

REVIEW

The opioid epidemic:

How did we get here and where do we stand?

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Background

For the last 5000 years opioid medications derived from the opium poppy have been utilized by various cultures for their analgesic properties. Over the last 2000 years opioids have become a cornerstone in the management of moderate to severe pain. As the use of these medications has become more widespread, it has become apparent that their beneficial properties might be overshadowed by their potential downsides.¹

Western, Arabian, and Chinese cultures have described cases of opioid addiction following opioid use dating back to the 16th century.² This frightening trend of opioid addiction subsequent to using opioids for their analgesic properties has persisted to the present day where it has reached epidemic-level proportions. As pharmaceutical companies became aware of this problem, they were quick in attempting to develop opioid medications that possessed the same analgesic properties but lacked addictive potential. Drugs such as meperidine, oxycodone, hydrocodone, methadone and oxycodone were all developed and originally marketed as opioid medications lacking addictive potential.²

Unfortunately, evidence has shown that each of these drugs possess a high addictive potential. During the 1980s, prescribing of opioid analgesics skyrocketed, in part due to this misinformed marketing.^{3,4} At the heart of this prescribing surge were two articles: one by Porter and Jick³ entitled "Addiction rare in patients treated with narcotics" and another by Portenoy and Foley⁴ entitled "Chronic use of opioid analgesics in non-malignant pain: report of 38 cases". Both of these articles demonstrated the safety of opioids in treating acute and chronic pain while largely downplaying the dangers associated with opioid use, namely their abuse and lethal potential. Pharmaceutical companies frequently cited these papers, using them to convince physicians of the safety of opioid analgesics in treating patients' pain. The strategy worked – opioid sales increased dramatically. Further fuelling the opioid prescription surge was the awareness of pain as the "5th vital sign". This idea was first presented by Dr. James Campbell in 1995 and led to patients' pain being regularly evaluated, often by physicians with no experience in pain management.⁵ Pain is often assessed using the Numeric Rating Scale (NRS) wherein patients rate their pain from 0 to 10 (0 = no pain; 10 = the worst possible pain). If non-steroidal anti-inflammatory

drugs (NSAIDs) and acetaminophen were ineffective for patients with significant pain on the NRS, they would often be prescribed opioids to relieve their pain. Opioid prescriptions were often guided by both a lack of education surrounding pain management, but also the ease of writing a prescription when physicians had little time to spend with their patients. Prescriptions of opioids increased dramatically as physicians aimed to normalize their patients' 5th vital sign.⁵ Unfortunately, this surge in opioid prescriptions also led to increases in opioid diversion, abuse, addiction, and frequently, overdose. Indeed, opioid overdose death rates increased 5-fold between 1980 and 2008 in the US.² Interestingly, this increased opioid prescribing rate did not lead to a reduction in patients' pain scores.²

Research has shown that opioid use is associated with immunosuppression, opioid-induced endocrinopathy, and paradoxical opioid-induced hyperalgesia.⁶ Furthermore, there are a myriad of side effects associated with opioid use, including (but not limited to) sedation, constipation, delirium and respiratory depression. Opioid-induced respiratory depression - leading to hypoxemia and ultimately cardiorespiratory arrest - is the primary cause of mortality associated with their use and is potentiated by various pulmonary conditions and the combined use of other CNS depressants.⁶ In light of more recent literature regarding the dangers of opioid use, the quantity of opioids dispensed in Canada (as measured by defined daily doses - DDDs) has declined from 238 million in 2012 to 226 million in 2016.⁸ Of note, although the number of DDDs has decreased, the overall number of prescriptions has increased from 20.2 million in 2012 to 21.5 million in 2016. While there is no national data available prior to 2016, opioid-related deaths in Ontario have ballooned from 366 in 2003 to 865 in 2016. A similar trend is seen in Quebec, where deaths have escalated from 62 in 2005 to 133 in 2015.^{7,8} Furthermore, the trend is moving east with Nova Scotia averaging 60 acute opioid toxicity deaths per year between 2011 and 2017 (Figure 1).⁹ This would suggest that though the number of pills dispensed has decreased, the number of opioid prescriptions and opioid-related deaths have increased.

