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Cover Art: Julian Rizos

Description: This cover art is based conceptually on the World Health Organization’s (WHO’s) Analgesic Ladder, a framework used by physicians to develop treatment plans for pain management. In this rendition, treatment modalities begin with over the counter non-pharmacologics then progress to prescription medications, opioids, nonprescription drugs and alcohol higher up. The ladder is more and more broken with each rising step, so in order to access more powerful analgesics, there is increasing risk of the ladder crumbling and succumbing to addiction, overdose, and death.

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Going blind: UWOMJ’s updated review process

“DEEP DOWN, ACADEMICS WANT THE SAME THING AS EVERYONE ELSE: ACCEPTANCE, WITH MINOR REVISIONS.”

@AcademicsSay

Though peer review can be controversial and is occasionally derided in the academic community, it is still widely recognized as an essential cornerstone of scientific communication. Peer-reviewed scientific journals first circulated in the 1660s, but it wasn’t until after the Second World War that peer review was widely implemented. In the decades that followed, leading journals deliberated on the merits of different peer review strategies, considering efficiency, efficacy, stringency, collegiality, and more recently, equity. The most common strategies today are:

- **open peer review**, wherein the authors’ and reviewers’ identities are disclosed throughout the review process
- **single-blind peer review**, wherein the identities of the reviewers are never disclosed to the authors
- **double-blind peer review**, which expands on single-blind review by also withholding the authors’ identities from the reviewers during the review process

Some journals have even implemented a triple-blind peer review, wherein the journal editors are also uninformed of the authors’ or reviewers’ identities during review, however this is still often too much of a logistic challenge for most journals. In a 2013 survey of over 4000 researchers, 76% considered double-blind an effective peer review strategy, while only 45% and 20% considered single-blind and open review to be effective. Despite this, most medical journals still follow a single-blind review process.

In 2015, in response to growing author and reader support, the Nature Publishing Group began to offer authors the option to submit manuscripts for double-blind review instead of their traditional single-blind review. Surprisingly, uptake of this option was only 12% in the 2 years that followed. Authors who opted for double-blind review were more likely to be affiliated with less prestigious institutions, and their manuscripts were less likely to be sent out for review (8% versus 23%) or accepted after review (25% versus 44%). These statistics may bias reviewers into thinking that double-blind submissions are of lesser quality. Such disparaging attitudes should not discourage journals or researchers from double-blind review, on the contrary, this demonstrates the crucial need for the universal uptake of double-blind review. Indeed, double-blind review has been shown to mitigate reviewer bias with respect to the author’s reputation, gender, country, and institution.

In the interest of offering students an educational peer review experience and eliminating any potential bias in our review process, the UWOMJ editorial team has successfully implemented a double-blind peer review process as of this issue. We hope that this push towards objectivity and equity will also strengthen the credibility of UWOMJ publications. We will continue our time-tested tradition of involving both peer and faculty reviewers for each submission accepted for review; while our peer reviewers will focus on the quality of communication, faculty reviewers will focus on content validity.

This development could not be possible without the contributions of our wonderful reviewers – your patience and feedback are greatly appreciated.

Alexander Levit
Co-Editor-in-Chief

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UWOMJ: 25, 50, & 75 years ago

UWOMJ: 25, 50, & 75 years ago is a new series featuring past perspectives and research of Schulich medical students as chronicled in the UWOMJ. This first edition was compiled by Chloe Gui.

25 YEARS AGO: FALL 1993, ISSUE 63(1)

A sample of infectious diseases research in Peru
Ross Mantle, Meds ’95

The following is a sample of eight concurrent research projects I was exposed to when I travelled to Peru in the summer of 1992 and stayed with Professor Robert Gilman, MD of John’s Hopkins University. [...] The wide diversity of tropical infective disease, coupled with the effects of altitude which can be observed in the Andes make Peru an attractive research arena for the infective disease specialist.

Helicobacter pylori (HP)

The relationship between HP, atrophic gastritis, and gastric ulcer, has been known for over five years, but is only just now becoming accepted in North American Centres. The further likely relationship between HP and gastric cancer is the subject of research effort by Dr. Gilman. In the third world HP infection rates typically see most of the population infected by age 20, and in some places 50% of the population are infected before one year of age. Rates of gastric cancer are higher and those of peptic ulcer lower than in the first world.

50 YEARS AGO: FEBRUARY 1968, VOLUME 38, NUMBER 3

Prognosis: Hopeless
Gary Koop, Meds ’69

There are a multitude of once “hopeless” conditions which made life very disagreeable to the patient at one time. It is quite safe to say that if euthanasia had been practiced in the past, our knowledge of these diseases would have come to a standstill and they would still be a source of human woe. Medicine says we must buy time; euthanasia says that the price of time is too high for what it is worth. It seems that medicine stops when euthanasia starts, and the latter can never be appropriate as one of the treatments to be used in the former.

[...]

There is a strong movement in favour of permission legislation on euthanasia in the Western democracies. The threat to the practice of medicine here comes not from politician interest on fulfilling certain goals of the state, but primarily from philosophies intent upon the preservation of the “good life”. The primary element of this supposed “good life” is freedom from pain. When we see what a large section of medical practice is devoted to the relief of pain, it would seem that we have accepted the philosopher’s definition of “the good life”. However, the larger goal of preservation of life is always foremost as is evident in our definition of the ideal analgesic (which, incidentally [sic], has not yet been discovered).

CAMSI Centennial Exchange, Inuvik, N.W.T.
Robert Birnbaum ’69

On August 12, 1967, 70 medical students, representing each of Canada’s 12 medical schools, met in Edmonton, Alta., for the beginning of the 2nd annual CAMSI summer school. This being our Centennial year, the summer school was to be held in Canada. The topic – ‘Frontier Medicine’. The frontier – Canada’s Arctic.
Wartime Abdominal Injuries

Charles Dyson

Since the Battle of France in 1940, military surgeons of the United Nations have had relatively limited opportunities (with the exception of those in attendance upon the North African, Russian or Chinese forces) to deal with abdominal injuries sustained upon the field of battle. Nothing in this war has yet been seen by the majority of our surgeons which could parallel the total casualties of the pitched week- or month-long battles of World War I. However, the present conflict has presented him with a new field of endeavour, for he must not only minister to the men who have been (and will be) injured on the field of battle, but he must also reckon with the injuries which total war visits upon the civilian population. As regards the latter group, the most fertile source of information is the English journals, whose writers have had extensive experience with casualties resulting from the indiscriminate bombings in the blitz of 1940.

A classification of wartime abdominal injuries divides them into four groups. This classification is intended only for convenience of discussion, and it should be remembered that considerable overlapping is possible:

1. Immersion blast injuries
2. Abdomino-thoracic injuries
3. Non-penetrating wounds of the abdomen
4. Wounds of the abdomen penetrating the cœlom.
“She is very illusive”: Substance abuse, gender roles and motherhood among the teenage girls of the Sioux Lookout Zone, 1969-1996

North de Pencier, Ian Puppe, Carrie Davis, Drishti Dhawan, Mithila Somasundaram, Gerald McKinley

ABSTRACT

From 1969 to 1996, the Indigenous teenage girls of the Sioux Lookout Zone of Northern Ontario grew up surrounded by poverty and rapid societal change. Substance abuse, vandalism, and suicide rates were rising, and families and health care providers were worried about the health of adolescents in their communities. This paper examines the instances teenage girls were mentioned in the collection of documents about the Sioux Lookout Zone Hospital at the University of Toronto Archives in order to analyze the challenges that these girls faced in gender role negotiations, substance abuse, and teen motherhood.

INTRODUCTION

The Sioux Lookout Zone Hospital was located in Northwestern Ontario. Up until 1996, it was funded by the federal government of Canada to provide racially segregated care to Status Indians. From 1969-1996, the Zone Hospital partnered with the University of Toronto medical school, Toronto General Hospital, and SickKids Hospital. University of Toronto physicians travelled to Sioux Lookout in shifts to staff the hospital, which allowed the university to teach its medical learners about Indigenous health.

METHODS

This paper uses an archival research method to study the collection about the Sioux Lookout Zone Hospital at the University of Toronto Archives. The collection contains numerous reports that analyze the challenges that the adolescents of the Sioux Lookout Zone faced during this era, which contributed to poor physical and mental health. This paper will analyze how teenage girls negotiated gender roles and dealt with substance abuse and the challenges of teen motherhood.

EMERGING THEMES

Teenage girls in the Sioux Lookout Zone lived in a gendered world, which reflected local social norms. A 1980 report on recreational activities for young people described community organizers taking teenage boys camping while “for girls there has been baking, making crafts, with the co-operation of the elderly ladies.” The teenage girls of the Sioux Lookout Zone were “expected to do work around the house” and were “less free to roam around” than teenage boys. Men enjoyed sports for recreation but women rarely participated. For example in one community, Pikangikum, “there were few organized evening activities and very little to do, for women, other than household chores.” From the 1970s onwards, “teenage girls were beginning to rebel against the traditional role of the woman.” It is beyond the scope of this paper to analyze to what extent and according to what tradition these domestic gender roles were in fact “traditional.” What is clear is that in this era, teenage girls were rebelling against the gender roles that were expected of them.

This rebellion often took the form of fighting with parents, choosing one’s own partner, sniffing gas, or drinking alcohol. There is also one mention in the collection of “girl gangs” though it is left to our imagination to determine what happened in a girl gang. Substance abuse, especially alcohol and gas sniffing, was a major problem among teenagers in general in the Sioux Lookout Zone from 1969-1996, including among teenage girls. “For many young girls who worked hard at home, gas sniffing seemed an escape and outlet from the daily routine.” However, restrictive gender roles expected of young women protected them from the enormous burden of substance abuse that fell on teenage boys. A report about gas sniffing in the Zone says that “young girls who are less free to roam around and who are expected to do work around the house, were rarely seen sniffing around town although many said they sniffed occasionally.” Blood tests for lead levels confirmed that women sniffed gas less frequently than men, and women also drank less alcohol than men.

Parents in the Sioux Lookout Zone often expected their teenagers to have an arranged marriage, and this was one of the gender expectations against which teenage girls rebelled. The collection describes several conflicts between young women and their parents over who and whether or not to marry. For example, one case study reports: “Her parents wanted her to get married but she didn’t want to. She was going out with a guy who was five years younger than herself. Her parents did not like that.” Another report describes a typical conflict between a teenage girl and her parent: “The parent, for example, wanted the daughter to marry a certain man and the daughter refuses. The child most often acted out by staying out late, not coming home, or sometimes making a suicide attempt.” The high stakes of this type of conflict are evident, especially as rates of teen suicide were rising in the Zone during this era. However, arranged marriage did not always lead to peace between parents and their teenage girls because “younger marriages also lead to conflicts in the home,” such as exacerbating pre-existing tension caused by the generation gap between girls and their parents.

Resisting arranged marriage was often tied to teen pregnancy. Teenage girls would rebel “by pregnancy and later marriage with a person not considered appropriate by the parents.” In 1972 in the
community of Webique, women tended “to have their first child
by the age of seventeen, and before they are married (in their mid-
twenties) most already have two to four children.” One case study
of a teenage mother is presented in depth in a report on motherhood
in the Zone from 1974, titled “Single (Unwed) Mother”:

“Eighteen years old, she was fairly fluent in English and was
Anglican by religion. Although with other Indians she was relaxed
and firmly [sic], she felt the stigma attached to unwed pregnancy,
a value imposed by white society when in white company… Like
the other mothers, this mother thought that seventeen or eighteen
was a good age to begin bearing children. She wanted a family of
about four to five children, though she wanted to be married before
having another child.”

This teenage mother’s case study shows that teen pregnancy
was common but that pregnancy before marriage was stigmatized,
though also common in the Zone. The ambivalence of health care
providers is evidenced by writings that indicated being a teenage
mother was more acceptable in the Zone than being an unwed
mother.

DISCUSSION

A limitation of my paper is that most of the writing about
teenagers in the Sioux Lookout Zone focuses on the problems
of teenage boys. Writers most often use the pronoun “he” when
referring to teenagers in the Zone, and as a result, young women are
excluded from the discourse. For example, “the teenager wanted
to say what he thought and felt and was groping with identity.” In
a 1969 report from the Ontario Ministry of Education, visitors to
the Zone discuss the difficulties teenagers face finding work: “The
amount of training he does possess doesn’t allow him to adequately
compete.” This use of the pronoun “he” to refer to the adolescent
in general may be a convention of English writing from the period,
but it still demonstrates a clear gender bias on behalf of the report
writers, who themselves were usually male. In some instances, when
talking about teenagers in general, it is more explicit that the author
means young men. For example, “the outlets for the non-student
are few; some of these young men can be observed participating as
musicians in the local rock bands.” In the 1969 report, visitors to
Sandy Lake noticed that “teenagers” had long hair as part of their
“hippy-type” fashion. Given that young women at the time would
have usually had long hair, regardless of the current hippie fashion,
this is another example of when “teenagers” was used by default
to describe only teenage boys. Sociologist Gill Jones writes that it
is common for the word “youth” to refer to young men instead of
young people in general, and in the Sioux Lookout collection, this
applies to the word “teenager” as well. The gender bias in the
writing about teenagers makes it unclear when teenagers in general
are being described compared to just teenage boys.

Teenage girls were specifically documented when they
negotiated expected gender roles and arranged marriage. Studying
these challenges that teenage girls faced is essential because rates
of suicide by teenage girls increased over the period that this paper
studies, and in the present day, rates of suicide are very high among
Indigenous teenage girls. They are even higher than among boys,
in contrast to non-Indigenous Ontario communities. It is very
unusual for suicide rates to be higher among girls than among boys
in any population, and it indicates that teenage girls in the Sioux
Lookout Zone are particularly marginalized.

CONCLUSION

The teenage girls of the Sioux Lookout Zone asserted
themselves against the control of their parents by experimenting
with alcohol and gas sniffing, by choosing their own partners and
by becoming mothers. However, conforming to traditional gender
roles protected young women to some extent from the scourges of
gas sniffing and alcoholism that affected all teenagers in the Zone.
Studying the historical challenges teenage girls faced is essential
to understanding the health of young women in the Sioux Lookout
Zone today.

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Mindfulness-based cognitive therapy for young adults with cancer

A report of benefits and challenges from the perspective of participants

Amanda Roth, Rinat Nissim, Mary Elliott

ABSTRACT

Introduction: Cancer diagnosis and treatment frequently involves physical and psychological symptoms, including anxiety, depression, fatigue, and sleep disturbances. The young adult population with cancer face unique struggles including poignancy in relation to self-concept, identity formation, independence, role development, loss of independence, and time away from school and peers. Mindfulness-based interventions are increasingly being evaluated for individuals with a cancer diagnosis. Mindfulness-Based Cognitive Therapy (MBCT) combines Mindfulness-Based Stress Reduction with aspects of cognitive behavioural therapy. This paper aims to briefly describe MBCT and its benefits and challenges in the young adult population with cancer.

Method: An analysis of themes was conducted of post-intervention semi-structured interviews that were conducted with a subsample of 14 participants to gain more detailed information regarding their perception.

Findings: Participants reported positive transformations including in how they cope.

Conclusions: Although a small sample size limits its generalizability, this study provides further evidence that MBCT can be successful in treating psychological symptoms in young adults with cancer.

BACKGROUND

In Canada, the number of individuals currently living with cancer is on the rise with an increase in the incidence of cancer in the young adult population. Diagnosis and treatment frequently involve physical and psychological symptoms, including anxiety, depression, fatigue, and sleep disturbances. Physical and emotional distress often continues following completion of cancer treatments. Various psychosocial interventions designed to enhance coping with stress and to improve quality of life have been developed. The young adult population faces unique struggles, including poignancy in relation to self-concept, identity formation, independence, role development, loss of independence, and time away from school and peers.

