Clinical Pharmacology: Advances and Applications

Dovepress
Taylor & Francis Group

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REVIEW

The Role of Danavorexton for Perioperative Opioid-Induced Respiratory Depression and Sedation: A Narrative Review

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Abstract: Opioid-induced respiratory depression (OIRD) and sedation are significant perioperative complications that limit safe and effective use of opioid analgesia. Current reversal agents, such as naloxone, are effective at treating OIRD but may negatively affect pain management, leaving a critical clinical gap in perioperative pain management. The orexin system has a pivotal role in wakefulness and respiratory drive. Danavorexton is a selective orexin-2 receptor agonist that targets this system to promote arousal and respiratory function. It has emerged as a pharmacological option for OIRD and reversal for opioid sedation without compromising analgesia. Additionally, studies have shown that danavorexton can enhance tidal volume and minute ventilation in patients who are being managed with opioids. This narrative review discusses the pathophysiology of OIRD, current reversal strategies, and the emerging evidence supporting the use of Danavorexton in perioperative care. Danavorexton represents a novel and potentially transformative adjunct that could improve postoperative recovery, reduce adverse opioid-related events, and enhance patient safety in the surgical setting.

Keywords: opioid-induced respiratory depression, danavorexton, orexin receptor agonist, perioperative sedation, opioid analgesia

Introduction

Opioids remain a necessity for perioperative analgesia due to their efficacy in controlling acute and post-surgical pain. However, their clinical utility is frequently limited by adverse effects, including opioid-induced respiratory depression (OIRD) and excessive sedation. OIRD represents the most critical threat, contributing to hypoxemia, hypercapnia, delayed post-anesthesia recovery, and increased perioperative morbidity and mortality. The current standard for reversing OIRD is naloxone, but it reverses both respiratory depression and analgesia, leaving postoperative patients in severe pain. This limitation has been increasingly problematic as perioperative opioid exposure rises with expanding surgical volume and increased comorbidities, especially in the aging population. Despite the frequency and severity of OIRD, clinicians currently lack an effective strategy that can reliably restore respiratory function without simultaneously reversing analgesia. This is a critical gap in perioperative management.

Early clinical trials of danavorexton have produced evidence supporting a pharmacologic agent capable of reversing OIRD and excessive sedation without compromising analgesia. Danavorexton (TAK-925), a selective orexin-2 receptor agonist, has demonstrated the ability to increase tidal and minute ventilation, counter opioid-induced sedation, and preserve analgesia in early clinical studies.[1–3] By specifically targeting the orexin-2 receptor (OX2R), danavorexton activates neural pathways that regulate both arousal and respiratory drive. The convergence of increasing OIRD burden, inadequate existing reversal agents, and newly available human data on orexin-2 receptor agonists makes a comprehensive review both timely and necessary. In this review, we will discuss the mechanisms of opioid-induced

https://doi.org/10.2147/CPAA.S575330
Received: 21 October 2025
Accepted: 10 January 2026
Published: 14 January 2026

respiratory depression and sedation, examine existing and emerging pharmacologic reversal strategies, and evaluate the potential clinical role of danavorexton as an adjunctive therapy in the perioperative setting.

Mechanism of Opioid-Induced Respiratory Depression and Sedation

The mu-opioid receptor (MOR) is part of the class of G-protein-coupled receptors (GPCR), which are seven-transmembrane receptors that are vital in facilitating cellular responses.[4] The mu-opioid receptor is activated by opioid analgesics like morphine, fentanyl, and heroin.[5,6] Following MOR activation, it can signal via G-protein signaling mechanisms (selectively G_i) or the β-arrestin pathway.[7] G_i is a heterotrimeric G protein (G_a, G_b, and G_g) that inhibits adenylate cyclase.[8,9] Via G_i, MOR affects different ion channels, including G-protein-coupled inwardly rectifying potassium channels (GIRK) and voltage-gated calcium channels (VGCC). β-arrestin 2 is a regulator of the signaling of the mu-opioid receptor that functions via desensitization and internalization.[8]