Opioid Use

Opioid prescriptions in the US have increased 4-fold since 1999, the most commonly prescribed medications

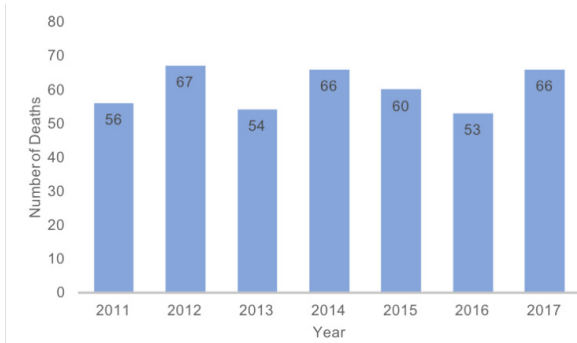


Figure 1: Number of opioid deaths in Nova Scotia between 2011 and 2017⁹

being oxycodone and hydrocodone. Notably, these are also the medications most commonly associated with opioid-related deaths.⁶ It has been shown that following low-risk surgery, up to 80% of patients are prescribed opioids for analgesia; 80% of which are oxy- or hydrocodone.⁶ As their pain dissipates, patients frequently keep their leftover medication instead of properly disposing of them.⁶ This behaviour, coupled with opioid over-prescribing, has contributed to the observed increase in opioid diversion, abuse and addiction. Several risk factors for chronic opioid use following surgery in the opioid naïve patient have been identified. These include: male sex, age >50, preoperative use of benzodiazepines and/or antidepressants, history of depression, history of alcohol/drug use, low socioeconomic status, and preoperative pain.⁶ Moreover, chronic opioid use does not only impact the patient. Leftover medications are often given to family or friends to treat their pain, laying the groundwork for a new cycle of misuse. A dramatic increase in opioid-related motor vehicle

fatalities, from 0.1% of all motor vehicle fatalities in 1995 to 7.2% in 2015, demonstrates that opioid use can continue to affect lives outside of those related to the patient.^{6,11}

The problem of opioid abuse recently reached a peak in 2014, when more individuals in the US died from drug overdoses than any other year on record and greater than 60% of these deaths involved opioids. As a result, the US Centers for Disease Control and Prevention released a compilation of 12 evidence-based guidelines for physicians prescribing opioid analgesics for chronic pain:¹²

Determining when to initiate or continue opioids

1. Opioids are not first-line therapy
2. Establish goals for pain relief and function
3. Discuss risks and benefits

Opioid selection, dosage, duration, follow-up, and discontinuation

4. Use immediate-release opioids when starting
5. Use the lowest effective dose
6. Prescribe short durations for acute pain
7. Evaluate benefits and harms frequently

Assessing risk and addressing harms

8. Use strategies to mitigate risk
9. Review Prescription Drug Monitoring Program (PDMP) data
10. Use urine drug testing
11. Avoid concurrent opioid and benzodiazepine prescribing
12. Offer treatment for opioid use disorder

