duloxetine (20, 30, or 60 mg) once daily at 8.00 PM in phase–I by computer generated randomization. Then they had cross-over to phase–II after a 2 week washout period. In phase–II, amitriptyline was replaced by duloxetine, and duloxetine was replaced by amitriptyline. Each treatment phase lasted for 4 weeks. Treatment was started with the lowest dose available of either drug, with weekly assessments with optional up-titration. Up-titration of dose was done after the assessment of the therapeutic response. Treatment related adverse events were assessed and recorded.

The primary study endpoint was the reduction in the mean pain score, as assessed by VAS after one, two, three, and four weeks in each phase. The secondary endpoint was quality of life, assessed using a Short-Form 36-item general health survey (SF-36) at the beginning and end of each treatment phase. DN-4 and VAS were used to assess the pain intensity. All subjects had weekly face to face study visits or telephonic conversations. Subjects were allowed to take a combination of paracetamol and tramadol (325 mg + 37.5 mg) as a rescue medication, three times a day during the study period with domperidone to counter nausea and/or vomiting as required basis.

**Statistical analysis:** The sample size was calculated on the basis of means and SDs observed in studies of duloxetine versus placebo and amitriptyline versus placebo in neuropathic pain other than chikungunya, the total number of patients included was 40. Patients who completed phase–I were included in intention-to-treat (ITT) analysis and patients who completed both phases were enrolled in per-protocol (PP) analysis. Values were expressed as mean ± standard deviation (age, VAS score, DN4 score, and SF-36 score) and as percentages. To compare the differences between amitriptyline and duloxetine group, the student's t-test was used for quantitative variables, and for qualitative variables the chi-square test, with Fisher's exact test, as needed, was used. Repeated measures ANOVA was used to determine the difference within the groups. A $p < 0.05$ (CL 95%) was considered statistically significant. SPSS (Statistical Package for Social Sciences) for Windows, version 23.0 was used to perform statistical analysis.

## 3. Results

The patients were randomly allocated into amitriptyline and duloxetine group in phase–I. Then they were crossed-over in phase–II after a two-week washout period. A total of 19 patients were dropped out from this study (7 patients before completing phase–I and 12 patients during washout, before entering phase–II). Patient disposition through the trial is shown in Figure 1.

No significant difference was observed in baseline scores, both before and after the cross-over in the two groups. Patient demographic and clinical characteristics are summarized in Table 1.

In intention-to-treat analysis (n=33), the mean VAS scores in the amitriptyline group after one, two, three, and four weeks were 5.06 ± 0.68, 4.06 ± 0.68, 3.18 ± 0.8,

**Table 1: Demographic and baseline clinical characteristics of the studied groups in phase–I**

| Variables | Amitriptyline (n = 20) | Duloxetine (n = 20) | p value |
|---|---|---|---|
| Age (y) | 36.05 ± 7.07 | 37.25 ± 5.15 | 0.234 |
| Gender [n (%)] | | | |
| Male | 11 (55) | 10 (50) | 0.829 |
| Female | 9 (45) | 10 (50) | |
| Neuropathic pain by DN4 score | 4.31 ± 0.47 | 4.23 ± 0.45 | 0.595 |
| Pain intensity by VAS score | 5.65 ± 0.94 | 5.45 ± 0.78 | 0.426 |
| Quality of life by SF-36 score | 50.83 ± 4.78 | 49.87 ± 4.71 | 0.524 |

*Data presented as Mean ± SD, unless specified in the table.*

and 2.62 ± 0.71, respectively. In the duloxetine group, mean VAS scores after one, two, three, and four weeks were 5.23 ± 0.90, 4.35 ± 1.05, 3.47 ± 0.87, and 2.58 ± 0.71, respectively. The mean reduction of VAS from baseline was seen in both groups with no significant difference between the two groups.