Mindfulness-based interventions are increasingly being evaluated for individuals with a cancer diagnosis. The most rigorously described mindfulness-based intervention in cancer is Mindfulness-Based Stress Reduction intervention (MBSR). This program arose from the Buddhist principle of mindfulness, described as “the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally, to things as they are.” MBSR provides a strategy for coping with stress from daily life and/or a variety of medical illnesses. Recent systemic literature reviews of studies that evaluated this program in individuals impacted by cancer concluded that MBSR was associated with improvement of the quality of life and reduction of symptoms of depression, anxiety, and fatigue. Another mindfulness-based intervention that has been utilized in cancer is the Mindfulness-Based Cognitive Therapy (MBCT). This intervention combines MBSR with aspects of cognitive therapy. It uses 8 weekly group sessions format and incorporates a psycho-education component, aiming at helping participants develop detached relationships with their thoughts to prevent the escalation of automatic negative thought patterns.

There is currently a gap in the literature as the majority of studies examining MBCT in the cancer population addressed patients over the age of 40, with younger ages being in the exclusion criteria. Recently, the MBCT program, modified for individuals with a cancer diagnosis (MBCT-Ca) has been launched at Princess Margaret Cancer Centre (PM) of the University Health Network (UHN) to answer the research question: what are the benefits and challenges of mindfulness-based cognitive therapy for young adults with cancer?

METHOD

The study was carried out at PM. It was approved by the UHN research ethics board. Young adult participants, who were referred to the MBCT-Ca at PM by their healthcare team (MBCT-Young Adult), were recruited from a pool of patients who attended the MBCT-Young Adult Groups. Participants were contacted by the research assistant and invited to take part in an interview, and those who provided consent were invited to participate in an in-depth qualitative interview. Post-intervention semi-structured interviews were conducted with a sub-sample of participants to gain more detailed information regarding their perception of the MBCT. The first author observed 2 MBCT-Young Adult groups and conducted the interviews and the analysis. The semi-structured interview explored participant’s experiences of the intervention and any associated benefits or challenges that they experienced during the intervention and afterward. Interviews were audio-taped and transcribed verbatim. Interviews were continued until theme saturation, where additional sampling did not lead to more information related to the research question, was achieved. An initial set of themes were coded, and a preliminary coding scheme was developed using NVivo. The codes were then revised to adjust for new information until no new codes emerged. The analysis was then verified by an additional coder.
RESULTS
Fourteen adolescent and young adult participants, both male and female, between the ages of 20 to 40 were interviewed. These participants had a history of breast, blood, brain, and lung cancers, and were interviewed within 6 to 12 weeks of the end of the MBCT intervention. No information was provided regarding treatment outcomes.

The analysis provided insight into the unique young adult-associated benefits and challenges. Many benefits of the MBCT-Young Adult were identified. Each of the participants came from different backgrounds and used the same mindfulness techniques. The themes that arose show many more benefits than challenges. The analysis indicated the following themes with regards to benefits of MBCT-Young Adult: developing in-the-moment tools, finding an emotional center, coping with pain, acknowledging that one's feelings are valid, and community and a sense of belonging. Some of the themes regarding challenges include: staying focused, finding the time to practice, and reminders of past experiences, facing difficulties or unwanted thoughts.

BENEFITS
Developing in-the-moment tools
The first of the themes that were identified by participants as providing brief, in-the-moment tools to use when stressful situations arise. This theme focuses on the awareness of what you are feeling and awareness of self. Developing these in-the-moment tools helped young adults with cancer cope with their anxiety. “...sit there and focus on your breath and try to relax and try to sort of calm yourself down. Be aware of what you're feeling...focus on it from a more neutral perspective, so you aren't being swayed by your emotions.”

Finding an emotional center
Finding an emotional center was a theme mentioned in multiple interviews as a benefit. Young adult participants described developing the ability to be grounded and centered. They spoke of how these skills helped in dealing with stressful situations arising out of their control and not typically faced at a young age. “Can the world please stop spinning for a little bit, so I can get my bearings, that kind of thing. It kind of brought me into a center that I didn't expect to find so quickly, an emotional center, but also a grounding sense of being in time and space.”

Coping with pain
Accepting the pain and coping with it was another theme that arose as a benefit to young adult participants. Recognizing the importance of looking out for aches and pains that last long periods of time are a part of being in remission. The worry that every pain may be a cancer relapse causes distress for many patients. Participants acknowledged the benefit of breathing spaces, which is an opportunity to pause, and relax, and decide what to do next, helped participants decide what to do with regards to pain management and the mental anguish associated with it. “Every little bump and scrape and bruise and pain, I think I’m getting cancer again... you need to develop any kind of tool, any kind of skill that helps you really channel into what you're feeling inside your body and what you're thinking inside your mind, and how to interact with it or not.” “I'll do the body scan, [and say to myself] you're not actually in pain, you're fine. Those quick things to break the record in my head has been really helpful.”

Acknowledging that one's feelings are valid
An important theme that arose was acknowledging one's feelings. The feelings that one has as a young adult cancer patient are unique; these participants developed the ability to acknowledge their feelings and accept them nonjudgmentally. Recognizing that they can sit with these feelings, and accepting them was an obstacle that many participants overcame in their journey of self-acceptance. “I kind of felt bad for feeling bad and I didn't understand why and I resented myself for that. I kind of felt like a privileged brat who didn’t appreciate the silver lining of it all. What I learned from the program very shortly after I started it was that was okay. It was okay to feel that way and it doesn't necessarily mean that you'll feel that way forever, so here's what you can do about it now.”

Community and sense of belonging
As a young adult, learning mindfulness in the group context created an immediate community, and provided participants with a sense of belonging, which they valued. “You know, I wanted to be in a community, so I thought, you know like everyone's going to mindfulness class. We have the same goals and if they're all from the community of the hospital, you know, I will have found a like-minded community.”

CHALLENGES
While the young adult participants said that there were no major challenges, some of the minor ones include the following:

Staying focused
A challenge that arose for many participants was staying focused and concentrating throughout the body scans, as their minds would wander throughout the practice. “The body scans. I had a really hard time sitting still...I had a really, really hard time sitting still and focusing on those.”

Finding the time to practice
Another theme described involved the challenge of being able to find the time to practice mindfulness throughout the week. The importance of dedicating time to practice was acknowledged, but it was difficult to make time for it. “I mean, really, I think the biggest challenge is the commitment and, practicing, actually doing the work and doing it every day.”

Reminders of past experiences, facing difficulties, or unwanted thoughts
The final challenge recognized by the participants was seeing other participants at different stages of illness or having to think about the area where cancer originated from during a body scan. “I guessed it’s with some of the meditations and some of the body scans. It just pulled me towards my past, like, through my breast to my past.”
CONCLUSION

Young adult patients with cancer are a unique group with different needs. Participants reported positive transformations, including in how they cope on a day to day basis, improvement of relationships as a result of learning how to respond instead of reacting, and how accepting their feelings and emotions improved their well-being. The importance of having a specific MBCT group for the young adult population was illuminated in this preliminary study. Adaptations to the program have been made to address the needs and challenges encountered.

“It’s probably one of the most important things I’ve done…. I can see a big difference in my personality and how I attack things that are stressful.”

REFERENCES

The legacy of Dr Earl Russell
A new era of pain medicine at Western University and Canada's first pain medicine residency program

Sandra Botros

ABSTRACT
Dr Earl Russell (1920-2008) was a Canadian anesthetist and pain specialist who spent the majority of his career as a Western University faculty member and a pain physician in Southwestern Ontario. Dr Russell obtained his medical degree at Western, graduating in the class of 1950, and went on to serve in the Korean War as a medical officer. It was in Korea that he began developing a keen interest in pain medicine, using self-taught anesthesia skills to help soldiers suffering from frostbite. He returned to Canada and focused the rest of his career on the practice and advancement of pain medicine, and endowed the Earl Russell Chair in Pain Management in order to fund future research and education in the field. This article highlights the importance of his contributions to the field, in particular through his creation of the Earl Russell Chair, and how this led to the first Pain Medicine residency program in Canada at Western University.

INTRODUCTION AND EARLY LIFE
Dr Earl Russell grew up on a family farm in Saskatchewan during the Great Depression. From the age of 10, he dreamed of becoming a country doctor like the local general practitioner, who came around to tend to people’s various needs, from setting broken bones to delivering babies. He credited the demanding work ethic of farm life for strengthening his dream, and managed a full-time workload on the farm throughout his elementary and high school education. He went on to study math and physics at the University of Saskatchewan, and qualified for medical school before serving in World War II as an Officer in the Royal Canadian Signal Corps. Upon his return, he started medical school at the University of Saskatchewan, and completed his degree at the University of Western Ontario, graduating in 1950.

Halfway through his intern year, he was sent to serve in the Korean War as a junior medical officer. He was placed with the 8055th Mobile Army Surgical Hospital (MASH) unit, which was the unit that inspired the popular television series, MASH. It was in Korea that Russell was thrown into the role of an anesthetist and developed his interest in pain medicine. It started one night when a surgeon approached him, asked “Do you know anything about anesthesia?” and recruited him to help with an appendectomy. From then on, anesthesia became his full-time role. His interest in pain management was sparked when he found himself deeply affected by the sight of wounded soldiers lying in the snow suffering from frostbite. This was a common occurrence, as soldiers often removed their gloves to fire their weapons. In an effort to relieve their pain, he taught himself to perform stellate ganglion blocks and many other anesthesia-related skills.

CAREER
When he returned from Korea, Dr Russell completed his training in anesthesia at Kingston General Hospital. After being certified in 1955, he spent 10 years working in Kingston and teaching medical students at Queen’s University. This included 2 years spent in Lagos, Nigeria, where he helped open the University of Lagos Medical School. He was recruited to Western’s faculty in 1968 for his skills in chronic pain management and obstetrical analgesia. He worked in the anesthesia departments at both Victoria Hospital and St. Joseph’s Hospital, and served as Chief of Anesthesia at Victoria Hospital. He was greatly respected and influential in several areas: these include establishing obstetrical epidurals as common practice in the early 1970s, many years before the rest of the country; and pioneering a telemedicine program that allowed doctors to see patients by video in Moose Factory, Ontario.

In 1982, Dr Russell officially “retired” as a Professor Emeritus at Western, but continued to run his very busy pain clinics in Ingersoll and Newbury, Ontario. He was dedicated to his chronic pain patients and continued to see over 100 patients a week until the age of 87. He simultaneously ran his own farm near London, and worked on it himself until the age of 85. Alongside his extensive professional accomplishments, he maintained a strong involvement within his church and the community throughout his life, and even established the Meals on Wheels program in London for seniors. When he died in 2008 at the age of 88, he left a lasting impression on the community of Southwestern Ontario. He is survived by his loving wife of 61 years, Marjorie, and his 4 children, 11 grandchildren, and 5 great-grandchildren. He was awarded a Distinguished Lifetime Achievement Award from the Canadian Pain Society in 2004 and an honorary Doctorate in Science from Western University in 2006.

LEGACY
Although Dr Russell dedicated his life and career to his patients as a clinician rather than a researcher, he had a profound impact on the future of research in pain medicine. His most important contribution was his endowment of the Earl Russell Chair in Pain Management. Dr Russell had truly fallen in love with the art of pain management, and had hopeful visions for its future. In a 1999 interview, Russell predicted, “Pain is so devastating, and its management so primitive...I’ll bet you in 10 or 15 years I just won’t recognize it.”
The Earl Russell Chair in Pain Management is a position established at Western in 2002 by Dr Russell through a $1.1 million donation. He donated another $1.6 million in 2008. Initially, the Chair had two major mandates. The first was to direct a multidisciplinary pain management clinic in London, and the second was to advance research and education in the field. The first holder of the position (2001-2005) was Dr Patricia Morley-Forster, an anesthesiologist. The current Earl Russell Chair is Dr Dwight Moulin, a neurologist, who has held the position since 2005, with the mandate now focused more on research and education. Both have been a driving force in making Dr Russell's dream a reality, and have described the lasting effects of Dr Russell's contribution on the field of pain medicine.1,4

Prior to the establishment of the Chair, research in the area was disconnected, with different specialties and disciplines separately initiating pain medicine research. These disciplines became united together under the support of the Earl Russell Chair and a multidisciplinary Scientific Advisory Board (with representation from anesthesiology, physiatry, rheumatology, psychology and neurology). The creation of this cohesive multidisciplinary program helped attract significant grant funding for research and pushed pain into the national spotlight. Several team members have held or hold CIHR grants. In addition, funding from the Canadian Foundation for Innovation and from the industry-established National Neuropathic Pain Patient Registry and Database has allowed for multiple studies addressing long-term outcomes of the management of neuropathic pain syndromes. Ultimately, this resulted in a surge of publications, detailed in the Annual Reports of the Western Pain Program.3 Emerging areas and relevant topics in the pain medicine program currently include functional MRI imaging, further studies on neuropathic pain, and the role of cannabinoids and lidocaine infusions in the management of chronic pain.1,4

Education has been another important focus, and was an area that Dr Russell recognized as vital to make the specialty more visible and attract more physicians. Pain education has historically been grossly underrepresented in medical school, despite the fact that it is the most common reason patients present to a doctor. Recently, Western has had substantial success in incorporating pain medicine into medical school and residency curriculums. This has come in the form of medical school lectures, resident half-days, monthly interdisciplinary pain rounds, and continuing medical education. Western was also the first medical school in Canada to offer a pain medicine selective; this has evolved into a mandatory core curriculum in pain assessment and management. Particular targets include the opioid epidemic and the role of opioid analgesics in the management of chronic pain.1,4

As a passionate clinician, Dr Russell wanted to ensure his endowment also directly improved clinical care in London. He envisioned one central multidisciplinary pain clinic, instead of smaller scattered ones. The creation of the Earl Russell Chair led to the opening of the St. Joseph’s Pain Clinic, first directed by Dr Morley-Forster. The clinic moved to a new and larger location in 2012, and provides multidisciplinary care from several medical specialties as well as a coordinated team of psychologists, nurses, pharmacists, social workers, occupational therapists, and physiotherapists. There is considerable demand for pain management care, and the clinic has a sizeable wait list, so this remains an exciting area of future growth as the specialty of pain medicine gains popularity.1,4

The most significant accomplishment to come from Dr Russell's legacy has been the creation of the first Pain Medicine residency program in the country, which was officially recognized by the Royal College of Physicians and Surgeons of Canada in 2014. This 2-year fellowship program at Western, which can be entered from any discipline, was a huge step forward for the specialty of Pain Medicine at a national level and for Western’s pain management program. The creation of the residency program was spearheaded by Dr Morley-Forster, who has worked towards this goal with the Royal College since 2006. She credited in part the connections and experience she gained as the holder of the Earl Russell Chair to make this a reality.2 Other universities have steadily followed in subsequent years, with eight programs having completed, or in the final phases of accreditation. Dr Geoff Bellingham, from the Department of Anaesthesiology and Perioperative Medicine, was the first Director of a Pain Medicine residency program in Canada, and he continues in that position at Western.

CONCLUSION

Dr Russell was an invaluable member of the Western faculty and he influenced the entire field of pain medicine. He was also a vital and irreplaceable part of the life of each patient he touched, and he worked tirelessly through his life to alleviate their suffering. His patients, the London community, and the Canadian medical community as a whole have been lucky to have him. As quoted from Dr Russell's 2006 speech at the Western convocation ceremony, showing where his heart truly lay in the practice of medicine, “In the sick room 10 cents worth of human understanding equals $10 worth of science.”

