# Inspire or expire: a matter of life or death

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# PART IV

# Summary and future perspectives

# CHAPTER 9

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# Summary, future perspectives and conclusions

## Summary

The opioid crisis has unfolded in distinct waves: first, a surge in prescription opioid use in the 1990s; second, a rise in heroin-related deaths starting in 2010; and currently, a dramatic increase in fatalities from synthetic opioids like fentanyl since 2013.[1] The widespread availability of potent synthetic opioids, often mixed with other substances (such as tranquillizers or stimulants) without the user's knowledge, results in more fatalities. Today, opioid use disorder is recognized as a global public health emergency, with devastating medical, psychological, social, and economic consequences. The ongoing epidemic serves as a stark reminder of the need for better healthcare provider training, more conscientious prescribing practices, and integrated approaches to pain management and harm reduction. Addiction, illicit markets flooded with ultra-potent synthetic substances, and respiratory depression create a potentially lethal triad that requires a deeper understanding to optimize prevention and adequate emergency response in opioid overdoses.

**In this thesis**, *Inspire or Expire, a Matter of Life or Death,* I focused on interrupting the fatal cascade of opioid-induced respiratory depression, apnea, and cardiac arrest. Through collaborative research with the U.S. Food & Drug Administration (FDA), I addressed critical gaps in our knowledge and evaluated strategies to reverse respiratory depression using optimized drug formulations and delivery routes (e.g., intramuscular vs. intranasal naloxone). And thereby preventing the pathophysiological cascade Opioid overdose → Irregular breathing → Respiratory depression → Hypoxia + Hypercapnia → cardiovascular collapse. These effects are often associated with loss of consciousness, severe acidosis, hypothermia and muscle rigidity. When no treatment is initiated (immediate resuscitation + naloxone), the victim might experience hypoxic brain damage or even death. The goal of my thesis was to transform the current crisis response by bridging pharmacological basic science with translational science using controlled experiments reflecting clinical practice.

The following conclusions can be drawn from these chapters:

In **Chapter 2**, we studied the application of principal component-based breath clustering for early recognition of opioid-induced respiratory depression. This pilot investigation utilized high-frequency flow sensor data from healthy volunteers who received intravenous fentanyl, resulting in apnea. By applying Principal Component Analysis (PCA) and fuzzy C-means clustering, we identified distinct breath clusters corresponding to normal breathing, compromised breathing, and impending apnea. This methodology demonstrated the potential to detect early signs of severe respiratory depression. Our findings suggest that machine

learning approaches could form the basis for advanced early warning systems, improving patient safety and intervention timing.

In **Chapter 3,** we developed an extensive pharmacokinetic-pharmacodynamic (PK/PD) framework to evaluate fentanyl-induced ventilatory depression in healthy volunteers. In this study, multiple clinical doses of fentanyl were administered during a sham surgical procedure, and key respiratory parameters such as minute ventilation and end-tidal $CO_2$ were measured. We compared three PK/PD modeling approaches: separate empirical analyses for ventilation and $CO_2$, and a physiological model that incorporated closed-loop conditions and $CO_2$ kinetics. The physiological model yielded a fentanyl potency parameter ($C_{50}$) that was significantly lower than those derived from the other models, suggesting it provides more realistic and clinically relevant estimates. These findings highlight the importance of incorporating physiological mechanisms into PK/PD modeling to better understand and predict opioid-induced respiratory depression in perioperative settings.

**Chapter 4** is a review article that examines the pharmacology of naloxone and its limitations in reversing opioid-induced respiratory depression under various scenarios. The chapter discusses the historical development of naloxone as a pure opioid antagonist and its mechanism of action. It addresses key challenges, including the limited efficacy of naloxone in reversing respiratory depression caused by long-acting or high-affinity opioids and in cases of polysubstance intoxication. The review also highlights the short half-life of naloxone and the risk of renarcotization, as well as the importance of distinguishing between opioid-induced respiratory depression and cardiac arrest. The chapter concludes by emphasizing the need for improved naloxone formulations, optimal dosing strategies, and complementary approaches to address the increasing threat of potent synthetic opioids.

