Gabepentinoids and Benzodiazepines in Medicare Part D

I have read with interest the observational study regarding risks of adverse outcomes associated with gabapentin and pregabalin use. The authors adeptly analyzed data in the US Renal Data System database, including Medicare Part D prescription drug events (i.e., claims), and identified positive associations of gabapentin and pregabalin exposure with adjusted hazards of first episodes of altered mental status, fall, and fracture requiring either an emergency room visit or hospitalization.

The study suffers from one unappreciated limitation. The authors attempted to adjust for the influence of concomitant use of benzodiazepines. Evidently, <0.5% of all patients in the study cohort used benzodiazepines. Such low utilization is clinically implausible but can be explained by the design of the Medicare Part D benefit during the study era (i.e., in 2011). The Medicare Modernization Act excluded benzodiazepines from Part D coverage between 2006 and 2012. This exclusion was eliminated by the Patient Protection and Affordable Care Act. The fact that the authors identified any use of benzodiazepines during the study era reflects the provision of “enhanced alternative coverage,” which generally offers a higher monthly premium in exchange for added value (e.g., reduced deductible, coverage of drugs not ordinarily included in the Part D benefit, reduced cost sharing in the coverage gap, etc.).

Benzodiazepine toxicity is positively associated with risks of altered mental status, fall, and fracture. Thus, because of inherent limitations of data ascertained from Medicare Part D, unmeasured confounding by benzodiazepine use cannot be discounted. Because of study design, unmeasured confounding by opioid use also cannot be discounted. Ultimately, polypharmacy is common among patients on dialysis, and therefore, observational studies of the efficacy and safety of single drugs or single classes of drugs should be interpreted cautiously. Gabapentinoid toxicity is an observable event, but the magnitude of the associations reported by Ishida et al. may be biased.

DISCLOSURES

E.D.W. is also an employee of NxStage Medical but reports no conflict of interest with this content.

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See related Letters to the Editor, “Authors’ Reply,” on pages 2771–2772.

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Authors’ Reply

We thank Weinhandl for his comments regarding our analyses using the US Renal Data System of the association between gabapentin and pregabalin use and adverse outcomes among patients on hemodialysis. We acknowledge that we were limited in our ability to reliably capture benzodiazepine exposure with our available data, because benzodiazepines were not covered by Medicare Part D until 2013.

Using more recent data from 2013, among a comparable cohort of 162,965 adult Medicare-covered patients on chronic hemodialysis with continuous Part D coverage during 2013, we found that the prevalence rates of gabapentin, pregabalin, and benzodiazepine use were 21% (n=33,900), 4% (n=7102), and 23% (n=37,112), respectively. The prevalence of benzodiazepine
The prevalence of concomitant use (defined as at least one instance of overlapping prescriptions in 2013) of gabapentin and benzodiazepine was 5.5% (n=8907), with a median overlap duration of 62 days (25th interquartile range, 28–152 days). Twenty-six percent of gabapentin users had concomitant benzodiazepine use, and 22% of gabapentin nonusers had concomitant benzodiazepine use. The prevalence of concomitant use of pregabalin and benzodiazepine was 1.3% (n=2054), with a median overlap duration of 57 days (interquartile range, 26–137 days). Twenty-nine percent of pregabalin users had concomitant benzodiazepine use, and 22% of pregabalin nonusers had concomitant benzodiazepine use.

Gabapentin and pregabalin use had virtually no association with benzodiazepine use on the basis of the point-biserial correlation (Table 1). The point-biserial correlation is mathematically equivalent to the Pearson correlation and can be interpreted on the same scale (0–0.5 is weak, 0.5–0.8 is moderate, and 0.8–1 is strong). Although Pearson correlations are not usually used for binary variables, such as medication exposure, they are, in fact, what a regression program uses to adjust one predictor for another one with a correlation of zero, indicating no adjustment.

Correspondingly, the effect of benzodiazepine use on event rates would need to be massive to explain away the gabapentin or pregabalin associations. Thus, confounding by concomitant benzodiazepine use was unlikely to have had a large effect on our results. The letter of Weinhandl also mentions the possibility of unmeasured confounding by opioid use, and we would like to note that we adjusted for concomitant use of opioids in our analyses. We appreciate the interest in our research, and thank you for the opportunity to elaborate on our methodology.

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DISCLOSURES

None.

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See related Letters to the Editor, “Gabepentinoids and Benzodiazepines in Medicare Part D,” on page 2771.

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