Letters to the Editor

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Diabetic Peripheral Neuropathic Pain: Is Gabapentin Effective?

Original Article: Treating Diabetic Peripheral Neuropathic Pain

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TO THE EDITOR: Contrary to the authors' statements, gabapentin (Neurontin) in dosages up to 3,600 mg per day is not more effective than placebo for the treatment of diabetic peripheral neuropathic pain. During discovery in a lawsuit filed in federal court, it was learned that the manufacturers of Neurontin systematically biased scientific evidence through data manipulation and suppression of negative studies to promote the drug for off-label uses.[1,2]

According to an article co-authored by Kay Dickersin, PhD, director of the U.S. Cochrane Center, the reporting practices used in trials funded by the makers of Neurontin "do not meet the ethical standards for clinical research."[2] The article further asserts that "reporting biases … increase the likelihood that interventions will appear to be effective when they are not."[2] The authors also suggest that "the 2005 Cochrane systematic review regarding the effectiveness of gabapentin for acute and chronic pain concluded that it is effective on the basis of published findings and should now be updated with the inclusion of unpublished information made available through litigation."[2,3]

By early 2000, there were three manufacturer-funded, double-blind, randomized, placebo-controlled trials of gabapentin. In one study published as a letter to the editor, Gorson and colleagues concluded that "gabapentin is probably ineffective or only minimally effective for the treatment of painful diabetic neuropathy at a dosage of 900 mg per day."[4] In the largest study conducted to date (325 participants) for diabetic peripheral neuropathic pain, the researchers concluded in their internal, unpublished manuscript that gabapentin in a dosage of 600 to 2,400 mg per day was not more beneficial than placebo. Backonja and colleagues concluded that gabapentin use resulted in positive outcomes, despite the high potential for unblinding from forced titration to 3,600 mg per day.[5] However, a subsequent independent reanalysis of the data revealed that Neurontin failed to provide significant relief of diabetic peripheral neuropathic pain compared with placebo in participants who remained blinded to treatment.[6]

Dr. Lindsay and colleagues may not be aware of the unpublished studies and data manipulation, leading them to inappropriate conclusions about the effectiveness of gabapentin for the treatment of diabetic peripheral neuropathic pain, just as in the 2005 Cochrane review.

Although this may be an isolated incident, it highlights the need for transparency and publication of all trial results, regardless of outcome. Morevoer, final study reports should be compared with the original protocol and the published study articles to ensure that information is not presented in a biased fashion. We urge physicians to be cautious consumers of published evidence in general, but especially in regard to gabapentin for diabetic peripheral neuropathic pain.

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Author disclosure: Drs. Hyatt, Daniel, and Millares were called as witnesses to testify in the matter of Neurontin Marketing, and Sales Practices Litigation. The other authors have no relevant financial affiliations to disclose.

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IN REPLY: We greatly appreciate Dr. Hyatt and colleagues bringing to light this breach of trust in the world of academia and scholarly publications. Since we submitted our article, a related Cochrane review on anticonvulsant drugs for acute and chronic pain has been withdrawn because of concerns about missing unpublished data.[1] We were unaware of the unpublished literature referred to in the legal proceedings referenced by Dr. Hyatt and colleagues. A new Cochrane review evaluating gabapentin for chronic neuropathic pain and fibromyalgia has since been published with rigorous evidence-based criteria.[2] The reviewers' study inclusion criteria set minimum standards for quality, validity, and size, and, more importantly, utilized the initiative on methods, measurement, and pain assessment in clinical trials (IMMPACT) criteria in their evaluation. Using these more stringent criteria, the Cochrane review concluded that gabapentin was effective in treating diabetic peripheral neuropathic pain at appropriate doses and treatment duration with a number needed to treat (NNT) of 5.8 for substantial benefit, where at least 50 percent pain reduction is achieved. Scores on the Patient's Global Impression of Change, a quality of life index, for significant and modest improvement had an NNT of 9.6 and 8.1, respectively.

Furthermore, excluding the studies assessed in the most recent Cochrane review, other well-designed, non–industry-sponsored studies support the use of gabapentin for this specific pain syndrome. One study found that gabapentin produced outcomes similar to those in patients using amitriptyline, a widely accepted treatment for diabetic peripheral neuropathic pain.[3] Additionally, a few small studies have evaluated gabapentin in combination with other agents. Synergistic outcomes in these trials have been seen with nortriptyline (Pamelor) and venlafaxine (Effexor).[4,5] Finally, evidence suggests that gabapentin use can decrease overall opiate requirements in some patients.[6]

Clearly, as Dr. Hyatt and colleagues have pointed out, the acts of the pharmaceutical company have called into question the results of several of the larger studies of gabapentin. However, we cannot conclude that gabapentin is ineffective for the treatment of painful diabetic neuropathy based solely on the indiscretions of the original manufacturer. Additionally, to address the concerns of Dr. Hyatt and colleagues regarding unblinding due to forced dose titration, no statistically significant differences in adverse effects were seen between gabapentin and placebo in any of the studies reviewed in the most recent Cochrane review.[2] We share the conclusions of the Cochrane reviewers that gabapentin, dosed appropriately, will provide pain reduction for patients with diabetic peripheral neuropathic pain similar in magnitude to that of other commonly used treatments. As the number of patients with diabetes mellitus continues to increase, focus on this quality-of-life issue remains important for our patients.

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