

## LETTER TO THE EDITOR

### TAPENTADOL: AN INITIAL ANALYSIS—FOLLOW-UP

To the Editor,

In the May/June 2010 issue of the *Journal of Opioid Management*, Dr Prommer authored a review article on tapentadol (immediate-release oral tablet formulation). We appreciate Dr Prommer's discussion on the topic and as a follow-up to the article, we would like to address several inaccuracies and provide correct information.

Although the author stated that tapentadol has a high binding affinity to all three ( $\mu$ ,  $\delta$ , and  $\kappa$ ) opioid receptors, we believe this misrepresents the 10-fold difference in affinity between the  $\mu$  opioid receptor ( $K_i = 0.096 \mu\text{M}$ ) and the other two opioid receptors ( $\delta$  opioid receptor  $K_i = 0.97 \mu\text{M}$  and  $\kappa$  opioid receptor  $K_i = 0.97 \mu\text{M}$ ).<sup>1</sup> Although tapentadol has been shown to bind to these three opioid receptor sub-types in experimental models, the literature and the approved prescribing information attribute tapentadol's analgesic effect to  $\mu$ -opioid receptor agonism (based on the 10-fold greater affinity for the  $\mu$  receptor) and norepinephrine reuptake inhibition.<sup>1,2</sup>

The author stated that tapentadol is structurally related to tramadol; however the chemical structure for tramadol was not provided for readers to compare and interpret whether there are any structural similarities or differences between the two molecules. Perhaps it would be helpful to present the two molecules side by side so that readers could visually identify those moieties within the two chemical structures that might be considered structurally related. Details regarding synthesis of tapentadol and tramadol are available in published literature.<sup>3,4</sup> It also may be informative to mention some of the differences in stereochemistry of the two molecules. Tramadol is a racemic molecule consisting of two enantiomers: (+) – 1R, 2R – tramadol and (-) – 1S, 2S – tramadol. Similar to the tramadol parent molecule, the pharmacologically-active M1 metabolite (O-desmethyltramadol), which is formed via metabolism by CYP2D6, also consists of two enantiomers (Figure 1). Unlike tramadol, tapentadol does not have stereoisomers and therefore exists as single, non-racemic molecules. In addition, a discussion of similarities and differences

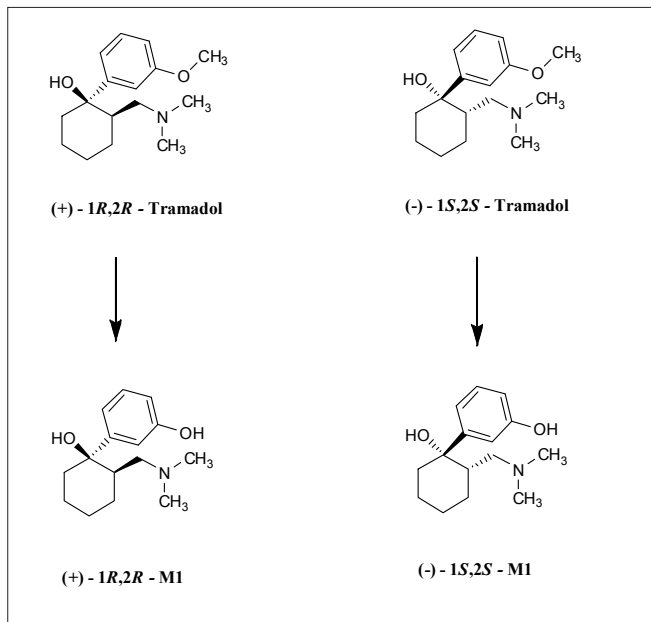
between tapentadol and tramadol was presented in a review article by Tzschentke in 2009.<sup>5</sup>

The author stated that tapentadol has a half-life of 24 hours, which is incorrect. The prescribing information reports the terminal half-life of tapentadol is "on average four hours after oral administration."<sup>2</sup> Accordingly, the mean terminal half-life of tapentadol has been reported to be approximately four hours in multiple publications on the pharmacokinetics of tapentadol in healthy subjects.<sup>6-8</sup>

The author was incomplete in discussing the excretion of tapentadol and its metabolites. Approximately 3 percent of orally administered tapentadol is excreted in the urine as unchanged drug.<sup>2,8</sup> Approximately 70 percent of tapentadol is excreted as direct conjugates (55 percent as tapentadol-O-glucuronide and 15 percent as tapentadol-O-sulfate) and approximately 27 percent is excreted as other metabolites, mostly indirect glucuronides (these indirect glucuronides include the 15 percent of an oral dose which first undergoes Phase I metabolism via cytochrome P450 enzymes followed by subsequent Phase II conjugation with glucuronic acid).<sup>2,8</sup> Fecal excretion of tapentadol is approximately 1 percent,<sup>2,8</sup> while a trace amount is excreted with expired carbon dioxide.<sup>6,8</sup>