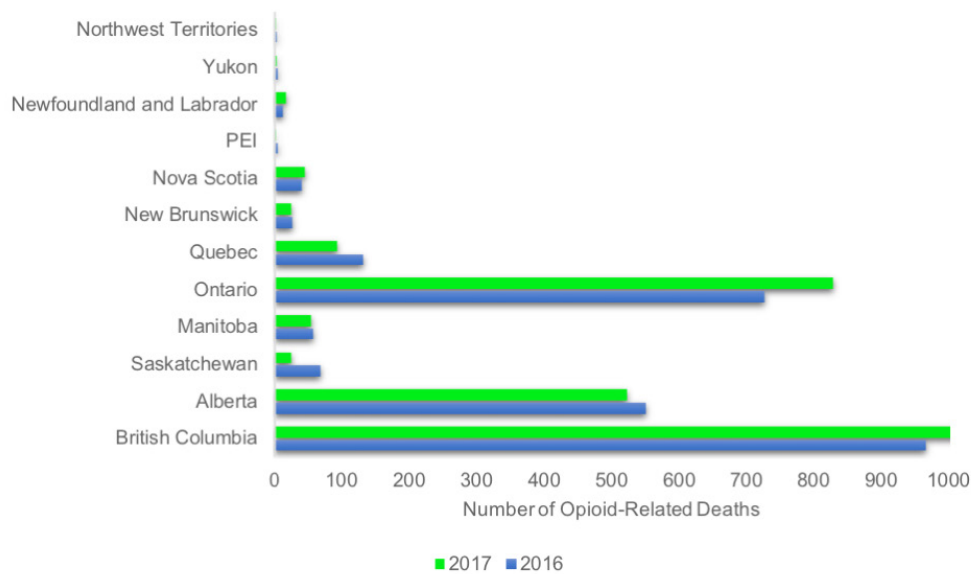


Figure 2: Number of opioid-related deaths by province in 2016 and 2017¹⁰

As previously mentioned, opioid analgesia may often fail as an intervention for chronic pain despite increasing dosage. This is due in part to the complexity of the condition. Chronic pain can be altered by several comorbid factors including depression, anxiety, poor coping skills, personality, sleep, and concurrent substance use disorders.^{13,14} The presence of chronic pain may exacerbate a patient's psychiatric, functional, and social difficulties, all of which can act to influence their opioid use. The importance of this cannot be understated as it demonstrates that chronic pain may best be treated using a multimodal approach in contrast to increasing opioid dosages.^{13,14}

Addressing the Opioid Crisis

1) Use of Opioid Adjuvants and Alternatives

The use of non-opioid adjuvants has recently gained traction as an option to reduce perioperative opioid use. These include non-opioid adjuncts (acetaminophen and NSAIDs), nerve blocks and block additives, among others. Kumar et al. describe several non-opioid adjuvants, some of which are outlined below.¹⁵ It should be noted that some opioid adjuvants also have significant abuse and diversion potential (most notably ketamine). Their use should be monitored accordingly:

1. Dexmedetomidine – an α_2 adrenoreceptor agonist. Dexmedetomidine possesses central antinociceptive activity thought to be mediated through α_2 stimulation in the dorsal horn. A 0.5-1 $\mu\text{g}/\text{kg}$ bolus \pm intraoperative infusion has been shown to decrease opioid consumption for 24 hours postoperatively, without a concurrent increase in patient pain scores.
2. Clonidine – also an α_2 adrenoreceptor agonist. Clonidine is primarily used as an antihypertensive medication but has also been shown to reduce opioid consumption for 24 hours postoperatively.
3. Ketamine – an N-methyl-D-aspartate (NMDA) receptor antagonist that decreases nociceptive transmission. Low-dose intravenous ketamine following surgery has been shown to reduce opioid use by 40%
4. Dextromethorphan – also an NMDA receptor antagonist. Perioperative administration (40-120 mg IM or 30-200 mg oral) of dextromethorphan has been shown to decrease pain up to 24 hours following surgery and morphine use for up to 48 hours.
5. Duloxetine – an oral serotonin-norepinephrine reuptake inhibitor (SNRI). Duloxetine elicits its antinociceptive effects by modulation of the descending inhibitory pain pathways. Several studies have demonstrated that its perioperative

use can decrease opioid consumption following surgery for up to 48 hours, though it does not alter pain perception.

6. Lidocaine – when administered intravenously, a bolus of lidocaine (1-3 mg/kg) followed by an infusion (1-2 mg/kg/h) can lower pain scores for up to 24 hours following surgery and decrease perioperative opioid use. It is currently recommended as part of the Enhanced Recovery After Surgery (ERAS) intraoperative protocol, particularly when epidural analgesia is not used.