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Pain management training in undergraduate medical education
Stephanie Fong, Patricia Morley-Forster

ABSTRACT
The pain curriculum in medical education across the globe is lacking, leaving medical trainees ill prepared to properly assess and design plans to address acute and chronic pain. Poorly managed pain has implications on the individual in the form of psychological, physical, and financial costs, and on the greater healthcare system and economy. Gaps in education have resulted in suboptimal opioid prescribing habits contributing to the current opioid epidemic, and the development of negative attitudes towards patients with chronic pain amongst healthcare providers. Studies researching existing pain education in undergraduate medical education in North America, the United Kingdom, and Europe have identified limited pain teaching, typically incorporated into other courses rather than given a designated place in the curriculum. Several barriers to improving the provision of pain education have been identified, including resource limitations and perceived importance in comparison to other content. Improving pain education in Canada should be a priority given recent updates to the Canadian Guideline for Opioid Therapy and Chronic Noncancer Pain which recommends a decrease to the maximum dose of morphine. Implementing these guidelines will require physicians to have the knowledge and ability to safely taper patients whose opioid doses exceed the upper limit. Enhancing pain education will require an interdisciplinary approach with students developing competence not only in the identification and appropriate management of pain, but learning the communication and motivational interviewing skills to display empathy and compassion when providing care to the chronic pain patient population.

INTRODUCTION
Pain has emerged as a global health issue, with studies from Europe, North America, Australia, and Asia suggesting 1 in 5 adults suffer from pain.1,2 Chronic pain is a problem affecting 1 in 5 Canadians over the age of 18.3 Unrelieved pain greatly impacts an individual’s functional status, quality of life, and health outcomes.4 From a health resource perspective, pain is the most common reason for patients to access healthcare, and chronic pain is the leading cause of long-term disability.5

In Canada, the unsafe prescribing of opioids has contributed to an increase in opioid related deaths over the last decade.6 On an individual level, the physical and psychological aspects of chronic pain result in lost productivity, absenteeism and early retirement. Moreover, the economic cost of underdiagnosed and undertreated chronic pain accounts for 3 to 10 percent of a nation’s Gross Domestic Product.7

Despite the prevalence of pain in clinical practice and its burden on healthcare systems, dedicated pain teaching in undergraduate medical education is often inadequate in terms of time devoted to the subject as well as the content presented to learners.1,2,4,6,8 Other systemic factors contributing to inadequate pain management include lack of provincial coverage for non-pharmaceutical pain management options and limited access to pain specialists and multidisciplinary pain clinics. This article focuses on the current landscape of pain education at the undergraduate medical level, describes how a lack of knowledge around proper opioid prescribing practices has contributed to current situation, and makes suggestions for future direction of pain education in medical school.

PAIN EDUCATION: CURRENT LANDSCAPE
In a 2009 survey of Canadian health sciences programs including medicine, nursing, dentistry, pharmacy, physical therapy, and occupational therapy, it was found that only one-third of programs had designated mandatory pain content in the curriculum, with two-thirds identifying “integrated” content that could not be quantifiable.9 Respondents highlighted the need for increased pain-related curriculum resources and the desire for interprofessional education opportunities. Given that a well-designed pain curriculum has been shown to significantly improve pain knowledge and beliefs of students, and enhance pain management practices, the authors advocate for increased pain content in health sciences programs.10

A 2011 study involving 117 American and Canadian medical schools, found that 80% of American medical schools and 92% of Canadian medical schools require pain related teaching. Pain content was most often incorporated within other required courses, producing a fragmented learning experience. The researchers found that many topics outlined in the International Association for the Study of Pain (IASP) core curriculum, a learning society that publishes internationally accepted standards for pain education, received limited or no coverage in the medical school curricula studied.11

Pain education in health sciences programs is also underrepresented in the United Kingdom (UK). A sample of 74 health sciences programs including medicine, dentistry, midwifery, nursing, occupational therapy, pharmacy, physiotherapy, and veterinary medicine across 19 institutions in the UK found that programs had an average of 12 hours of pain content, with the greatest amount of content found in veterinary medicine and physiotherapy.12

The Advancing the Provision of Pain Education and Learning study aimed to determine levels and methods of undergraduate
medical education in pain management at 242 schools across 15 European countries. During a six-year degree program, medical students received an average of 12 hours of pain management training, an amount the authors cited as disproportionate to the prevalence and burden of pain. Most schools studied (55%) incorporated pain content into non-pain specific courses. Thirty-one percent incorporated a dedicated pain module in the curriculum, an approach most common in France where it was present in 87% of school’s surveyed within that country.1

OPIOID PRESCRIBING PRACTICES

Given the limited pain management training offered to medical student learners, new medical graduates are faced with clinical presentations they are unable to adequately assess and managing.5,11 They may harbour negative attitudes towards patients presenting with pain based on their mentors’ reaction to chronic pain patients.161921 In a study of medical residents in the United States, 59% of respondents rated their medical school preparation to manage chronic non-cancer pain as “fair” or “poor” while 30% used negative or derogatory terms to describe patients with chronic pain.12

The 2017 update of the Canadian Guideline for Opioid Therapy and Chronic Noncancer Pain provides recommendations for safer and more effective opioid prescribing practices. One recommendation is a reduction in the upper dose of prescribed opioids from 200 mg morphine equivalent per day to 90 mg morphine equivalent per day, a change based on evidence showing correlation between higher opioid doses and increasing risk of death. The new guidelines indicate patients on a dose greater than 90 mg should undergo a trial of tapering to the lowest effective dose. However, most physicians will not graduate with the training in how to taper opioids slowly without precipitating significant withdrawal symptoms. This may lead to patient resistance or refusal to further tapering.6

In the United States, where pain curricula reflect those in Canada, approximately half of all opioid prescriptions are written for indications for which there is little or no evidence.7 Practitioners should be more vigilant about not starting patients with problems such as acute low back pain and fibromyalgia on opioids. Additionally, physicians should educate patients on opioid use prior or at hospital discharge, as studies have shown patients discharged from hospital with an opioid prescription are at increased risk of future chronic opioid use and that contributes to morbidity and mortality.7,14 It has been identified that 10% of opioid naive patients started on opioids for short term pain management post-surgery develop chronic opioid use.6

PAIN EDUCATION: FUTURE DIRECTIONS

Common recommendations that have emerged from studies on undergraduate pain education include increasing the curriculum time devoted to pain assessment and management, and incorporating an interprofessional approach to undergraduate medical teaching.14,8,10 Ideally, pain education in medical school would include psychology, physiotherapy, pharmacy, family medicine, physical medicine, anesthesiology, neurology, and addiction medicine. Learners should be comfortable not only with opioid prescribing practices, but also competent in prescribing non-opioid and non-pharmacologic pain management options.

In addition to the medical science component of pain education, communication skills and motivational interviewing are integral aspects of learning to manage chronic pain patients who can feel as though their pain is minimized by being labelled as drug-seeking.9 Researchers have suggested that pain education should include intellectual, emotional, technical, and ethical dimensions.4 A survey of pain medicine leaders within the American Academy of Pain Medicine ranked awareness of acute and chronic pain, competence in clinical appraisal, promotion of compassionate practices, displaying empathy toward the patient, and knowledge of terms and definitions for substance abuse as the top five learning objectives for medical students.17 Another important aspect of a pain curriculum involves the exposure to best practices in the clinical setting by working with mentors up to date in the field.9

The International Association for the Study of Pain (IASP) is an organization that brings together clinicians, scientists, and policymakers to support the study of pain and translate knowledge into improved pain management for patients. The IASP has created a series of curricula outlines for healthcare providers within the interdisciplinary team that are helpful for establishing courses on acute, chronic, and cancer pain at the undergraduate and graduate levels.18

The pain curriculum at the Schulich School of Medicine and Dentistry at Western University has undergone a continuous evolution since the introduction of an elective pain course in 2001 offered to students in their final year. Over the years, the elective course grew from eight to twenty hours in duration. In 2018, the course length was shortened, but was made a mandatory component of the final year curriculum. The focus of the course is on safe opioid prescribing with the aim of promoting the development of clinicians who are knowledgeable about chronic pain conditions, empathetic to patients’ experiences with pain, and aware of the risk-benefit ratio of opioids as a tool with which to manage pain.

CONCLUSION

Despite the significant global burden of pain and the growing numbers of deaths from opioid misuse, medical school pain curricula continue to be limited and fragmented. Challenges to incorporating a more robust pain curriculum into undergraduate medical education include perceived importance in comparison to other content; limited time, resources and staff knowledge; and a diffusion of responsibility for pain education to non-pain specific courses.7 Having a roster of health professionals with pain education experience to act as mentors for trainees can help learners gain more confidence in managing chronic pain.10 Greater knowledge and confidence in management abilities are correlated with more positive attitudes towards chronic pain patients.19 Improving the pain curriculum in medical schools should be prioritized, although
it is recognized that learning is lifelong and the incorporation of pain education at the postgraduate and continuing medical education levels is essential in developing and maintaining best practices.\textsuperscript{11,12} Learning objectives should include not only knowledge acquisition of assessment and therapeutic options, but also exploration of attitudes to allow students to recognize their own biases and prejudices.\textsuperscript{5,9,13}

REFERENCES
Working towards developing an interprofessional pain management curricula for clinicians

Zoe Letwin

ABSTRACT

Pain management receives minimal attention in the education of healthcare professionals. An environmental scan was conducted to assess the current pain management educational programs with a focus on interprofessionalism within a competency-based education framework in order to determine gaps before implementing the future master’s-level Interprofessional Pain Management degree program to be implemented at Western University. This paper outlines the methods used in the scan, keywords for the search, and key findings. The findings highlight several current interprofessional pain management programs, the need for a conceptual framework for interprofessional pain education, consistent core values/principles, and competency-based education embedded in interprofessional pain management and future directions.

INTRODUCTION

Pain is the most common reason patients visit their clinicians; however, pain management receives little attention in the education of healthcare providers. Evidence indicates that health professionals lack adequate knowledge and skill to properly assess and provide strategies to manage pain for their patients. The purpose of this feature article is to share the existing literature by conducting an environmental scan on interprofessional pain management educational programs in preparation for developing the Interprofessional Pain Management (IPM) master’s level degree program at Western University. This program would be based on a new “collaborative team integrated competencies” framework intended for all healthcare professionals with specific focus on allied health providers. Focusing on interprofessional education is a primary objective as developing interprofessional pain management educational programs in preparation for developing the Interprofessional Pain Management program at Western University. This paper outlines the methods used in the scan, keywords for the search, and key findings. The findings highlight several current interprofessional pain management programs, the need for a conceptual framework for interprofessional pain education, consistent core values/principles, and competency-based education embedded in interprofessional pain management and future directions.

METHOD

The environmental scan was conducted to establish the current environment of pain management. Environmental scans consist of several steps including defining the keywords involved, which includes interprofessional education, pain management and competency-based education. The second step then reviews existing information from like-minded organizations, such as other academic institutions. The final step is to gather the data and analyse it to determine existing educational programs that consist of interprofessional components and/or CBE. The following keywords and Boolean operators were used: “competency-based education”[MeSH Terms] OR “(competency-based education” OR “competency based education” OR “curriculum” OR “curriculum”[MeSH Terms] OR “Health Personnel/education”[Mesh] AND (“pain management”[MeSH Terms] OR “pain management” OR “pain”) AND (“patient care team”[MeSH Terms] OR “patient care team” OR “interprofessional relations”[MeSH Terms] OR “interprofessional”).

PubMed was utilized to conduct this high-level environmental scan as this database provides summaries and full texts of systematic reviews that are easily accessible. PubMed also has a focus on medical education. The search provided 340 results initially. Only full texts, peer-reviewed articles in English within the last 10 years were included. Clinical guidelines, literature that did not have a primary focus on pain, interviews, drug-based pain management and surveys were excluded from the scan.

RESULTS

Of the results, 48 articles were reviewed. The findings described an interprofessional team as health professionals providing common and specific educational expertise to support the team. A variety of conceptual frameworks were identified along with consistent core values/principles and a brief description of competency-based education paired with interprofessional curricula. Of the literature reviewed, there was only one MSc Interprofessional Pain Management program in the UK at Cardiff University. It is offered as a part-time 14-week e-learning module with a primary focus on blogging as a method of assessment. The findings were useful, but still did not provide enough adequate information. This proved to be a good model to follow, but is limited due to the length of the program. It would only serve as an introduction to interprofessional pain management for clinicians.

DISCUSSION

Overview

In reviewing the available literature, it was evident that there is little emphasis on pain management education in a variety of health provider curricula. Findings show that even when health professionals do have access to pain assessment information, they...
do not appear to use it in their treatment planning or reinforce the need for pain education. This can be improved, however, and health professionals need to be taught to recognize the prevalence and consequences of pain, but also how to work together to diminish it. Findings recommend that including pain management in healthcare education is crucial due to the importance and frequency of pain in society. Throughout the literature reviewed, there was little evidence of master’s level programs that solely focus on pain management in an interprofessional healthcare setting within a competency-based framework.

**Interprofessionalism**
Interprofessionalism in the environmental scan included collaboration between health clinicians in dentistry, medicine, nursing, occupational therapy, pharmacy, physiotherapy, and social work. Within the clinical sites, there has been less progress in interprofessional pain education at the advanced ‘trainee’ stage of learning. On balance, the bulk of the work indicates that interprofessional educational initiatives may be most successful when integrated early in the socialization and educational experience of diverse professionals. Interprofessional collaboration has been identified as a key factor for effective pain management.

The literature reviewed not only focused the need for interprofessional pain management with clinicians, but also included patients as collaborative partners to address their care in a non-hierarchical design. Findings demonstrated that when patients participate in their pain care, they are more satisfied and experience better outcomes. Patient stories were highly regarded as the patient introduces how pain impacts their life. Since patients are credible judges of their pain, patient self-reports serve as the basis for planned intervention by assessing pain intensity, location, and characteristics as well as pain-related interference with activity. In reviewing assessment tools on pain management, Pain Management Index (PMI) scoring card were used to assess levels of pain. While the majority of the focus is on the primary stakeholders, including students and faculty, patients and clinical facilitators are vital in interprofessional collaboration.

**Pedagogical Practices for Interprofessional Pain Management**
As the purpose of this environmental scan is to review existing interprofessional pain management curricula with an emphasis on competency-based education, it was important to highlight the successful pedagogical practices in order to start developing a conceptual framework. An example includes the ‘Pain-IPE Placement’ that was piloted in Toronto, which included five weekly 2 hour tutorials. The goal of the placement was to provide an opportunity for trainees to participate in collaborative-learning models and apply theoretical pain concepts as well as core interprofessional competencies. According to one study reviewed, the literature on pedagogical constructs of the ‘how’ to teach interprofessionally to improve collaborative pain care is nonexistent; therefore, only pedagogical practice models that were successfully practiced in interprofessional pain management were included in the scan. Interprofessional learning is a challenge across many post-secondary institutions in Canada; it was found that an innovative hybrid incorporating both online and face-to-face learning has been proven to be successful. The literature suggests a variety of learning modalities including: simulation, online modules, face-to-face sessions, small groups, patients as educators, case-based learning, tutorials and problem-based learning. In a study on the effectiveness of an interprofessional workshop on pain management for medical and nursing students, over 90% of students agreed that learning with students in other professions in these workshops was valuable.