Opioids are valuable pain relievers with side effects. Their side effects include respiratory depression, constipation, sedation, and vomiting. Respiratory depression is potentially a lethal side effect of opioid usage.[10] Opioid induced respiratory depression (OIRD) is defined as reduced respiratory rate, hypercapnia/hypercarbia, and/or reduced oxygen saturation.[11] It has an incidence rate of 0.5% in opioid users.[12] Opioids interact with the central nervous system via MOR, which contribute to the development of Opioid induced respiratory depression.[13] This opioid and CNS interaction leads to decreased respiratory drive, upper airway obstruction, and sedation.[10]

Aside from opioid and MORs in the CNS interaction, certain MOR signaling pathways have been implicated in opioid-induced respiratory depression. Previous studies on β -arrestin two knockout mice showed that adverse opioids effects, including the opioid induced respiratory depression, is mediated mainly by the b-arrestin signaling pathway.[14] This led to widespread proposals that the Gi signaling pathway of MOR is the good pathway that mediates analgesia and the positive effects of opioids, while the β-arrestin signaling pathway is the bad pathway that mediates most opioid induced side effects, including respiratory depression.[9] It also supported the proposal that opioid medications that specifically target the Gi pathway over the β-arrestin pathway are beneficial. It is important to know that some recent studies do not support this proposal of the β-arrestin signaling pathway mediating respiratory depression. This includes a study conducted in three labs that showed that fentanyl and morphine induced constipation and respiratory depression in β-arrestin2 knockout mice.[15]

Numerous risk factors are associated with opioids induced respiratory depression, including obstructive sleep apnea, patients with multiple comorbidities (for example: a patient with renal disease), elderly patients (older than 60 years), female sex, cardiac and neurological disease, combined usage with sedatives, chronic obstructive pulmonary disease, smoking status, multiple opioid prescribers, the first day of opioid use, and combined use with Central nervous system (CNS) depressants.[10,16] Patients with renal disease have an accumulation of opioids and their metabolites which can suppress the respiratory drive. Combining opioids with CNS depressants can lengthen opioids respiratory depression effects.[10] Though all opioids like morphine, oxycodone, fentanyl, and heroin can cause respiratory depression, some opioids have been more associated with respiratory depression than others. The most lethal one is fentanyl, which recorded close to 30,000 out of the 60,000 opioid overdose deaths in the United States in 2017.[11,17–19] Fentanyl is a potent and cheap synthetic opioid that is widely used clinically during surgeries and illegally as a drug of abuse.[19]

Studies have shown that OIRD is dose-dependent and correlates with sedation level and analgesia.[20] Studies have also shown that low doses of opioids do not change the tidal volume, while high doses of opioids decrease the tidal volume.[21] Though OIRD is dose dependent, the risk factors play a role, and the type of opioid being used also affects the occurrence of OIRD. For example, different studies have shown Fentanyl to be seventy times more potent than morphine, cause a rapid onset of OIRD, cause a lesser tidal volume, and cause rapid brain hypoxia compared to other opioids like morphine, heroin, and oxycodone.[18,19]

Orexin System and Pharmacologic Profile of Danavorexton

Orexins, also called hypocretins, are excitatory hypothalamic neuropeptides that are endogenous ligands for G-protein coupled receptors- orexin receptor 1(OX1R) and orexin receptor 2 (OX2R), which bind to orexin 1 and orexin 1 2, respectively.[22–24] Orexins are two neuropeptides, namely orexin A (hypocretin 1) and orexin B (hypocretin 2), derived

from the same precursor, prepro-hypocretin.[22] Several brain regions project to orexin neurons. The orexin neurons project to various brain areas, including intrahypothalamic innervation, noradrenergic locus coeruleus, histaminergic tuberomammillary nucleus, serotonergic raphe nuclei, dopaminergic ventral tegmental area, medial thalamus, and cholinergic basal forebrain.[22]

