Opioids and Chronic Neuropathic Pain

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Chronic neuropathic pain is a serious problem resulting from injury to the central or peripheral nervous system; it affects more than 2 million Americans. Despite advances in our understanding of the pathophysiology and molecular biology of neuropathic pain, its clinical management remains disappointing and controversial. Antidepressants and anticonvulsants have been demonstrated to provide analgesia but are effective in less than half of patients half the time.[1] Opioid treatment of neuropathic pain is often discouraged, because of concern about ineffectiveness, the potential for the development of tolerance, the risk of addiction, and limiting side effects.[2]

In this issue of the *Journal*, Rowbotham et al.[3] report on the efficacy of opioids in reducing the severity of treatment-refractory neuropathic pain in patients with either a central or a peripheral neuropathic pain syndrome. They performed a double-blind, randomized, controlled trial comparing low doses of the μ-opioid agonist levorphanol with high doses of the drug; patients titrated their own doses over an eight-week period in order to balance adequate analgesia with tolerable side effects. There was a 36 percent reduction in pain among patients receiving high-dose therapy, as compared with a 21 percent reduction among patients receiving the low dose. Study patients who received the high dose and completed the trial had pain reduction as great as 48 percent, and 66 percent of them reported moderate or better pain relief. Although improvement in pain was also associated with improvements in functioning, affective distress, and ability to sleep, the changes observed were not significantly different between the low-dose and high-dose groups.

This clinical trial supports the concept of opioid responsiveness — defined as the degree of analgesia obtained following the escalation of the dose to the point of analgesia or intolerable side effects — in neuropathic pain syndromes.[4] The trial mimics a typical clinical setting and highlights the need for individualizing the drug, the dose, and the titration schedule. This study adds to the expanding literature of randomized, placebo-controlled trials of opioids in patients with central or peripheral neuropathic pain that show that opioids work.[5] The data show that patients with peripheral neuropathic pain seem to be more likely to have responses to opioids than those with pain from central lesions, and opioids appear selectively to reduce spontaneous and touch-evoked allodynia in trials using quantitative methods for sensory testing.[6] Together, these studies challenge the traditional view that neuropathic pain is opioid-resistant and now provide the scientific basis for developing a rational approach to the opioid treatment of neuropathic pain.

What the study does not address is the long-term efficacy of opioids. Few clinical trials have addressed this issue, and even in those, only a small percentage of patients, ranging anywhere from 7 percent to 17 percent, have continued to receive long-term opioid therapy one to two years after the clinical trial ended.[6] In contrast, data from surveys conducted in pain clinics show that subgroups of patients continue to maintain analgesia with the use of long-term opioid therapy.[7] To advance the treatment of neuropathic pain and to establish the role of opioid therapy, a series of important, clinically relevant research questions needs to be addressed. Can we predict which patients may benefit from such therapy? Which opioid analgesics are the most appropriate to use? To what extent will tolerance develop, and what are the risks posed by long-term opioid treatment?

Numerous patient-related factors can influence the responsiveness to opioids.[4] These factors range from a patient's previous exposure to opioids (which may necessitate higher initial doses) to a wide variety of pharmacogenomic factors influencing both the pharmacokinetics and the pharmacodynamics of opioids.[8] For example, a polymorphism of the *MDR1* gene may determine the toxic effects in a patient after the administration of morphine. DNA-sequence variance in the *CYP2D6* gene prevent the O-demethylation of codeine to morphine, thus dramatically affecting its analgesic effects. Polymorphisms in μ-opioid receptors, variations in populations of opioid receptors, and sex differences also appear to play a part in the variable responses to opioids. Such variability argues for trials of opioids in patients with neuropathic pain as we refine other predictive approaches, including sophisticated pharmacogenomic screening.

The choice of an opioid for neuropathic pain should be based in part on the intensity of pain re-

ported by the patient. According to the guidelines for analgesia developed by the World Health Organization, strong opioids such as morphine, hydromorphone, fentanyl, levorphanol, oxycodone, and methadone are the common choices for patients with moderate-to-severe pain.

New studies have identified unique properties of some of the μ-opioid drugs in the treatment of neuropathic pain. In the study by Rowbotham et al., levorphanol was used. It differs from morphine in its broader interactions with not only the μ_1 receptor but also with both κ and δ receptors, and it has been shown to provide analgesia in animals that are tolerant to morphine.[9] In fact, levorphanol has been suggested as an alternative for pain management in morphine-tolerant patients on the basis of these studies in animals.

Methadone also has unusual properties that other μ-opioid–agonist drugs do not have: it inhibits the reuptake of norepinephrine and serotonin.[10] Drugs with similar actions are known to be effective against neuropathic pain. Methadone is a racemic mixture of the *d*- and l-isomers, and both bind to the N-methyl-D-aspartate (NMDA) receptor, a known modulator of neuropathic pain.[11] Studies in animals show that *d*-methadone is antinociceptive in an animal model of neuropathic pain, in which it blocks the action of the NMDA receptor. These studies suggest that methadone analgesia may result from the *d*-isomer's potentiating of the opioid antinociceptive effects of l-methadone, as well as its attenuating of the development of morphine tolerance through its antagonist activity at the NMDA receptor. Clinically, switching to methadone therapy in patients who have been receiving high doses of morphine, hydromorphone, fentanyl, or levorphanol is associated with improved pain relief at doses of methadone that are as low as 10 percent of a calculated equianalgesic dose.[12] Clinical studies are necessary to define the relevance of these new discoveries to the analgesic mechanisms of methadone.

These data argue for the use of various opioid drugs in rotation in patients with chronic neuropathic pain in order to maximize analgesia and minimize side effects. There have been no clinical trials testing the rotation of opioids, with aggressive management of side effects, with the goal of expanding the role of opioids in the treatment of neuropathic syndromes. Studies in patients with cancer suggest that 80 percent of patients seen by an inpatient pain-consultation service require at least one switch of drugs, 44 percent require two, and 20 percent require three.[13]

In their trial, Rowbotham et al. did not observe the development of tolerance to analgesia and did not assess tolerance to other side effects of opioids. Tolerance to each of the effects of opioids develops at a different rate, and the rapid development of tolerance to the respiratory depressant effects of opioids allows for the safe escalation of doses. Incomplete cross-tolerance is commonly observed when patients are switched from one opioid to another, often allowing patients to maintain effective analgesia with fewer side effects. Long-term studies in patients with neuropathic pain would allow for further assessment of the phenomenon of tolerance and encourage strategies to reduce or alter the development of tolerance. According to studies in patients with cancer, the risk of addiction with long-term opioid therapy is low, but only longitudinal studies will provide the necessary evidence base to support the conclusions of existing retrospective analyses and surveys.

In addition to the biologic issues, concern on the part of both patients and physicians about addiction, physicians' lack of knowledge about and training in pain management and opioid-drug therapy, scrutiny of physicians' prescribing practices by drug regulators and insurance companies, and increased abuse of prescription drugs all serve as powerful disincentives influencing physicians' decisions about trying opioids in patients with neuropathic pain. Given our lack of data about how to manage chronic neuropathic pain, we must focus urgent attention on the needs of suffering patients.

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