**Consistent Core Values/Principles**
Within the literature there were common themes on how to provide adequate pain management through interprofessional collaboration. The following is a list of consistent core values and principles identified:

- Accountability
- Advocacy
- Characterizing entrustment
- Collaboration
- Communication
- Compassion
- Comprehensive care
- Continuum of learning
- Coordinated planning
- Cultural inclusiveness
- Diversity
- Empathy
- Ethical treatment
- Evidence-based practice
- Equality
- Health disparities reduction
- Identification of each profession and their expertise
- Informed decision-making
- Interprofessional teamwork
- Justice
- Patient-centred care
- Privacy and confidentiality
- Shared views
- Synthesises theory and practice
- Staff continuity
- Student participation
- Reflection
- Reviewing policy and practice critically from different perspectives
- Unity

**Competency-Based Education**
Some have suggested that competency-based curricula work best in interprofessional healthcare settings. This may be due to the findings in the environmental scan that highlight the purpose of interprofessional pain management programs with a competency-
based framework, which is to provide a shared view of pain for all healthcare professionals and enable them all to demonstrate competence to come to an agreement on pain management.\(^8\) Interprofessional competency frameworks have much to offer educators when introducing interprofessionalism to learners; the frameworks can serve as a guide to inform curricula in combination with appropriately aligned learning activities and assessments.\(^4\) Furthermore, in competency-based education, the competencies are aligned with the clinical practice and reality rather than simply the scientific expertise.\(^1\) It has been shown that the absence of core competencies may in part be a reason for the scarcity of pain education found in post-secondary programs.\(^1\) These competencies may be absent as the current curricula focus on traditional ways of teaching including didactic methods; impersonal topics, such as, anatomy and physiology; and does not address complex issues faced by patients, family members or clinicians.\(^7\)

**CONCLUSION**

The environmental scan identified several interprofessional pain management curricula. It is widely accepted that in order to maximize quality in patient care, all healthcare professionals need to work effectively in interprofessional teams.\(^5,10,16,17\) In order to address the literature gaps further, it would be beneficial to further review the pedagogical tools in order to successfully implement an interprofessional pain management master's level program with a focus on collaborative team integrated competencies and the primary purpose of best serving those that suffer from pain.

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An overview of the opioid crisis
Framing the opioid crisis in the context of the global drug problem

Tiago Ribeiro, Sasha Ayoubzadeh

ABSTRACT
The objective of this paper is to highlight the current state of the opioid crisis in Canada, framing it in the context of the global drug problem. The effects of the Opioid Crisis seen in London are part of a larger crisis occurring in North America. The USA has declared the opioid crisis a national emergency and we can expect a similar statement here in Canada as opioid related hospitalizations and deaths continue to rise. Although media attention continues to increase, we continue to see worsening statistics highlighting a flaw in how this complex issue is currently being addressed. Much like how attempts to prevent worsening of the opioid crisis have failed, globally, attempts to reduce the use and misuse of all illicit drugs have failed. Two key documents written by The Global Commission on Drug Policy will be reviewed to provide further insight while highlighting the need to challenge how we currently approach not just the opioid crisis but also the “war on drugs”.

INTRODUCTION
An average of 4 overdose related deaths per day – an alarming statistic. This number, released by the British Columbia (BC) Coroners Service, indicates the number of overdose related deaths occurring daily in BC between January 1, 2017 and October 31, 2017. Accordingly, there has been a 70.4% increase in the number of illicit drug overdose-related deaths in BC from 2015 to 2016. This dramatic increase is indicative of the increasing trends seen nationally. In Ontario, as of 2015, the annual death rates have almost quadrupled since 1991, going from a total of 144 to 734 overdose-related deaths annually. This reflects an average of 2 overdose-related deaths occurring daily. When we assess the problem locally, it becomes clear that London has also been affected. The London-Middlesex county ranked 11th in Ontario for high-strength opioid use in 2015. Furthermore, London ranked 13th in Ontario for opioid-related deaths in 2013, and the opioid crisis has been on the rise since. This has all contributed to London officially declaring a public health emergency in 2016 due to HIV and hepatitis outbreaks, which has been associated with increased intravenous drug use (IVDU).

Nationally, Canada finds itself in the midst of an opioid crisis, with an average of 16 hospitalizations daily related to opioid poisoning. Moreover, the rate of Emergency Department (ED) visits continues to rise, increasing by almost 50% in the past 5 years in Ontario. Although the opioid crisis has roots in overprescription by medical practitioners, illicit fentanyl and heroin use continues to increase and contribute to the high rates of overdose. According to a statement given by Dr. Theresa Tham, Canadian Chief Public Health Officer, fentanyl deaths “more than doubled in the first 3 months of 2017 compared to the same period in 2016”. Not only does the opioid crisis come at a high social cost, but there is also significant financial burden from opioid-related costs to the Canadian healthcare system, costing approximately $15 million in 2011. Furthermore, this calculated cost is a conservative estimate as it does not account for those arriving to the ED but not being admitted, those receiving treatment in the community and outpatient services, and those admitted for injuries or accidents related to opioid use.

Internationally, the opioid crisis occurring in Canada is not unique. The United States, Europe, China, Saudi Arabia, Lebanon, and Australia all have alarming rates of opioid abuse. Reports show a worldwide increase in opioid abuse, especially in middle- and high-income countries. Although some data is available, the United Nations continues to work with many countries to improve data collection on opioid abuse as this remains a barrier to fully understanding the extent of this issue. What is clear at this time is that the “war on drugs” has proven ineffective in decreasing substance abuse rates. The United States have declared their opioid crisis a national emergency, and the Canadian government is under pressure to do the same. Given the increasing burden of the opioid crisis both on healthcare systems and societies, it has become clear that there is need to change how this issue is addressed.

Considering the current state of the opioid crisis and drug problem locally and internationally, it was felt to be both important and informative to share the main findings and recommendations from 2 key documents released by The Global Commission on Drug Policy (GCDP). The GCDP is an international group composed of political figures, intellectuals, and business leaders who work together to “bring to the international level an informed, science-based discussion about humane and effective ways to reduce the harm caused by drugs to people and societies”. By looking globally, this organization highlights important lessons from around the world that can be useful as we move forward and think of new strategies to address both the opioid crisis and illicit drug use. Two recent reports will be summarized within this article: The GCDP’s 2016 report, “Advancing Drug Policy Reform,” and their recent position paper titled “The Opioid Crisis in North America”.

“THE OPIOID CRISIS IN NORTH AMERICA”
The 2017 position paper was written following recognition of the opioid crisis in both Canada and the United States. Through its position paper, the GCDP highlights the complexity of the crisis and refers to the many contributing factors, including: increase in...
prescription opioids, increase in non-medical opioid use, inadequate treatment services, and an increase in the use of synthetic opioids. Through their analysis, the report considers the history of health policy and economics and how that has led to the position we are in today. The GCDP’s main recommendations include working towards finding the appropriate balance in regulation to provide proper pain care while minimizing the possibility of misuse of these medications and making a concerted effort towards proven harm reduction and treatment measures currently available. These recommendations are meant to minimize the negative outcomes of the current crisis. However, the GCDP continues to advocate for decriminalization of personal use and possession of illicit drugs as a strong step towards a definitive solution. Below are some of the important points made in the position paper:

- The healthcare systems in Canada and the United States are not set up to effectively care for those with addiction; treatment is still dominated by abstinence-focused programs even though substitution therapy has continually proven to reduce mortality.
- The prejudice many still hold against substitution therapy negatively affects the opioid crisis, leading to overregulation and decreased access to methadone treatment.
- Given the demographics of those most affected by chronic pain and those who most often overdose, the epidemic seems to be driven by illegal rather than medical use of opioids.
- Though guidelines to reduce opioid prescriptions have led to a decrease in medical supply, incidence of overdose is still going up. This highlights that without providing adequate treatment and harm reduction measures, we fail those our healthcare system aims to serve. Individuals are left to seek out illicit sources with unknown purity and potency, increasing their risk of overdose.

**“GLOBAL COMMISSION ON DRUG POLICY 2016 REPORT – ADVANCING DRUG POLICY REFORM”**

The GCDP’s 2016 report describes full decriminalization and removal of all punitive responses of drug possession and use as an essential step in drug policy reform towards regulation. The report offers strong support in the form of relevant research and lessons from different systems around the globe with a focus on serving those impacted most, drug users. Below are some of the report’s supporting points:

- Prohibition has failed - such policies have led to social and health consequences for all of society. Today, violations of human rights and unjust law enforcement continue to occur which does not serve society’s effectively.
- Regulating the drug market gives governments the power to bring positive economic, health, and societal changes while taking the power away from illegal markets.
- Penalizing possession of drugs for personal use - when no risk is present to others - is an unjustified violation of an individual’s right to privacy and thus in conflict with the principles of personal autonomy and human dignity.
- Criminalization has fueled the global pandemic of HIV and hepatitis C as criminalization pushes people away from beneficial services such as needle and syringe programs and towards risky behaviors to avoid law enforcement.
- Well-implemented decriminalization programs globally are promising examples. Decriminalization in conjunction with a substantial effort towards harm reduction and treatment services has been effective.

**CONCLUSION**

Criminalization of drug use has not been effective at addressing the root cause of substance abuse nor has it achieved the goal of reducing or eliminating drug use. Evidenced by an increased incidence of drug use, hepatitis C and HIV outbreaks, and overpopulated prisons, an overhaul in drug policy is necessary. Much like the global drug problem, the opioid crisis is one that we as a society continue to fail to address properly. Overdose numbers continue to rise at an alarming rate, without an appropriate increase in proven reduction measures. The stigma and cultural viewpoints that bias our societal views on drug use may be clouding our ability to decide on effective action that will address these problems. Through research at an international level and consolidation of global lessons, the GCDP’s reports serve to spark new ways of thinking about addressing these challenges in hopes of leading to true productive change for the betterment of societies globally. It is time to challenge our current failed approaches to dealing with drug crises to make room for novel, effective methods that better serve those in need.

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Bluewater Health
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Understanding therapies selected for managing pain associated with spinal cord injuries
Aneta A Surmanski

ABSTRACT
Pain is a common consequence in patients who are suffering from a spinal cord injury (SCI). Such pain affects nearly all aspects of life including mood, physical function, and social activities. Management of pain must be preceded with a thorough clinical examination which characterizes pain according to a classification scheme. The International Spinal Cord Injury Pain classification system divides pain into three tiers: according to type (nociceptive or neuropathic), according to subtype (localization of pain), and according to the source. Neuropathic pain is predominately treated with three different types of pharmaceutical therapies – antidepressants, anticonvulsants, and analgesics. Multiple studies have shown amitriptyline, gabapentin, and pregabalin as being the most efficacious. Nociceptive pain is mainly treated with analgesics and physiotherapy, often together. Moreover, spasticity associated with nociceptive pain is treated with antispasmodics and physiotherapy. Non-traditional means of therapy, specifically transcutaneous electrical nerve stimulation, have demonstrated a favourable effect on pain. Nevertheless, finding an optimal treatment remains difficult and largely empirical. A stronger understanding of the mechanisms behind each pain type is needed in order to provide therapies that are better suited at targeting the source of the pain while minimizing possible side effects often seen in the SCI population. An integrated approach that fine tunes the combination of pharmacological and nonpharmacological therapies is needed for optimal management in SCI pain.

INTRODUCTION
Pain associated with spinal cord injury (SCI) is a debilitating disorder that affects nearly 81% of individuals 1 year post-injury, and 82.7% of individuals 25 years post-injury.1 Chronic pain associated with SCI has been shown to not only affect daily activities, such as exercise and ability to work, but can also impact mental well-being and quality of life.2,3 A major challenge to those with SCI is that long-term prognosis of pain often worsens over time following injury, creating a difficult obstacle to recovery by contributing to disability and decreasing the patient’s overall capacity in rehabilitation.2,3

Pain associated with spinal cord injury is classified according to the International Spinal Cord Injury Pain Classification and can be subdivided into two groups: neuropathic and nociceptive.4,5 Furthermore, neuropathic pain is further divided based on localization of pain: at-level, below-level or other, relative to site of injury, whereas nociceptive pain is divided into musculoskeletal, visceral or other pain. In addition, pain associated with spasticity is a problem often seen in SCI patients and may be managed using similar therapies as nociceptive pain.5

Treatment options vary for these subtypes of SCI pain and several guidelines, specifically CanPainSCI and Paralyzed Veterans of America (PVA), are available to guide physicians in recommending the appropriate course of treatment. These guidelines provide an in-depth analysis for screening, diagnosis and treatment for pain associated with SCI.6,7

Elucidating effective ways to alleviate pain remains an important factor in the recovery process, and understanding the specific mechanisms underlying these pain subtypes is vital in establishing proper efficacious treatment.5,8 Therefore, the objective of this review paper is to outline common mechanisms underlying pain subtypes in detail in order to describe how treatment options work to alleviate pain.

NEUROPATHIC PAIN MANAGEMENT
Neuropathic pain originates from the dysfunction or damage to the somatosensory system.4 This form of pain affects 29-75% of the SCI population.4 Etiology stems from structural damage to the neuron, which results in functional changes in neuronal signalling pathways, such as molecular changes in ion channels and -aminobutyric acid (GABA) metabolism.9 These changes may lead to neuronal hyperexcitability, permanent changes in nociceptive thresholds, and hypofunction of natural inhibitory signals.10,11 Hyperexcitability often results in the spontaneous generation of pain, and changes in nociceptive thresholds may pathologically amplify stimuli.11 Furthermore, natural inhibitory signals play a vital role in dampening or turning off specific signalling pathways. Disinhibition provokes neuronal excitation and spontaneous activity by prolonging synaptic transmission.5,14-16 In addition, nerve injury may also cause reduced expression of opioid receptors, which in turn lowers sensitivity of those neurons to inhibition by opioid agonists.13

Pain location with respect to region of injury allows for subclassification of pain type and therefore allows physicians to recommend an appropriate course of treatment.5,6 Neuropathic pain at the level of injury is typically caused by nerve root compression and often results in numbness, pain, and tingling along the course of the nerve. Such pain is usually not related to the spinal cord itself but can be due to any number of etiologies, such as nerve root pathology or changes in supraspinal structures.14 Pain below the level of injury often originates from direct spinal cord trauma, causing changes in sensory function, but can also originate from other etiologies.4,5

Due to the complex nature of this chronic condition, neuropathic
pain responds poorly to a single pharmaceutical drug. According to CanPainSCI guidelines, antidepressants, anticonvulsants, and analgesics are first-line pharmaceutical therapies used to treat neuropathic pain. Currently, amitriptyline, pregabalin, and gabapentin have the best documented properties and should be prescribed first. Recent studies have shown a significant decrease in nerve pain experienced by patients treated with either pregabalin or gabapentin, compared to placebo. Gabapentin serves to reduce activity of voltage-gated calcium channels and increase GABA biosynthesis, both of which attenuate neuronal hyperexcitability. In addition, pregabalin also reduces neuronal hyperexcitability by increasing extracellular concentrations of GABA in the brain.

Second-line treatment includes the use of opioids, specifically tramadol. These potent drugs may be used on their own or concurrently with other medications; however, risk of drug abuse and motion for side effects, such as gastrointestinal problems and cognitive deprivation, may complicate long-term use. Third-line therapy is transcranial direct current simulation, which shows a favourable effect on pain suppression. It modulates cortical excitability and decreases the perception of pain. Furthermore, evidence shows that transcutaneous electrical nerve stimulation either alone or with visual illusions and microsurgical lesioning of the dorsal root entry zone conferred neuropathic pain relief in patients that were resistant to other treatments. Both procedures are considered fourth-line therapy and are a last resort for patients experiencing neuropathic pain.

Although these treatment options convey promising outcomes, such therapies can impact other areas of function, specifically bowel and bladder management. For example, evidence shows that tricyclic antidepressants and opioids may cause constipation and increased urinary retention, among other side effects. Therefore, it is necessary to optimize these pharmacological treatments in individual patients in order to minimize these special side effects, while maximizing overall efficacy on pain management.