Orexins have been shown to affect feeding, reward processes, and the sleep/wake states. Previous studies showed that the lack of orexin led to narcolepsy (a sleep disorder) in humans, rodents, and dogs.[25,26] The orexin system mediates the waking drive and promotes wakefulness via the regulation of wakefulness-promoting monoaminergic and cholinergic hypothalamic neurons. The orexin two and orexin two receptors are linked to sleep/wake control.[24,27] This is further supported by medications like suvorexant and Lemborexant, which are dual orexin receptor antagonists. These medications are approved by the Food and Drug Administration (FDA) for the treatment of insomnia and impaired nocturnal sleep disorders.[24] A study in rats also showed that orexin neurons fire during wakefulness but not during sleep.[1]

Since studies have shown that the orexin system is involved in the sleep/wake states, medications have been developed to either promote wakefulness by being agonists of the orexin system or promote sleepiness by being antagonists of the orexin system.[2,24] Some studies have also shown that activation of orexin 2 receptors enhances respiratory function and preserves the analgesic effects of opioids.[3] One such medication is Danavorexton (TAK-925). Danavorexton has been used in mice- both wild-type and narcolepsy-model, humans with narcolepsy type 1 and 2, primates, and healthy men. In all these subjects, danavorexton has been a wakefulness-promoting agent. Danavorexton produces its effect via its mechanism of action as an orexin 2-receptor selective agonist.[2] It binds to the orexin two receptor, which stimulates inositol phosphate. This leads to calcium activation, arrestin recruitment, and Extracellular signal-regulated kinases 1 and 2 (ERK1/2) phosphorylation.[28] Danavorexton is administered as intravenous infusions in most studies. A study administered 11mg as low-dose and 19mg as high-dose. Its plasma concentration is proportional to the dose administered and plateaus at 3–4 hours of infusion start. It also has reduced clearance in older patients.[3,29]

Danavorexton has been shown to treat narcolepsy type 1 and narcolepsy type 2.[2] Narcolepsy is a rare sleep disorder characterized by severe sleepiness. It can be either type 1 or type 2. Type 1 narcolepsy has undetectable levels of orexin-1 in the cerebrospinal fluid (CSF) and is characterized by excessive daytime sleepiness, disrupted nocturnal sleep, hypnagogic/hypnopompic hallucinations, sleep paralysis, and cataplexy, while type 2 narcolepsy has normal orexin A CSF levels and shares a lot of type 1 features except cataplexy.[30] In a study on mice with type 1 narcolepsy, treating them with danavorexton for 7 days prevented the occurrence of cataplexy in these subjects. Danavorexton also increased the mean sleep latency in human subjects with narcolepsy by up to 40 minutes.[2] Danavorexton is also an arousal agent that promotes recovery from anesthesia. It also promotes opioid sedation recovery in animals without compromising the analgesic effects of opioids.[28]

Different Pharmacologic Strategies for Reversing Opioid-Induced Respiratory Depression and Sedation

Opioids are indispensable in the field of anesthesia, but their extensive side effect profile often results in complications in perioperative settings. Commonly considered the most important adverse effect, respiratory depression leads to the greatest morbidity and mortality.[31–33] A study found that of 92 cases of OIRD 22% suffered anoxic brain injury, with 55% of cases resulting in death.[32] With the ubiquity of opioids for analgesia in the perioperative setting alongside their tendency to cause adverse events, numerous agents have been proposed to reverse OIRD.

Naloxone remains the gold standard for the reversal of opioid induced respiratory depression; however, it has its own limitations. Naloxone is a non-selective competitive inhibitor of the MOR with a rapid onset of action (6.5 minutes) and relatively short half-life (33 minutes).[31,34] While rapid onset is desirable, a short half-life offers the possibility of renarcotization by any opioid with a half-life greater than its own.[31] Naloxone's non-selective targeting of MORs also has the unwanted effect of reversing opioid-induced analgesia.[12] In the perioperative setting, this leaves patients in immense discomfort. Thus, the search remains underway to find an agent that reverses OIRD and sedation without affecting analgesia.

