



OPINION ARTICLE

**REVISED** Respiratory concerns of gabapentin and pregabalin: What does it mean to the pharmacovigilance systems in developing countries? [version 2; peer review: 2 approved]

Sunil Shrestha <sup>1,2</sup>, Subish Palaian <sup>3</sup>

<sup>1</sup>Department of Pharmacy, Nepal Cancer Hospital and Research Center, Lalitpur, Nepal

<sup>2</sup>Department of Pharmaceutical and Health Service Research, Nepal Health Research and Innovation Foundation, Lalitpur, Nepal

<sup>3</sup>Department of Clinical Sciences, College of Pharmacy and Health Sciences, Ajman University, Ajman, United Arab Emirates

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**Abstract**

Gabapentin and pregabalin, commonly known as gabapentinoids, have been widely used globally. This paper highlights the serious breathing problems due to using gabapentin and pregabalin which was warned by the United States Food and Drug Administration on December, 2019. In this article, we tried to recommend suggestions for controlling these adverse drug reactions (ADRs). Safety reports of gabapentin and pregabalin should be obtained from concerned manufacturers and reviewed for respiratory depression effects. There should be strict prescription monitoring and drug use evaluation studies. Concurrent use of gabapentin and pregabalin with other respiratory depressants such as opioids should be strictly monitored. Educating patients can help in the early detection of ADRs due to gabapentin and pregabalin. Anecdotal reports on these medications should be encouraged.

**Keywords**

Gabapentin, Pregabalin, pharmacovigilance, Developing countries

**Open Peer Review**

**Reviewer Status**

	Invited Reviewers	
	1	2
<b>version 2</b> (revision) 25 Feb 2021		 report
<b>version 1</b> 22 Jan 2020	 report	  report

1. **Sue E Jordan**, Swansea University, Swansea, UK

2. **Tetsu Ohnuma** , Duke University Medical Center, Durham, USA

Any reports and responses or comments on the article can be found at the end of the article.

**Corresponding author:** Sunil Shrestha ([sunilcresta@gmail.com](mailto:sunilcresta@gmail.com))

**Author roles:** **Shrestha S:** Conceptualization, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Palaian S:** Conceptualization, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

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**REVISED Amendments from Version 1**

In response to the reviewer's comments and suggestions, we have made a few changes in the recommendations and conclusion sections of the article. Being widely used medications, it is recommended that vulnerable patients for developing respiratory side effects due to gabapentinoids should be identified in order to prevent exposure. The changes made in the revised version highlights two additional high risk population category for developing gabapentinoids induced respiratory depression such as patients with concurrent opioid use and patients administered with gabapentinoids on the day of surgery. The abstract was also amended in line with the recommendations section mentioning the risk of respiratory suppression when opioids are combined with gabapentinoids. Further, we cited literature confirming gabapentinoids induced respiratory suppression during the immediate post-operative period in a dose-dependent fashion among people who underwent total hip and knee arthroplasties. In the conclusion section, two new points have been added emphasizing the need to exercise more caution while gabapentinoids are used in patients concurrently with opioids, and the need for establishing effective safety monitoring and reporting systems to identify signals and its proper dissemination. The revised version of the article has three new references, 21–23, added to it.

**Any further responses from the reviewers can be found at the end of the article**

**Introduction**

Gabapentin and pregabalin, commonly known as gabapentinoids, have been widely used globally. Gabapentin is an anticonvulsant agent used in treating various illnesses such as amyotrophic lateral sclerosis, analgesia, anxiety, neuralgia, restless legs syndrome and bipolar disorder<sup>1</sup>. Pregabalin is commonly used to treat painful diabetic neuropathy, fibromyalgia, diabetic neuropathy, cancer chemotherapy-induced neuropathic pain, post-herpetic neuralgia, trigeminal neuralgia, and post-operative pain<sup>2,3</sup>. Pregabalin also acts to be an effective treatment therapy in refractory partial-onset seizures and the existing data recommends that pregabalin may be favorable as adjunctive therapy in adults with generalized or social anxiety disorder<sup>3</sup>.

As per the available safety data, the use of gabapentin and pregabalin may cause neuropsychiatric related adverse drug reactions (ADRs) followed by hepatic, cutaneous and hematological reactions<sup>4</sup>. Suicidal ideation, cognitive impairment, motor incoordination, dizziness are also severe forms of ADRs associated with gabapentinoids<sup>5</sup>. The use of pregabalin is associated with hematological ADRs, and gabapentin is also associated with liver toxicity.