NOCICEPTIVE PAIN MANAGEMENT

Nociceptive pain is characterized as pain that follows when non-neural tissues, specifically musculoskeletal (MSK) tissues (bone, joint, muscle) are damaged. Patients in this category have a normal, functioning somatosensory nervous system but often experience mechanical instability, muscle trauma, and inflammation. MSK-related pain can originate from the initial trauma, postural abnormalities, and overuse of joints and muscles. Shoulder pain is the most common type and often results from overuse or muscle instability due to lack of core strength post-injury. Pain may also arise from spasticity, which affects muscle tone and contraction. Nociceptive pain can be further classified into visceral pain, which refers to pain generated in thoracic, abdominal, or pelvic viscera. Visceral structures are highly sensitive to a specific subset of stimuli, including stretch, inflammation, and ischemia, and generation of such stimuli may arise from bowel irregularities and side effects from certain medications.

First-line therapy for nociceptive pain includes analgesics and physiotherapy. Analgesic medications, such as non-steroidal anti-inflammatory drugs and certain steroids, can help relieve pain caused by inflammation by blocking enzymes responsible for prostaglandin synthesis. On the other hand, physiotherapy strives to prevent and treat the overuse of muscles and joints by teaching patients how to properly stretch and increase strength, while attempting to maintain or regain motor tasks. Evidence shows that physical activity alone is capable of improving quality of movement, coordination, and flexibility but has also been shown to reduce depression, pain and stress. Moreover, physiotherapy can address poor posture, abnormal gait, and muscle overuse, which can all contribute to nociceptive pain. Second-line treatment consists of weak opioids, such as codeine, which help modulate pain by binding to receptors in the brain, spinal cord, and other nervous tissue responsible for analgesia. These therapies must be used with caution due to the risk of building tolerance and potential development of gastrointestinal problems.

According to the PVA Guidelines for preservation of upper limb function post-SCI injury, MSK pain originating from upper extremities is managed using similar principles as in the non-SCI population. Healthcare providers must educate patients to minimize frequency and force of repetitive tasks as well as to avoid extreme positioning of the shoulder. Additionally, flexibility and resistance training should be integrated into the overall fitness program in order to enhance muscular endurance and promote appropriate limb positioning. On the other hand, visceral pain is treated based on underlying etiology, which may stem from distension of hollow organs and, most commonly, side effects from medications, i.e. constipation associated with opioid use. Treatment options include analgesics and spasmyotics.

Spasticity is classified as the involuntary activation of muscles which often results in increased muscle tone and frequent phasic stretch reflexes. Such alterations in motor control lead to uncontrollable muscle spasms and pain and interfere with movement, gait, and speech. Treatment for spasticity is centered on treating spasticity itself or managing pain associated with spasticity. Antispasmodics, like baclofen, and physiotherapy represent the first-line treatment for spasticity itself. Baclofen works as an inhibitory neurotransmitter analog by blocking excitation pathways in the spinal cord, thereby promoting muscle relaxation.

Lastly, non-traditional means of treatment, specifically cognitive-behavioural counselling and psychotherapy, have also been shown to provide significant advantages both on their own or in conjunction with more traditional therapies. Psychotherapy teaches patients how to develop better coping mechanisms to deal with both neuropathic and nociceptive pain as well as to decrease stress and improve overall quality of life.

CONCLUSION

Pain associated with SCI is complex and requires a combination of treatment modalities, specifically pharmacological
methods, physical therapy, and psychological counselling. Although individualizing treatment is very important, there are common considerations in the SCI population that are not present in other populations. These include impairment in bladder and bowel function, limited range of mobility, and impact on overall rehabilitation.20 With these careful considerations in mind and availability of more up-to-date guidelines, physicians can offer better combinational therapy options suited for each pain subtype associated with SCI.

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FEATURE ARTICLE

The case for a student run clinic in London
Yara Abou-Hamde, Adam Hopfgartner

ABSTRACT

Student Run Clinics (SRCs) are an emerging form of primary healthcare involving the collaboration of students and licensed health care professionals. SRCs aim to identify healthcare needs in the community and to meet those needs with supervised clinical and non-clinical services, education, and outreach. The SRC model provides students with direct patient interaction to complement classroom learning and develop extracurricular clinical skills.

The Alliance of Students Providing Interprofessional Resources and Education (ASPIRE) is a new interdisciplinary student group from the University of Western Ontario, Fanshawe College, and the University of Waterloo. Using established Canadian SRCs as a framework, ASPIRE is working to start a London-based SRC. A recent review of healthcare needs and social determinants of health completed by ASPIRE for the City of London identified a high incidence of mental health conditions and HIV in the community. Furthermore, the adequate provision of primary healthcare in London is complicated by transportation issues, financial constraints, and language barriers among underserved and minority populations. These concerns may be addressed by care provided by professional students from various disciplines organized by ASPIRE.

The future of ASPIRE includes health promotion in the London community with presentations on topics such as opioid addiction and overdose prevention, diabetic foot care, and smoking cessation. ASPIRE will continue to work towards a transition into a larger role in health promotion and health advocacy, with the ultimate goal of establishing an SRC in the City of London.

INTRODUCTION

Student run clinics (SRCs) are models of healthcare delivery where students assume a leadership role in the provision of care under the supervision of licensed healthcare professionals. These clinics aim to fill gaps in the healthcare needs of their local communities; for example, they may operate for extended hours, or involve a team of interprofessional students in the care of complex patients. Moreover, SRCs benefit student volunteers by exposing them to clinical encounters, health promotion, and interprofessional work prior to graduation. Today, there are more than seven SRCs in operation across Canada. According to Holmqvist et al., Canadian SRCs place a common emphasis on health equity, interprofessionalism, and student leadership.1

CANADIAN SRC EXAMPLES AND SERVICES PROVIDED

The first SRC became operational in Canada in the year 2000, and involved students at the University of British Columbia. Today, the Community Health Initiative by University Students (CHIUS) is an interdisciplinary student and resident-led team that has partnerships with both the Vancouver Native Health Clinic and Three Bridge Clinic.5 At the Three Bridge Clinic, chronic pain management is a core topic that students discuss with their patients. At the Vancouver Native Health Clinic, medical and nursing students provide services that focus on such topics as mental health concerns and chronic disease. These include taking health histories, performing physical exams, and creating personalized care plans.

One of the most successful SRCs in Canada is run by the Student Wellness Initiative Toward Community Health (SWITCH) in Saskatoon, Saskatchewan. SWITCH operates out of the Westside Community Clinic.3 Services offered include speech language pathology, physical therapy, occupational therapy, and cultural supports. The clinic also offers nutrition advice, assistance with transportation, and homework help.

In Ontario, there is currently one SRC that is fully operational. The Interprofessional Medical and Allied Groups for Improving Neighbourhood Environment (IMAGINE) clinic is based in Toronto.4 Patient identification and OHIP cards are not required to access care at this clinic. Services provided by IMAGINE include the treatment of acute conditions such as infections and wounds, preventative strategies, physiotherapy exercises, medication management, and counselling regarding harm reduction and social work issues. The drop-in clinic operates on Saturdays from 10 am to 2 pm.

A number of other SRCs across Canada provide similar services in their local communities, including ones in Regina, Edmonton, Calgary, Winnipeg, Halifax, and St. John’s.

POTENTIAL IMPACT OF A LONDON-BASED SRC

Enhancing healthcare education and augmenting the treatment of underserved populations are two mechanisms through which an SRC can positively impact healthcare in London.5 Medical students volunteering in an SRC gain valuable experience independent of the official curriculum. This practical environment improves clinical knowledge and skills, provides collaborative experiences, fosters positive attitudes towards interprofessionalism, and develops comfort with in-need populations. Recent evidence indicates improved educational outcomes among medical students involved with SRCs.5,6 Students are given a chance to mature in their future role as a medical professional through autonomous clinical experience under the supervision of medical professionals.8 Students from educational backgrounds outside of the health sciences benefit from an improved understanding of the healthcare
system and issues faced by underserved populations. SRCs also promote interest in primary care after graduation, specifically in targeting underserved populations. However, the benefits of the SRC approach are not isolated to student learning.

SRCs have been shown to improve specific health care outcomes in the general and underserved populations. The success rates of preventative medicine counselling, hyperlipidemia management, and depression screening have been shown to equate or exceed national averages in the United States. In particular, significant improvements in diabetic care in underserviced populations have been associated with treatment at SRCs. This includes indicators of diabetes control such as cholesterol level, HbA1c level, glycemic control, and blood pressure. Additionally, the SRC approach can improve diagnostic accuracy, promote greater compliance, decrease return visits, and increase patient satisfaction.

A new interdisciplinary student group from the University of Western Ontario, Fanshawe College, and the University of Waterloo has taken the first steps towards establishing an SRC in London. The Alliance of Students Providing Interprofessional Resources and Education (ASPIRE) aims to help relieve the pressure on a healthcare system that is struggling to meet the needs of the community. As an initial step, ASPIRE recently completed a needs assessment, composed of a review of the healthcare needs and social determinants of health within the City of London; the city is home to 383,822 inhabitants as of 2016. The high incidence of mental health conditions (up to 22% in certain pockets of the city with lower socioeconomic status) and increasing HIV rates (5.9 to 9.0 cases per 100,000 between 2005 and 2015 compared to the provincial average decline of 7.4 to 5.5 cases per 100,000) are two major concerns. Additionally, the three most prevalent chronic conditions presented to primary healthcare providers in communities across Canada, including London, are hypertension, arthritis, and chronic pain. These are all chronic conditions that professional students, including those from medicine, nursing, physiotherapy, and occupational therapy, can help manage; this can be done by creating personalized treatment plans, reviewing medications, and making appropriate referrals.

Major barriers to primary care identified in the assessment include distance to a primary care provider, the added financial burden of transportation to and from healthcare appointments, lost pay from time taken off work, and long wait times. This can be addressed by an SRC through extended hours of operation and the provision of transportation support if funding and/or donations can be secured. Transitional barriers between provincial and federal funding and inadequate access to mental health services are additional limitations faced by Indigenous communities. Furthermore, immigrants may struggle to navigate a foreign healthcare system and to communicate through language barriers. These issues may be addressed by eliminating the need for a provincial health card when providing patient care at an SRC, and by holding workshops to inform newcomers about the intricacies of the Canadian healthcare system.

Not surprisingly, creating a student run clinic also comes with potential barriers. One of the biggest barriers to implementation is cost. This includes funding necessary for marketing and volunteer recruitment, clinical equipment, and the provision of supports such as nutritional meals and bus tickets. Avenues of funding can be explored include grants, financial supports through partnering with educational institutions, community fundraising, and individual donations. However, all of these avenues do require large continuous efforts in order to maintain adequate funding. Ultimately, the current operation of several SRCs across Canada and the United States is a testament to the fact that these clinics can be successful with community efforts.

**ASPIRE HEALTH PROMOTION**

Although a London-based SRC is still in the works, ASPIRE has already embarked on a health promotion project serving the London community. Interdisciplinary teams of student volunteers have put together presentations on such topics as opioid addiction and overdose prevention, diabetic foot care, and smoking cessation. The first set of presentations is scheduled to take place in the community in mid to late November 2017. The hope is that the design and implementation of these presentations will serve as a stepping stone for ASPIRE to transition into a bigger role in health promotion and health advocacy in the city. Such exercises will also help develop the skill set of student volunteers and give them the opportunity to work interprofessionally early on in their careers.

**CONCLUSION**

More research still needs to be done on the outcomes of student run clinics, especially those in operation in Canada. Preliminary literature has demonstrated their utility to both students and community members. It is no secret that the Canadian healthcare system is strained, and that this strain is likely to increase with our aging population. Chronic health conditions, including pain syndromes, will continue to require a sizeable portion of healthcare resources. As such, an interdisciplinary student-led health team working under supervision has the potential to make a significant impact on the management of these conditions in a local setting.

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The etiology of spaceflight-associated hearing loss

Mason Kadem

ABSTRACT
Since the Apollo space missions, spaceflight-associated hearing loss has been considered a medical risk. NASA has given over a million dollars to astronauts as compensation for their hearing loss. The cause of spaceflight-associated hearing loss is unknown. Currently, research has shown sensorimotor and perceptual performance deteriorates after spaceflight. Certainly, the resulting hearing loss may not be caused by a unitary phenomenon, but rather due to a combination of factors endured during space flight. While presumed to be noise-induced, no link has been established between hearing loss and noise exposure during spaceflight; thus, countermeasures to reduce noise alone may be ineffective. Assessing the cause of spaceflight associated hearing loss may provide insight into novel neural, functional, and structural manifestations which could improve the safety and efficacy of terrestrial and space habitats.

INTRODUCTION
For the past 45 years, temporary and permanent hearing loss has been an outcome of long-duration spaceflight.\(^1-5\) In 33% of astronauts, the spaceflight environment caused permanent hearing damage, and in some cases astronauts were unable to further pursue spaceflights as a result.\(^6\) A comparison of air and bone conduction thresholds pre- and post-flight shows temporary threshold shifts (ie, shift in auditory thresholds) in 100% of returning astronauts, with permanent threshold shifts in 81%.\(^7\) The temporary hearing loss observed is atypical for noise-induced loss.\(^2\)

Several environmental changes, unique to space, are known to affect hearing ability (ie, hearing sensitivity and acuity). For example, the introduction of solvents, antibiotics and carbon monoxide can synergistically interact with noise (as low as 58 dB) to produce hearing loss.\(^8,9\) While these functional changes may result from changes in environmental gas, other environmental changes such as reduced gravitational strength and increased noise levels have the potential to affect not only functionality, but also the structure of the auditory system. Noise levels may affect the auditory structure via changes to the hair cells, or ribbon synapses; the decreased gravitational force (ie, microgravity) may also have implications both on, and downstream from, peripheral hearing structures as well as the auditory cortex.\(^7\) Thus, this review will discuss the potential link between the spaceflight environment and hearing loss. Namely, this review will explore whether hearing loss is attributed to noise levels, microgravity, or both. Hearing loss due to the individual or combined effects of sensory, structural, or perceptual components will be addressed.

PAUCITY OF SPACEFLIGHT KNOWLEDGE
Research in space is expensive, low in power, and logistically complex. While Earth-based models (eg, parabolic flights, head-down bed rest) have been developed to mimic aspects of spaceflight, they don’t fully mimic the spaceflight environment. Potential contributors to hearing loss can also be investigated by comparing the general population to individuals who share similar experiences as astronauts (eg, military pilots). For instance, military pilots are shown to experience hearing loss.\(^2\) Terrestrial methods act as surrogates for elucidating mechanisms behind spaceflight-associated hearing loss.

Currently, the methodologies for assessing hearing loss in space are scarce. Threshold-based audiograms, used to measure hearing status, are unsuccessful due to noise interference in the International Space Station (ISS).\(^2\) Moreover, microgravity-induced physiological changes (eg, headward fluid shifts, increased intracranial pressure) impede hearing tests.\(^7\) While magnetic resonance imaging (MRI) is not conducted in space, the ISS is equipped with an electroencephalogram which can be used to assess functional integrity of the auditory system. Despite the inability to use MRI in space, assessing the effects of spaceflight on brain structure has been attempted by evaluating retrospective longitudinal MRI scans pre- and post-spaceflight.\(^10\) Results from this study showed decreased gray matter in the temporal and frontal regions attributed to neuroplasticity. Collectively, spaceflight studies have shown that sensorimotor and perceptual performances deteriorate in spaceflight conditions.\(^5,11-14\) The paucity of spaceflight knowledge is attributed to the resource limitations of the spaceflight environment, the inability of Earth-based models to fully mimic the spaceflight environment, and the heterogeneity in methods.

