Comment on "Parkinsonism Associated With Gabapentinoid Drugs: A Pharmacoepidemiologic Study"

We have read "Parkinsonism associated with gabapentinoid drugs: a pharmacoepidemiologic study" by Pacheco-Paez and colleagues with great interest.[1] As the use of gabapentinoid drugs increases, any information on their possible long-term side effects is warranted. Based on the VigiBase database, the researchers concluded that both gabapentin (GBP) and pregabalin (PRG) have 2.16 to 2.43 times higher reporting odds ratios (RORs) for developing parkinsonism than nonusers, indicating possible adverse reactions.

However, in our opinion, the lack of numerous important factors (e.g., age, indications, and comorbidities) prevents from identifying any causative relationships between gabapentinoid usage and reported parkinsonism.

While GBP has numerous on-label indications (e.g., epilepsy, peripheral neuropathic pain caused by diabetic neuropathy, and postherpetic neuralgia), it may be used in restless legs syndrome (RLS), essential tremor (ET), and central- or spasticity-related pain efficiently. Besides, PRG has an indication for generalized anxiety and the off-label use for chronic low-back pain. Gabapentinoid drugs are more frequently prescribed in patients with older age, higher comorbidity index, and diabetes.[2] Reimbursement and costs can also have an impact on the use of these drugs. Based on the publicly available Hungarian National Health Insurance Fund data, the vast majority of real-life gabapentinoid usage is associated with diabetic neuropathic pain (72.2% and 89.5% for GBP and PRG, respectively).

The interpretation of the VigiBase data without relevant clinical data is very limited because some of the gabapentinoid indications (e.g., type 2 diabetes mellitus [T2DM], RLS, or ET) may be associated with higher risks for developing parkinsonism.[3,4] For example, T2DM may increase the risk by 41%.[4] Therefore, the underlying T2DM supposedly is not a negligible factor behind the increased RORs observed with gabapentinoid usage.

To compensate for this weakness and assess "the robustness" of their findings, the researchers made some efforts. They tried to exclude cases where other drugs capable of inducing parkinsonism were used, but some concomitant medications (e.g., trimetazidine[5]) were not taken into consideration. The reported risks for parkinsonism concerning amitriptyline and duloxetine, drugs having similar indications with gabapentinoids, were also compared. Although amitriptyline might have similar indications for neuropathic pain, it has numerous contraindications, mainly attributed to cholinergic side effects and significantly more pharmacological interactions, limiting its use in T2DM and the elderly. Therefore, we believe that the comparison between gabapentinoids versus duloxetine was more feasible. Table 2 shows that GBP and PRG usage is associated with 0.91 (95% confidence interval [CI]: 0.86–0.96) and 1.15 (95% CI: 1.09–1.22) higher risks for reported parkinsonism compared to duloxetine users. Considering that gabapentinoids are more frequently prescribed in the elderly,[2] where development of parkinsonism is more probable, these differences (–9% to +15%) seem to be neither strikingly outstanding nor clinically relevant. Moreover, these data may suggest that GBP and PRG have similar RORs for signaling parkinsonism compared to duloxetine. This may also indicate that not the gabapentinoid-usage alone, but other clinical factors (e.g., T2DM and older age) might be responsible for the increased reporting of parkinsonism. Therefore, we believe that the methods applied by Pacheco-Paez and colleagues are unable to answer the question of whether gabapentinoid usage can be associated with parkinsonism.

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Reply to: Comment on "Parkinsonism Associated With Gabapentinoid Drugs: A Pharmacoepidemiological Study"

We read with interest the comments by Pinter and colleagues about our article in which we suggested an association between exposure to gabapentinoids (gabapentin, pregabalin) and the occurrence of parkinsonism.[1] The authors discussed several points.

First, they underlined the lack of description of numerous important factors, like age, in the description of the study population. In fact, because of editorial recommendations (limits to the number of tables and words), it was not possible to present all our data in the article. In fact, we previously verified that there was no difference between the study groups. For example, the mean age was 63.2 10.8 years in cases and 63.6 11.1 in noncases for gabapentin and 63.8 11.4 in cases and 64.4 11.5 in noncases for pregabalin, which were not significantly different.

Second, Pinter and colleagues discussed the underlying putative role of diabetes mellitus. They mention that type 2 diabetes mellitus increases the risk of parkinsonism by 41%. In fact, there are many publications about diabetes mellitus and Parkinson's disease (PD), and there have been major conflicting results; some studies described an association and others have been unable to find such an association.[2,3] Pinter and colleagues also pointed out that trimetazidine, a nonantipsychotic drug known to induce parkinsonism,[4] was not in the list of excluded drugs which cause parkinsonism in our analysis. Thus, we repeated a sensitivity analysis that excluded trimetazidine as well as drugs used in diabetes (i.e., insulins and oral hypoglycemic drugs, class A10 in the ATC [Anatomical Therapeutic Chemical] classification; these drugs were used as a proxy for diabetes) in addition to the drugs listed in our article. We found that ROR (reporting odds ratio) values remained statistically significant: 2.11 (95% confidence interval: 2.04–2.19) for gabapentin and 2.38 (2.30–2.46) for pregabalin. The results clearly did not change with or without inclusion of diabetes and trimetazidine.

Third, Pinter and colleagues recall that we used amitryptiline and duloxetine as control drugs given that they have similar indications than gabapentinoids. Of course, the indications are close, but not similar; because of their unique pharmacological profile, it was not possible to find drugs that have similar indications to gabapentinoids. Moreover, they claimed that amitriptyline has cholinergic side effects. Amitriptyline, like all imipraminic antidepressants, possesses atropinic (i.e., anticholinergic and not cholinergic) properties, which is totally different from a clinical point of view. The results all consistently point toward an increased ROR for pregabalin regardless of the comparator (amitriptyline, duloxetine). We emphasized this in our last paragraph in which we concluded that there is "an association between parkinsonism and gabapentinoid drugs, mainly pregabalin."

Fourth, Pinter and colleagues discussed the clinical importance of our results, indicating that they are "neither strikingly outstanding nor clinically relevant." Once again, they should consider that, as clearly indicated in the Methods, ROR values only represent the risk of reporting and not the absolute risk value, which has a clearly different clinical meaning.[5-7] However, these results should be interpreted in view of the very large and increasing use of gabapentinoids, as underlined in the Introduction.

Finally, we would like to emphasize that, as we stated in the article, the results report on a pharmacovigilance signal[8,9] and only suggest an association between exposure to gabapentinoids and the occurrence of parkinsonism. These results warrant replication in population-based pharmacoepidemiological studies.

We thought that it was important to present this alert given the widespread use of gabapentinoids and the putative clinical consequences in the field of movement disorders.

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