

# REVIEW ARTICLE

## Risk factors for prolonged opioid use and adverse events following orthopedic surgery

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### Abstract

Over the past few years, the field of opioid research has been aimed at targeting the opioid crisis affecting communities across Canada. One way that health care workers have been contributing to this field is by identifying risk factors that predispose patients to prolonged opioid use. Given opioids have long been used for post operative pain control in orthopaedics, this article aims to address some of the more common and severe risk factors seen in orthopedic surgery patients. Included with each of the risk factors are potential mitigation strategies to reduce the risk of opioid dependence or adverse effects, including medication interactions.

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### Background

Opioids have been used for thousands of years, both for medication as well as other cultural purposes. Over the years, the opium poppy has been referred to by a number of names, including the “Joy Plant” by the ancient Sumerians, and has been widely praised for its analgesic effects. Over the past 150 years, however, an extensive number of opioids have been synthesized in labs, facilitated by the advent of the hypodermic needle in the 1850s<sup>1</sup>.

The first documented cases of opioid addiction can be traced back to the 16th century in western, Arabian, and Chinese cultures. In the United States, opioid addiction was previously known as “the soldier’s disease” due to the use of morphine in Civil War soldiers who subsequently became addicted. For years, drug manufacturers have been trying to develop non-addictive opioids. In fact, some of the most popular opioids used today including hydromorphone (Dilaudid) and oxycodone (OxyContin) were originally marketed as non-addictive alternatives for morphine<sup>2</sup>.

The use of opioids is associated with a number of very common side effects including sedation, dizziness, anorexia, and nausea/vomiting. It is also associated with more severe, and potentially life-threatening side effects such as respiratory depression and hypotension<sup>3</sup>. Naloxone is a competitive opioid antagonist used to treat opioid overdose, including the associated respiratory depression, the incidence of which appears to be highest within the first 24-hours after surgery<sup>4,5</sup>.

In Nova Scotia, opioid-related death rates are

among the lowest in the country, lying approximately 75% below the national average<sup>6</sup>. In 2020, approximately 45 Nova Scotians died from opioid overdoses, down from 57 the year before<sup>7</sup>. Since 2011, benzodiazepines have contributed to ~56% of the opioid-related deaths in the province, and anti-depressants to another 21%<sup>8</sup>. Importantly, despite the fact that Nova Scotia has relatively low rates of opioid deaths, it is estimated that in over 90% of these deaths, victims received their opioids from pharmaceutical sources (e.g. prescriptions)<sup>6</sup>. This emphasizes the need for health care professionals to closely examine their prescribing habits and tailor them to the individual patient.

Orthopedic surgery has been previously identified as a significant contributor to the overall number of opioid prescriptions in the United States, with orthopedic surgeons contributing upwards of 10% of opioid prescriptions in 2009<sup>9</sup>. For the most part, these prescriptions are written by residents, and there has been growing concern over the lack of education new physicians are receiving in this regard<sup>10-13</sup>. In addition to this, it appears as though a large proportion of patients are not disposing of their leftover medication properly, further contributing to the number of opioids in the community<sup>14-17</sup>.

There are several risk factors that have been associated with prolonged opioid use and adverse events following orthopedic surgery including, but not limited to anxiety and depression, pre-/perioperative opioid use, alcohol misuse, and larger discharge prescriptions. Others that should be noted, but will not be further discussed here include increased BMI, age under 65,

lower socio-economic status, and a history of chronic pain<sup>18–20</sup>. The aim of this article is to provide an overview of these risk factors and discuss ways to minimize the potential for harm and/or abuse.