In **Chapter 5**, we compared the efficacy of intramuscular (IM) versus intranasal (IN) naloxone in reversing fentanyl-induced apnea in a randomized, crossover, open-label trial. Both opioid-naïve individuals and chronic opioid users were studied. Intravenous fentanyl was administered to induce apnea. The primary outcome was the number of naloxone doses required for full restoration of breathing. Our results demonstrated that IM naloxone was more effective, requiring fewer doses and achieving faster reversal compared to IN naloxone. Pharmacokinetic analysis revealed higher peak plasma concentrations following IM administration, explaining the observed efficacy differences. These findings suggest that IM naloxone formulations may be preferable in emergency settings, particularly for high-potency synthetic opioid exposure (e.g. during mass casualty events).

**Chapter 6** addresses the question of the efficacy of intranasal naloxone for reversal of moderate respiratory depression induced by potent synthetic opioids. In collaboration with the FDA, we evaluated the effectiveness of a 4 mg intranasal naloxone spray in both opioid-naïve individuals and daily opioid users exposed to fentanyl or sufentanil. We found that intranasal naloxone restored minute ventilation within minutes, however, reversal of end-tidal $CO_2$ was delayed, especially during sufentanil exposure in opioid-naïve participants. The study was limited by its continuous opioid infusion design and high participant discontinuation due to withdrawal symptoms. Overall, the findings suggest that while a single 4 mg intranasal naloxone dose is effective for moderate opioid-induced respiratory depression, it may be insufficient for high-dose overdoses, underscoring the need for further research on optimal dosing and delivery methods.

In **Chapter 7,** we discussed mechanism-agnostic respiratory stimulants as potential alternatives for reversing drug-induced respiratory depression, particularly in cases where naloxone is less effective. This review explores four promising classes of respiratory stimulants tested in humans: potassium channel modulators acting on the carotid bodies, NMDA receptor antagonists, orexin receptor-2 agonists, and ampakines. The mechanism of action, clinical data, and limitations for each class were evaluated. The chapter concludes that while several agnostic respiratory stimulants show promise, further research should focus on optimizing dosing strategies, evaluate safety, and assess efficacy in severe respiratory depression, including apnea.

In **Chapter 8,** we studied the safety and efficacy of danavorexton (TAK-925), an orexin receptor 2-selective agonist, in reducing opioid-induced respiratory depression in a controlled phase 1 trial. Healthy male volunteers were administered danavorexton or placebo during remifentanil-induced respiratory depression. Danavorexton significantly increased ventilation, tidal volume, and respiratory rate compared to placebo, and also decreased sedation without compromising analgesic effects. In this small sample size, side effects were mild and transient. These results demonstrate that danavorexton effectively reverses opioid-induced respiratory depression and sedation, a promising new approach for managing respiratory depression in the perioperative setting.

## Future perspectives

The research presented in this thesis highlights significant advances in understanding and addressing opioid-induced respiratory depression, while simultaneously revealing critical gaps that require further investigation. As we look towards the future, several key areas emerge as priorities for continued research and development to combat the persistent challenges of the opioid crisis.

**Optimizing management of opioid withdrawal symptoms**

One of the most significant barriers to effectively reverse opioid overdose is the precipitated withdrawal following naloxone administration. Symptoms ranging from mild discomfort to severe physiological distress not only cause suffering but may also discourage bystanders from administering naloxone and can result in aggressive responses from individuals experiencing withdrawal. Current approaches to managing these symptoms clinically often rely on α2-adrenergic agonists like clonidine, and in some cases even deep propofol sedation, as described in Chapter 5 and 6.

Future research should focus on developing specific pharmacological interventions that can be co-administered with naloxone to mitigate withdrawal symptoms while similarly stimulating respiration. The development of "withdrawal-sparing" formulations that combine naloxone with agents that attenuate withdrawal symptoms could significantly improve outcomes in overdose situations. Additionally, exploration of protocols that involve titrated administration of naloxone to achieve respiratory stimulation without precipitating severe withdrawal symptoms could enhance the safety and acceptance of overdose reversal interventions.

**Advancement of mechanism-agnostic respiratory stimulants**

The limitations of naloxone in addressing respiratory depression from high-affinity opioids and polysubstance use underscore the need for mechanism-agnostic respiratory stimulants. These agents, which stimulate breathing regardless of the underlying cause of respiratory depression, represent a promising frontier in overdose management.

