of neuropathic pain could be retarded evidently by systematic administration of mefloquine.\(^3\) Although it was a small sample research, the effect of mefloquine was very precise.

Since mefloquine is confirmed as a selective connexin (Cx) 36 blocker,\(^4,5\) we chose it as a tool for verifying the contribution of Cx36 in the pathologic process of neuropathic pain. And we therefore suggested that Cx36 could be a new target for pain management. We certainly realized the possibility of neurologic and psychiatric adverse effects of mefloquine. In our study, we sought to find out the active isomer of mefloquine \([−]−(11R, 12S)\)-mefloquine\] for further investigation. Our future effort is to try developing a new analgesic with more specificity for the target site and substantially reduced toxicity by molecular modification. That work is bound to need multilateral cooperation with plenty of time, before the new drug is officially certified.

Last, we would like to emphasize that our work is just in the stage of animal investigation. We totally agree with Dr. Nevin’s words, that is, any attempt for off-label prescribing of the drug for analgesia would clearly be unethical without precautions. There should be more laboratory studies until expansion of clinical researches.

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Competing Interests
The author declares no competing interests.

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Questions Regarding “Efficacy of Duloxetine in Chronic Low Back Pain with a Neuropathic Component”

To the Editor:
A recent article in ANESTHESIOLOGY by Schukro et al.\(^1\) concluded that duloxetine is superior to placebo for the treatment of chronic low back pain (LBP) associated with neuropathic pain in the lower limb. I commend the authors for their efforts in adding to the literature on therapies for this subgroup of patients with LBP. However, I have a few questions regarding the methodology of this article and some suggestions that may be useful for future investigations on this topic.

First, the title of the publication is confusing because it gives the impression that trial participants had pain with a neuropathic component in their lower back. Several recent publications (including some referenced by the authors) have focused on this aspect of LBP.\(^2–4\) However, the focus of treatment in the trial by Schukro et al. was radicular pain in the lower limb. Second, the diagnosis of radiculopathy secondary to intervertebral disc herniation or spinal canal/foraminal stenosis should have been confirmed through documentation of neurologic deficits on physical examination or the use of magnetic resonance imaging or electrodagnostic studies.

I respectfully submit that diagnosing radicular pain on the basis of the distribution and characteristics of pain is suboptimal, especially in the context of a clinical trial. Two references\(^5,6\) quoted by the authors in support of this approach are more than 40 yr old, and some of the other more recent publications\(^7,8\) referenced by Schukro et al. are investigations that focused on identifying neuropathic back (and not leg) pain.

Third, pain scores should have been measured distinctly for LBP and radicular pain in the lower limb. A recent study by Cohen et al.\(^9\) that compared the efficacy of gabapentin and epidural steroid injections in patients with lumbosacral radicular pain demonstrates the importance of rigorous inclusion criteria supported by diagnostic modalities and serial measurement of pain in different locations. Another potential option is to consider patients with only neuropathic LBP.\(^10\)

In addition, the authors could have considered the use of a measurement tool to evaluate the neuropathic component of the pain over time (pre and post treatment). The Neuropathic Pain Symptom Inventory is an example of such a tool that has the ability to detect the effects of treatments for neuropathic pain over time.\(^11\) The authors used painDETECT\(^\text{®}\) (at baseline and at 4 weeks after the intervention), but this is a screening tool for neuropathic pain and, as acknowledged by the authors, it may not have the sensitivity to reflect the change in the neuropathic component of pain over time. Last, although the authors have provided some information about calculation (and recalculation) of the sample size, the final number of participants (25) seems unusually low. Can the authors kindly provide SDs that were used for the first and second calculations of sample sizes?
Correspondence

Competing Interests

The author declares no competing interests.


References


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In Reply:

We thank Dr. Bhatia for taking an interest in our article,1 and are pleased to address the comments in detail.

We deliberately refrained from using the term “radiculopathy” in our title, as this would in fact have implied that dorsal nerve root compression or mechanical lesion was confirmed in our patient sample by magnetic resonance imaging or electrophysiology, as suggested in the Letter to the Editor. We decided not to require a technical confirmation for patient inclusion because the presence or absence of a visually identified mechanical compression would not have influenced the study results. This makes a difference to trials on invasive, localized therapeutic approaches like epidural corticoid injections, e.g., as reported in the referenced article by Cohen et al.,2 where an identified lesion is the target. The primary aim of our trial, however, was to investigate whether or not systemic duloxetine is efficacious in reducing chronic low back pain (CLBP) in patients with a clinically diagnosed radicular neuropathic component. These patients—although frequently seen—were excluded from former studies on the efficacy of duloxetine in CLBP.3–6 We think that these patients may currently be undertreated in terms of addressing their neuropathic pain symptoms.

It is recognized that the International Association for the Study of Pain definition of neuropathic pain may be problematic in CLBP, as there is sometimes a lack of correlation between neurologic lesion and symptoms in these patients.7,8 Recent guidelines on neuropathic pain assessment9 clearly state that there is still no accepted standard for diagnosis of neuropathic pain, and that the relevance of clinical examination for distinguishing neuropathic from nonneuropathic pain is well documented. Therefore, we combined a clinical examination and diagnosis of radicular leg pain by two independent, experienced pain specialists, who were not involved in the study, with the additional assessment using the painDETECT questionnaire. Combining the validated painDETECT screening tool with a clinical diagnosis of radicular leg pain increases the probability of identifying the target group of CLBP patients with a clear neuropathic pain component.

We referenced a study by Baron et al.,10 which also uses the wording “Chronic Low Back Pain with a Neuropathic Component” in its title. In the Letter to the Editor, the quoted study has been misinterpreted as focusing only on patients with a neuropathic pain component localized in their lower back without neuropathic leg pain. Baron et al. enrolled patients who scored “positive or unclear” in the painDETECT questionnaire and additionally clinically tested them for the presence of radicular leg pain at baseline. Patients were clinically diagnosed with lumbar radicular pain in 70% of cases. Therefore, this study investigated a mixed population suffering from low back pain with or without a radicular neuropathic component, although a two-thirds majority actually suffered from CLBP combined with radicular pain.

We agree with Dr. Bhatia in that differentiation between duloxetine’s relative therapeutic effect on either leg or back pain would have added further information.

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