In addition to the use of non-opioid adjuvants, the use of nerve blocks with or without general anesthesia has been associated with decreased perioperative pain scores and opioid usage.^{15,16} For example, continuous interscalene blocks have been shown to have a prolonged analgesic effect for up to 24-48 hours postoperatively, working to reduce opioid consumption. Additionally, patients undergoing hysterectomy who received an epidural reported lower postoperative opioid consumption and pain scores in comparison to those who underwent general anesthesia. Block additives, such as dexamethasone and clonidine, can work to increase the efficacy of nerve blocks by significantly increasing the duration of action of the block, helping to further reduce opioid consumption and patient pain scores.^{15,16}

As mentioned above, chronic pain can be modulated by several comorbidities, including depression, smoking and anxiety.^{13,14} For individuals with a history of these conditions, Hah et al suggest that these patients may benefit from preoperative and ongoing postoperative cognitive behavioural therapy (CBT) in order to help curtail the risk of opioid abuse and misuse.⁶ Furthermore, Vetter et al suggests the implementation of a Transitional Pain Service (TPS), where applicable.¹⁷ The TPS is a longitudinal program pioneered at Toronto General Hospital which focuses on at-risk and vulnerable surgical patients who are without adequate support for pain management. Participants in the program must meet the following criteria: a) history of chronic pain; b) previous or current psychological comorbidities; and c) be consuming large amounts of opioids either pre- or post-operatively. As such, the goal is to tackle the issues of chronic pain and opioid use pre- and post-operatively. Patients enrolled in TPS programs are treated with conventional pharmacotherapy, such as gabapentinoids and tricyclic antidepressants (TCAs), in addition to perioperative psychological and holistic treatments. Teams involved with TPS are large, multidisciplinary teams composed of an anesthesiologist/pain medicine specialist, internal medicine hospitalist, addiction medicine specialist,

pain psychologist, licensed social worker, and advanced practice registered nurse. The aim of TPS is to aid those patients who are at high risk of long term, excessive opioid consumption and in turn, limit opioid abuse, addiction, and diversion.¹⁷

2) *Naloxone in Managing Acute Overdose*

Now synonymous with opioid overdose, Naloxone (allyl-noroxymorphone) was first recognized in the early 1960s. Before then opioid overdose was treated with levallorphan, a compound that, itself, could cause respiratory depression at high doses. When allyl-noroxymorphone treatment was compared with levallorphan, it was found to be 2-6 times as potent and also did not cause respiratory depression or any other unpleasant side-effects even at high doses.¹⁸ Further studies have demonstrated the risk of several side-effects, including pulmonary edema, seizures, arrhythmias and hypertensive crisis. It is difficult, however, to determine if these side-effects are caused by the administration of naloxone, the underlying disease processes, or other drugs that have been ingested or administered.^{19,20} Overall naloxone is considered a safe and effective treatment for opioid overdose.²⁰

Since then, naloxone (commonly sold in Canada under the trade name Narcan) has become a staple in the treatment of opioid overdose. Naloxone was first distributed to heroin users in 1995 in Germany and England,²¹ with community opioid overdose prevention programs following soon after, rapidly becoming commonplace in North America and Europe.²² These programs, aimed at teaching members of the community about recognizing and responding to opioid overdose, typically included a few core components: recognizing the signs of overdose, strategies to prevent overdose, risk factors for opioid overdose, appropriate response to opioid overdose, and how to administer naloxone in the event of an overdose.²² These programs have been shown to increase bystander knowledge of prevention, risk factors and recognition of opioid overdose. Further, there is evidence that the use of these programs increases the bystander use of appropriate overdose strategies.²² One study, performed in Massachusetts between 2006 and 2009, evaluated the correlation between implementation of their Overdose Education and Naloxone Distribution (OEND) programs and the rate of opioid related deaths from overdose. They found that regions implementing OEND programs were associated with lower rates of opioid related deaths from overdose when compared with regions with no OEND implementation.²³

In many provinces in Canada, Naloxone kits are available free of charge to those at risk of an opioid overdose or those who may witness an overdose.²⁴⁻²⁷ In

Nova Scotia, and several other provinces, individuals must complete a brief training session prior to obtaining the kits, the content of which is akin to the aforementioned prevention programs.²⁴ Emergency departments across North America have also developed their own opioid overdose protocols and varying naloxone dosages, the details of which are beyond the scope of this article.¹⁹ This demonstrates that life-saving methods that are used in emergency departments can also be employed in a similar way for overdoses that occur in the community.

