Reviewer’s report

Title: A Serious Adverse Drug Reaction Probably Induced by Clonazepam: a case report of Myotoxicity

Version: 0 Date: 09 Aug 2019

Reviewer: Mervyn Eadie

Reviewer's report:

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While I thought this was an interesting account, though necessarily lacking in some desirable details because of circumstances outside the authors' control, I felt that it might be safer to relate the problem encountered to the use of clonazepam in the presence of valproate, since clonazepam was never the only drug present when the probable adverse reaction occurred, and to put less emphasis on the speculative nature of the muscle pathology presumed to present.

No description is provided of the neurological findings at the time the patient's epilepsy was investigated before any treatment commenced, and also no details of the clinical findings during the presumed adverse reaction. Partly because of the lack of this information a number of questions need to be raised in the Discussion section of the paper, and answers provided. Thus how certain is the diagnosis of early-life poliomyelitis? Could this young woman really have had some very slowly progressive early-onset type of muscle wasting disease of neurological or myopathic origin, and the epilepsy treatment simply accelerated its progress? A long-standing myopathic disorder might be more likely in view of the high creatine kinase level during the adverse reaction.

Because the patient was always taking valproate, even though the probable myopathy seemed to vary with clonazepam intake, could it be that there was a metabolic interaction between valproate and clonazepam leading to the presence of a myotoxic valproate metabolite. Valproate has a considerable number of known metabolites and the formation of some of them has been related to occasional but serious liver toxicity, though reports of this have largely ceased to occur in recent years. At the least, I think it might be wise to bring out the point that clonazepam was never the sole antiepileptic drug present.

A post-polio syndrome has been described on a number of occasions, though as far as I can make out its exact spectrum of manifestations and cause remain unclear, but it might be worth mentioning this though I think the high creatine kinase level makes it likely that you are correct
in believing that the issue is muscle toxicity, though the detail of its pathogenesis has to be speculative.

Without some mention of matter such as the above I suspect your confidence that clonazepam by itself was the cause of the muscle problem, and your ideas of the nature of the muscle microscopic pathology may be questioned by some readers.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
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Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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