**Respiratory concerns with gabapentin and pregabalin**

Respiratory depression, a highly mortal condition, due to gabapentin and pregabalin has been emerging for the past few years even in patients who were not on opioids, though post-marketing studies showed similar effects among patients taking these medications concurrently along with other respiratory suppressants<sup>6</sup>. In December 2019, the United States Food and Drug Administration (US FDA) issued a drug safety alert on serious breathing problems with gabapentin and

pregabalin noticed when used along with central nervous system (CNS) depressants or in patients with lung problems. US FDA reviewed data from the FDA Adverse Event Reporting System (FAERS)<sup>7</sup> database of almost five years, i.e. from January 1, 2012 – October 26, 2017, which revealed 49 cases gabapentinoid-induced respiratory depression. Out of 49, most cases (n=34; 69.3%) were reported with pregabalin and 30.6% (n=15) cases were reported with gabapentin. Of these cases, 92% reported either a respiratory risk factor, including age-related loss of lung function, or the use of a CNS depressant. This report also revealed that 24% percent (n=12) of the 49 patients with respiratory depression died due to respiratory depression and were taking gabapentinoids.

**What do the recent respiratory problems of gabapentin and pregabalin mean for pharmacovigilance in the developing world?**

Since these ADR reports are from developed countries, it is difficult for regulators in developing countries to take decisions on these two medications that are also abundantly used in the developing world. For example, in India, there are escalating sales of gabapentin and pregabalin and while comparing the sales in 2017 to those in 2019, it was found that sales of gabapentin and pregabalin increased by 25% and 16%, respectively<sup>8</sup>.

As is well documented in the literature<sup>9–11</sup>, pharmacovigilance programs in developing countries lack robust reporting of ADRs and underreporting is a common issue. To bring any regulatory changes such as labeling changes or even ultimately banning the medications, one needs evidence, which largely is lacking at this point among developing countries<sup>12</sup>.

There have often been issues like this in the past where safety concerns emerge, mainly from the developed world, with drugs like selective cyclooxygenase-2 inhibitors (coxibs)<sup>13</sup>, cerivastatin<sup>14</sup> and glitazones<sup>15</sup>, and the developing world, due to lack of stringent pharmacovigilance mechanisms, is left with little or no choice but to follow the actions taken by the developed world. In addition, developing countries lack options for communicating pharmacovigilance information<sup>16</sup> among key stakeholders, including consumers, which is another concern. It is astonishing that many developing countries where large quantities of medicines are used still lack strong mechanisms to monitor the safety of their products.

**Recommendations**

In the current scenario, safety reports of gabapentinoids should be obtained from concerned manufacturers and reviewed for respiratory depression effects. As understood, manufacturers are an important partner in the pharmacovigilance process with the unique advantage of formulation related information. The periodic safety update reviews (PSURs) submitted by the manufacturers of gabapentinoids can be an important source for new signal detection<sup>17</sup>. In addition, the pharmaceutical manufacturer also has an obligation to report serious ADRs to the regulatory authorities<sup>18</sup>.

Healthcare professionals should be watchful and report ADRs associated with gabapentinoids. Spontaneous reporting of

suspected ADRs in the past have been crucial in detecting ADRs at an early stage<sup>19</sup>.

Labeling changes should be made, and a drug can be banned if needed<sup>20</sup>. New warnings are necessary to incorporate into prescribing information, including package inserts about possible respiratory depression<sup>8</sup>. Concurrent use of these drugs with other respiratory depressants should be strictly monitored. Anecdotal reports on these medications should be encouraged as they can be crucial in detecting ADRs<sup>21</sup>. If noticed, causality and severity assessments should be made for the suspected ADRs.