Pre-marketing adverse events were reported in pooled data from nine Phase II/III studies that administered multiple doses.<sup>2</sup> These nine studies included 2,178 patients treated with tapentadol. The full prescribing information for tapentadol immediate-release oral tablet reports the most common (reported by  $\geq 10$  percent in any tapentadol-treated group) adverse events to be nausea, dizziness, vomiting, and somnolence. The most common adverse events that led to discontinuation (occurring in  $\geq 1$  percent of patients) from tapentadol treatment were dizziness, nausea, vomiting, somnolence, and headache.<sup>2</sup>

The author stated that in vivo drug-drug interaction studies involving tapentadol have not been performed, which is inaccurate. Studies in healthy subjects found there were no changes in the pharmacokinetic parameters of tapentadol when acetaminophen and aspirin were given concomitantly. Naproxen and probenecid slightly increased the exposure to tapentadol measured by the area under the serum concentration time curve, but these



**Figure 1. Enantiomers of Tramadol and O-desmethyltramadol (M1).**

changes were not considered clinically relevant and no change in dose is required.<sup>2,6</sup> The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.<sup>2,9,10</sup>

The author stated that no formal studies were conducted in special populations; however, the prescribing information discusses top-line results of pharmacokinetic studies involving patients with impaired renal function (including mild, moderate, and severe renal impairment) and patients with hepatic impairment (including mild and moderate hepatic impairment).<sup>2</sup> These pharmacokinetic studies were subsequently presented at the 2010 Annual Meeting of the American College of Clinical Pharmacology and published as abstracts several months after Dr. Prommer's review article was published.<sup>11,12</sup> Furthermore, population pharmacokinetic analyses (also published after this review article) of pooled data from over 10,000 serum pharmacokinetic samples from healthy subjects and patients with moderate to severe pain has been published.<sup>13</sup>

To date, there are four published Phase III clinical studies for immediate-release (IR) tapentadol; two are safety and efficacy studies in a postoperative pain model,<sup>14,15</sup> one is a safety and efficacy study in an outpatient, non-surgical pain model,<sup>16</sup> and the last is a safety study evaluating tapentadol exposure for up to 90 days.<sup>17</sup> The author did not

include information on the severity of pain that was required to be eligible for randomization in the Phase III studies; patients were included if they met criteria for moderate to severe ( $\geq 4$  based on the 11-point Numerical Rating Scale; 0 = no pain and 10 = worst pain imaginable; in the non-surgical model, criteria for inclusion was  $\geq 5$ ) acute pain. The author stated that tapentadol IR was compared to oxycodone IR in Phase III studies, which is not exactly correct. To clarify, tapentadol IR was compared to placebo in these efficacy and safety studies<sup>14-16</sup> which employed oxycodone IR as an active control to confirm sensitivity of the pain model. These studies were not designed for primary head-to-head comparisons of tapentadol IR to oxycodone IR for the primary endpoints of reduction in pain intensity. Pre-specified and post-hoc analyses for non-inferiority of tapentadol IR to oxycodone IR for pain intensity reduction were conducted in the three safety and efficacy studies as part of a stepwise comparison approach.<sup>14-16</sup>

Other points of clarification in the summary of clinical data include the allowance of acetaminophen as rescue therapy as discussed only occurring in one of the bunionectomy studies;<sup>14</sup> the other bunionectomy study permitted a variety of rescue medications but the use was specified to manage pain prior to randomization.<sup>15</sup> For the Phase II dental study,<sup>18</sup> the author stated that the primary endpoint was total pain relief over eight hours, which is accurate, but an incorrect abbreviation was used. The correct abbreviation for total pain relief is TOTPAR.

The author was correct to state that equianalgesic dosing studies have not been performed. However, the author's statement of similar analgesic efficacy was based solely on a single-dose Phase II study.<sup>18</sup> We suggest your readership also consider the four Phase III studies that conducted non-inferiority analyses between tapentadol IR and oxycodone IR for analgesic efficacy. In one bunionectomy study,<sup>14</sup> tapentadol IR 100 mg administered in repeated doses was non-inferior to oxycodone IR 15 mg in analgesic efficacy in the treatment of acute postoperative pain as measured using the primary efficacy variable of SPID<sub>48</sub> in a post-hoc analysis. In another bunionectomy study<sup>15</sup> individual comparison of tapentadol IR 50 and 75 mg administered in repeated doses were non-inferior to oxycodone IR 10 mg in analgesic efficacy as measured using the primary efficacy variable of SPID<sub>48</sub> in a prespecified analysis. In the end-stage joint disease study, the

analgesic efficacy of tapentadol IR and oxycodone IR was similar in the relief of osteoarthritis pain based on the mean SPID over two, five, and 10 days of treatment; tapentadol IR 50 and 75 mg were non-inferior to oxycodone IR 10 mg in pain relief as measured with 5-Day SPID in pre-specified secondary efficacy analyses.<sup>16</sup> In the 90-day safety study, evaluation regarding efficacy was limited by the lack of a placebo arm and comparisons of pain relief between tapentadol IR 50 or 100 mg and oxycodone IR 10 or 15 mg were not conducted.<sup>17</sup>

