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Tramadol and Mortality in Patients With Osteoarthritis

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To the Editor

Confounding by indication occurs when the clinical indication for selecting a particular treatment, such as severity of disease, also affects outcomes.[1] Even with careful data analysis, intractable confounding can occur because the data set does not contain data detailed enough to allow investigators to adjust sufficiently for comorbidities and disease severity.

A cohort study of patients aged at least 50 years with osteoarthritis found that tramadol use was associated with increased 1-year mortality compared with use of non-steroidal anti-inflammatory drugs (NSAIDs).[2] This study probably represents an example of intractable confounding by indication.

First, in unmatched analyses, patients assigned to receive tramadol had more comorbidities and were more severely ill in every parameter than patients treated with NSAIDs. Physicians likely avoid prescribing oral NSAIDs when patients have severe comorbidities and choose tramadol instead. While the authors of this study used a propensity score to match disease severity and comorbidity prevalence for identified comorbidities, they could not fully adjust for all the ways that patients who received tramadol were more severely ill than patients who received NSAIDs. For example, information on the severity of comorbidities is not generally available in the Health Improvement Network database used for this analysis. Among the comorbidities, hypertension was adjusted for, but the severity of hypertension or level of blood pressure (hypertension is a common reason for physicians to avoid NSAIDs) were not. For every comorbidity, there was no measure of disease severity, and disease severity is associated with mortality risk.

Second, why would mortality be increased in tramadol users when they are not receiving tramadol? In the analysis, the mean duration of tramadol treatment was 22 days, and an intention-to-treat analysis over 1 year was presented; most tramadol users were actually not receiving tramadol at the time of their death.

Third, among patients receiving tramadol vs NSAIDs, the risk of 1-year mortality was highest for cancer mortality. How could tramadol increase 1-year cancer mortality? Because patients with cancer were reported as excluded, the high cancer mortality within a few

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months of follow-up suggests the exclusion was not successful. Tramadol would be prescribed for managing pain in patients with cancer.

Confounding by indication probably accounts for the increased mortality seen in patients receiving tramadol vs patients receiving NSAIDs in the study by Dr Zeng and colleagues. Tramadol may not pose any mortality risk; in some instances, confounding by indication cannot be eliminated.

References

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