Are there any opioids with a potency somewhere between that of tramadol and hydromorphone that are associated with a lower risk of nausea than tramadol and hydromorphone?
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There is considerable variation amongst opioids in terms of their potency and activity at opioid receptors.[1-4] Based on equianalgesic dosing tables, several opioids are classified as high potency such as fentanyl, hydromorphone, and oxymorphone.[1,3] Relative to these agents, lesser potent opioids include morphine, oxycodone, hydrocodone, and methadone, while codeine, tramadol, and tapentadol are the weakest in potency. (See Table 1 for selected agents and equianalgesic dosages).

Table 1: Equianalgesic dosage for selected opioids.[1,3]

Agent	Equianalgesic dose (mg)*
Fentanyl	0.125 mg (IM)
Oxymorphone	1 mg (IM), 10 mg (PO)
Hydromorphone	1.5 mg (IM), 7.5 mg (PO)
Hydrocodone	5-10 mg (PO)
Morphine	10 mg (SC/IM), 30 mg (PO)
Oxycodone	10 mg (PO)
Methadone	Variable
Tapentadol	50-100 mg (PO)
Tramadol	50-100 mg (PO)
Codeine	120 mg (PO)

*Equivalent to 10 mg of morphine; IM=intramuscular; PO=by mouth; SC=subcutaneous

Opioids commonly cause gastrointestinal (GI) adverse events such as nausea, vomiting, and constipation, which are mediated via stimulation of the chemoreceptor trigger zone in the medulla.[1-4] There are limited data regarding comparative incidence of nausea between various opioid agents. Per *Goodman and Gilman*, all clinically useful opioid agonists produce some degree of nausea and vomiting, and at equianalgesic doses, the incidence of these side effects is not significantly lower comparing opioid agonists to morphine.[2] Table 2 summarizes the incidence of nausea for selected opioids based on data from placebo-controlled trials.

Table 2: Incidence of nausea based on placebo-controlled trials.[5]

Agent	Incidence of nausea
Hydromorphone*	N/A
Hydrocodone	7% – 8%
Morphine	7% to >10%
Oxycodone	15% – 23%
Methadone**	N/A
Tapentadol	21% – 27%
Tramadol	15% – 40%

N/A=not available; *for hydromorphone: listed as “common;”
**for methadone: listed as “most frequently observed.”

As shown in Table 2, hydrocodone and morphine appear to have the lowest incidence of nausea relative to other opioid agents; however, these comparisons are indirect. In addition to these data, 2 randomized, double-blinded placebo-controlled trials were identified which assessed the efficacy of immediate-release (IR) tapentadol compared to IR oxycodone in patients with end-stage joint disease or post-operative bunionectomy pain.[6,7] Both trials established the non-inferiority of tapentadol relative to oxycodone and found lower incidences of GI adverse events (nausea, vomiting, constipation) in patients who received tapentadol. Based on the results of these 2 studies, Etropolski et al conducted a phase 3b randomized, double-blinded, multicenter trial assessing the efficacy and tolerability of tapentadol versus oxycodone in patients with end-stage joint disease.[8] Unlike the earlier trials, Etropolski et al directly evaluated GI adverse events with a validated bowel function diary (BFD). Although the primary tolerability endpoint evaluated opioid-induced constipation (number of spontaneous bowel movements), treatment-emergent adverse events (TEAEs) such as nausea and vomiting were also assessed. Patients were included in the trial if they had moderate-to-severe pain and were between the ages of 18 to 80 years. There were numerous exclusion criteria including seizure disorder, severe renal or hepatic impairment, stroke, transient ischemic attack, or mild/moderate traumatic brain injury.

Patients were randomized to tapentadol IR 50 mg or 75 mg, oxycodone IR 10 mg, or placebo every 4-6 hours for 14 days.[8] This was followed by 28 days of extended-release (ER) tapentadol, controlled-release (CR) oxycodone, or placebo (note: specific doses were not provided). A total of 598 patients were randomized to treatment, of which 596 were part of the safety analysis. It was noted that baseline demographics were similar between groups. In terms of nausea and vomiting, more patients in the oxycodone IR group reported nausea (40%) compared to patients in the tapentadol IR (17% for 50 mg, 20% for 75 mg) and placebo groups (7%, $p<0.001$ for each vs. oxycodone IR). Similarly, for vomiting, patients in the oxycodone IR group experienced more days of vomiting compared to the tapentadol IR groups ($p<0.001$ for 50 mg; $p=0.003$ for 75 mg, number of days not reported). The authors also noted that nausea and vomiting were more common in the oxycodone CR group compared to the tapentadol ER group (results not reported). In addition to adverse events, fewer patients discontinued tapentadol IR and placebo compared to oxycodone as a result of TEAEs (14% for tapentadol IR 50 mg; 7% for tapentadol 75 mg; 3% for placebo; 29% for oxycodone IR). Similar results were also reported for the CR and ER products in which more patients discontinued oxycodone CR compared to tapentadol ER (6.6% for oxycodone CR; 2% for tapentadol ER).

Etropolski et al concluded that tapentadol IR had better tolerability compared to oxycodone IR in terms of GI adverse events such as nausea, vomiting, and constipation.[8] The authors also noted that these results confirm the results from earlier studies.[6,7] Limitations of the trial include a lack of assessment of use of anti-emetic agents by patients despite documentation of use of fiber products, stool softeners, and suppositories.[8] In addition, use of other pharmacologic agents that may cause GI adverse events was not addressed. Finally, the subjective nature of reporting nausea symptoms should also be considered when evaluating the results of the study.

In conclusion, there are limited data regarding the comparative incidence of nausea across the opioid class. Placebo-controlled trials have shown a lower incidence of nausea with hydrocodone and morphine, but these trials only allow for indirect comparisons.[5] In addition, 3 randomized controlled trials have demonstrated a lower incidence of nausea with tapentadol compared to oxycodone.[6-8] In terms of opioid potency, it is unknown what role it plays in the development of nausea or vomiting.

Although 3 trials showed that tapentadol had a favorable GI tolerability profile, it is premature to recommend this agent over other opioids. At this point, additional comparative trials are needed in order to more fully determine which opioids are associated with a lower risk of nausea.

References:

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