### Anxiety and Depression

Of all of the risk factors predicting prolonged opioid use after orthopedic surgery, anxiety and depression are by far the two most common<sup>20–23</sup>. While the pathophysiology of these illnesses is not well understood, it is generally accepted that they are the result of neurotransmitter imbalances, leading to changes in emotion and subsequent physiological changes including fatigue, difficulty concentrating, and insomnia<sup>24</sup>. The link between opioids and anxiety has been studied since the 1970s and a considerable body of research demonstrates that opioids have potent anxiolytic effects in people with anxiety, thus it is not surprising that this population would be more prone to consuming opioids after their prescription has run out due to the symptomatic relief caused by opioids<sup>25</sup>. Furthermore, the presence of opioid receptors in the amygdala supports this idea and introduces a potential mechanism as this region of the brain is linked to fear and anxiety<sup>26</sup>. Patients going through opioid withdrawals tend to be more prone to panic attacks, a phenomenon that can be mimicked through the use of naloxone in healthy patients<sup>27,28</sup>. Taken together, this suggests a close-knit relationship between opioid signalling and anxiety.

Opioids have been studied as treatments for depressive episodes since around the late 19th century due to the euphoria that is associated with their use<sup>29</sup>. The general consensus surrounding this is that patients/animals with depression show diminished endogenous opioid signalling compared to healthy individuals<sup>30</sup>. This means that these patients may be more prone to long-term opiate use in an attempt to replace signalling that has been lost due to their illness. On top of this, opiate use at the time of a traumatic response is known to impair memory consolidation, and prolong the emergence of depressive symptoms after a traumatic experience, such as surgery<sup>30</sup>.

Two common medication classes used to treat anxiety and depression include benzodiazepines (BZDs) and Selective Serotonin Reuptake Inhibitors (SSRIs)<sup>24</sup>. BZDs may enhance the depressant effects of opioids, including respiratory depression, and increase the risk of death four-fold, so patients should be given the lowest possible opiate dose to achieve therapeutic benefit<sup>31</sup>. In this case, immediate release opioid formulations are preferred. These patients should also be counselled on the use of naloxone. Opioids are currently contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or who have ceased MAOI use within the

past 14 days due to the increased potential for serotonin syndrome, as certain opioids are known to inhibit serotonin transporters<sup>3</sup>.

### Pre-/Perioperative Opioid Use

Another major risk factor for prolonged opioid use following orthopedic surgery is pre-operative opioid use<sup>21,22,32</sup>. This is likely because reward pathways associated with opioid use have already been activated for extended periods of time, thus increasing the likelihood that these patients will continue using opioids long-term. Research has also shown that patients with more frequent pre-operative opioid dosing were between 2-12 times more likely to exhibit prolonged opioid use, depending on their pre-operative dose<sup>33</sup>. In terms of mitigation strategies, chronic pre-operative opioid users should have a discussion with their surgeon to determine the lowest dose needed to provide analgesia, keeping in mind they may require a higher dose than opioid-naïve patients. Extra care should also be given to re-iterate the importance of educating on naloxone use for anyone using chronic opioid prescriptions.

When it comes to peri-operative opioid dosing and prolonged opioid use, the mechanism is much less understood. Currently, opioids are used during surgery to both reduce the dose of anesthesia required for sedation as well as for prophylactic pain control<sup>34</sup>. In terms of peri-operative risk management, other analgesics, such as high-dose acetaminophen have proven to be effective in reducing post-operative opioid consumption and nausea/vomiting with a potentially significant reduction in pain<sup>35,36</sup>. The reason that high dose acetaminophen reduces post-operative opioid consumption may, in fact, be the same reason why peri-operative opioid use is a risk factor for prolonged post-operative opioid use in the first place. A recently published narrative review examining medication adherence determined that in 6 out of the 10 studies included in the review, having prior exposure to a medication made patients more likely to use that medication in the future when given the choice<sup>37</sup>.

### Alcohol Misuse

The third risk factor of importance is alcohol misuse<sup>20,38,39</sup>. In Canada, it is estimated that upwards of 1 in 5 adults would fit the definition for “problematic drinking”, so understanding this interaction is important in treating pain in patients with alcohol use disorders<sup>40</sup>.

