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Use of real-world data to understand self-harm risk in people prescribed gabapentinoids

Consider routine follow up, especially after medication has been stopped

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Gabapentinoids, including gabapentin and pregabalin, are a class of drugs that have anticonvulsant, analgesic, and anxiolytic properties and are broadly approved for treating epilepsy and neuropathic pain disorders. However, in recent years, off-label use has been increasing for a wide range of related conditions,[1] including psychiatric disorders (eg, major depression and bipolar disorder), sleep disorders (including insomnia), and postoperative acute pain management, for which the evidence of treatment efficacy and tolerability remains limited.[2]

Randomised controlled trials are considered gold standard evidence for the assessment of treatment efficacy because the design allows for the balancing of confounding factors between treatment groups, given sufficient statistical power. However, randomised controlled trials are both costly and time consuming and studies often struggle to recruit a sufficient number of participants to meaningfully estimate treatment effects.[3] Additionally, randomised controlled trials often have short follow-up periods, making assessment of long term treatment effects challenging, particularly in the case of relatively rare outcomes, such as self-harm and mortality. These limitations were apparent in a 2008 US Food and Drug Administration (FDA) report that concluded, after reviewing randomised controlled trials of 11 antiepileptic drugs, including gabapentin and pregabalin, that the medications were collectively associated with an 80% increased risk of suicidal behaviours over an average of around three months follow-up.[4] However, specific estimates linked with suicidal behaviours for gabapentin (odds ratio 1.57; 95% confidence interval (CI) 0.12 to 47.66) and pregabalin (1.88; 0.41 to 13.58) lacked precision and were not informative due to a small number of outcome events across drug and control groups.

Yuen and colleagues address many of these limitations by examining the associations between prescriptions of gabapentoids and subsequent risks of self-harm in the UK between 2000 and 2020. They used data from the Clinical Practice Research Datalink (CPRD), which covers around 1500 GP practices in the UK and broadly representative of the wider population.[5] The authors examined four distinct follow-up periods for each individual: 90 days before the treatment period; the treatment period; the 14 days following the end of treatment; and any other period (which acted as the reference category). To account for confounding by indication, where people who are prescribed certain medications have different background risk factors to those prescribed other medications or no medication during the time period examined, the authors adopted a self-controlled or within-individual design.[6,7] This design compared outcome rates within the same individual across the four periods, which inherently accounted for unmeasured and time constant confounders within the individual, including genetic risks, childhood environment, and early onset conditions. The authors additionally accounted for age, seasonality, and co-prescribed opioid and psychotropic medications as time varying confounders.

The main findings indicated that the incidence rate of self-harm increased by 69% (adjusted incidence rate ratio 1.69; 95% CI 1.55 to 1.85) during the 90 day period before the initiation of treatment compared with the reference period. This increase was fully attenuated during the treatment period (showing no association with self-harm), but was elevated threefold in the 14 day period after treatment had ended. This finding suggests that gabapentinoids are unlikely to be linked to self-harm risk. These results are potentially important in allowing clinicians and their patients to weigh up risks and benefits of these medications, particularly in people with co-occurring mental health problems and background risk factors for suicide.

However, a number of important limitations should be considered when interpreting the findings. Firstly, the self-controlled design is only informative for individuals who have at least one self-harm episode in the follow-up period (n=10 002), which implies that the findings may not generalise to the large majority of patients who did not have such events (n=864 273). Individuals with no mental health diagnoses but with a history of self-harm (n=760) had higher incidence rates of self-harm occurring during their treatment periods compared with reference periods (adjusted incidence rate ratio 1.82; 95% CI 1.40 to 2.37), as shown in the appendix. Secondly, the authors conducted more than 20 sensitivity analyses, which are interpreted as being consistent with the main findings. However, some important differences are of note, such as in young adults (aged 24-44 years, n=4214), who were shown to have significantly elevated incidence rates of self-harm occurring during their treatment periods compared with reference periods (adjusted incidence rate ratio range 1.19 to 1.40), which was not consistent with the main findings. Additionally, one limitation that is shared with other studies using healthcare registers and electronic health records is that treatments were measured using prescription drug records, and therefore, whether the medication was only collected and not taken is not clear. This approach introduces misclassification bias, as some individuals who did not take the medicine are incorrectly classified as

having taken the drug. Future research may benefit from pooling analyses across multiple large scale databases using a common analytical pipeline to determine whether differences in findings stem from methodological variations or reflect true effects.[8]

This research can also be viewed in the wider context of observational studies on gabapentinoids. Another population based self-controlled study,[9] which included 10 026 people in Sweden but based in secondary care, reported consistently increased risks of suicidal behaviours occurring during treatment periods across all age groups. The investigation by Yuen and colleagues shows the importance of testing associations in primary and secondary care, and their novel approach of considering periods before and after treatment is an important contribution. Clinically, their results suggest that routine and periodic follow-up of people prescribed gabapentinoids should be considered, particularly in the weeks after medication has been discontinued. Whether young adults and people with no psychiatric diagnoses need more supervision while taking gabapentinoids requires further research to clarify.

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