In per-protocol analysis (n=21), mean VAS scores in the amitriptyline group after one, two, three, and four weeks were 5.80 ± 0.78, 5.10 ± 0.56, 4.30 ± 0.48, and 3.40 ± 0.51, respectively. In the duloxetine group, mean VAS scores were 5.63 ± 1.02, 4.81 ± 0.87, 3.81 ± 0.98, and 2.90 ± 0.70, respectively. The pain intensity was reduced in both groups but there was no significant difference between the groups. Figure 2 shows change of pain intensity in the different time intervals.

The global SF-36 score in the amitriptyline and duloxetine groups after four weeks was 61.05 ± 3.10 and 61.08 ± 2.42, and after ten weeks was 58.68 ± 5.89 and 59.71 ± 4.29 respectively. The eight domains of SF-36 score in the amitriptyline group, General health, Physical function, Limitation of activities, Emotional well-being, Social activities, Bodily pain, Vitality, and Mental health scores were 50.55 ± 1.66, 80.11 ± 7.07,88.13 ± 11.02, 62.87 ± 4.47, 51.11 ± 6.50, 42.60 ± 5.66, 48.52 ± 2.92, and 55.55 ± 1.66, respectively; while in the duloxetine group, these values were 50.55 ± 1.66, 82.22 ± 6.66, 89.38 ± 6.25, 64.88 ± 3.64, 56.66 ± 8.16, 45.22 ± 5.54, 50.55 ± 3.03, and 56.11 ± 2.20, respectively. There was no significant difference between the two groups but SF-36 score was significantly increased from baseline in both groups. Figure 3 shows the eight domains of SF-36 score.

The rescue medication was consumed by19 (73%) patients in the amitriptyline group and 18 (64%) patients in the duloxetine group. In the amitriptyline and duloxetine group, 19 (73%) and 19 (68%) patients required dose up-titration, respectively. No statistically significant differences between the frequencies of dose up-titration requirement and rescue medication use were observed between the two groups. Adverse effects were common in both the amitriptyline and duloxetine group. There were no statistically significant differences in frequencies of these adverse effects between the two groups, with the exception of dry mouth, which were significantly more common in amitriptyline group. Table 2 lists the frequency of adverse effects in the amitriptyline and duloxetine group.

