

## LETTER TO THE EDITOR

### EREM VERSUS IV PCA META-ANALYSIS

Dear Editor:

I read the recent meta-analysis by Sumida et al.<sup>1</sup> with some interest. As an anesthesiologist in clinical practice with more than 4+ years of experience with extended-release epidural morphine (EREM), I would like to point out a few caveats with respect to reporting the incidence of respiratory depression based on only three of the original dose finding studies that led to the approval of EREM. The readers of this journal need to understand the nature of a dose-finding clinical study and the inherent limitation of a study designed to focus on the safety and efficacy of a single agent. Dose-finding studies are designed knowing that some of the doses used may fall outside the range that is ultimately approved by the US Food and Drug Administration, such as EREM doses  $\geq 25$  mg. As the 20 mg EREM dose has fallen out of favor, this dose is no longer commercially available on the marketplace. Although EREM doses less than 10 mg are not FDA approved, our experience has been that patients achieve good analgesia with doses  $\leq 10$  mg in conjunction with multimodal analgesia and preemptive management of expected side effects from neuraxial opioids. Therefore, it is critical for physicians to read the product label to understand that for any given level of pain, patients differ widely in their opiate requirements. It is critical to adjust the dose of EREM for each individual patient, taking into account the patient's age, body mass, physical status, prior experience with opiate analgesics, risk factors for respiratory depression, and medications to be coadministered before or during surgery.

If you take a deeper look into the pooled adverse events profile derived from seven multicenter trials (1 phase I, 3 phase II, and 3 phase III) among patients administered single-dose epidural EREM (5, 10, 15, or 20 mg), placebo (IVPCA fentanyl), standard epidural morphine 5 mg, or IV PCA morphine, you will see that the incidence of respiratory depression is similar between the EREM 5 mg, 10 mg, IV PCA with fentanyl, IV PCA with morphine, and standard release epidural morphine sulfate 5 mg (Table 1).<sup>2</sup>

It is significant to note that the rates of hypoxia, somnolence, and decreased oxygen saturation were similar to or lower than the 5 and 10 mg doses of EREM when compared with IV PCA or standard release epidural morphine 5 mg.<sup>2</sup>

My experience with EREM over the past 4+ years in more than 300 joint arthroplasty patients has been with an average EREM dose of 9.7 mg, range 5-15 mg.<sup>3</sup> When we initially used the recommended doses in early 2005, our incidence of respiratory depression was similar to the reported incidence in the package insert and from major clinical trials with doses more than 10 mg of EREM, but as we decreased the dose, incorporated multimodal analgesia, and preemptively treated nuisance side effects typical of neuraxial hydrophilic opioids, our incidence of respiratory depression with EREM is now less than 1 percent. This incidence is similar to or lower than the reported incidence after neuraxial opioids of 0.01-7 percent.<sup>4,5</sup>

Although the randomized nature of the clinical trial provides scientific validity, the environment is artificial and does not always represent clinical practice because patients are randomly assigned to the treatment drug and dosed without benefit of clinical judgment. In clinical practice, patient's needs, comorbid medical conditions, and/or overall health as well as clinical practice guidelines are considered in determining an appropriate drug treatment. For example, in the study by Viscusi et al.,<sup>6</sup> among the patients who received the FDA-approved doses of 15 and 20 mg, three patients received opioid antagonist treatment for respiratory depression. Of these three patients, one was aged 75 years and another was morbidly obese (BMI = 41 kg/m<sup>2</sup>). In clinical practice, the overall health and pre-existing medical conditions of these two patients would have been considered before selecting a drug treatment and dose.

It is also important to recognize that the clinical trial of EREM did not permit the use of multimodal analgesia. In clinical practice, the multimodal approach for pain management in postoperative patients is a common practice and has proven to be quite effective for pain management. In my clinical practice, patients generally receive lower doses of EREM ( $\leq 10$  mg) in conjunction with other modalities such as peripheral nerve blocks, NSAIDs, and oral APAP.

**Table 1. Pooled adverse event profile**

Adverse event	Control groups			EREM groups		
	Placebo (n = 78)	Standard MS 5 mg (n = 97)	IV PCA MS (n = 55)	5 mg (n = 121)	10 mg (n = 141)	15 mg (n = 197)
↓ O2 sat, n, percent	4 (5.1)	6 (6.2)	20 (36.4)	4 (3.3)	10 (7.1)	13 (6.6)
Hypoxia, n, percent	0	2 (2.1)	5 (9.1)	3 (2.5)	6 (4.3)	8 (4.1)
Somnolence, n, percent	2 (2.6)	3 (3.1)	5 (9.1)	1 (0.8)	5 (3.5)	6 (3.0)
Respiratory depression, n, percent	0	1 (1.0)	1 (1.8)	0	1 (0.7)	10 (5.1)

In summary, I thank Sumida et al. for providing me an opportunity to elaborate on the side-effect profile as well as my own clinical experience with respect to EREM. Through time and experience, we have improved the safety profile of EREM in our facility. Other clinical trials may also be ongoing to determine the lowest effective dose in conjunction with multimodal analgesia to improve the safety profile of EREM.<sup>7,8</sup> We await the results of these trials.

Robert H. Blackshear, MD  
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## AUTHOR'S RESPONSE

Dear Editor:

We appreciate Dr. Blackshear's interest on our meta-analysis.<sup>1</sup> Dr. Blackshear highlights several important issues and limitations particularly when applying results of either clinical trials or meta-analyses of these trials to clinical practice. Certainly, Dr. Blackshear has extensive clinical experience with extended-release morphine (EREM) and should be commended in reducing the doses of EREM and carefully avoiding EREM in high-risk patients. We agree that by using the lowest efficacious dose of neuraxial opioids<sup>2</sup> and applying other techniques (eg, multimodal analgesia) to reduce the dose of opioid used may potentially result in a reduction in opioid-related side effects including respiratory depression. Nevertheless, the incidence of respiratory depression, while potentially decreased with lower doses of EREM, remains a concern. We would like to reiterate that vigilance, through prevention, detection, management, and treatment, remains essential with any form of post-operative opiate use. This is reflected in recently published practice guidelines by the American Society of Anesthesiologists for the prevention, detection, and

management of respiratory depression associated with neuraxial opioid administration.<sup>2</sup>

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1. Sumida S, Lesley MR, Hanna MN, et al.: Meta-analysis of the effect of extended-release epidural morphine versus intravenous patient-controlled analgesia on respiratory depression. *J Opioid Manag.* 2010; 5: 301-305.

2. American Society of Anesthesiologists Task Force on Neuraxial Opioids, Horlocker TT, Burton AW, Connis RT, et al.; Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. *Anesthesiology.* 2009; 110(2): 218-230.

## ERRATUM

In the November/December issue of *Journal of Opioid Management*, the article titled "The analgesic potential of cannabinoids," the first author's last name was spelled incorrectly. It should read Elikkottil. The corrected reference is: Elikkottil J, Gupta P, Gupta K: The analgesic potential of cannabinoids. *Journal of Opioid Management.* 2009; 5(6): 341-357.

## *Call for Papers*

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