

Dear Editor-in-chief

We are grateful to the reviewers for the helpful and valuable comments on our manuscript [ID: 34998] with the title “**Topiramate induced peripheral neuropathy: A case report and review of literature**” which we are submitting and wishing to be published in World Journal of Clinical cases. We have addressed all reviewers' comments on an item-by-item basis, as indicated on the attached pages and considered their corrections within the main text. We hope that the explanations and revisions of our work are satisfactory. We have specified where changes have been made (yellow color). We hope that the revised version of our manuscript is now suitable for publication in World Journal of Clinical cases and we look forward to hearing from you at your earliest convenience.

Response to comments of Reviewer 1

The case presented is interesting.

Reviewer:

The manuscript could be improved by reducing repetition and reducing the amount of words used.

Author:

Providing that there is a review of literature which included all reports of antiepileptic drugs induced peripheral neuropathy, in the revised version, I avoided redundancy, repetitions and reduced the number of words to less than 3000 instead of 5000 and number of references to 45 instead of 55. I followed the journal style for case articles.

Reviewer:

There are several grammatical and spelling mistakes that need to be corrected. e.g. in the title and other places "Topirmate" should be "Topiramate"

Author:

I revised the text for grammar and spelling mistakes. Topiramate was corrected throughout the whole text.

Reviewer:

The manuscript is a single-author manuscript but the author use the plural "we" frequently even in places where "I" is most appropriate.

Author:

Page 8, line 14: I feel that there is only one occasion in the text where I can use "I" instead of "we" as follow:

"As the patient is seizure free on TPM after several years of ineffective other AEDs therapies, I was unable to do re-challenge testing"

Reviewer:

Some sections need to be corrected for tenses e.g. in some sentences had is used instead of has, were instead of are, was instead of are etc.

Author:

The manuscript has been revised for typo and grammatical errors by a colleague who na ĩve language is English.

Reviewer:

Abbreviations should be defined in the places they are first used. In the second last line of the introduction names of drugs are abbreviated without referring to the full name.

Author:

Page 4 and 5: In the second last line of the introduction, the full names of drugs were referred before they were abbreviated

Reviewer:

The first line of the case presentation section needs to be corrected. It suggests that in 2017 the patient "presented with recurrent frequent attacks (at least two ictal attacks per week) of generalized tonic clonic convulsions" although in other sections the patient is described as "seizure free".

Author:

Page 6, lines 2 and 3: The first line of the case presentation section was corrected as follow: "A 37-year-old well-nourished woman presented at the year 2010 with frequent attacks (two or more ictal attacks per week) of generalized tonic clonic convulsions."

Reviewer:

There is a section written in bold "Long-term phenytoin administration" this should be corrected to conform with the rest of the manuscript

Author:

This section was corrected to conform with the rest of the manuscript.

Response to comments of Reviewer 2

Reviewer:

Causality assessment is very important in this case report as topiramate is used for treatment of neuropathy. It can be done either on basis of Naranjo's scale or WHO scale

Author:

Page 5, lines 12 and 13: we clarified the cause of assessment of the patient as follow: Two years after starting TPM therapy (2015), the patient developed persistent distal numbness in lower extremities. We also checked the probability scoring as recommended by the reviewer and found that it is 7 (i.e. probable). Thus we added this to the text as follow **(the last two lines in page 6):** " and according to the Naranjo adverse drug reaction (ADR) probability scale (ADR score = 7)^[34]."

We already mentioned in **Page 8, lines 13-15** the following: "As the patient is seizure free on TPM after several years of ineffective other AEDs therapy, I was unable to do re-challenge testing (stopping and re-starting the treatment to be sure that it was the cause peripheral neuropathy)."

Thus TPM is a probable diagnosis of patient's peripheral neuropathy and not definite.

Reviewer:

In literature review most of the discussion revolves round phenytoin. It would be nice to focus on topiramate and its related side effects

Author:

As this is also a review of literature and not only a case report, we discussed in details the reports of AEDs induced peripheral neuropathy in which most are related to PHT which is an old and first generation AED but share similar anticonvulsant mechanism of action as TPM which is blockade of sodium channel.

Page 4, lines 10-21: In the introduction section, the side effects of TPM have been mentioned and I explained that most of them are due to the carbonic anhydrase inhibition properties of TPM as follow: "TPM has many adverse side effects. Some are very common (>10% incidence) including dizziness, weight loss, paraesthesia in the face, mouth and extremities (pins and needles which occur in 12-14% of patients), somnolence, nausea, diarrhea and fatigue. Others are common (1-10% incidence) including disturbance in attention, memory impairment, amnesia, cognitive disorder, psychomotor slowing, abnormal coordination, tremors, sedation, vomiting, vertigo, tinnitus, dry mouth, abnormalities of taste and abdominal discomfort. However, most of these adverse effects are mild/moderate, transient and related to higher doses and/or rapid dose titration rate. Thus, these side effects can be reduced or prevented by starting TPM at low doses and gradually increasing the dosage^[9]. Also, TPM has some rare and serious side effects which necessitate drug withdrawal and replacement by alternative, these include acute angle glaucoma, acute myopia, decreased sweating and increase in body temperature, confusion, speech arrest^[10], manifest metabolic acidosis^[11] and urolithiasis of clinical importance^[12]. Most of these side effects are related to the carbonic anhydrase enzyme inhibition properties of TPM."

There are only two articles for TPM related topics which are:

Page 11, lines 14-16: "Boylu et al.^[28] reported mild prolongation in the distal latency of median sensory, ulnar sensory and sural nerves with diminished nerve conduction velocities with chronic CBZ therapy but not with VPA, OXC or TPM."

And **Page 11, lines 19-2; Page 12, lines 1 and 2:** "In an experimental study, Zafeiridou et al.^[33] observed a differential effect for LCM, PHT and TPM on peripheral nerve excitability. The authors reported inhibition of compound action potential of the sciatic nerve of an adult rat after 48 hours period of LCM exposure at concentrations higher than the therapeutic level (>25µg/ml). An acute and immediate increment of the latency and decrement of the amplitude of the nerve compound action potential were observed at LCM concentrations of 62.57-125.15 µg/ml. However, in contrast to LCM, PHT resulted in an acute decrement in

the amplitude of the nerve compound action potential as well as an increment in the latency of the compound action potential even at sub-therapeutic levels (5µg/ml). Reduced compound motor action potential amplitude was also observed with TPM at concentration of 33.94µg/ml (supra-therapeutic).

Reviewer:

Check for spellings stoking ----- correct spelling two places barbiturates----- correct spelling

Author:

We corrected the spellings throughout all the text.

Response to comments of Reviewer 3:

Reviewer:

Interesting case, worth to be published. The paper is too long, 5000 + words, much more than most case presentations. Please check with the policy of the journal.

Author:

We checked the style of the journal for case reports. We reduced the number of words of the manuscript to less than 3000.

Reviewer:

I was not able to find any image in this manuscript, the case needs some records of of electroneurology or other documents of the patient.

Author:

We added the significant electrophysiological records of the patient as figure 1.

Reviewer:

References list longer than usual for case report

Author:

We reduced the number of references to 45.

With this article, we included 1 figure which we wish to publish.

As a corresponding author: I certify that the article entitled “**Topiramate induced peripheral neuropathy: A case report and review of literature**” is original, has been written by the stated author and has not been published and is not being submitted for publication, in whole or part elsewhere.

Thank you for reviewing our manuscript.

Again, we appreciate the valuable comments of the reviewers.