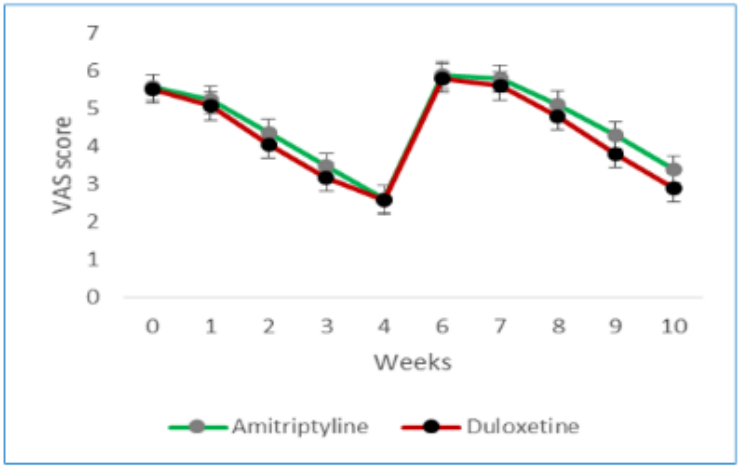


**Figure 2: Weekly pain intensity in the two studied groups.**

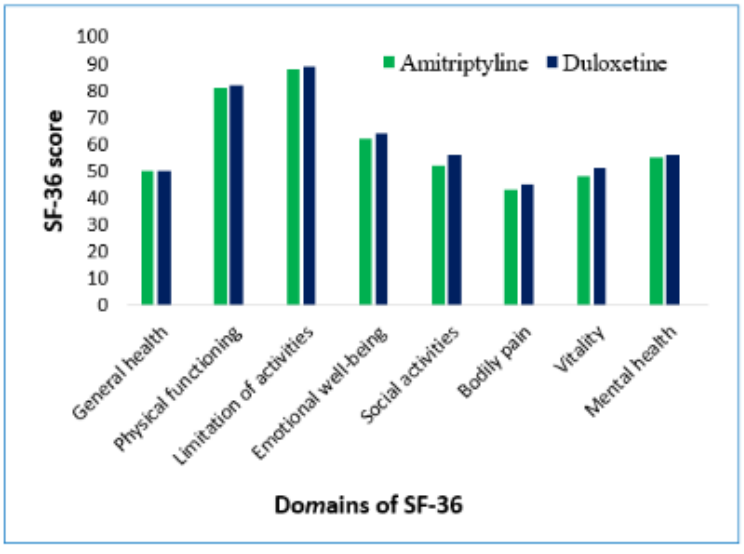


**Figure 3: Eight domains of SF-36 score in the studied groups**

## 4. Discussion

Very few studies were found regarding the pharmacological treatment of neuropathic pain in patients with chikungunya and comparative studies about the use of antidepressants and anticonvulsants, amitriptyline, duloxetine, and gabapentin or pregabalin,[2, 5, 8, 12] The initial treatment of neuropathic pain recommended by the National Institute for Health and Care Excellence (NICE) guideline. The European Federation of Neurologic Societies (EFNS) and NeuPSIG include TCAs, duloxetine, and gabapentinoids.[14, 17]

A randomized, double-blind, cross-over, active-control trial, was done by Kaur et al.[15] to compare the efficacy and safety of duloxetine and amitriptyline in painful diabetic neuropathy. In this study, 58 patients received amitriptyline and duloxetine orally once daily at bedtime in

the doses of 10, 25, and 50 mg and 20, 40, and 60 mg, respectively, each for 6 weeks with optional dose up-titration fortnightly.

**Table 2: Frequency of adverse events**

| Events | Amitriptyline (n=26) | Duloxetine (n=28) | p value |
|---|---|---|---|
| Dry mouth | 12 (46%) | 7 (25%) | 0.013 |
| Drowsiness | 10 (38%) | 6 (21%) | 0.239 |
| Anorexia | 2 (8%) | 3 (10%) | 0.655 |
| Nausea | 3 (11%) | 4 (14%) | 0.705 |
| Diarrhea | 1 (4%) | 1 (3%) | 1.000 |
| Fatigue | 9 (34%) | 5 (18%) | 0.285 |
| Constipation | 2 (8%) | 4 (14%) | 0.414 |
| Insomnia | 1 (4%) | 2 (7%) | 0.564 |

*Values are expressed as absolute number, within parenthesis are percentage over column total.*

A single-blinded placebo washout was given for 2 weeks between the two treatments and a single-blinded placebo run-out phase of 4 weeks was given at the end of the treatment period. Good, moderate, and mild pain relief was achieved in 55%, 24%, and 15% of patients, respectively, on amitriptyline and 59%, 21%, and 9% of patients, respectively, on duloxetine.

Boyle et al. performed a study to compare amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic neuropathic pain. Each treatment group had a single-blind, 8-day, placebo run-in followed by 14 days of lower-dose and 14 days of higher-dose medication. A total of 83 patients were enrolled and randomized. Amitriptyline, duloxetine, and pregabalin reduced BPI severity, BPI interference, and VAS score when compared with placebo.[13]

In the clinical trial by Bansal et al. comparing the efficacy and safety of pregabalin and amitriptyline in painful diabetic peripheral neuropathy, amitriptyline, in doses of 10, 25, and 50 mg at night time and pregabalin, at doses of 75, 150, and 300 mg twice daily, by optional titration were used. The duration of drug treatment was 5 weeks followed by a placebo washout period for 3 weeks between the two drugs. Good, moderate, and mild pain relief were noted in 21 (48%), 6 (13%), and 7 (15%) patients on pregabalin and 15 (34%), 5 (11%), and 12 (27%) patients on amitriptyline, respectively.[22]

Schukro et al.[20] conducted a prospective, randomized, placebo-controlled, double-blind crossover trial to assess the efficacy of duloxetine in chronic low back pain with a neuropathic component. Chronic low back pain with a VAS score greater than 5 and a neuropathic component that was assessed clinically and by the painDETECT questionnaire (score > 12) was required for inclusion. VAS was significantly lower in the duloxetine phase compared with the placebo corresponding to an average pain reduction of 32% after four weeks.