SPACEFLIGHT AND NOISE
High levels of noise (>75 dB) are known to cause hearing loss, impede the cardiovascular system and imbalance homeostasis, and decrease cognitive performance.\(^15-17\) To investigate whether the ambient ISS noises played a role in hearing loss, Abel et al recorded ISS noise environments (72 dB) and played them back for prolonged periods (70-h), then assessed the follow-up auditory function.\(^18\) Three testing conditions were created to test the effects of ISS noise on normal function: (1) no noise (n = 5), (2) exposure to continuous noise (70-h) taped in ISS environment (n = 10), and (3) noise during the day only (n = 10). Five groups (n = 5 per group) were tested sequentially over 5 weeks, and testing lasted 4 days. The first day was for baseline tests and familiarization with environment chamber, and testing in the respective conditions began on the evening of the first day. Post-exposure tests took place 3 hours after termination of the study (4th day).
To assess auditory function in the middle ear, an ear inspection and tympanometry were conducted, followed by psychoacoustic tests, which detected auditory function in each ear. Speech understanding was tested using the Four Alternative Auditory Feature Test of consonant discrimination. There were no effects on auditory thresholds, or ability to discriminate consonants in quiet and noisy backgrounds. While these data support the notion that spaceflight-associated hearing loss may not be due to environmental noise on the ISS, the 70-h exposure paradigm may not have been long enough to exert effects on hearing ability. Exposure to noise and vibration has been shown to cause threshold shifts and hair cell loss more than exposure to noise alone, and in the study by Abel et al, vibrations were not delivered.23 Future work involving duration and intensity of noise level exposure and how they tie into respective vibrational effects are required to test the spectrum of noise stimuli experienced on the ISS and the implications for hair cell health in the context of hearing loss.

MICROGRAVITY

Another factor that plays a significant role in perception and sensory processing is microgravity, a force in space that is 1 millionth of the gravity on Earth. Microgravity impacts vestibular system function where disturbance in illusory perceptions and errors in sensory localization are observed.3,14,20 The auditory system evolved from the vestibular system.2,22 The same process could be at work in auditory processing. Vestibular disturbances in space affect musculoskeletal postural balance causing back pain, and incur changes in the vestibulospinal reflex and vestibulo-ocular reflexes (vestibular innervations to the visual system) causing headaches.23 These effects are shown to last even after returning from spaceflight.13,20

In a hallmark study conducted by Clément et al, researchers wanted to observe how visual perception is affected during spaceflight, precisely as a result of microgravity. Findings from these tests indicate that astronauts on the ISS show bias in the perception of their environment. Specifically, the astronauts underestimated distances and depths and overestimated heights while in orbit relative to their responses on Earth.23 These data highlight that perceptual-motor changes take place during adaptation to spaceflight. The same changes could be at work in auditory processing. If gravity can impede the processing of visual information, and given the intricate link between the vestibular, visual and auditory systems, what influence would it have on auditory processing?

The innate processes surrounding organization of external stimuli, in addition to learned experience, enables organization of the perceptual world. Microgravity alters how the environment is perceived in space, with lasting effects upon returning from spaceflight. Perhaps a reference point is set by the brain with regards to gravity and how proper motor control, visual representation, and visually guided movement are executed in the context of this “set-point” gravity level. The microgravity effects may arise due to a discrepancy between what is experienced versus what is expected. Alternatively, the gravitational change may impact the mechanistic properties of the peripheral auditory system. Ear bones (ossicles) move fluid inside the year that, in turn, stimulate hair cells, which send signals to upper areas of the brain. The fluid within the ear will have a different mass (mass*acceleration of gravity) in microgravity relative to Earth which may affect oscillo functionality. Cochlear hair cells, like vestibular hair cells, can change their ribbon synapses, or the mechanosensitive channels in the ear can change affinity. Hearing loss in space may then be a result of structural or functional deficits in the peripheral auditory system.

CONCLUSION

Despite the paucity and heterogeneity of spaceflight studies, findings from these studies offer insight into sensory, structural and functional changes during spaceflight that may have serious implication on hearing loss. Rewiring cortical organization to adapt to an artificial environment may be unlikely in permanent hearing loss, as individuals can adapt back rather quickly. Certainly, the gravitational environment is changing how the peripheral auditory system functions and how the sound signals are transduced and propagated. Longitudinal work needs to be conducted to address the myriad of factors present in the space environment, and their synergies with microgravity and noise, to predict hearing loss risks linked to long duration space travel to mars, and beyond.

REFERENCES


Management of fibromyalgia syndrome
Cognitive-behavioral therapy (CBT) for healthcare professionals

Joshua Y Lee, Stacey D Guy, Michael J Lukacs, Zoe A Letwin, Mohamad F Fakhereddin, Iyad J Al-Nasri, Shahan Salim

ABSTRACT
Fibromyalgia syndrome is a chronic pain condition that affects 440,000 Canadians above the age of 12. People with fibromyalgia report lifelong biological, emotional, cognitive and social complications. Recent clinical practice guidelines indicate management of symptoms is limited outside of analgesics. Cognitive-behavioral therapy (CBT) is one emerging treatment that displays promise for these individuals. CBT helps individuals to realize their maladaptive thought processes and how these can affect their own emotional response as well as the significance they attribute to potentially noxious stimuli. In conjunction with a physical exercise program, CBT shows promise in both the management of pain, and an improvement of quality of life.

INTRODUCTION
Pain, and management of pain, is complex and multifaceted. Chronic musculoskeletal pain is described as persistent or recurrent pain experienced regularly for a period of 3 to 6 months, affecting specific or widespread regions of the body. Fibromyalgia syndrome (FMS), a controversial chronic pain condition, is classified as a rheumatologic disorder that is characterized by generalized somatic pain. Fibromyalgia syndrome affects approximately 440,000 Canadians above the age of 12, which is 1.5% of household populations. Fibromyalgia syndrome is most commonly reported in females aged 40 years and older. Costs associated with FMS are extremely high with 75% of those costs being attributed to lost productivity.

People with FMS report lifelong biological, emotional, cognitive, and social complications. Management of the somatic symptoms of FMS historically involved a myriad of therapies such as opioids, exercise, nerve blocks, and physiotherapy. During the acute stages of pain, analgesics vary in effectiveness in eliminating symptoms. In the chronic stages, however, treatments tend to focus on management, rather than elimination of symptoms, and seek to enhance overall quality of life. As such, management goals focus on an improvement in health-related quality of life, maintenance of function, and a reduction of major symptoms. Cognitive-behavioral therapy (CBT) is often used to help individuals manage their FMS-related pain, as a way of improving mood, and fostering healthy coping skills.

This paper aims to educate readers on the pathophysiology of FMS and the basics of CBT – an evidence-based management therapy. Although the spectrum of CBT has broadened considerably since its inception, current strategies including mindfulness-based cognitive therapy (MBCT), dialectical behavior therapy (DBT) and acceptance and commitment therapy (ACT), arguably belong to the same family and are seen as extensions of traditional CBT. As an introduction to CBT in practice, we will describe the foundational principles of CBT in the context of FMS in adults, provide a summary figure for reference, and discuss implications for practice.

PATHOPHYSIOLOGY
While the underlying cause has yet to be fully elucidated, many factors have been identified in the development of FMS including genetic, environmental, and psychological factors. The generalized somatic pain is sometimes referred to as central sensitization, a dysregulation in nociceptive signaling within the central nervous system. With respect to heritability, FMS has a strong familial component. First order relatives of individuals with FMS are 8.5 times more likely to have the disease. In terms of specific genetic targets, it has been demonstrated that genes responsible for normal regulation of nociception can be down-regulated, which leads to hypersensitivity to pain. Specific polymorphisms of serotonin transporters (5-HTT) can cause lower serum levels of serotonin resulting in higher pain sensitivities.

Development of FMS has also been linked to a number of environmental and psychosocial factors. Acute trauma or illness has been linked to the onset of the disease process. Psychological stressors such as low social support or early childhood trauma have been shown to be strong predictors of widespread pain development. Psychological factors play a large role in the triggering and persistence of FMS. In combination with a genetic predisposition, both environmental and psychosocial factors can trigger an abnormal amount of physiological stress, resulting in a dysregulation of a hypersensitive system. Thus, psychological therapies may aid in reducing anxiety-related symptoms of FMS and improving overall function.

THE PRINCIPLES OF TRADITIONAL CBT
Cognitive-behavioral therapy was first introduced as a psychotherapeutic approach for depression in the early 1960s by Dr Aaron Beck. Since then, CBT has been implemented in the treatment of many different chronic pathologies often associated with anxiety or depression. Based on an information-processing model, CBT operates under the principle that any stimulus (external or internal) is subject to personal bias. These biases can distort an individual’s perception of a particular experience, leading to “cognitive errors” (eg, overgeneralizing, taking specific details out of context, or assigning personal significance to a situation). These errors are often the result of “dysfunctional beliefs” that...
become incorporated into long-term cognitive patterns. Once triggered by external events or stimuli, these patterns can produce extreme thought processes or behaviors often seen in pathological conditions. The following formula may help to conceptualize the primary principle behind CBT:

**Situation (event, stimuli) + Beliefs (core beliefs, attitudes, assumptions, automatic thoughts) = Reaction (emotional reaction and behavioral consequences)**

Cognitive-behavioral therapy is often implemented in a clinical setting via 3 distinct strategies: cognitive, behavioral, and situational. These strategies often overlap when put into practice. A brief summary is provided in Figure 1. The examples provided in the figure have been shown to be effective in treating FMS and often incorporate multiple CBT strategies. Since there is no standardized definition of what constitutes a formal CBT treatment, we have categorized each of the examples according to the definition outlined by Beck. Generally, these approaches focus on normalizing one's behavior and thought processes to produce more adaptive and realistic reactions to a given situation or stimuli. Based on the multidimensional nature of these strategies, it becomes apparent that an interdisciplinary approach is often required to modify cognitive processes and behaviors.

**STUDIES USING CBT TO MANAGE FMS**

In 2002, Turk introduced a diathesis-stress model of chronic pain which provided a more comprehensive understanding of complex pain conditions. He proposes that it is one's pre-existing sensitivity to anxiety in combination with trauma (actual or perceived) that eventually leads to disability. Turk describes “sensitivity” as a combination of dimensions including fear of pain, catastrophizing (ie, a tendency to envision worst-case scenarios), and causal attribution (ie, assigning personal significance to an event). Depending on a person's attitude and environment, these factors may result in a perpetual avoidance of anything that may cause pain. With an emphasis on addressing cognitive and behavioral processes, CBT can be used to address these core elements of disability as outlined by the diathesis-stress model.

Four clinical practice guidelines have been produced to address the screening, diagnosis, management, and monitoring of FMS. The European League Against Rheumatism clinical practice guidelines (2017) recommends CBT as a nonpharmacological therapy for individuals with poor coping skills, and mood disorders. There is no universal definition of CBT. For this reason, traditional CBT, mindfulness, operant therapy, and self-management education have been considered cognitive-behavioral therapies in FMS studies. A 2017 meta-analysis of 29 randomized controlled trials (N=2509) concluded CBT is tolerable, and effective in both the short and long term for reducing symptoms and disability of FMS. Specifically noted is a ≥50% pain relief (RD 0.05 [95% CI 0.02 to 0.07]), health-related quality of life ≥20% (RD 0.13 [95% CI 0.00 to 0.26]), reduction in negative mood (SMD -0.43 [95% CI -0.62 to -0.24]), improvement in disability (SMD -0.30 [95% CI -0.52 to -0.08]), and a reduction in fatigue (SMD -0.27 [95% CI -0.50 to -0.03]).

A combination approach using CBT and physical exercise is thought to be especially beneficial for management of FMS. Although physical exercises may prove painful for those with fibromyalgia or other chronic pain disorders, clinicians often described that CBT therapies may help reduce the pain experience. It has been shown that positive treatment outcomes can be generated via a combination of CBT and exercise when tailored to an individual's pain presentation (pain-avoidance, beliefs, thought processes etc.). CBT complements exercise by allowing individuals to more fully participate through improved coping skills. In addition, CBT facilitates long-term adaptations for individuals in an exercise program by setting goals centered on activities of daily living and increasing physical activity regardless of symptoms.

One issue with the implementation of CBT in a clinical setting is that it has been employed in a variety of different formats, thus creating uncertainty for clinicians in choosing which applications to implement. Traditionally, CBT treatments have encompassed a wide range of techniques ranging from problem solving to self-monitoring. That being said, the fact that CBT follows basic principles allows for both a flexible and pragmatic adoption of a variety of interventions. Through identification of noxious stimuli and maladaptive beliefs that may cause a negative emotional reaction, clinicians can select what type of therapy may prove most effective. For example, if an individual's response seems to be more influenced by maladaptive beliefs, a cognitive strategy may be the most appropriate selection. Conversely, situational strategies may prove most effective if an individual's negative behavioral response is triggered by a specific stimulus. Behavioral strategies may be employed throughout an intervention such that individuals have the appropriate tools to monitor their own emotional state. By its very nature, CBT allows for a multi-faceted strategy in dealing with the consequences of FMS through a combination of cognitive, behavioral, and emotional approaches.

**CONCLUSION AND IMPLICATIONS**

Fibromyalgia syndrome is a rheumatic disorder characterized by chronic pain. People with FMS suffer from physical, psychological, and social complications. While pharmacological management is available, a psychological strategy, CBT, is an effective and tolerable alternative, or combination therapy choice. Healthcare professionals can apply three strategies to help patients manage FMS: cognitive, behavioral, and situational. These strategies are suited to the clinical setting as they allow for flexibility in application and provide an individualized approach. Cognitive-behavioral therapy is a viable and effective management strategy for people with FMS.
Management of Fibromyalgia: Cognitive-Behavioral Therapies (CBT) for healthcare professionals

Table 1: Clinical implementation of CBT

<table>
<thead>
<tr>
<th>Cognitive factors</th>
<th>Behavioral factors</th>
<th>Situational factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive therapy</td>
<td>Objective monitoring of one’s own symptoms (numeric rating of intensity, frequency, duration, etc.)</td>
<td>Controlled and repetitive exposure to certain stimuli. Systematic desensitization.</td>
</tr>
<tr>
<td>Self-instruction training</td>
<td>Meditation, conscious/neutral awareness of one’s body, promote more parasympathetic activity</td>
<td>Autogenic training, therapeutic/graded exercise, social abilities training, communication/assertiveness training, planning/pacing activity, visual/graded imagery techniques, pain education, gamified rehab.</td>
</tr>
<tr>
<td>Behavioral rehearsal of skills</td>
<td>Adopting a desired set of skills through modeling, role-playing, rehearsal, and positive feedback</td>
<td>Overcoming negative thoughts, cognitive restructuring, planning/pacing activity, pain education.</td>
</tr>
<tr>
<td>Problem-solving training</td>
<td>Objectively and accurately defining the problem. Encourage rational problem solving by minimizing impulsiveness, carelessness or avoidance</td>
<td>Overcoming negative thoughts, cognitive restructuring, planning/pacing activity, pain education.</td>
</tr>
<tr>
<td>Behavioral activation</td>
<td>Increasing engagement in pleasant activities, increasing behaviors that counter avoidance.</td>
<td>Pleasant activity scheduling, social abilities training, planning/pacing activity, visual/graded imagery techniques.</td>
</tr>
<tr>
<td>Behavioral contacting</td>
<td>A statement or agreement outlining positive and negative consequences of performing certain behaviors.</td>
<td>Pain diary, cognitive restructuring.</td>
</tr>
<tr>
<td>Habit reversal</td>
<td>Identification of habits or tics, and countering these habits with more benign actions (e.g. applying lotion to hands instead of biting nails) or through therapist/social reinforcement.</td>
<td>Social abilities training, biofeedback, gamified rehab.</td>
</tr>
</tbody>
</table>

Figure 1. Clinical implications of CBT
FEATURE ARTICLE

REFERENCES

The role of medical cannabis in the opioid crisis

Lucy Samoilov, Claire P Browne

ABSTRACT

Opioid use increased dramatically in the 1990s upon introduction of newer, more relaxed regulations. As opioid prescriptions for pain increased, a parallel increase in opioid abuse and addiction occurred; this phenomenon is widely known as the opioid crisis. Cannabis had long been considered a recreational drug until legislation in 2001 allowed highly limited access to the drug for medicinal purposes. Although small-scale clinical trials show promising results for the use of cannabis in pain management, it is not currently indicated for chronic or severe-to-moderate acute pain, for which opioids are typically considered the standard of care. The impending legalization of recreational cannabis may mark a turning point in pain medicine as the general public becomes able to self-medicate with cannabis. This increased availability may lead individuals prescribed opioids to combine or replace them with cannabis, with potential positive impacts. There is growing evidence that cannabinoid compounds present in cannabis are able to augment opioid-induced pain relief. Increased availability of cannabis is linked to decreased opioid-related mortality and hospitalizations; furthermore, cannabis might act as a tool to treat opioid addiction. Cannabis does possess adverse effects and addiction risk, and expanded research into its properties is needed. However, its relatively decreased risk profile and potential positive effects indicate that it may serve an important role in addressing the opioid crisis.