One promising approach for maintaining analgesia while reversing OIRD is the use of agents that stimulate respiration and can be administered alongside opioids. These respiratory stimulants act on various receptors, allowing MORs to maintain their analgesic action.[31,35]

Serotonin (5-HT) has been shown to modulate respiratory neurons in the pre-Botzinger complex via the actions of 5-HT receptors ($5\text{-HT}_{1A/7}$, 5-HT_{2}, 5-HT_{4}, 5-HT_{7}).[31,36] 5-HT receptor stimulation enhances the activity of these respiratory neurons, thereby stimulating breathing, without affecting opioid induced analgesia.[12,33] A study found that coadministration of the 5-HT_{4} agonist, BIMU-8, when admisitered to fentanyl-induced apneic rats, resulted in recovery of respiratory minute volume (RMV) (70.6 ± 18.1% of baseline RMV) without significant effect on antinociception.[36] BIMU-8 however, is not available for human use at this time. A surrogate $5\text{-HT}_{4(a)}$ agonist, mosapride, revealed poor efficacy in a human trial; mosapride administration in morphine-induced respiratory depression yielded no effect on ventilatory response but did preserve analgesia.[37] Currently the lack of agonists with specificity to individual 5-HT receptor subtypes limits future clinical trials.

Ampakines are an allosteric modulator of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. AMPA receptors are transmembrane receptors for glutamate throughout the CNS, and being present in the pre-Botzinger complex, play a role in stimulating respiratory drive.[12] It was found that in fentanyl-induced respiratory depression in rats, administration of the ampakine CX546 resulted in significant recovery of respiratory rate with persistence of analgesia.[38] A study of the ampakine LXC001 in mice resulted in similar recovery of respiratory rate but also revealed that LXC001 may have dose dependent analgesic effects independent of opioids.[39] In 2016, stage 2 clinical trials were underway to examine the ampakine, CX1739's effectiveness in humans, however this trial has not yet concluded.[12] A human trial of CX717 revealed partial improvement in all respiratory parameters when administered prior to alfentanil.[31] Presently, while animal trials are abundant, ampakines have yet to undergo extensive human trials and lack safety and toxicity studies.

Doxapram has a heavily contested mechanism. One leading hypothesis is the involvement of K2P channels present in type 1 glomus cells of the carotid bodies.[12] A dose-dependent relationship seems to exist between doxapram and stimulation of respiration. At low doses, doxapram is found to act at the carotid bodies, while at high doses, doxapram acts on medullary neurons.[12] Doxapram administration in rabbits resulted in increased tidal volumes and a decrease in PCO2 following morphine injection, with no observed effect on analgesia.[40] A human trial revealed a short half-life (3 minutes) following a single dose, with benefits to respiratory rate ceasing after 15 minutes.[34] This short half-life introduces risk for renarcotization, similar to that of naloxone. In another human trial, continuous infusion of doxapram during alfentanil-induced respiratory depression resulted in dose-dependent increased clearance of alfentanil due to doxapram's analeptic effect of increased cardiac output.[34] This increased clearance did not result in reversal of OIRD.[34] Doxapram's considerable side-effect profile of headache, nausea/vomiting, hypertension, sweating, flushing, muscle spasms, and panic attack significantly limits its clinical use.

A comparison of the different pharmacologic strategies is provided in Table 1.

Clinical Applications of Danavorexton in the Perioperative Setting

Danavorexton is a promising adjunct to opioids in the perioperative setting. A clinical trial of 13 healthy male participants found that, when compared to placebo, administration of high dose (19 mg over 90 minutes) intravenous danavorexton in remifentanil-infused patients (titrated to achieve 30–40% depression of minute volume) yielded an increase in both minute and tidal volumes (8.2 L/min, 312 mL/min, respectively).[3] In the same study, high dose danavorexton was found in increase patients' RASS and VAS scores without changing pain tolerance.[3] With these findings and their potential generalization to other opioids, danavorexton may prove invaluable in post-anesthesia care through accelerated PACU recovery and decreased occurrence of postoperative adverse events. While optimistic for its future, Danavorexton currently has a few barriers to implementation. Due to limited perioperative trial data, FDA approval remains distant, and IV administration may pose logistical challenges to future studies.

