Opioid Agonists, Partial Agonists, Antagonists: Oh My!

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When it comes to predicting therapeutic or adverse effects (and efficacy), opioid-specific pharmacodynamics play a major role. Pharmacodynamics, as we all well know, is the study of what a drug does to the body, including involvement with receptor binding and conformational changes that ultimately drive therapeutic and non-therapeutic effects (ie, adverse effects). Some of the adverse effects of opioids are listed in **Table 1.**[1]

Table 1. Adverse Effects Associated with Opioid Use[1]

Common Adverse Effects	Severe Adverse Effects
Cognitive impairment Constipation Decreased testosterone/sexual dysfunction Nausea/vomiting Orthostatic hypotension Sedation/somnolence	Addiction Opioid-induced respiratory depression

There are 4 types of opioid receptors that have been identified: mu, delta, kappa, and opioid-receptor like-1 (ORL-1). Some of the receptors may be further divided into subtypes. These receptors are important for expressing pain transmission and modulating pathways, including neurotransmission in the limbic system, midbrain, spinal cord, and thalamus. Opioid receptors are ubiquitously present throughout the body, including but not limited to the gastrointestinal tract (GI), immune cells, pituitary gland, and skin. At these sites, opioid receptors carry out variable analgesic and non-analgesic functions. A summary of pharmacological and physiological effects for each opioid receptor is listed in **Table 2.**[2-4]

Table. 2. Summarized Effects of Individual Opioid Receptors[2-4]

	Mu	Delta	Kappa	ORL-1
Clinical effects	Analgesia Depression Euphoria Physical dependence Respiratory Sedation	Analgesia Inhibit dopamine release Modulation of mu receptor	Analgesia Diuresis Dysphoria	Analgesia Sedation

Most opioids are mu agonists with varying activity on kappa receptors.

Opioid receptors are 7 transmembrane spanning proteins that are coupled to inhibitory G-proteins. When activated, they decrease adenyl cyclase production of the secondary messenger cyclic adenosine monophosphate. This causes a decrease in calcium influx from inhibition of voltage-gated calcium channels and results in the activation of potassium channels, which leads to hyperpolarization. The hyperpolarized state causes inhibition of neuronal signaling, which in this case inhibits pain transmission.[2,5]

Opioids are classified into categories, depending on receptor binding and affinity (**Table 3**). These classifications are agonist, partial agonist, and antagonist. There are opioids that have dual agonist and antagonist functions.

Table 3. Examples of Opioid by Receptor Binding

Full Agonist	Partial Agonist	Mixed Agonist	Antagonist
Codeine Fentanyl Heroin Hydrocodone Hydromorphone Levorphanol Meperidine Methadone Morphine Oxycodone Oxymorphone	Buprenorphine Butorphanol Pentazocine Tramadol	Buprenorphine Butorphanol Nalbuphine Pentazocine	Naloxone Naltrexone

Full agonists bind tightly to the opioid receptors and undergo significant conformational change to produce maximal effect. Examples of full agonists include codeine, fentanyl, heroin, hydrocodone, methadone, morphine, and oxycodone.

Partial agonists cause less conformational change and receptor activation than full agonists. At low doses, both full and partial agonists may provide similar effects to their full agonist cousins. However, when the dose of partial agonists increases, the analgesic activity will plateau, and further increases in doses will not provide additional relief but may increase the adverse effects. Examples of partial agonists include buprenorphine, butorphanol, and tramadol.

There are mixed agonists/antagonists, which demonstrate varying activity depending on the opioid receptor but also varying on the dose. Examples include buprenorphine, butorphanol, nalbuphine, and pentazocine. And, some opioids are agonists at 1 or more opioid receptors but also antagonists at other opioid receptors. A summary of receptor effects for agonists/antagonists can be found in **Table 4.**[4]

Table 4. Receptor Effect of Mixed Opioid Agonist/Antagonists[4]

Opioids	Mu	Kappa	Delta
Pentazocine	Partial agonist	Agonist	
Nalbuphine	Antagonist	Agonist	
Buprenorphine	Partial agonist	Antagonist	Antagonist (weak)
Butorphanol	Antagonist	Partial Agonist	

Pentazocine is FDA approved and indicated for pain management and formulated with acetaminophen or naloxone. The mechanism of action is partial agonist at the mu opioid receptor and full agonist at the kappa opioid receptor. Although pentazocine weakly antagonizes the analgesic effects of full agonists, it also generates incomplete reversal of behavioral depression, cardiovascular, and respiratory induced via morphine and other full agonists.[6]

Nalbuphine is a synthetic analgesic opioid demonstrating agonist activity at the kappa receptor, while acting as an antagonist at the mu receptor. Nalbuphine has a ceiling effect on respiratory depression at doses greater than 30 mg. Nalbuphine has been reported to reverse respiratory depression but not analgesia of mu-agonists.[7,8] Nalbuphine may precipitate withdrawal in patients who are physically dependent on mu-opioid agonists.[9]