Most of the studies assessed the efficacy of either amitriptyline or duloxetine with placebo or other groups of drugs in patients with diabetic peripheral neuropathic pain, but the comparison between these two drugs was rare.[13, 15] An extensive search of the literature revealed no head to head comparison between amitriptyline and duloxetine in the treatment of post-chikungunya neuropathic pain.

In our study, the demographic and baseline clinical characteristics were statistically similar ($p > 0.234$). The reduction of pain intensity within the groups was statistically significant ($p < 0.001$) after two, three, and four weeks in phase–I but no significant difference was observed between the two groups ($p > 0.326$). In diabetic neuropathic pain, there was significant improvement in pain with both medicines ($p < 0.001$) with no significant difference between the two treatments.[15]

In phase–II, the reduction of pain intensity within the groups was statistically significant ($p < 0.001$) after two, three, and four weeks with no significant difference between the two groups ($p > 0.577$). In patients with painful diabetic neuropathy, various randomized controlled studies showed no significant difference between the efficacy of amitriptyline and duloxetine, although improvement with both treatments was significant ($p < 0.001$).[13, 15, 22]

The reduction of pain intensity was more in phase–I than in phase–II in the amitriptyline group. The difference was statistically significant after three and four weeks between two phases ($p < 0.011$). It may be due to the appearance of unwanted events, particularly dry mouth, limiting dose up-titration in the amitriptyline group in phase–II. In the duloxetine group, there was no significant difference in pain intensity between phase–I and phase–II ($p > 0.128$). It was observed that the reduction of pain intensity after one week of treatment was not significant in both groups ($p > 0.167$).

The improvement of quality of life with both medicines was statistically significant ($p < 0.001$) but there was no significant difference ($p > 0.863$) between the two treatments in phase–I of our study. In a placebo controlled study on chronic low back pain with neuropathy, duloxetine treated group showed significant

improvement of quality of life (SF-36) compared to the placebo group.[20]

In phase–II, the quality of life was significantly improved with both treatments ($p < 0.001$) but their difference was not statistically significant ($p > 0.245$). Boyle et al. did not find any significant difference in the improvement of quality of life (SF-36) between the treatment groups. In a placebo controlled trial on duloxetine, significant improvement of quality of life was observed in duloxetine group compared to placebo group.[20]

In our study, no significant difference in eight domains of SF-36 scores was observed (General health, Physical function, Limitation of activities, Emotional well-being, Social activities, Bodily pain, Vitality, and Mental health) between the two groups ($p > 0.134$). Nor any statistically significant difference was observed in dose up-titration requirement and rescue medication consumption between the two groups ($p > 0.786$).

The adverse events with both agents were comparable to those reported in other studies.[13, 15, 20, 22] Dry mouth was significantly more common in the amitriptyline group than the duloxetine group ($p < 0.013$) which is consistent with previous studies related to neuropathic pain.

We did dose up-titration gradually from 10-50 mg and 20-60 mg daily for amitriptyline and duloxetine respectively. These doses were lower than the recommended dose range 25-150 mg and 60-120 mg for amitriptyline and duloxetine respectively. These recommended dose ranges are for diabetic peripheral neuropathic pain as it is associated with structural damage to the nerve tissue.[25] On the other hand, post-chikungunya neuropathic pain occurs as a result of dysfunction of the nervous system.

## 5. Limitations

The limitations of the current study are blinding and lack of a placebo arm. The observed reduction in pain intensity, as well as improvement in the quality of life, suggests the therapeutic efficacy of amitriptyline and duloxetine in post-chikungunya neuropathic pain.

## 6. Funding

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## 7. Conflict of interests

The authors declare that there were no potential conflicts of interest relevant to this study.

## 8. Acknowledgement

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