Potassium channel modulators like ENA-001, which act on the carotid bodies to stimulate breathing, have shown promise in human studies of moderate opioid-induced respiratory depression.[2] Furthermore, ENA-001 was able to reverse a xylazine/fentanyl-induced respiratory depression in rats.[3] However, their efficacy in severe respiratory depression and apnea remains to be established. Future research should focus on determining appropriate dosing for various depths of respiratory depression and developing formulations suitable for

community use, such as intramuscular or intranasal preparations.

Orexin receptor agonists, exemplified by danavorexton (TAK-925), have demonstrated significant potential in reversing opioid-induced respiratory depression without affecting analgesia.[4] The development of these agents should be accelerated, with emphasis on evaluating their efficacy in more severe respiratory depression scenarios and exploring their potential use in combination with naloxone. Long-term safety studies and the development of formulations suitable for both hospital and community settings will be crucial for translating this promising approach into practice.

Ampakines represent another class of respiratory stimulants that modulate AMPA receptors in brainstem respiratory networks.[5-7] While compounds like CX717 and CX1739 have shown promise in early human studies, more comprehensive safety data and efficacy assessments in deeper levels of respiratory depression are needed.[5, 8, 9] The development of ampakines specifically optimized for respiratory stimulation, rather than repurposing compounds initially developed for cognitive enhancement, could lead to more effective therapies.

Research into the combined use of different classes of respiratory stimulants, such as carotid body modulators with centrally acting agents like orexin agonists or ampakines, may yield synergistic effects that provide more robust reversal of respiratory depression with fewer side effects. Such combined approaches may be particularly valuable for addressing polysubstance overdoses involving both opioids and non-opioid respiratory depressants.

**Development of analgesics without respiratory depression**

The ultimate solution to opioid-induced respiratory depression lies in developing effective analgesics that do not compromise respiratory function. Several promising approaches are currently being pursued in this direction, offering hope for safer pain management options in the future.

Biased opioid receptor agonists represent one of the most promising approaches. These compounds selectively activate G-protein signaling pathways while minimizing recruitment of β-arrestin pathways, which are associated with respiratory depression and other adverse effects. Preclinical studies with compounds like SR-17018 have demonstrated sustained analgesic efficacy without severe respiratory compromise when given chronically to animal models.[10] Further development and clinical testing of these biased agonists could potentially revolutionize pain management by providing opioid-level analgesia without respiratory risks.

The recent FDA approval of suzetrigine (Journavx) in 2025 marks a significant milestone as the first new non-opioid analgesic on the market in over two decades.[11, 12] This development represents an important step forward, but additional novel analgesic classes are needed to address the full spectrum of pain conditions that are currently being treated with opioids. Promising targets include nerve growth factor (NGF) monoclonal antibodies, transient receptor potential vanilloid 1 (TRPV1) antagonists, and selective sodium channel blockers.

**Immunologic and supramolecular countermeasures**

The development of monoclonal antibodies (mAbs) targeting synthetic opioids, like fentanyl, represents a shift from receptor-based antagonism to molecular strategies that prevent opioids from reaching their targets. The most developed candidate, CSX-1004, is a fully human monoclonal antibody with a high affinity for fentanyl and shows a high efficacy in preclinical studies, including a first-in-human study.[13, 14] In a non-human primate model, CSX-1004 demonstrated protection against repeated fentanyl challenges for 3-4 weeks, producing up to a 15-fold reduction in fentanyl potency.[14]

Vaccination strategies against fentanyl and other opioids represent a promising approach for more long-term overdose prevention. The University of Houston has developed a fentanyl vaccine that generates anti-fentanyl antibodies capable of binding to fentanyl and thereby preventing brain entry.[15] The first human clinical trials are planned in 2025.

A final strategy is using supramolecular hosts, building on the clinical success of sugammadex for neuromuscular blockade reversal.[16] One of the drugs is Calabadion-1, which reversed fentanyl-induced respiratory depression in rats, including reversal of muscle rigidity.[17] Another compound is Subetadex-a-methyl (SBX-Me), which is a polyanionic cyclodextrin scaffold. Rat studies found that recovery times from fentanyl decreased from ~35 minutes to ~17 minutes, and from carfentanil from ~172 minutes to ~59 minutes.[18]

**To conclude**, significant progress has been made in understanding opioid-induced respiratory depression and in testing the efficacy of reversal strategies. In the future, the evolving opioid crisis demands continuous innovation in both reversing overdoses and preventing them.

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