ANSWERING REVIEWERS

Dear editor,

Thank you very much for the editorial staff and reviewer's hard-work in processing our manuscript (No.43309). The comments are all valuable for refining our paper. We have studied the comments carefully and revised the manuscript. The revised portion have been marked in the manuscript and the main corrections in the manucript and the responds to reviewers' comments are as following:

To reviewer #1 (code: 00504462)

1) Dear Sir, It is interesting your manuscript as you have a complicated patient of a common disease with a uncommon etiology. It was interesting also, how you propose to be treated, even though right now cannot be generalized but proposed for a research protocol for validate it. One more suggestion is that it is too long, and need to be synthesized, which should not be any problem for you. Hope to hear from you soon.

Answer: Thank you for your kindly review of our manuscript and your encouraging comments. We have made the refinement according to your suggestion and adjusted the manuscript structure based on the journal requirements. We have restrcutured the abstract and case presentation section. Conclusion section have also been provided according to the science editor's comments. However, in order to describe this unusual case with complicated history and long-term follow-up in detail and further disccuss the suspected etiolgy, the revised manuscript may seem long.

To reviewer #2 （code: 03469734）

1) ***Long form d (day) must be written: insomnia for 20 years and exacerbation in 20 d.***

Answer: Thank you for carefully reviewing our manuscript. The guidelines for how to accurately write common units and quantities indicate that short

form d should be written after Arabic numerals and 20d can be used in numerical narration. We have revised other non-standard units in the updated manuscript.
(http://www.wjgnet.com/bpg/gerinfo/189)

2) ***Generic name (atorvastatin) should be used instead of lipitor.***

Answer: Thank you for patiently reviewing our manuscript and listing the mistakes in the original manuscript. We have made the corrections in the revised manuscript.

3) ***All medications mentioned in the discussion section should be written in case.***

Answer: We have restructured the "Case Presentation" part according to the journal requirements and all medications mentioned in the discussion section have all been written in the "History of present illness" and "History of past illness" part chronologically.

4) ***Was there any change in the dose of quetiapine?***
Antipsychotics can lead to bruxism. As you say, there is no case reports associated with quetiapine. However, side effects of this drug include bruxism, even in textbooks is also included. One of the side effects of quetiapine is the grinding of teeth.
(https://www.drugs.com/sfx/quetiapine-side-effects.html)
Quetiapine is also used in the treatment, as it can lead to bruxism!
(Zandifar A, Mohammadi MR, Badrfam R. Low-Dose Quetiapine in the Treatment of SSRI-Induced Bruxism and Mandibular Dystonia: Case Series. Iran J Psychiatry. 2018 Jul;13(3):227-229. PMID: 30319707)
"Another problem seen in patients on high doses of Quetiapine is bruxism, more commonly know and teeth grinding. This results in further damage to teeth and irritation to gums. A reduction in dosage may also help reduce side

effects, making it well worthwhile discussing this possibility with your doctor. However, it is equally necessary to weigh up the pros and cons of Quetiapine before altering the dosage."
(Drummond, E. (2006) The Complete Guide to Psychiatric Drugs New Jersey: Wiley & Sons Stein, G. & Wilkinson, G. (2007), Seminars in General Adult Psychiatry Royal College of Psychiatrists)