Providing education and treatment for opioid overdose in the community is an important step in combating the sequelae of the opioid epidemic on the front lines. Reduction in fatal overdose rates in regions with access to overdose education and treatment methods has shown early promise. Though the rates of fatal overdoses have declined in these areas, the core of the opioid issue must be tackled from higher powers, including governmental bodies and the medical institution as a whole.

3) *Current Strategies to Manage the Opioid Epidemic*

In 2010, the National Pain Centre at McMaster University developed the original Canadian Guideline for Safe and Effective Use of Opioids for Non-Cancer Pain.²⁸ This guideline outlined several important recommendations for physicians to adhere to when prescribing opioid medication in order to help prevent adverse outcomes. Given more recent research surrounding opioid prescribing, an updated version of the guideline titled “The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain” was released by the National Pain Centre at McMaster University in 2017. The updated document outlines the following ten recommendations for opioid-prescribing physicians:²⁹

1. Pain in patients with chronic non-cancer pain should be addressed by optimization of non-opioid pharmacotherapy and non-pharmacologic therapy in place of opioid therapy (strong recommendation).
2. Patients with chronic non-cancer pain, who have persistent problematic pain despite optimized non-opioid therapy, can be trialled on opioid therapy (weak recommendation).
3. Opioid therapy is advised against in patients with chronic non-cancer pain with an active substance use disorder (strong recommendation).
4. In patients with an active psychiatric disorder and chronic non-cancer pain, who have persistent problematic pain despite optimized non-opioid therapy, it is suggested that the psychiatric disorder be stabilized prior to trialling opioid therapy (weak recommendation).

5. In patients with chronic non-cancer pain with a history of substance use and persistent pain despite optimized non-opioid therapy, it is suggested that physicians continue non-opioid therapy rather than trialling opioid therapy (weak recommendation)
6. In patients with chronic non-cancer pain beginning opioid therapy, it is suggested that prescribed doses remain less than 90 mg morphine equivalents per day (strong recommendation).
7. In patients with chronic non-cancer pain beginning opioid therapy, it is suggested that prescribed doses remain less than 50 mg morphine equivalents per day (weak recommendation).
8. In patients with chronic non-cancer pain currently using opioid therapy, it is suggested that physicians rotate to other opioids if pain persists rather than keeping the opioid the same (weak recommendation).
9. In patients with chronic non-cancer pain currently using ≥ 90 mg morphine equivalents daily, it is suggested that opioids be tapered to lowest effective dose, potentially including discontinuation (weak recommendation).
10. In patients with chronic non-cancer pain currently using opioids and experiencing challenges in tapering, a formal multidisciplinary program is recommended (strong recommendation).

Since the publication of these guidelines in the Canadian Medical Association Journal in May of 2017, they have been adopted by the majority of medical colleges across Canada; in British Columbia, Alberta, Ontario, and Nova Scotia.³⁰⁻³³ In addition to these guidelines, many provinces are taking further steps to address the opioid crisis. Examples include the implementation of harm reduction programs in Alberta, development and implementation of Prescription Monitoring Programs in New Brunswick and Newfoundland and Labrador, and the development of further evidence-based standards regarding opioid prescribing in Ontario.³⁴⁻³⁷ The hope is that with the advent of these guidelines, physicians will have a framework for decisions surrounding opioid prescribing.²⁹ Further, implementation will ultimately lead to decreases in opioid abuse, diversion and dependence.

In 2017, the Association of Faculties of Medicine of Canada (AFMC) concluded that pain, addiction to pain medication and medical management of pain were not adequately addressed in either the undergraduate or postgraduate Canadian medical curricula.³⁸ Following this observation, AFMC has begun the process of developing and implementing a curriculum addressing these deficiencies. Key aspects of the curriculum

would include: the diagnosis and assessment of pain; treatment of pain; safe prescribing, monitoring and discontinuation of pain medication, focusing on opioids; adverse effects of opioids; and prevention of misuse and medication diversion, among others.³⁸ The current proposal is to develop and implement the curriculum from early 2019 through to mid-2020 at selected medical schools, with evaluation of the curriculum being completed by the end of 2020.³⁹

Since the AFMC's 2017 report was released, their 2018 update praised several Canadian medical schools for developing courses or curricula around these topics. Most notable were a Year-4 clerkship course in pain management and the opioid crisis at UBC, a course on safe prescribing practices for several medications at Memorial University and an integrated program at Dalhousie University for Residents in PGME.⁴⁰ Education of the next wave of physicians is paramount to ensure they enter the workforce with a thorough understanding of the benefits and dangers of opioids. It is expected that the knowledge of the impact opioids can have on a patient's quality of life will shape prescribing practices of the next generation of physicians from the outset.

