LETTERS TO THE EDITOR

Is "Tolerance" Seen With Morphine Related to the Metabolite?

I read "Understanding Opioid Tolerance in Cancer Pain" by Jormain Cady, ARNP, MS, AOCN®, in the November/December 2001 *Oncology Nursing Forum* ([*ONF*], Vol. 28, pp. 1561–1568) and was grateful for a very interesting and informative piece.

Under the "Risk" subhead, the author mentions that there was difficulty in the animal model in "differentiating whether the evidence was true tolerance to opioids or an opioid-induced hyperalgesic state" (p. 1562) because high concentrations of $MS0_4$ or its metabolites have been associated with these types of neurotoxicities. With our new understanding of the neurotoxicities associated with accumulation of M3 glucuronide of morphine (e.g., hyperalgesia, delirium, myoclonus), is it possible that much of the "tolerance" seen with morphine might relate to the metabolite and not true tolerance? Additionally, do the other opioids—oxycodone, hydromorphone, fentanyl—exhibit an equal amount of tolerance as that seen is $MS0_4$?

My question is born out of an experience that I had eight years ago, before my mother passed away from renal cell carcinoma. She had only one kidney left, with diffuse metastasis to the bone. Her last weeks were spent in a significant amount of confusion and what seemed to me to be intense pain, despite the continued efforts of hospice to manage the pain. My lingering question is what would have been the outcome had we switched her to hydromorphone?

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The Author Responds

Thank you for your thoughtful question. Tolerance is defined as a requirement for increasing the amount of opioid to achieve the same analgesic effect and is not necessarily associated with the neurotoxicity you describe (hyperalgesia, delirium, monoclonus). Certainly, higher doses of opioid analgesia may contribute to these symptoms regardless of whether clinically significant tolerance is present. Although it is understood that incomplete cross-tolerance develops between opioids, other pure opioid agonists (e.g., oxycodone, hydromorphone) do not appear to have a significantly different risk for tolerance development. A trial of an alternative opioid, such as hydromorphone, may have temporarily reduced your mother's total opioid requirement to achieve comfort. However, given her clinical condition (renal insufficiency and possible other electrolyte abnormalities associated with this), whether this intervention would have had any meaningful or sustained impact on her confusion is difficult to determine.

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Does Venlafaxine Affect Libido?

I appreciated "Venlafaxine for the Control of Hot Flashes: Results of a Longitudinal Continuation Study" (*ONF,* Vol. 29, pp. 33–40) by Debra Barton, RN, PhD, and colleagues. Have the authors ever used this drug to treat reduction in libido or noticed anecdotally any changes in libido/sexual function? I see a lot of suppressed libido secondary to opioids.

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The Author Responds

Unfortunately, some people who have been on venlafaxine for a long time report some decreased libido that they believe is secondary to the drug. Nonetheless, in a randomized, placebo-controlled trial (Loprinzi et al., 2000), we saw no detrimental effect from venlafaxine on libido at all during the four-week study period; in fact, libido increased in each of the patient groups on this trial. It might have been that the hot flash reduction seen in this trial decreased night sweats so that women slept better, thereby improving their libido on subsequent evenings. The long-term effect of venlafaxine on libido is not clear, as long-term placebo-controlled trials examining libido issues in women (as opposed to sexual dysfunction issues in men) have not been conducted, to my knowledge. The *Physician's Desk Reference* (2002) cites "orgasm disturbance" in women, which is 2% compared to placebo and also is thought to be dose dependent. This number does not appear to be based on extensive research. Some of the newer antidepressants have been claimed to be associated with sexuality problems. However, little actually is established about the incidence of sexual dysfunction with these newer antidepressants.

I routinely ask the women for whom I care who have been on venlafaxine for more than six months whether they have noted any libido changes that they feel are attributed to the medication, and the majority answer no. To definitively answer the question of whether 75 mg of venlafaxine daily negatively affects libido over time, a placebo-controlled trial of at least six-months duration using the low dose of venlafaxine ideally would be conducted.

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Loprinzi, C.L., Kugler, J.W., Sloan, J.A., Mailliard, J.A., LaVasseur, B.I., Barton, D.L., et al. (2000). Venlafaxine in management of hot flashes in survivors of breast cancer: A randomised controlled trial. *Lancet, 356,* 2059–2063.

Nurse Practitioners in Academic Setting Looking for Answers

The group of practitioners to which I belong enjoyed "The Emerging Role of the Oncology Nurse Practitioner: A Collaborative Model Within the Private Practice Setting" (*ONF,* Vol. 28, pp. 1425–1431), by Nancy Jo Bush, RN, MN, MA, AOCN®, ONP, and Tammy Watters, RN, MSN, ONP. We are a group of three struggling nurse practitioners (NPs) with many of the same practice issues but within an academic practice setting. We have some questions about practice time issues.

How many patients do you see in a given day per week? How many days do you see patients? Do your MD colleagues support your taking time for office management of such patients? If so, how much time do you take per week? Is that time you want or time your MD colleagues request you take?

We are in a position where two new surgical oncology MDs have been added to the practice. They expect a 20% volume increase in our workload. We are expected to be in clinic every day seeing 15–30 patients. How usual is this load in your experience?

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