Can a dose reduction in a pure opioid agonist, such as morphine, result in increased analgesia?
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Opioids are among the oldest known agents used to treat pain.[1] The term "opioid" refers to any compound that acts at opioid receptors.[2] There are 3 major classes of opioid receptors (mu, kappa, and delta), each with multiple subtypes, as well as several poorly defined minor classes.[1,3] The mu, kappa, and delta receptors are composed of similar sequences (e.g., all have 7 transmembrane segments, an extracellular amino terminus, and an intracellular carboxy terminus), but the individual receptors are disparate in their distribution within the central and peripheral nervous system, and they mediate unique clinical effects. A summary of the functions of each type of receptor is shown in Table 1.

Table 1. Opioid receptors and their functions, adapted from *Basic and Clinical Pharmacology*.[2]

Functions	Opioid receptor types		
	Mu	Delta	Kappa
Supraspinal and spinal analgesia	√	√	√
Sedation	√	--	--
Inhibition of respiration	√	--	--
Slowed gastrointestinal transit	√	--	√
Modulation of hormone and neurotransmitter release	√	√	--
Psychomimetic effects	--	--	√

√=applies; -- = does not apply

Opioid drugs include full agonists, partial agonists, and antagonists.[2] Opioids may also differ in receptor binding affinity. Though the majority of currently available opioid drugs act primarily at the mu receptor, binding of an opioid is not limited to 1 receptor type, and the relative affinity for the different receptors accounts for the clinical effects.[1] The affinity of selected opioids is outlined in Table 2. Of note, opioid compounds may bind to different parts of an individual receptor – for example, alkaloids such as morphine bind to the transmembrane portion of a receptor while other ligands may bind at the extracellular loops – and binding results in conformational changes to the receptor, further leading to G protein activation/inactivation.[3] Per *Goodman and Gilman*, different ligands may induce different conformational changes in the receptor, leading to divergent intracellular events, translating into different clinical effects.

Table 2. Selected opioids and their affinity for each major class of opioid receptor, adapted from *Basic and Clinical Pharmacology*.[2]

Drug	Opioid receptor types*		
	Mu	Delta	Kappa
Morphine	+++		+
Hydromorphone	+++		
Oxymorphone	+++		
Methadone	+++		
Meperidine	+++		
Fentanyl	+++		
Sufentanil	+++	+	+
Levorphanol	+++		

Drug	Opioid receptor types*		
	Mu	Delta	Kappa
Codeine	±		
Hydrocodone	±		
Oxycodone	++		
Pentazocine	±		±
Nalbuphine	--		++
Buprenorphine	±	--	--
Butorphanol	±		+++

*+ indicates level of affinity (+++ = highest; + = lowest); all of these agents are full agonists. ± indicates partial or weak agonist; -- = antagonist

Administration of opioid drugs may lead to a complex sequence of events.[2] For example, though an opioid such as morphine may act primarily at the mu receptor, this action may lead to the release of endogenous opioids that act at the delta and kappa receptors. Additionally, opioids may act simultaneously at multiple sites, including both the ascending pathways involved in transmission of pain but also descending or modulatory pathways.

Several sources note that frequent or repeated doses of morphine or related compounds are associated with gradual **loss** in analgesic effectiveness.[2-4] Consequences described include desensitization,[3] tolerance,[2-4] and physical dependence. Desensitization, or acute tolerance, is thought to occur with acute agonist occupancy of the opioid receptors (over minutes to hours).[3] Per *Goodman and Gilman*, short-term desensitization involves phosphorylation of the receptors, leading to uncoupling of the receptors from their G proteins and/or internalization of the receptors. Tolerance refers to a decrease in maximum achievable effect of a drug, usually occurring over weeks to months. Tolerance is surmountable with higher doses of the drug and is reversible over time after the drug has been discontinued. Physical dependence is characterized by withdrawal or an abstinence syndrome when an antagonist is administered or when there is an abrupt dose reduction or discontinuation of the drug. The mechanism for development of opioid tolerance and physical dependence is poorly understood, but there are several hypotheses, including receptor uncoupling (described above) and issues in the recycling of receptors (disruption in the normal process of receptor endocytosis followed by resensitization of the receptor and recycling to the plasma membrane).[2] In addition to these consequences, hyperalgesia, or an increase in sensation of pain, is thought to occur with persistent administration of opioids.