Summary

For the last 2000 years, opioid use has been integral in the management of moderate to severe pain. Though efficacious in treating pain, we are currently in the midst of an opioid epidemic as we are learning that these medications have significant side effects. They possess a high addiction potential and research has shown that opioid use may also be associated with immunosuppression, opioid-induced endocrinopathy, and paradoxical opioid-induced hyperalgesia. Furthermore, the side effects associated with opioid use include sedation, constipation, delirium, respiratory depression and death. Despite the known issues surrounding these medications, they are still being prescribed at an alarming rate, leading to a year-over-year increase in opioid-related hospitalizations and mortality. In light of this, the CDC recently released a set of guidelines for physicians to adhere to when prescribing opioids in hopes of curbing the current epidemic. Indeed, while the guidelines are helpful, physicians and patients should be made aware of risks, potential alternatives to opioids in treating pain and options to mitigate opioid use. These include the use of opioid adjuvants (e.g. Dextromethorphan), the use of nerve blocks as an alternative to general anesthesia, and at-risk patient involvement in programs such as TPS. Further, governmental bodies and medical curricula alike are aiming to combat the opioid epidemic from the lens of the initial prescriber. While we may be in

the midst of an opioid epidemic, the accumulation of changes such as these may begin to slowly, but surely, help to curtail our overreliance on opioids.