The interactions between alcohol and opioids are two-fold. Firstly, both of these drugs are central nervous system (CNS) depressants, therefore use of alcohol and opioids increases the risk of respiratory depression and other serious side effects<sup>41</sup>. Second, alcohol and opioids

are known to activate similar pathways within the body, conferring analgesic and euphoric effects in the short term, and therefore activating similar reward pathways in the brain. Furthermore, acute alcohol withdrawal is known to cause hyperalgesia, resulting in a cycle of pain and pain relief, so by consuming opioids, patients would be able to circumvent some of the unwanted symptoms of alcohol withdrawal<sup>42</sup>. While the exact proportion of patients who use opioids and alcohol concurrently is currently unknown, the most recent estimate as of 2020 is approximately 20% of opioid users<sup>43</sup>. People who regularly consume alcohol are more likely to then consume opioids, a phenomenon that would be facilitated by the administration of post-operative opioids following surgery<sup>44</sup>.

Given the increased risk for respiratory depression and other serious side effects, alcohol and opioid co-administration should be considered carefully. Patients should be encouraged to avoid alcohol while taking opioids, however, they should also be made aware of overdose symptoms, such as excessive sedation and respiratory depression. Again, special consideration should be made regarding naloxone training. Patients being treated for alcohol use disorder can safely take opioids as they do not interact with disulfiram, acamprosate, or ondansetron<sup>3</sup>.

### Discharge Prescription/Opioid Reducing Protocols

An additional consideration when it comes to prolonged opioid use is the amount of opioids a patient receives at discharge. There has been a considerable amount of recent research into this topic. The general consensus is that surgeons/physicians are prescribing more medication than is necessary for patients, with upwards of 50-80% of the pills going unused<sup>45-47</sup>. Currently, the American Academy of Orthopedic Surgeons recommend no more than 400 morphine milligram equivalents (MMEs) following orthopedic surgery which is equivalent to 50 tablets of hydromorphone (Dilaudid) 2mg<sup>48</sup>. This is in stark contrast to what has been happening in the US, where the average discharge prescription is up to double the recommended amount. However, in more recent years, there has been a steady decline in opioid prescribing<sup>48,49</sup>. Originally, it was thought that larger discharge prescriptions would result in fewer refills, thus saving time, however this appears to not be the case and as previously mentioned, many patients do not know how to properly dispose of leftover medication<sup>50-52</sup>. Because of this, patients can use these pills for other purposes, including non-surgical pain, where opioids may not be indicated, leading to an increased risk of prolonged use, and inappropriate use by other members of the household.

Given the ongoing opioid epidemic, there has been growing interest in developing opioid reducing protocols around the world. Some states in the US, such as Florida, have introduced laws restricting the amount of opioids a patient is allowed to be prescribed<sup>49</sup>. While the methodologies and protocols tend to vary greatly, most opioid sparing protocols were able to reduce the number of opioids prescribed at discharge by 50-75%. This, in turn, has been associated with fewer refills and fewer leftover pills, with no decrease in patient satisfaction or increased pain levels<sup>49,50,53,54</sup>. In Canada, most provinces have a prescription monitoring program (PMP) or drug information system (DIS) which allows healthcare workers to monitor patients' prescriptions province-wide.

### Risk Factors for Adverse Events

Opioid prescribers should also be aware of which patients are at an increased risk for severe adverse events, namely respiratory depression. Medications that might increase a patient's risk of opioid induced adverse events can be classified into to major categories: sedatives and other CNS depressant drugs, as well as those that can cause constipation due to additive effects. There are also various medical conditions that may predispose a patient to higher rates of respiratory depression and those include pre-existing cardiac disease, respiratory diseases (including asthma and chronic obstructive pulmonary disease), smoking, renal disease, and obstructive sleep apnea<sup>3</sup>. Patients are also typically prescribed a laxative when taking opioids, however, depending on what other medications they are currently taking, they may require a dosage adjustment.

### Conclusions

There are a number of risk factors associated with prolonged opioid use following orthopedic surgery and while not be an exhaustive list, this article presents the most common and critical risk factors. Also presented are mitigation strategies to reduce the risk of developing an opioid use disorder as well as adverse effects. With the ongoing opioid epidemic, it is important for health care workers, especially those working with post-operative patients, to stay up to date with current opioid prescribing guidelines. Given the complex interaction involving opioids, it is also important to keep in mind the concept of patient-oriented care, and tailor prescriptions to the individual patient rather than the surgical procedure.

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