INTRODUCTION: THE OPIOID CRISIS

The opioid crisis has continued to dominate Canadian health news headlines, and the alarming epidemic shows no signs of abating. Canada is second only to the U.S. in the use and abuse of opioids, with 13% of the population relying on these drugs for pain relief. Among users, 2% reported using opioids for non-medicinal purposes, constituting opioid abuse. In the past, opioids were falsely promoted as low-risk and non-addictive; they are now recognized for their notoriously addictive properties (5.5% addiction risk). In 2016 alone, there were over 2,400 opioid-related deaths across Canada.

Originally, opioids were approved in Canada for select populations such as terminal cancer patients. This changed in 1996, when OxyContin was approved for moderate-to-severe pain in all patients. This decision heralded a turning point in pain management and precipitated the current opioid crisis. Opioid use, abuse, and overdose rates have skyrocketed since opioids were approved for use in the chronic pain patient population. A Canadian study found that among opioid-dependent patients admitted to the Centre for Addiction and Mental Health in Toronto, 37% reported receiving opioids from physician prescriptions versus 21% obtained illicitly.

Although there is certainly an iatrogenic component to the opioid crisis, it is particularly difficult to eliminate their use in pain management. No drugs have yet been able to match their powerful and effective pain-relieving properties. Opioids remain the standard of care for many cases of severe acute or chronic pain despite their side effects and potential for addiction and overdose.

CAN CANNABIS BE USED TO ADDRESS THE OPIOID CRISIS?

Another healthcare issue making recent headlines is the legalization of recreational cannabis in Canada, projected to occur on July 1, 2018. These seemingly disparate issues - the opioid crisis and cannabis legalization - could connect in interesting ways. Although cannabis is best known for its psychoactive (“high”-) inducing properties, it may have a role to play in pain medicine and in mitigating the opioid crisis.

Cannabis has been approved for medical use in Canada since 2001 under the Marihuana Medical Access Regulations (MMAR). These regulations were introduced by Health Canada after seriously ill and dying patients fought for their right to pain relief without fear of prosecution, as marijuana was then broadly criminalized. Since then, the regulations have been replaced twice to accommodate modifications; the current iteration is the Access to Cannabis for Medical Purposes Regulations (ACMPR). Under these regulations, doctors can prescribe medical cannabis for any condition they believe it will aid. While guidelines have yet to be set for recreational cannabis, accessibility is likely to increase greatly. Interestingly, the federal government recommends maintaining a separate legal framework for medical prescription of cannabis.

PHARMACOLOGY OF CANNABIS

Cannabis, also known as marijuana, is generated from the bud and flowers of the plant Cannabis sativa. A variety of preparations are available, including smoked, vaporized, edible oil, or capsule form. Cannabis consumption leads to euphoria, altered perception, and decreased anxiety by acting on the endocannabinoid system. In this pathway, endocannabinoid neurotransmitters act on cannabinoid receptors 1 and 2 (CB1 and CB2). CB1 is the most abundant G-protein-coupled receptor in the human brain, and initiates signalling pathways responsible for anxiety, eating, growth, and learning. Its activation also facilitates the dopamine reward pathway, which is heavily implicated in addiction and substance dependence. CB1 inhibition can decrease the ability of substances to activate the dopamine pathway; examples include nicotine, ethanol, cocaine, and opiates.

Cannabis contains a multitude of active compounds; here, we will highlight two of importance: Δ9-tetrahydrocannabinol (THC) and...
and cannabidiol (CBD). THC is the most abundant compound in cannabis and the sole molecule with psychoactive effects.\textsuperscript{14,15} As a partial agonist of the CB1 receptor, THC produces effects such as euphoria, decreased pain response, and tachycardia.\textsuperscript{20,21} Synthetic THC and its analogues have been used as antiemetics, appetite stimulants, and neuropathic pain relievers.\textsuperscript{22} CBD is the second most abundant compound in cannabis.\textsuperscript{26} It acts as an inverse agonist of CB1 and can cross-react with other receptor systems.\textsuperscript{16,28} CBD possesses antipsychotic effects and can modulate nausea, inflammation, seizures, and anxiety.\textsuperscript{15,30,28}

**IMPACT OF CANNABIS LEGALIZATION**

Although medical cannabis has occasionally been utilized for pain management, its legalization will have important implications for the field. Broader recreational use will facilitate more rigorous studies to remedy the relative paucity of cannabis research.

Initial investigations of cannabis for pain management are promising. Cannabis has mild-to-moderate analgesic properties and can manage chronic pain in some patients.\textsuperscript{15} Cannabis also decreases patient-reported pain when used in conjunction with opiates.\textsuperscript{21} A study of individuals with chronic pain showed a 64% decrease in opiate use when taken alongside medical cannabis.\textsuperscript{24} Other studies describe patient substitution of medical cannabis for opioids or discontinuation of opioid use.\textsuperscript{25,26} This reported augmentation of opioid analgesia is likely due to the effect of cannabis on opioid pathways. As noted above, there is a crossover between the endocannabinoid and dopamine systems; CBD, and to a lesser extent THC, can also interfere directly with opioids by increasing dissociation rates from opioid receptors.\textsuperscript{27} Further investigation into the mechanism of such effects are ongoing.

The ability of CBD to dampen the rewarding effects of opioids, combined with its inability to activate the reward pathway, makes it a promising treatment for addiction and substance abuse.\textsuperscript{28} Preliminary studies show that CBD can help prevent opioid relapse, modulate drug-seeking behaviours, and improve abstinence.\textsuperscript{28,29} However, these investigations use purified CBD or nabiximol, an oral spray containing cannabis extract. It is not yet known whether cannabis consumption will produce similar effects.

Cannabis legalization could help mitigate the opioid epidemic in broader, systemic ways. American states where medical cannabis is legalized have lower rates of opioid-related hospitalization and overdose-related mortality.\textsuperscript{29,30} This may be due to patient substitution of cannabis for opioids, augmentation of pain relief translating to decreased opioid doses, or decreased polypharmacy rates. Legalization of recreational marijuana may also lead to a decrease in opioid-related deaths, as reported in a Colorado study.\textsuperscript{31} It is worth noting that cannabis overdose is very rare, and no cannabis-related overdose deaths have yet been recorded.\textsuperscript{32} These findings suggest that opioid-related healthcare expenses may decrease upon cannabis legalization.

**CHALLENGES AND RISKS OF CANNABIS**

Medical cannabis is not specifically indicated for any condition, including chronic pain. This has likely lead to underutilization - only 7% of Canadian doctors have written a recommendation for medical cannabis prescription.\textsuperscript{23} As the standard of care for pain management is often opioids, a doctor may not consider cannabis as a first line treatment. Health Canada has also discouraged the use of medical cannabis; it states that “[d]ried marijuana is not an approved drug or medicine in Canada” and “[t]he Government of Canada does not endorse the use of marijuana.”\textsuperscript{24} This position, combined with its public perception and complicated legal status, has likely served to deter prescription of cannabis.

Research regarding the use of cannabis in pain management is limited. Although randomized-controlled trials are being conducted, methodologies vary widely and many are currently in pilot stages.\textsuperscript{33} This has led to conflicting results and speaks strongly to the need for larger, more tightly controlled trials. In addition, much is unknown regarding the therapeutic use of cannabis in combination with opioids, including vital information on dosage and safety.\textsuperscript{19,30} This is further complicated by variability in levels of THC, CBD, and other compounds across cannabis strains.\textsuperscript{27}

Physicians should also be alert to the signs of cannabis use disorder, lest one epidemic be replaced with another. Approximately one in ten adults who have used cannabis can be classified as cannabis-dependent; it is more likely in men and younger users.\textsuperscript{28} Cannabis use disorder is characterized by cravings, changed behaviours, problematic usage habits, and altered mental status.\textsuperscript{22,28} THC has also been linked to negative mental health outcomes such as psychotic disorders. The association is strongest in adolescent consumers, and may be related to family history and overall consumption.\textsuperscript{29} Additionally, some studies have reported an association between cannabis use in opioid users and future opioid misuse or dependence.\textsuperscript{40} Given the expected expansion in cannabis use upon legalization, these reports are concerning. It will be important to monitor patients for symptoms or behaviours related to dependence.

**POTENTIAL OF CANNABIS RESEARCH**

Research was previously complicated by accessibility and possession laws, and was limited in applications; legalization will make necessary studies easier to conduct. For example, direct comparisons of opioids and cannabis could indicate whether it could replace opioids for certain conditions, or provide another option where opioids are ineffective or contraindicated. It will also be important to further investigate the use of cannabis as a complement to opioids. Combination therapy may have increased efficacy due to additive effects, facilitating lower doses of each drug; this could decrease side effect rates and mitigate tolerance. Furthermore, medical cannabis may be a therapeutic tool for opioid-dependent patients. Studying the ability of CBD-high cannabis strains to alleviate opiate withdrawal symptoms and prevent relapses could prove enlightening.
CONCLUSION

Currently, opioids remain the drug of choice for pain relief, despite their risk of serious adverse events and addiction. Evidence is accruing regarding the efficacy of cannabis for pain relief, both as monotherapy and in combination with opioids; its ability to interfere in addiction biochemistry is intriguing. Although cannabis carries its own risks, they are less severe than those of opioids. If prescription or self-medication with cannabis leads to a decrease in opioid use, the reduction in risk and harm would be significant. In the long term, cannabis has the potential to decrease burden on the healthcare system and relieve opioid-related morbidity and mortality.

REFERENCES


Botulinum toxin therapy in amputee pain management
A scoping review
Ramona Neferu, Ricardo Viana, Tom Miller, Michael Payne

ABSTRACT
Background: Post-amputation pain is common, occurring in up to 85% of patients. The pain can be related to the etiology of amputation, post-surgical healing, or prosthetic use. Pain syndromes may arise from a variety of tissue pathologies and can be broadly categorized into residual limb pain (RLP) or phantom limb pain (PLP). Botulinum toxin (BTX) has been found to be effective in treating a variety of neuropathic pain conditions. This scoping review summarizes the use of BTX in RLP and PLP management of patients with a major extremity amputation.

Methods: A literature search was conducted using PubMed, Web of Science, Cochrane Library, Scopus, and Google Scholar. Sixteen studies were included. Most studies excluded did not address BTX use in amputee pain management. Extracted data were categorized by either RLP or PLP.

Results: Two randomized controlled trials (RCTs), 10 case series, and 4 case reports were included (total 68 patients, 82 amputations). Seven studies addressed BTX use in both RLP and PLP, 5 studies address RLP exclusively, and 5 additional studies exclusively addressed PLP. Toxin types, injection techniques, and dosages varied between the studies. Negative results were reported in 2 RCTs and 2 case series showing 30% of patients with RLP and 50% patients with PLP did not benefit from BTX.

Conclusion: Literature for BTX in PLP and RLP is broad but lacking rigour for definitive conclusions to guide usage. There were more positive results for BTX use in RLP than in PLP. Case reports and patient series show promising results for both PLP and RLP, indicating future research should be directed at adequately-powered prospective trials.

INTRODUCTION
Post-amputation pain is a major concern in the amputee population, as it impedes rehabilitation and interferes with quality of life. It is estimated to affect up to 85% of patients and remains a challenging condition to treat, often requiring a multimodal approach to pain control. Post-amputation pain can be broadly categorized into residual limb pain (RLP) or phantom limb pain (PLP). There is a strong correlation between RLP and PLP, with patients often having difficulty distinguishing one category from another.

Residual limb pain has multiple etiologies, both neuropathic and nociceptive. These may include but are not limited to: infection (osteomyelitis, cellulitis), failure of flap closure, vascular insufficiency/claudication, bone spurs, heterotopic ossification, unusual mechanical stress at prosthesis-residual limb interface, soft tissue inflammation around the prosthesis from improper prosthetic fit, stump bursitis, neuroma, complex regional pain syndrome, cutaneous lesions (abrasions, ulceration, folliculitis, and eczema), and painful muscle contractions or dystonias.

Phantom limb pain typically occurs within the first 6 months after a limb amputation and can last several years after the amputation in the distribution of the amputated limb. Its description varies from neuropathic-like characterizations such as sharp, shooting, or electrical-like, to more nociceptive-like descriptions such as dull, squeezing, or cramping. The mechanism underlying phantom pain perception remains poorly understood, but it is thought to involve supraspinal, spinal, and peripheral mechanisms. Current treatment modalities attempt to target one or more of these areas to achieve pain control. For example, mirror therapy, deep brain stimulation, guided imagery/biofeedback/hypnosis, and opioids/anticonvulsants attempt to target somatosensory cortical reorganization in phantom limb pain. In addition, spinal cord stimulation targets functional changes in the dorsal horn of the spinal cord after deafferentation from a peripheral nerve injury. Finally, injections with local anesthetic or botulinum toxin, pulsed radiofrequency, or peripheral nerve stimulation attempt to target peripheral mechanisms such as neuroma formation, in which afferent fibers can develop ectopic activity, mechanical sensitivity, and chemosensitivity to catecholamines.

Botulinum toxin (BTX) is a potent substance derived from Clostridium botulinum bacteria and has been used for a variety of medical conditions, most commonly in disorders of excessive muscle contraction. Its benefit lies in its interference with acetylcholine neurotransmitter release at the neuromuscular junction by cleaving proteins in the Soluble N-ethylmaleimide-sensitive factor Attachment protein REceptor (SNARE) complex at the presynaptic nerve terminal, leading to decreased muscle contraction. In addition, BTX has been found to be effective in treating a variety of neuropathic pain conditions, but its antinociceptive effect remains unclear. Its effect on neuropathic pain appears to be independent from its effect on muscle contraction, with postulated mechanisms involving inhibition of SNARE complex-mediated vesicular release of substance P and glutamate, as well as reduction in vanilloid receptor activity involved in integrating noxious stimuli. There are seven types of toxins recognized, labeled A through G. Current BTX formulations include onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, CA, USA), abobotulinumtoxin A (Dysport®, Ipsen Ltd., Berkshire, UK), incobotulinumtoxinA (Xeomin®, Merz, Frankfurt, Germany, and Prosige®, Lanzhou Institute, Lanzhou,
China), and rimabotulinumtoxinB (MyoBloc®, Malvern, PA, USA and NeuroBloc®, Elan Pharmaceuticals, San Diego, CA, USA). The formulations differ in production and potency.9

Although there have been a multitude of trials studying the use of BTX in neuropathic and nociceptive pain,6,9 there are currently no guidelines for the use of BTX in post-amputation pain, and studies are mostly limited to case reports and small case series. In this scoping review, the current available literature on the use of BTX in post-amputation pain will be summarized, with the goal of providing context for future adequately-powered prospective trials to guide BTX usage in post-amputation pain.

