

One from Column A and One from Column B

May I Take Your Order?

MANAGEMENT of neuropathic pain is not an easy task, especially after pain is well established. Practitioners choose from a bewildering array of ingredients to create their own menus, based on local taste and local experience, with little literature serving up a gold-standard, prize-winning combination. “Morphine *versus* Mexiletine for Treatment of Postamputation Pain: A Randomized, Placebo-controlled, Crossover Trial”¹ from the Hopkins pain group is a study likely to make it easier to transcend local tastes and narrow down the menu choices.

“Morphine *versus* Mexiletine for Treatment of Postamputation Pain” carries weight because it is the unusual, well-designed and controlled, decent-sized trial in a patient population that has been largely neglected. Furthermore, the patients studied have established pain, where other investigations have tackled postamputation pain earlier, with interventions starting in the perioperative period² often yielding results that do not deliver a clear take-home message.³ The effectiveness of amitriptyline and gabapentin in the treatment of postamputation pain remains uncertain, depending in part on the timing of instituting therapy. In one randomized, double-blind, placebo-controlled, crossover study,⁴ gabapentin provided better pain relief than placebo in 14 patients with postamputation pain, with an average duration of postamputation pain in this study of 18 months. However, another randomized, placebo-controlled clinical trial, published by Nikolajsen *et al.*⁵ in this journal, suggested that immediate postoperative treatment with gabapentin (median dose of 2,100 mg/day) did not reduce the incidence or intensity of postamputation pain in 46 patients. The study was sufficiently powered to detect a clinically significant (> 40%) reduction in the incidence of phantom pain. Robinson *et al.*⁶ found similar results, comparing the effects of amitriptyline (up to 125 mg/day) *versus* placebo in 39 patients with postamputation pain lasting more than 6 months. Certainly the timing of instituting therapy is one reason for heterogeneous results in studies directed at finding the optimal drug regimens for patients with neuropathic pain.

This Editorial View accompanies the following article: Wu CL, Agarwal S, Tella PK, Klick B, Clark MR, Haythornthwaite JA, Max MB, Raja SN: Morphine *versus* mexiletine for treatment of postamputation pain: A randomized, placebo-controlled, crossover trial. ANESTHESIOLOGY 2008; 109:289-96.

On the one hand, the study can be distilled as a simple affirmation that morphine is better than mexiletine in providing pain relief in the setting of postamputation pain. Perhaps not a surprise, but the results are clean *and* useful, given the paucity of similar studies. In a systematic review of published evidence supporting treatment regimens for acute and chronic phantom pain, Halbert *et al.*⁷ identified 186 articles. Of these, only 6 were randomized, controlled trials with parallel groups or crossover protocols. Fortunately for practicing physicians, Raja *et al.* have a history of practical clinical studies on pain including treatment of postherpetic neuralgia,⁸ the role of coping strategies in chronic pain,⁹ and a practical approach of prescribing opioids in controversial settings,¹⁰ as well as outcomes after regional anesthesia and analgesia.^{11,12} These studies are difficult to perform and difficult to fund, and further congratulations are due to the Hopkins group for getting the attention of reviewers from the National Institutes of Health in funding their work.

“Morphine *versus* Mexiletine . . .” is certainly not a complete solution. The maximum oral dose of morphine in the study (180 mg) afforded only moderate pain relief, did not mediate improved function over mexiletine, and was associated with significant side effects. In addition, the practical issues of managing tolerance and dependence over time with high doses of opioids are not addressed. Furthermore, most patients with neuropathic pain are treated with combination drug therapy, a practice supported by a recent study¹³ in patients with diabetic neuropathy and postherpetic neuralgia, in whom combined morphine (60 mg) and gabapentin (2,400 mg) afforded better pain relief than morphine alone (120 mg). Because of the difficulties inherent in managing patients on high doses of morphine, we hope that Raja *et al.* will use this baseline monotherapy success with morphine to identify even better therapies for postamputation pain, using opioid-sparing combination therapies. In addition, we look forward to learning how long the morphine regimen described in the current study will sustain pain relief, and whether combination therapies provide more easily managed and sustained pain relief.

According to the outline of Raja’s study published at the National Institutes of Health clinical trial Web page, data about the effect of the different treatment drugs on function as well as quantified sensory testing were gathered. This design reflects the opinion of many experts in the field that improved treatment of chronic pain will evolve as treatments become mechanism based.¹⁴ Quantified sensory testing could be useful to better differen-

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tiate and define distinct chronic painful conditions on a molecular level,¹⁵ preferably after standardization of protocols within a clinical trial network.¹⁶

In this context, unseen data gathered by Raja's group combined with the current study could propel the field forward and provide much needed guidance. A study providing evidence that opioid therapy increases quality of life and function in a quantified sensory testing-defined subset of chronic pain patients could provide compelling rationale to institute chronic opioid therapy for a nonmalignant condition. "Morphine *versus* Mexiletine," like a good menu choice from column A, whets the appetite for a main course in column B.

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