References

- Canadian Institute for Health Information (CIHI). Opioid-related harms in Canada. Ottawa, ON: CIHI; 2017.
- Yaster M, Benzon H, Anderson A. "Houston, we have a problem!": The role of the anesthesiologist in the current opioid epidemic. *Anesthesia & Analgesia*. 2017;125(5):1629-1431.
- Porter J, Jick H. Addiction rare in patients treated with narcotics. *N Engl J Med*. 1980;302:123.
- Portenoy R, Foley K. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25:171-186.
- Morone N, Weiner D. Pain as the 5th Vital sign: exposing the vital need for pain education. *Clinical Therapeutics*. 2013;35(11):1728-1732.
- Hah J, Bateman B, Ratliff J, Curtin C, Sun E. Chronic opioid use after surgery: implications for perioperative management in the face of the opioid epidemic. *Anesthesia & Analgesia*. 2017;125(5):1733-1740.
- Canadian Centre on Substance Use and Addiction (CCSA). Canadian drug summary: prescription opioids. Ottawa, ON: CCSA; 2017.
- Canadian Institute for Health Information (CIHI). Pan-Canadian trends in the prescribing of opioids, 2012 to 2016. Ottawa, ON: CIHI; 2017.
- Nova Scotia Department of Health and Wellness. Nova Scotia's opioid use and overdose framework. Nova Scotia, Canada: Department of Health and Wellness; 2017.
- Special Advisory Committee on the epidemic of opioid overdoses. National report: Apparent opioid-related deaths in Canada (January 2016 to September 2017) Web-based Report. Ottawa: Public Health Agency of Canada; March 2018.
- Benzon H, Anderson TA. Themed issue on the opioid epidemic: what have we learned? Where Do We Go From Here? *Anesthesia & Analgesia*. 2017;125(5):1435-1437.
- Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain – United States, 2016. *MMWR Recomm Rep* 2016;65(No. RR-1):1-49.
- Maher D, Cohen S. Opioid reduction following interventional procedures for chronic pain: a synthesis of the evidence. *Anesthesia & Analgesia*. 2017;125(5):1658-1666.
- Webster L. Risk Factors for Opioid-Use Disorder and Overdose. *Anesthesia & Analgesia*. 2017;125(5):1741-1748.
- Kumar K, Kirksey M, Duong S, Wu C. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. *Anesthesia & Analgesia*. 2017;125(5):1749-1760.
- Dunn L, Durieux M. Perioperative use of intravenous lidocaine. *Anesthesiology*. 2017;126(4):727-737.
- Vetter T, Kain Z. Role of the perioperative surgical home in optimizing the perioperative use of opioids. *Anesthesia & Analgesia*. 2017;125(5):1653-1657.
- Sadove M, Balagot, R, Hatano, S, Jobgen, E. Study of a narcotic antagonist – N-allyl-noroxymorphone. *JAMA*. 1963;183(8):666-668.
- Clarke SFJ, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope *Emergency Medicine Journal*. 2005;22:612-616.
- Wermeling D. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. *Therapeutic Advances in Drug Safety*. 2015;6(1):20-31.
- Sporer KA, Kral AH. Prescription Naloxone: A novel approach to heroin overdose prevention. *Ann Emerg Med*. 2007;49(2):172-177.
- Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med*. 2014;8(3):153-163.
- Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis *BMJ* 2013;346:f174.
- Nova Scotia Take Home Naloxone Program. What is naloxone?. Nova Scotia, Canada: Nova Scotia Health Authority; 2018.
- Government of Ontario. "Recognize and temporarily reverse an opioid overdose". April 30, 2018. <<https://www.ontario.ca/page/get-naloxone-kits-free>>. (27 December 2018).
- Alberta Health Services. "Get Naloxone". Drug Safe Opioids. <<https://www.albertahealthservices.ca/info/Page16025.aspx#getnaloxone>>. (27 December 2018).
- Prince Edward Island. "Preventing opioid-related overdoses". <<https://www.princeedwardisland.ca/en/information/health-and-wellness/preventing-opioid-related-overdoses>>. (27 December 2018).
- Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. Canada: National Opioid Use Guideline Group (NOUGG); 2010. Available from: <http://nationalpaincentre.mcmaster.ca/opioid/>.
- Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ et al. Guideline for opioid therapy and chronic noncancer pain. *CMAJ*. 2017;189:E659-66.
- College of Physicians and Surgeons of British Columbia. Practice Standard. British Columbia, Canada: CPSCB, 2018.
- College of Physicians and Surgeons of Alberta. Standard of practice prescribing: drugs associated with substance use disorders or substance-related harm. Alberta, Canada: CPSA, 2018.
- College of Physicians and Surgeons of Ontario. Opioid position statement. Ontario, Canada: CPSO, 2018.
- College of Physicians and Surgeons of Nova Scotia. "College endorses new Canadian guideline for opioid prescribing". <<https://cpsns.ns.ca/college-endorses-new-canadian-guideline-for-opioid-prescribing/>>. (28 December 2018).
- Government of Alberta. "Opioids Report". 2017. <<https://www.alberta.ca/opioid-reports.aspx>>. (28 December 2018).
- Government of New Brunswick. "Prescription monitoring program and drug information system". 2017. <<http://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/PrescriptionMonitoringProgramandDrugInformationSystem.html>> 28 December 2018
- Government of Newfoundland Labrador. "Stronger communities through improved health care". 2016. <<http://www.releases.gov.nl.ca/releases/2016/health/1121n04.aspx>> (28 December 2018).
- Government of Ontario. "Ontario taking action to prevent opioid abuse". 2016. <<https://news.ontario.ca/mohltc/en/2016/10/ontario-taking-action-to-prevent-opioid-abuse.html>>. (28 December 2018).
- The Association of Faculties of Medicine of Canada (AFMC). Report on the AFMC response to the Canadian opioid crisis. Ottawa, ON: AFMC; 2017.
- The Association of Faculties of Medicine of Canada (AFMC). Request for proposal: curriculum development and evaluation services AFMC opioid response project. Ottawa, ON: AFMC; 2018.
- The Association of Faculties of Medicine of Canada (AFMC). UPDATE: Report on the AFMC response to the Canadian opioid crisis. Ottawa, ON: AFMC; 2018.