Author’s response to reviews

Title: Case report Pregabalin induced visual hallucinations – A rare adverse reaction

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Reply to Reviewers for the manuscript:
PHAT-D-19-00101R1
Pregabalin induced visual hallucinations – A rare adverse reaction
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BMC Pharmacology and Toxicology

Synopsis:
The authors would like once again to thank the reviewers for acknowledging the importance of our article and for the valuable comments they provided concerning the manuscript. We prepared a revision note highlighting in detail the amendments based on each reviewer comments. We are very happy that all the reviewers have acknowledged that this is a well written and well researched case report and all of them have supported publication after minor revision only. Pregabalin is a very hot topic nowadays and every well written case report is important.
Please note that all amendments made in the original manuscript are clearly highlighted in the revised manuscript and discussed below.

Dear editor our case is different from other case reports and this information can be found in page 7, line 10: In contrast to these studies which suggest that visual hallucinations from pregabalin are mainly attributed to rapid titration, our study indicates that this side effect may be dose depended and can appear in cases of slow titration as well, as happened in our case.

Review comments from the Reviewer 1

• Reviewer 1 / Comment 1: I suggest the authors add a brief formal assessment of the likelihood the adverse event was caused by pregabalin - using the Naranjo algorithm.

Authors reply: In page 8, line 31 we added: We have performed a formal assessment of the likelihood the adverse event was caused by pregabalin, using the Naranjo algorithm and the score was 7, which shows that this is a probable adverse drug reaction due to pregabalin.

Authors reply: In page 8, line 31 we added: This adverse drug reaction is listed in the medication label.

Reviewer 1 / Comment 3: Generic medication names (pregabalin), and medical specialties (neurologists, general practitioners, psychiatrists, etc.) are common nouns and not capitalized when they are not at the beginning of a sentence.

Authors reply: We have used smalls letters for all these words when there are not in the beginning of the sentence.

Reviewer 1 / Comment 4: A space is missing between two words in the last sentence ("clarifythe")

Authors reply: This has been amended.

Review comments from the Reviewer 2

Reviewer 2 / Comment 1: The authors should check a reference [20]. "Clin Toxicol 2013; 51 (4): 320" was not picked up on PubMed search engines.

Authors reply: This reference is correct.

Reviewer 2 / Comment 2: The description "Norgaard et al. reported a 38 year-old man was self-administering 8.4 g pregabalin daily" in the Discussion (Page 5; Lines 46-50), is about pregabalin abuse. At least, the previous sentence, the authors should describe pregabalin abuse. A reference (Clin Drug Investig, 2016, 36 (9): 735-742) about pregabalin abuse had better be used.

Authors reply: We have separated this paragraph into two smaller paragraphs. In the beginning of the second paragraph we have added a sentence about pregabalin abuse and we have used the reference provided by the reviewer (reference 20). Pregabalin as a medication can cause dependance, which on some occasions can lead to abuse. All the other references from thereafter have been amended accordingly.

Review comments from the Reviewer 3

Reviewer 3 / Comment 1: Introduction Pregabalin is an isomer (analogue) of gamma-aminobutyric acid (GABA). I would say with more precision "Pregabalin is a 3-isobutyl derivative of gamma-amino butyric acid (GABA)"

Authors reply: This has now been amended accordingly.

Reviewer 3 / Comment 2: What means exactly: in "over-excited" presynaptic neurons ? This phrase is not clear Is it true also in patients with anxiety ?

Authors reply: We have completely removed the word "over-excited" so that we do not cause any confusion.
• Reviewer 3 / Comment 3: Page 6, line 16th Psychotic symptoms…..Only vigabatrin and topiramate are cited. I would add also other AEDs.. At least also zonisamide may cause psychosis. In addition, I would add or change the reference (Besag et al., is not updated!)

Authors reply: We have changed this sentence in order to include all the antiepileptic medication: Psychotic symptoms caused by antiepileptic medication (AEDs) are infrequent; however, AEDs have been associated with the provocation of psychosis or worsening of pre-existing symptoms [11]. We have also used a more up to date reference changing the existing one as per the reviewer’s request. This is reference 11.

• Reviewer 3 / Comment 4: At the end of discussion, regarding the hypothesized pathophysiological mechanisms causing visual hallucinations it is affirmed "In predisposed individuals, an increase of pregabalin plasma levels might result in relative over-attenuation of inhibitory systems, and thus result in abnormal over-synchronization" It is not clear to me what exactly means this phrase. In particular "over-attenuation of inhibitory systems" and how this mechanism may cause hallucinations

Authors reply: We have removed the word over-attenuation. We have added one more sentence with the appropriate reference in an attempt to try to explain a bit more this mechanism. We believe that it is difficult to try and explain it more as this is only a hypothesis and as we had already mentioned in the text: More data is needed to understand the pathophysiology of pregabalin induced hallucinations and psychotic symptoms.

and thus significant reduction of glutamate levels [28]. According to glutamatergic theories of schizophrenia, glutamate dysfunction, for example a significant reduction of glutamate levels caused by pregabalin could be the cause of hallucinations and other psychotic symptoms.

Alternatively the whole paragraph could be removed, but we think that this is correct in general as per reviewer 1 and 2 and now has been improved after the reviewer 3 comments and it is a lot better.

Authors’ Note
A set of additional references have been included into the text and the reference list