Table 1 Pharmacological Strategies for Reversing Opioid-Induced Respiratory Depression

Author (Year)	Agent	Route of Delivery	Effect on Respiratory Depression	Effect on Analgesia	Adverse Effects	Barriers to Clinical Use
Boom et al (2012)[31]	Naloxone	Intranasal, intramuscular, intravenous	Reversal of OIRD	Reversal	Anxiety, Aggression, Nausea, Vomiting, Diarrhea, Abdominal Pain,	
Leighton et al (1989)[41] Manzke et al (2003)[33] Wang et al (2007)[36]	5-HT Receptor Agonists	Oral, intravenous, subcutaneous	No response in human trials Increase respiratory rate in animal models	Preserved analgesia	Nausea, fatigue	Lack of human trials Lack of agonists with high specificity
Dai et al (2019)[39] Imam et al (2020)[35] Ren et al (2006)[38]	Ampakines	Oral	Partial reversal in human trial Increase respiratory rate in rats	Preserved analgesia	Fatigue	Lack of human trials
Dahan et al (2018)[12] Gregoretti and Pleuvry (1977)[40]	Doxapram	Intravenous	Increase respiratory rate in human trial	Preserved analgesia	Headache, Nausea/Vomiting, Hypertension, Sweating, Flushing, Muscle Spasms, and Panic Attack	Lack of human trials IV access required Extensive side effect profile

https://doi.org/10.2147/CPAA.S575330

Research Needs

While van Lemmen et al shows promise, danavorexton must undergo further clinical trials before reaching the PACU.[34] Of available studies, danavorexton has only been evaluated in healthy males aged 23–30. Future trials need to examine the safety in adults with pre-existing conditions (COPD, OSA, HTN) as well as differing patient populations. Future trials should also examine optimal dosing of danavorexton and its hemodynamic effects on these varying patient populations. As clinical trials progress, we remain hopeful that danavorexton may serve to make perioperative patient care safer and more efficient.

Conclusion

Opioid-induced respiratory depression and sedation remain as significant challenges in perioperative practice, especially as current reversal strategies compromise analgesia and risk for re-narcotization. These challenges are particularly concerning in high-risk populations, including elderly patients, those with multiple comorbidities, and patients receiving potent opioids where even brief periods of respiratory compromise can lead to severe morbidity or mortality.

Danavorexton represents a mechanistically distinct approach that directly addresses this unmet need. Alternative pharmacologic strategies, including serotonin receptor agonists, ampakines, and doxapram, have been explored as potential options, but clinical adoption has been limited. The clinical implications of danavorexton have the potential to be significant, including improved postoperative safety, reduced need for opioid dose reduction, and accelerated post-anesthesia care unit (PACU) recovery. Danavorexton could shorten hospital stays, improve workflow efficiency, and decrease the incidence of opioid related adverse effects.

Further research is needed to validate these findings as current evidence remains limited.

Larger and diverse clinical trials are needed to confirm efficacy across different opioids and patients populations, as its only been tested on mice, healthy men, and humans with narcolepsy. It is also necessary to determine optimal dosing protocols, and assess long-term outcomes. Regulatory approval also remains pending, and logistical considerations, including the need for intravenous administration, must be addressed before widespread clinical adoption. Future research should also explore potential interactions with other perioperative medications, patient-specific risk factors, and cost-effectiveness, to fully define the therapeutic role of Danavorexton in perioperative care. Danavorexton offers a promising therapeutic option by addressing a significant unmet need in perioperative opioid management. Its unique ability to reverse OIRD while preserving analgesia presents as a potential alternative in the evolution of analgesic protocols and enhanced recovery pathways.

Compliance with Ethical Guidelines

This article is based on previous studies and contains no new studies with human participants or animals performed by any authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding or sponsorship was received for this study or publication of this article.

Disclosure

The authors report no conflicts of interest in this work.

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