While these medications are used widely, it is also crucial to identify the vulnerable population at a high risk of developing respiratory side effects. It is evident that concurrent opioid use increases the risk for respiratory depression<sup>22</sup>. Further, a retrospective study involving 175,787 patients who underwent colorectal surgery reported administration of gabapentinoids on the day of surgery was associated with an increased risk of pulmonary complications<sup>23</sup>. In another retrospective analysis involving 858,306 patients who underwent total hip and knee arthroplasties, gabapentinoids showed respiratory suppression during the immediate post-operative period in a dose-dependent fashion<sup>24</sup>. The patients on these two medications (and the ones closely chemically related to them) should be provided with proper counseling. Educating patients can help in the early

detection of ADRs and active participation of patients can help identify adverse events and ADRs, describe ADRs, and ultimately prevent drug-related harm<sup>25</sup>. Hospital drug and therapeutics committees play a crucial role in situations like this by disseminating information within the hospital<sup>26</sup>. Social media may also play a crucial role in the signal generation of suspected ADRs in these situations<sup>27</sup>. Hospitals using these medications should develop risk management plans associated with gabapentinoids usage and must disseminate any safety issues to concerned authorities.

## Conclusions

Drug safety is a constantly evolving process and one must be vigilant on the use of these medications. It is suggested to exercise more caution while these drugs are used in patients and concurrent opioid administration. It is also essential to establish effective safety monitoring and reporting systems to identify signals and its proper dissemination. Healthcare professionals, especially prescribing physicians, nurses and pharmacists should be more cautious about using these medications in vulnerable people. Patient education and prescription restrictions of gabapentin and pregabalin may be needed until more data are available.

## Data availability

No data is associated with this article.

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# Open Peer Review

Current Peer Review Status:  

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## Version 2

Reviewer Report 26 February 2021

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**Tetsu Ohnuma** 

Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, USA

Thank you for addressing my points. I don't have further comments to make.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Perioperative multimodal analgesics

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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## Version 1

Reviewer Report 17 August 2020

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**Tetsu Ohnuma** 

Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, USA

This is an interesting article on a relevant topic. It is well written and important points are clearly presented.

Gabapentinoids, gabapentin and pregabalin, are being increasingly dispensed for indications outside US FDA labelling, particularly as part of multimodal analgesia in the perioperative setting.

Emerging evidence from pre-clinical, human volunteer, inpatient, and outpatient studies suggests that their use in combination with opioids may increase the risk of respiratory depression. In our recent studies, use of gabapentinoids on the day of surgery was associated with increased risk of postoperative pulmonary complications in patients who underwent colorectal surgery<sup>1</sup>. We also found that in-hospital use of both gabapentin and pregabalin had dose dependent associations with pulmonary complications in the immediate postoperative period after total hip and knee arthroplasties<sup>2</sup>.

The adverse effect of perioperative use of gabapentinoids can occur in all countries. While differences in risk across different populations are unclear (for example, the prevalence of pulmonary complications after concurrent use of opioids with gabapentinoids may differ among races), we suggest that a caution be warranted when these drugs are used in combination with opioids. Obviously, it is essential to establish effective safety reporting systems to detect signals of adverse events and disseminate the information to all relevant sections.

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**Is the topic of the opinion article discussed accurately in the context of the current literature?**

Yes

**Are all factual statements correct and adequately supported by citations?**

Partly

**Are arguments sufficiently supported by evidence from the published literature?**

Partly

**Are the conclusions drawn balanced and justified on the basis of the presented arguments?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Perioperative multimodal analgesics

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Reviewer Report 31 July 2020

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### Sue E Jordan

College of Human and Health Sciences, Swansea University, Swansea, UK

Thank you for the opportunity to review this interesting short opinion paper.

The SmPCs for gabapentin and pregabalin include respiratory problems under 'undesirable effects'; however, as the authors say, there are no recommendations to apply this to practice. This applies in all countries, particularly post-industrial societies. Our trial and observation study found too many unaddressed respiratory problems <sup>1,2</sup>.

Whilst I concur with the sentiments expressed, I feel these should be placed in the context of full patient monitoring for the full range of possible adverse effects of prescribed medicines. Respiratory depression is extremely important, as indicated, but it is also important to check patients for other possible undesirable effects of medicines and unmedicated problems, including pain, sedation and falls. We have shown the effectiveness of this approach, and would like to see it more widely adopted<sup>1,2</sup>. Our website gives free access to our strategy.  
<http://www.swansea.ac.uk/adre/>.

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**Is the topic of the opinion article discussed accurately in the context of the current literature?**

Yes

**Are all factual statements correct and adequately supported by citations?**

Yes

**Are arguments sufficiently supported by evidence from the published literature?**

Yes

**Are the conclusions drawn balanced and justified on the basis of the presented arguments?**

Yes

**Competing Interests:** No competing interests were disclosed.



**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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