In the context of opioid tolerance, it is unclear whether a reduction in opioid dosage may lead to increased analgesia. The American Academy of Neurology asserts that the idea of tolerance being overcome by dose escalation is controversial.[5] The Washington State Agency Medical Directors' Group corroborates this statement, recommending that providers avoid ongoing dose escalation to overcome opioid tolerance.[6] The Centers for Disease Control and Prevention notes that patients who do not experience clinically meaningful pain relief within 1 month of opioid initiation are unlikely to experience pain relief with longer-term use – presumably, this could include use of opioids at higher doses.[7] Per the Institute for Clinical Systems Improvement, in patients experiencing opioid tolerance, clinicians should assess the appropriateness of the medication and consider either an adjuvant analgesic or opioid rotation.[8]

With regard to opioid-induced hyperalgesia, a reduction in opioid dosage is recommended for consideration by the Institute for Clinical Systems Improvement and the American Society of Interventional Pain Physicians.[8,9]

From a search of the literature, few studies were identified in which the effects of opioid dose reduction on analgesia were evaluated. A retrospective and prospective chart review was conducted by Harden et al to determine if patients receiving chronic opioid therapy could be tapered to lower opioid doses without an increase in pain.[10] They included adult patients prescribed opioids for ≥90 consecutive days at a Veterans Affairs Medical Center. The primary endpoint was percent reduction in morphine equivalents (ME) over a 12-month period. In total, 50 patient charts were included. The mean age of participants was 54 years (range: 25 to 71) and the majority (72%) had 1 or 2 pain diagnoses. The most common pain diagnosis was back pain (35%), followed by joint-related pain (15%) and osteoarthritis (14%). Thirty-six percent of patients had baseline opioid doses <200 mg ME/day; 34% had baseline doses between 201 and 400 mg ME/day, 16% had baseline doses between 401 and 600 mg ME/day, and 14% had baseline doses >600 mg ME/day. Over the 12-month period, there was a mean reduction in opioid doses of 46%. In months 0-3, 53% of patients reported less pain; comparatively, in months 3-6, 36% of patients reported less pain, and in months 6-12, 40% of patients reported less pain. Overall, 70% of patients experienced either no change in pain or less pain compared to baseline during the study period (0-12 months). From these findings, Harden et al concluded that patients on chronic opioid therapy may be successfully tapered to lower opioid doses without necessarily experiencing more pain.

Other than the study by Harden et al, a case report was identified in which Vorobeychik et al described an improvement in opioid analgesic effect following opioid dose reduction.[11] The patient was a 56-year old male with recurrent squamous cell lung carcinoma and spinal metastases, experiencing severe pain despite increasing doses of oxycodone, morphine, and hydromorphone (all administered by patient-controlled analgesia [PCA]). He had been admitted to the hospital 4 times in 5 months for inadequate pain control. Prior to his most recent admission, the palliative care team increased the dose of the hydromorphone PCA to a maximum of 13 mg every 10 minutes with a basal rate of 27 mg/h, equating to >50,000 mg/day of oral morphine. When the patient was admitted for the fourth time for persistent pain, the providers suspected potential opioid-induced hyperalgesia and reduced his hydromorphone dose by 40-50% and initiated methadone at a dose of 10 mg twice daily. Within 4 days, the patient's pain was reduced from 7-10/10 to 3/10.

Though the case report and chart review suggest that improvement in pain may occur following opioid dose reduction, the data are insufficient to conclude that the observed reduction in pain resulted from an improvement in opioid analgesic effect.[10,11] In the case report, for example, addition of another analgesic agent may have contributed to the reduction in pain intensity, and, potentially, the patient may have experienced resolution of hyperalgesia.[11] Importantly, the observational nature of both studies is a limitation to consider; the case report, in particular, is a weak form of evidence as it is anecdotal.[10,11]

In summary, the pathophysiology of pain and the mechanisms by which opioids act and/or exert their clinical effects are complex. There are multiple types of receptors to which opioids may bind, and opioids differ in their binding affinity as well as binding sites.[1-4] With regard to the effects of opioid dose reduction, there is insufficient evidence to suggest that this practice may lead to increased analgesia.[10,11]

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