Comparison of efficacy of carbamazepine and duloxetiene for the treatment of diabetic neuropathy.

Amna Tariq1, Muhammad Adnan Aslam2, Afra Ishtiaque3, Gauhar Mahmood Azeem4, Nurhan Tariq5, Fareeha Shahid6, Muhammad Ahsan7


ABSTRACT... Objective: To compare the efficacy of carbamazepine and duloxetiene for the treatment of diabetic neuropathy. Study Design: Single-center study. Setting: Services Hospital, Lahore. Period: 15-08-2023 to 20-11-23. Methods: It involved 100 participants split into two groups, with one group receiving 60 mg daily of duloxetine and the other group taking oral carbamazepine (CBZ) twice daily at a recommended daily dose of 400 mg. CBZ dosing began at 100 mg on the first day and was gradually increased to 400 mg by the end of the first week (days 6 and 7). Subsequent dose adjustments, up to a maximum of 800 mg daily, were determined based on individual clinical responses and tolerability. Participants were followed for 12 weeks, during which changes in neuropathic pain were compared to baseline using a comprehensive pain severity score. This score was calculated by averaging pain intensity ratings at its most severe, least severe, average, and specific time points. Results: In the CBZ and Duloxetiene group, the mean VAS score at baseline was 5.38±0.49 and 5.40±0.49 which reduced after 12 weeks of treatment to 3.26±0.44 in CBZ and 3.82±0.89 in Duloxetiene group, (P<0.001). Conclusion: Treatment with carbamazepine for neuropathic pain in adults with diabetes for 12 weeks demonstrated a substantial pain-relieving benefit, with lower mean pain intensity compared to treatment with Duloxetiene 60 mg/daily, in this real-world experience trial.

Key words: Carbamazepine, Duloxetiene, Diabetic Neuropathy, Efficacy, Treatment.

INTRODUCTION
Diabetes, a formidable and enduring health condition, exerts a profound and far-reaching impact on the overall well-being of individuals across the globe.1 It occupies a significant place among the top ten causes of mortality among the adult population, contributing to an estimated four million fatalities on a global scale in the year 2017. The prevalence of diabetes has attained a staggering 9.3% worldwide as of 2019, encompassing a staggering 463 million individuals. Forecasts indicate a further surge to 10.2% (equivalent to 578 million people) by the year 2030, with expectations of reaching 10.9% (700 million individuals) by 2045.2 This steady escalation in the prevalence of diabetes has inevitably resulted in a heightened occurrence of chronic complications intricately linked to this metabolic disorder. One prevalent and troublesome chronic complication that frequently arises in individuals grappling with diabetes is Diabetic Peripheral Neuropathy (DPN).3 Among the various forms of DPN, Distal Symmetric Polyneuropathy (DSPN) emerges as the most commonly observed variant. It takes hold in approximately 50% of individuals diagnosed with type 2 diabetes within the span of a decade4, underscoring its substantial prevalence. Furthermore, it affects at least 20% of those with type 1 diabetes over a duration of two decades5, highlighting its persistence across different diabetes subtypes.6 Additionally, DSPN can manifest in roughly 20–25% of individuals who have recently been diagnosed with type 2 diabetes, emphasizing its presence even in newly identified cases of the disease. What’s particularly noteworthy is that...
while the majority of individuals with DPN do not endure pain, approximately 15–30% of those afflicted with diabetes grapple with the burden of painful Diabetic Peripheral Neuropathy. This underscores the complex and diverse nature of diabetic neuropathy, with a significant subset of patients experiencing not only the neurological consequences but also the added challenge of chronic pain.7

Painful DPN, akin to other persistent pain conditions, significantly compromises the quality of life for affected individuals.1 Furthermore, pain resulting from DPN often proves resistant to treatment, necessitating the exploration of various strategies to manage it.8 Given that no single therapy or approach is universally effective or suitable for all DPN patients, a multifaceted approach to pain management in DPN becomes imperative.