Although the author stated the dosing range recommendation of tapentadol, it is important to remind prescribers that the dosing regimen should be individualized for each patient according to the intensity or severity of pain being treated, the patient's previous experience with similar drugs, and the ability of the prescriber to monitor the patient as discussed in the full prescribing information.<sup>2</sup>

NUCYNTA® (tapentadol) immediate-release oral tablets are indicated for the relief of moderate to severe acute pain in patients 18 years of age or older. This indication does not restrict use to specific causes of acute pain. However, during the premarketing evaluation of tapentadol, no studies were conducted for the immediate-release tablet formulation of tapentadol using a neuropathic pain model. There are published Phase III studies for the extended-release (ER) tablet formulation in treating moderate to severe chronic pain due to diabetic peripheral neuropathy,<sup>19</sup> chronic low back pain<sup>20</sup> and chronic pain related to osteoarthritis<sup>21</sup> of the knee. In addition, a study evaluating dose conversion between IR and ER formulations also has been published.<sup>22</sup>

The author's summary of the mechanism of analgesic action is not consistent with the full prescribing information<sup>2</sup> and published<sup>1,3</sup> literature. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake.<sup>2</sup> As written, the author's statement that "Tapentadol is a mu, delta, and kappa agonist that works by blocking the uptake of norepinephrine" misrepresents the 10-fold higher binding affinity for the mu receptor (compared to delta and kappa), and inadvertently convolutes tapentadol's two separate and distinct analgesic mechanisms of action: mu-opioid agonism and norepinephrine reuptake inhibition. Other statements in the conclusion section are not substantiated (ie, "touted as an improvement on the previous opioid with effects on descending modulation Tramadol"

and "Although affinity studies suggest potency equivalent to a step-3 opioid, its ability to activate G proteins seems less than morphine") or are not given appropriate context or interpretation (ie, "Clinical trials conducted so far suggest a lower potency than morphine" and "Tapentadol has a lower bioavailability than tramadol") since "potency" and "bioavailability" are not directly correlated to analgesic efficacy.

Thank you for the opportunity to correct some inaccuracies and present some contextual information to your readership regarding tapentadol immediate-release oral tablets.

Kind Regards,  
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## AUTHOR'S RESPONSE

In response to the letter to the editor by Nelson and co-workers, I would like to make a few comments. As the article was an initial analysis, the updated information on metabolism and drug interactions are appreciated. The binding affinities described for tapentadol were listed and it is clear that the drug has a greater affinity for the  $\mu$  opioid receptor by ten fold over the  $\delta$  and  $\kappa$  opioid receptor. Other affinities were listed for completeness as I feel any drug purported to have opioid characteristics should have the interaction at other opioid receptors characterized. These show that the drug *has high affinities* to the  $\delta$  and  $\kappa$  opioid receptors. To emphasize that this is only a  $\mu$  opioid agonist also neglects the interactions that exist between opioid receptors and their relationship to the development of tolerance.<sup>1</sup> It should also be remembered that all *three* opioid receptors can produce analgesia. Binding affinities and  $\mu$  agonism alone do not explain the mechanism of action of this drug. Despite the reported high affinity for the  $\mu$  opioid receptor, the argument for it being a  $\mu$  agonist loses its "potency" if you will. Studies using measures of G-protein activation such as [<sup>35</sup>S] GTP $\gamma$ S binding show a potency less than morphine.<sup>2</sup> In preclinical models for neuropathic pain, inflammatory pain, and models for acute nociception, which are described in the article, tapentadol shows antinociceptive, antihyperalgesic, and/or antiallodynic effects, which were consistently weaker than morphine in terms of antinociceptive effect.<sup>2</sup> Even when attempts to improve bioavailability were performed, such as by administering the drug intraperitoneally,

these effects were not improved. In acute nociceptive behavioral studies, such as hot-plate testing, *morphine was two to three times as potent as tapentadol*. In the tail flick test, another acute nociceptive model, morphine was twice as potent. In models measuring mechanical allodynia, such as sciatic nerve ligation, morphine was twice as potent as tapentadol. Preclinical models also suggest that the primary analgesic activity of tapentadol may lie in its ability to block norepinephrine uptake. Antagonists such as yohimbine can reverse its analgesia to greater extent than naloxone, which leads one to suspect that in addition to the limited opioid affinity studies that this drug functions less as an opioid, and more of an agent that can affect descending pain modulation through its inhibition of the uptake of norepinephrine. I feel that as far as we know now, the true opioid potency of this drug should still be questioned and to suggest that this drug acts as a full  $\mu$  agonist likewise convolutes its true nature.

Yours truly,

Eric Prommer, MD

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