PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Gabapentin for the Treatment of Pain Manifestations in Children with Severe Neurological Impairment- a Single Centre Retrospective Review
AUTHORS	Collins, Aedin; Mannion, Rory; Broderick, Annemarie; Hussey, Séamus; Devins, Mary; Bourke, Billy

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Julie Hauer Institution and Country: Boston Children's Hospital United States Competing interests: None
REVIEW RETURNED	27-Mar-2019

GENERAL COMMENTS	Thank you for collecting this important data. In the first paragraph I would add "severe" cognitive impairment so as to not confuse readers that all children with cognitive impairment have this high rate of pain frequency (i.e. those with intellectual disability that is severe to profound have a much higher rate of pain, not those with mild to moderate). I would suggest adding central neuropathic pain along with visceral hyperalgesia as reasons for GI symptoms, as discussed briefly in reference 5. My main concern is lack of information regarding dosing of gabapentin and pregabalin. It is unclear if lack of response to gabapentin in some was due to inadequate dosing. Reference 5 indicates average gabapentin dose, with higher dose in the younger group. I would suggest adding this information to enhance the results of this case series. What was the time frame over which 4 lost benefit from gabapentin? Was the dose adjusted when this was noted? How long were individuals on pregabalin for comparison? Did elevated liver enzymes return to normal in the 1 case? What other medications was this patient on that might increase the risk of elevated liver enzymes or was there a recent illness that can result in a transient increase? (though I recognize this last question may not fit into the word count) I would recommend taking out of table 1 the section "Reason for change to pregabalin" as it is included in table 2 and therefore redundant. One the one hand I am so grateful for this added information indicating the first line role of gabapentinoids in symptom management for this group of children. On the other hand I would like to see further information as to the outcome when used.

	This includes information when switched to pregabalin, including does the benefit continue? Does it make sense to switch to another gabapentinoid versus adding a 2nd medication with a different mechanism of action? (information about a 2nd medication with a different mechanism of action discussed in the AAP clinical report "Pain Assessment and Treatment in Children With Significant Impairment of the Central Nervous System" Thank you for this important effort!

REVIEWER	Reviewer name: Lefteris Zolotas Institution and Country: Royal Derby Hospital, UK Competing interests: None
REVIEW RETURNED	02-May-2019

GENERAL COMMENTS	This short paper summarises the effectiveness and safety of gabapentinoids in a cohort of 42 children with severe neurological impairment (SNI) and pain and/or distress symptoms. Use of gabapentinoids for neuropathic pain and other types of pain has been increasing including the paediatric population. However evidence around efficacy and safety remains poor in children. Therefore the information a retrospective cohort can provide is always useful The study has a number of limitations: The studied population poses a significant challenge: in children with SNI pain and distress due to other causes are not always distinguishable. Therefore it is difficult to distinguish between the analgesic and sedative properties of this class of drugs. The study does not use definitions of pain and also standardised pain scales (partially a result of the nature of studied population) The study is prone to bias associated with this type of studies (retrospective) I think the authors' conclusion is well phrased and reflects the above limitations. I think it is worth mentioning these limitations in the paper. Also I think the conclusion that adverse effects are "rare" should be avoided. The cohort is very small to draw any conclusions on frequency.

VERSION 1 – AUTHOR RESPONSE

In response to the comments made by Reviewer 1, Julie Hauer:

Thank you for your comments.

I have edited the article as suggested by changing cognitive impairment to severe cognitive impairment and adding central neuropathic pain as a reason for the symptoms and removed the replication from within the tables.

The starting dose of gabapentin was 5 or 10mg/kg/day working up to 20mg/kg/tds. All four children who lost response had worked up to the maximum dose and all but one of the patients who did not have a response to gabapentin were also on 20mg/kg/tds.

The final patient was on 10mg/kg/tds.

The mean duration of gabapentin treatment in the 4 patients who lost effect from gabapentin was 25 months and all were on 20mg/kg/tds. Follow up of patients who changed to pregabalin ranged from 4 to 26 months with a mean of 13.5 months. I have added this information into the body of the article.

The patient with raised transaminases was also on prophylactic azithromycin, melatonin, amitriptyline, mst, nitrofurantoin, oramorph and lansoprazole. There were no documented viral illness or other causes for their raised transaminases. I was unable to include this information in the article due to word count restrictions.

The number of patients who switched to pregabalin is small. Of the 6 who switched because of ongoing symptoms, 4 of whom had no response and 2 minimal response to gabapentin, 2 had good response to pregabalin, 2 minimal and 2 had no response. The 3 patients who switched cause the efficacy of gabapentin had worn off over time had minimal response to pregabalin. Pregabalin had good effect in one of the children who switched due to lethargy and a minimal effect in the other. The final child had a good response to pregabalin. Due to restriction in word count, this detail is not included in the article.

In response to the comments made by Reviewer 2, Lefteris Zolotas:

I acknowledge the limitations of this study. Unfortunately, the stringent restriction on length make it difficult to detail them as suggested. I have however inserted an acknowledgement that there are limitations given the retrospective nature of the study. I would be happy to expand further on the limitations if the editor so requests. I have removed the comment regarding adverse effects being rare.

Thank you for your comments.