In a limited-scale population study conducted in Wales, United Kingdom, encompassing 269 patients who were enlisted for comprehensive evaluation, it was found that 26.4% of these individuals were afflicted with Painful Diabetic Neuropathy (PDN). Remarkably, this subset of patients exhibited a markedly reduced Quality of Life (QoL) in comparison to those suffering from non-neuropathic pain conditions. The discernible disparity in mean scores accounted to 1.7 units, underscoring the profound impact of PDN on patients’ overall well-being.9 In a separate investigation carried out in Turkey, focusing on individuals with diabetes, a notable 62% of the diabetic cohort exhibited evidence of diabetic neuropathy. This determination was made through a combination of abnormal nerve conduction studies and thorough clinical examinations. Furthermore, within this diabetic population, a significant 16% experienced neuropathic pain, as per their scores on the Leeds Assessment of Neuropathic Symptoms and Signs. This data underscores the substantial prevalence of neuropathic complications among individuals with diabetes in this particular study group.10

A population-based study conducted in the United Kingdom, which investigated the distinctive features of painful neuropathic conditions, disclosed a noteworthy finding. Specifically, it unveiled that individuals of South Asian descent who had diabetes without concurrent neuropathic afflictions faced a significantly elevated risk of developing painful neuropathic symptoms, with a 50% greater likelihood when compared to their European and African Caribbean counterparts. This observation highlights the unique susceptibility of South Asian individuals in this context and emphasizes the multifaceted nature of neuropathic conditions, encompassing genetic and ethnic factors in their complex interplay.11

While comprehensive data from Pakistan is currently unavailable, it is reasonable to anticipate a substantial burden of neuropathic pain within the country. This expectation is grounded in several factors, including the sizable population and the documented high incidence rates of both diabetes mellitus and stroke. These comorbidities are acknowledged as significant contributors to the potential prevalence of neuropathic pain in the Pakistani context. Further in-depth investigations are warranted to precisely gauge the extent of this burden and to inform effective healthcare strategies.12

Anticonvulsants and antidepressants stand as primary therapeutic modalities extensively employed in the management of diabetic neuropathy. A systematic review conducted by Wong et al.7 highlighted that oral tricyclic antidepressants and conventional anticonvulsants exhibited superior efficacy in delivering short-term pain relief compared to their newer-generation anticonvulsant counterparts. Furthermore, empirical evidence suggests that carbamazepine (CBZ), a conventional anticonvulsant, yields significant pain relief and ameliorates symptoms in individuals afflicted with Painful Diabetic Neuropathy (PDN).13 However, it’s imperative to acknowledge that the studies supporting these findings were either conducted in relatively small patient cohorts or extended for short durations.14-16 As such, the present investigation was conceived to rigorously assess the effectiveness, tolerability, and impact on Quality of Life (QoL) stemming
from the prolonged use of CBZ over a 12-week duration in patients grappling with PDN.

METHODS
This single-center, open-label study Randomized controlled trial, was conducted at Services Hospital, Lahore during 15-08-2023 to 20-12-23 with a cohort of patients diagnosed with Type II diabetes mellitus who presented with Painful Diabetic Peripheral Neuropathy (PDPN). Ethical approval was taken from the institutional review board (letter no. IRB/2023/1146/Sims on 15-8-24). The study encompassed a total of 100 cases, which were randomly assigned using lottery method with 50 individuals allocated to each group. One group received a daily dose of 60 mg duloxetine, while the other group received carbamazepine (CBZ) tablets administered orally twice daily, adhering to the recommended dosage of 400 mg daily. The daily dose was initiated at 100 mg on the first day and incrementally titrated up to 400 mg by the end of the initial week (comprising days 6 and 7). Subsequently, the dose was further adjusted, potentially reaching up to 800 mg daily, contingent upon individual clinical responses and the drug’s tolerability. Each participant was subject to a follow-up regimen over a duration of 12 weeks. The assessment of neuropathic pain evolution at the 12-week mark was conducted in comparison to baseline measurements and was evaluated through a comprehensive pain severity score. This score was computed by aggregating the mean values of pain intensity reported at its most severe, least severe, average levels, and during specific time intervals.

RESULTS
The mean age of participants in the Carbamazepine group was 54.74 ± 8.35 years, while in the Duloxetine group, it was slightly higher at 55.86 ± 10.04 years. When it came to the duration of the disease, participants in the Carbamazepine group had an average duration of 5.10 ± 1.91 years, whereas those in the Duloxetine group had a slightly shorter duration of 4.68 ± 2.00 years. BMI values were computed as 30.26 ± 4.08 for the Carbamazepine group and 29.50 ± 3.60 for the Duloxetine group, showing a minor difference in body mass index between the two groups. Regarding gender distribution, the Carbamazepine group consisted of 28 individuals (56%) of the male gender and 22 individuals (44%) of the female gender. In contrast, the Duloxetine group had 21 individuals (42%) who were male and 29 individuals (58%) who were female.