Answer: There is no change in the dosage of quetiapine. We are very sorry that we have not described in detail the dosage change of medications in the original manuscript. In the updated manuscript, we have revised the sentence of "The patient insisted on the same drug recipe" as "The patient insisted on the same drug recipe and the final stable medication doses were venlafaxine 150 mg/d, quetiapine 100mg/d and lorazepam 2.0mg/d across 7 years" and the sentence of "However, none of those medications have been reported to induce DB or other movement disorders" as "However, none of those medications have been reported to induce DB".
Before further discussion of quetiapine on bruxism, we would like to thank you again for the valuable suggestion which will definitely improve the quality of our manuscript. As you state, quetiapine can lead to tardive dyskinesia and bruxism (uncommonly, 0.1% to 1%).
(https://www.drugs.com/sfx/quetiapine-side-effects.html)
Unfortunately, we failed to find reports associated with quetiapine-induced bruxism. In recent years, early/late-onset tardive dyskinesia (TD) induced by quetiapine have been reported.
(Walsh R A , Lang A E . Early-onset tardive dyskinesia in a neuroleptic-naive patient exposed to low-dose quetiapine[J]. Movement Disorders Official Journal of the Movement Disorder Society, 2011, 26(12):2297-2298.)
(Hou Y C , Lai C H . Late-onset Quetiapine-related Tardive Dyskinesia Side Effects in a Patient with Psychotic Depression[J]. Clinical Psychopharmacology &

Neuroscience the Official Scientific Journal of the Korean College of Neuropsychopharmacology, 2014, 12(2):163-5.)

It should be noted that bruxism has not been mentioned in reports related to quetiapine-induced TD, though it can be a clinical feature of TD as stated in textbook.

(Stein, G. & Wilkinson, G. (2007), Seminars in General Adult Psychiatry, Royal College of Psychiatrists, 269-270.)

A newly released article suggests low-dose quetiapine can be used in the treatment of SSRI-induced bruxism. It is interesting quetiapine is also used in the treatment of tardive dyskinesia , as itself can lead to tardive dyskinesia. Its treatment effect may be explained by its low D2 receptor occupancy and antagonism at the 5HT2A and H1 receptors. Its transient dopamine receptor occupancy may account for its risk of TD. Accordingly, quetiapine can be thought to possess the possibility to treate or exacerbate bruxism theoretically for it blocks a subset of dopamine and serotonin receptors. However, Further studies are needed to ascertain the differential effects of quetiapine in terms of bruxism.

(Ono S , Suzuki Y , Shindo M , et al. Improvement of tardive dyskinesia and dystonia associated with aripiprazole following a switch to quetiapine: case report and review of the literature[J]. Journal of Clinical Pharmacy and Therapeutics, 2012, 37(3):0-0.)

(Tomruk N B, Saatcioglu O, et al. Aripiprazole-induced tardive dyskinesia treated with quetiapine: a case report[J]. Acta Neuropsychiatrica, 2011, 23(4):188-190.)

And we totally agree with you that it is necessary to weigh up the pros and cons of quetiapine before altering the dosage. This is exactly why we suggest the maxillary buccal-pterygoid splint as a noninvasive approach before changing the medication regimen without evidence-based researches.

5) Bruxism associated with stroke has been reported of Tan. Was there any lesion in the basal ganglia in the cerebral MRI?

(Tan EK, Chan LL, Chang HM. Severe bruxism following basal ganglia infarcts:insights into pathophysiology. J Neurol Sci. 2004;217(2):229–32.)

Even the brain regions affected by the fMRI study are shown.

Yılmaz suggested that the bruxism group showed less activation in the right inferior parietal lobule [Brodmann areas (BA) 39, 40 and partially 7] and dorsal posterior cingulate area (BA 31). It also supports your theory.

(Yılmaz S. To see bruxism: a functional MRI study. Dentomaxillofac Radiol. 2015;44(7):20150019. doi: 10.1259/dmfr.20150019.)

Answer: There was no leison in the basal ganglia in the cerebral MRI. When the patient in our case was admitted to the psychology department of the Huifu Xi branch of Guangdong General hospital, the head MRI and MRA showed multiple remote ischemic areas at the bilateral frontal lobe and parietal cortex. Unfortunately, follow-up MRI and MRA was lacked. We have no way of knowing whether there was any progressive leision in the brain region when the patient developed diurnal bruxism. Likewise, we can not trace the change of the funtional area of brian during the splint therapy process. We have stated this limitation in our manuscript.