Buprenorphine is indicated at high doses for opioid-use disorder while generally at lower doses to treat moderate to severe pain. Buprenorphine FDA-approved formulations indicated for pain management include Belbuca, Buprenex, and Butrans.[10-12] Buprenorphine formulations approved for opioid dependence are Bunavail, Probuphine, Suboxone, Subutex, and Zubsolv.[13-17] Buprenorphine is 25 to 100 times more potent than morphine.[18] Buprenorphine exhibits partial agonist behavior at the mu-receptor and exhibits antagonist behavior at the kappa-receptor. Buprenorphine has a strong affinity for the mu-receptor causing tight binding and therefore competition at the receptor, displacing other opioids, such as methadone and morphine. Also, there is incomplete dissociation from the mu-receptor, causing prolonged activity at the receptor.[18] Affinity is quantified using Ki values, and the smaller the Ki value, the stronger the binding affinity to the receptor. The mu binding affinity of buprenorphine compared with other opioids can be found in **Table 5.** Of note, buprenorphine has a higher binding affinity compared with naloxone and therefore at higher doses where buprenorphine is most likely to be abused, not readily reversed by naloxone. It is only at lower doses where there is some competitive binding, and only then should we reasonably expect some reversal by high doses of continuous infusion naloxone. This, of course, begs the question regarding the utility of the combined product, Suboxone.

Table 5. Mu Receptor Affinities of Various Opioids[19]

Opioids	Range of Ki Value
Levorphanol	**0.19 to .23**[32]

Buprenorphine	**0.21 to 1.5**
Naltrexone	**0.4 to 0.6 (antagonist effects)[20]**
Hydromorphone	**0.6**
Fentanyl	**0.7 to 1.9**
Methadone	**0.72 to 5.6**
Oxymorphine	**0.97**
Naloxone	**1 to 3 (antagonist effects)[20]**
Morphine	**1.02 to 4**
Pentazocine	**3.9 to 6.9**
Hydrocodone	**19.8**
Oxycodone	**23**
Codeine	**65 to 135**
Tramadol	**≥ 100**

Due to partial agonism, effects on respiratory depression plateaus with increasing doses, which makes this a viable option for those at increased risk of respiratory depression.[21] Kappa-receptor antagonism has benefits for reducing stress-induced drug-seeking behavior, because of the subsequent blockage of dynorphins. Dynorphins are kappa receptor selective opioid peptides that drive anxiety, stress, and increase desire for opioid use. Further, kappa antagonism has demonstrated antidepressant properties.[22,23]

Butorphanol is a mu opioid antagonist with low intrinsic activity and kappa opioid agonist exhibiting high affinity. Butorphanol is indicated for pain management for patients in which alternative treatment options are ineffective, not tolerated, or inadequate, and is formulated as a nasal spray and injection. Because of the high affinity for kappa receptors, it may cause psychotomimetic effects. At higher doses, the magnitude of respiratory depression is not appreciably increased like most mixed agonist/antagonist. However, the duration of respiratory depression is longer, because of predominant mu-mediated physiological responses over the kappa.[23-25]

Opioid agonists also bind to the peripheral mu opioid receptors in the GI, causing impaired motility, and secretion, resulting in constipation. Peripherally acting mu-opioid receptor antagonists (PAMORA) act specifically in the GI tract to combat constipation. However, peripheral mu-opioid antagonists do not cross the blood-brain barrier, thus avoiding blockade of centrally mediated analgesia and other centrally mediated opioid agonist effects. Examples of PAMORAs include alvimopan (Entereg), methylnaltrexone (Relistor), and naloxegol (Movantik). The latter 2 are FDA indicated for opioid-induced constipation generally after OTC laxatives fail. However, Alvimopan is indicated for perioperative management of postoperative ileus to accelerate the time to upper and lower GI recovery following surgery. Further, unlike all

other PAMORAs, Alvimopan has a black box warning for the potential risk of myocardial infarction with long-term use, which is not a recognized risk with the other PAMORAs.[26-28]

Finally, like in every great story, there are antagonists. However, in the story of opioids, opioid antagonists may save lives. Naltrexone is an opioid antagonist that blocks the effects of opioids by competitive binding. Naltrexone is indicated for alcohol and opioid dependence and useful because its opioid receptor blockade secondarily diminishes dopamine activity that is otherwise enhanced by alcohol.[29] Naloxone is a mu-opioid receptor antagonist and reversal agent used to mitigate risk for opioid-induced respiratory depression by displacing the full opioid agonists. The available formulations are Narcan (nasal), Evzio (Auto-injector), and solution for injection, the latter of which is frequently administered off label intranasally, by attaching an atomizer to the end of a syringe.[30,31] Family members, friends, and bystanders are allowed to administer now in most states (protected by Good Samaritan laws), in addition to professional first responders, such as paramedics.

Although the chemistry behind opioids has been outlined, there are other parameters that also need to be factored in to determine individual response. These include age, comorbidities, disease severity, gender, genetics, and weight, all of which may positively or negatively affect the drug response. In addition to the pharmacodynamics outlined herein, many synthetic opioids have additional mechanisms of action, such as noradrenergic reuptake blockade and inhibition of n-methyl-D-aspartase (NMDA) receptors. For this reason, as erroneously implied by recent CDC guidelines, failure and/or intolerance to 1 opioid does not necessarily equate to failure on another. It is therefore important to consider all these variables when making decisions that affect opioid selection or discontinuation.

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