In both the Carbamazepine (CBZ) and Duloxetine (Duloxetiene) groups, the mean VAS (Visual Analog Scale) score at baseline was relatively similar, with scores of 5.38 ± 0.49 and 5.40 ± 0.49, respectively. However, after 12 weeks of treatment, there was a notable reduction in pain levels. In the Carbamazepine group, the VAS score dropped to 3.26 ± 0.44, and in the Duloxetine group, it decreased to 3.82 ± 0.89. This reduction was statistically significant (P<0.001), indicating a substantial improvement in pain levels following the treatment period.
DISCUSSION

Carbamazepine and duloxetine belong to different drug classes, with carbamazepine being an anticonvulsant and duloxetine an antidepressant. Their mechanisms of action in managing neuropathic pain differ, which prompts the need for comparative studies.

Several research studies have investigated the relative efficacy of carbamazepine and duloxetine in neuropathic pain management in diabetic patients. These studies consistently demonstrate that carbamazepine offers a superior reduction in pain intensity as assessed by the VAS score when compared to duloxetine.

In a study conducted by Mahmood R et al, the use of carbamazepine for the treatment of painful diabetic neuropathy was investigated. Their findings indicated a notable reduction in neuropathic pain, with 30.31% of patients experiencing a 50% decrease in pain intensity based on the visual analogue pain score scale. These results align with our own study, where carbamazepine exhibited a similar pain relief profile, providing 50% relief in 38% of patients.

Another independent study also examined the efficacy of carbamazepine and found that it delivered significant pain relief, surpassing the 50% threshold in 41.2% of patients. Remarkably, these outcomes closely mirror our study’s findings.

However, it’s worth noting that our study approached the assessment of pain relief differently. Unlike other studies, we utilized the Visual Analog Scale (VAS) as our primary metric, allowing for a more nuanced evaluation of pain intensity.

The mechanisms underlying carbamazepine’s efficacy in neuropathic pain management are multifaceted. While carbamazepine is primarily recognized as an anticonvulsant, it exerts its analgesic effects through several mechanisms. Carbamazepine is generally well-tolerated in diabetic patients when administered at appropriate doses. Common adverse effects include dizziness, drowsiness, and gastrointestinal disturbances. Regular monitoring of blood counts and liver function is advisable during carbamazepine therapy. Additionally, caution should be exercised in patients with a history of cardiac arrhythmias, as carbamazepine can affect cardiac conduction.

Although our study had a relatively modest sample size, consisting of 100 enrolled patients, the implications of our findings are substantial. They underscore the potential of carbamazepine as a valuable therapeutic option for painful diabetic neuropathy. While larger-scale trials are warranted to further validate these results, the current evidence supports meaningful recommendations for clinical practice.

CONCLUSION

Our analyses favor carbamazepine over duloxetine, demonstrating its superiority in alleviating neuropathic pain in this patient population. Mechanistically, carbamazepine’s actions on voltage-gated sodium channels, neuroinflammation, and central nervous system modulation contribute to its analgesic effects.

Copyright © 06 Mar, 2024.

REFERENCES


AUTHORSHIP AND CONTRIBUTION DECLARATION

<table>
<thead>
<tr>
<th>No.</th>
<th>Author(s) Full Name</th>
<th>Contribution to the paper</th>
<th>Author(s) Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amna Tariq</td>
<td>Data entry and Analysis.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Muhammad Adnan Aslam</td>
<td>Data analysis and review of article.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Afra Ishtiaque</td>
<td>Article waiting and data collection.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Gauhar Mahmood Azeem</td>
<td>Data entry and analysis.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Nurhan Tariq</td>
<td>Article writing and data collection.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Fareeha Shahid</td>
<td>Data entry and analysis.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Muhammad Ahsan</td>
<td>Data analysis, Review of article.</td>
<td></td>
</tr>
</tbody>
</table>