METHODS

A literature search from 1996 to 2016 was conducted using the following databases: PubMed, Web of Science, Cochrane Library, Scopus, and Google Scholar.

The following search terms were used: Botox; botulinum; BoNT; BTX; amputee; amputation; stump; residual limb; phantom; limb deficiency. All citations from relevant articles were checked to identify additional relevant sources. Boolean search operators were used: ((Botox OR botulinum OR BoNT OR BTX)) AND ((amputee OR amputation OR stump OR residual limb OR phantom OR limb deficiency)).

Inclusion criteria included: English abstract; human studies; use of BTX for pain management in major extremity amputation or congenital limb deficiency proximal to wrist or ankle.

RESULTS

A total of 79 unique records were obtained. After inclusion criteria were applied, 16 studies were included in this scoping review (2 randomized controlled trials (RCTs),10-12 10 case series,12-22,25 and 4 case reports,20-22,24,25), including 6 abstracts (1 meeting abstract,16 2 poster abstracts,21,24 and 3 foreign language articles with English abstracts,21,22,25). Of these, 8 studies assessed outcomes of BTX use in both PLP and RLP (2 RCTs,10,11 5 case series,15-17 and 1 case report18), 4 studies addressed RLP only (3 case series,12,16,19 1 case report17), and 4 additional studies addressed PLP only (2 case series,22,25 2 case reports,21,25). The study results are summarized in Table 1 and Table 2 for RLP and PLP respectively. Table 3 shows aggregated demographic data, with the exception of one case series for which demographic data were not available from its published meeting abstract.16

DISCUSSION

Although all 16 included studies evaluated the effects of BTX on post-amputation pain, there was a notable variation in the emphasis on pain management between each study. For example, it should be noted that 6 studies10,12-14,16 evaluated the reduction in residual limb hyperhidrosis as the primary outcome of interest with BTX treatment; residual limb pain and/or phantom limb pain were secondary variables. However, given the limited literature on using BTX therapy to treat post-amputation pain, RLP and PLP results from the quoted studies were included in the analysis to achieve a comprehensive scoping review.

Due to the heterogeneity of primary outcomes in the included studies, there was a wide range of toxin serotypes, total administered toxin dose, and injection techniques. Toxin serotypes included rimabotulinumtoxinB (NeuroBloc®, MyoBloc®), onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), unspecified botulinum toxin type A (BTX-A) and unspecified botulinum toxin type B (BTX-B). The majority of studies used varying formulations of the more widely studied BTX-A; only 4 of 16 studies evaluated the use of BTX-B. Of note, 2 of 6 studies that focused on the treatment of residual limb hyperhidrosis as the primary outcome used BTX-B.10,11 There appears to be a similar variety of the toxin serotypes between positive and negative studies for RLP or PLP.

In studies focusing on hyperhidrosis as the primary outcome,10,12-15,24 BTX injections were generally performed intradermally in a grid pattern ranging from 1 cm² to 6 cm². Positive results in post-amputation pain management were seen in 50% of these studies.12,13,24 In the remaining studies focusing on post-amputation pain as the primary outcome, BTX injections were primarily performed intramuscularly in trigger points. Of note, 100% of these studies showed positive results.16-20,22,23 Intraneuroma,17 perineuroma,25 and subcutaneous16 injections were also described, also with positive results in post-amputation pain.

Total doses for BTX-A ranged from 100 units intramuscularly, or 200 to 500 units intradermally. Total doses for BTX-B ranged from 2500 to 5000 units intramuscularly, or 1750 to 20000 units intradermally. There did not appear to be an obvious relationship between dosage and efficacy of BTX-A or BTX-B for post-amputation pain, but there may be more benefit in intramuscular administration rather than intradermal administration despite the lower dosages used in intramuscular administration. One RCT used relatively large dosages of 10000 to 20000 units of intradermal BTX-B,16 with lack of positive findings in post-amputation pain management despite positive findings seen in observational studies at lower dosages of BTX-B at 1750 units intradermally and 2500 to 5000 units intramuscularly.13,16 Conversely, another RCT used moderate dosages of 250 to 300 units of BTX-A intramuscularly, subcutaneously, and intraneuroma, leading to some improvement in RLP.16 This is in contrast to a case series that used higher dosages of 300 to 500 units of BTX-A intramuscularly and found no significant improvement in post-amputation pain,14 while studies that used lower dosages of 100 units BTX-A intramuscularly showed benefit in post-amputation pain.15,17,19,20

Outcome measures in all studies was dependent on patient reporting via pain severity scoring systems, including visual analog scales (VAS), numeric rating scales (NRS), and Likert scales. Based on these outcome measures, beneficial results of BTX treatment for post-amputation pain were seen in several observational studies. For example, in one case series, patients’ PLP severity decreased from 9 to 2 on a 100-point VAS for up to 12 weeks after abobotulinumtoxinA (Dysport®) intramuscular injections (200 to 500 units), allowing for better prosthesis tolerance and use.25 A case report showed reduction of pain medication such as intrathecal morphine by 40% at 12 months of quarterly injections with 100 units
of onabotulinumtoxinA (Botox®) and elimination of all other pain medications, remaining “almost pain-free.” Kern and colleagues have also described a reduction of postamputation pain by 60% to 80% in 4 patients, with a 50% to 90% reduction in pain attack frequency such as from monthly to weekly, and a reduction in pain duration from 120 minutes to 10 minutes per day.10,11 In another case report, PLP ceased within 4 weeks of BTX injection, and the patient remained pain-free at the 1-year follow-up.12

Despite these positive results, from this scoping review, 30% of patients with RLP (19 patients of 62), corresponding to 37.5% of amputations (27 amputations of 72) did not benefit from BTX. In patients with PLP, 50% of patients (23 patients of 46), corresponding to 57% of amputations (31 amputations of 54) did not benefit from BTX. These negative PLP results stem from 2 RCTs10,11 and 2 case series of 8 and 4 patients respectively.14,15 However, the 2 RCTs were limited in sample size and may not have been adequately powered. For instance, the study by Pasquina et al with 7 subjects in the BTX study arm did not comment on power calculations,16 while the study by Wu et al acknowledged the small sample size of 4 subjects in the BTX study arm limited the study’s power. It should also be noted that the results from one case series with positive results for BTX use in post-amputation pain were not included in the data analysis, as the number of subjects in the study was not published.16

CONCLUSIONS

These data suggest there is more evidence for the use of BTX in RLP than in PLP, and more evidence for intramuscular injection technique than intradermal injection technique. However, this evidence is limited to pooled data from case reports and small case series, some of which measured BTX effects on pain, prosthesis use, and function as secondary outcomes. Therefore, there is a need for larger RCTs or systematic reviews to study the effect of BTX on post-amputation pain. BTX appears to have the potential to provide post-amputation pain relief, and may facilitate more effective amputee rehabilitation by offering one aspect of the multi-modal approach to amputee pain management.

REFERENCES

Table 1. Summary of studies incorporating botulinum toxin (BTX) use in residual limb pain (RLP).

<table>
<thead>
<tr>
<th>Study Author</th>
<th>Study Design</th>
<th>Subjects, No. (Amp., No.)</th>
<th>Toxic Serotype (Commercial name)</th>
<th>Total Dose, Units</th>
<th>Injection Site (Pattern)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasquini et al. (2016)</td>
<td>RCT</td>
<td>1 (10) in BTX study arm</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>10000 to 20000</td>
<td>Intradermal (35 cm² to 6 cm²)</td>
<td>RPL reduction (100 mm VAS)</td>
<td>Negative (p&lt;0.05)</td>
</tr>
<tr>
<td>Wu et al. (2012)</td>
<td>RCT</td>
<td>8 (8) in BTX study arm</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>250 to 300</td>
<td>Intramuscular, subcutaneous, or intracutaneous</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>Improvement in both groups (Botulin: p&lt;0.002; Lidocone/Depomedrol: p&lt;0.06) at 1 month. Botulin: p&lt;0.59; Lidocone/Depomedrol: p&lt;0.96 at 6 months</td>
</tr>
<tr>
<td>Alvarado-Saldaña et al. (2017)</td>
<td>Case series</td>
<td>14 (0)</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>100 to 200</td>
<td>Intradermal (2 cm² to 4 cm²)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>RLP significantly reduced after 3 months (NRS 3 from baseline 5.5, p&lt;0.008)</td>
</tr>
<tr>
<td>Kern et al. (2018)</td>
<td>Case series</td>
<td>9 (9)</td>
<td>onabotulinumtoxin B (Myobloc®)</td>
<td>1750</td>
<td>Intradermal (4 cm² to 6 cm²)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>RLP significantly reduced after 3 months (NRS 3 from baseline 5.5, p&lt;0.008)</td>
</tr>
<tr>
<td>Chambon et al. (2018)</td>
<td>Case series</td>
<td>9 (9)</td>
<td>BTX-A (Unspecified)</td>
<td>300 to 500</td>
<td>Intradermal (1 cm² to 4 cm²)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>Negative (p = 0.89)</td>
</tr>
<tr>
<td>Fruitall et al. (2011)</td>
<td>Case series</td>
<td>4 (8)</td>
<td>onabotulinumtoxin B (Myobloc®)</td>
<td>200 to 300</td>
<td>Intradermal (3 cm² to 4 cm²)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>Negative study: Paper claims &quot;no effect on RLP&quot;; RLP decreased by 1.5 +/- 0.6 on Likert scale</td>
</tr>
<tr>
<td>Kern et al. (2020)</td>
<td>Case series</td>
<td>4 (4)</td>
<td>BTX-A (Unspecified)</td>
<td>100</td>
<td>Muscle trigger points (unspecified pattern)</td>
<td>Patient-reported RPL reduction (0 to 10 VAS)</td>
<td>Case 2: RLP decrease from NRS 6 to 0 lasted 10 weeks, leading to better prosthetic tolerance</td>
</tr>
<tr>
<td>Kern et al. (2020)</td>
<td>Case series</td>
<td>4 (4)</td>
<td>onabotulinumtoxin B (Myobloc®)</td>
<td>2500 to 5000</td>
<td>Muscle trigger points (unspecified pattern)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>Decreased RLP for 4 to 12 weeks (all cases). Case 2: VAS 4.5 to 1.5 (average pain). VAS 10 to 2 (max pain). Pain frequency and duration decrease (weekly to monthly, hours to minutes).</td>
</tr>
<tr>
<td>Kern et al. (2020)</td>
<td>Case series</td>
<td>4 (4)</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>100</td>
<td>Muscle trigger points (unspecified pattern)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>Case 1: VAS 95 to 6.5, VAS 10 to 2 for 3 months.</td>
</tr>
<tr>
<td>Kemet et al. (2020)</td>
<td>Case report</td>
<td>1 (1)</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>400 (100 every 3 mo. for 1 y)</td>
<td>Muscle trigger points (unspecified pattern)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>Almost pain-free after 12 months; intraarticular morphine reduced to 40% initial dose; all pain treatments ceased</td>
</tr>
<tr>
<td>Nguyen et al. (2020)</td>
<td>Case report</td>
<td>1 (1)</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>RPL reduction as per patient reporting</td>
<td>Decrease in stump pain due to decreased muscle spasms</td>
</tr>
</tbody>
</table>

Table 2. Summary of studies incorporating botulinum toxin (BTX) use in phantom limb pain (PLP).

<table>
<thead>
<tr>
<th>Study Author</th>
<th>Study Design</th>
<th>Subjects, No. (Amp., No.)</th>
<th>Toxic Serotype (Commercial name)</th>
<th>Total Dose, Units</th>
<th>Injection Site (Pattern)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasquini et al. (2016)</td>
<td>RCT</td>
<td>3 (10) in BTX study arm</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>10000 to 20000</td>
<td>Intradermal (14 cm² to 4 cm²)</td>
<td>RPL reduction (100 mm VAS)</td>
<td>Negative (p&lt;0.05)</td>
</tr>
<tr>
<td>Wu et al. (2012)</td>
<td>RCT</td>
<td>4 (4)</td>
<td>BTX-A study arm (10/17 in BTX arm)</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>250 to 300</td>
<td>Intramuscular, subcutaneous, or intracutaneous</td>
<td>RPL reduction (2 to 10 VAS)</td>
</tr>
<tr>
<td>Kern et al. (2018)</td>
<td>Case series</td>
<td>9 (9)</td>
<td>onabotulinumtoxin B (Myobloc®)</td>
<td>1750</td>
<td>Intradermal (2 to 4 cm²)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>Decreased PLP severity after 3 months (NRS 3 from baseline 5, p&lt;0.008)</td>
</tr>
<tr>
<td>Chambon et al. (2018)</td>
<td>Case series</td>
<td>9 (9)</td>
<td>BTX-A (Unspecified)</td>
<td>300 to 500</td>
<td>Intradermal (1 cm² to 3 cm²)</td>
<td>RPL reduction (100 mm VAS)</td>
<td>Negative (p = 0.39)</td>
</tr>
<tr>
<td>Fruitall et al. (2011)</td>
<td>Case series</td>
<td>4 (8)</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>200 to 300</td>
<td>Intradermal (1 cm² to 3 cm²)</td>
<td>RPL severity (7-9 Likert scale)</td>
<td>Negative study: Paper claims &quot;no effect on PLP&quot;; RLP decreased by 1.5 +/- 0.6 on Likert scale</td>
</tr>
<tr>
<td>Kern et al. (2020)</td>
<td>Case series</td>
<td>4 (4)</td>
<td>BTX-A (Unspecified)</td>
<td>100</td>
<td>Muscle trigger points (unspecified pattern)</td>
<td>Patient-reported RPL reduction (0 to 10 VAS)</td>
<td>Case 1: &quot;pronounced reduction in PLP&quot;</td>
</tr>
<tr>
<td>Kern et al. (2020)</td>
<td>Case series</td>
<td>4 (4)</td>
<td>onabotulinumtoxin B (Myobloc®)</td>
<td>100</td>
<td>Muscle trigger points (unspecified pattern)</td>
<td>RPL reduction in pain frequency, duration, intensity (3 to 10 VAS)</td>
<td>RLP reduced by 60 to 80% in all cases. 90% reduction in pain frequency (3 patients): Pain duration shortened from 120 min to 5 to 10 min and pain intensity reduction from VAS 9 to 1 to 2 (2 patients).</td>
</tr>
<tr>
<td>Jin et al. (2019)</td>
<td>Case series</td>
<td>3 (3)</td>
<td>abobotulinumtoxin A (Dysport®)</td>
<td>200 to 500</td>
<td>Intramuscular (4 to 12 points)</td>
<td>RPL reduction (2 to 10 VAS, CGT)</td>
<td>Response within 3 to 4 days and marked improvement for up to 11 weeks, allowed for reduction of pain medications in all cases. Case 1: VAS 9 to 10 to 0 to 2; Case 2: VAS 7 to 10 to 1 to 2; Case 3: VAS 6 to 8 to 1 to 2</td>
</tr>
<tr>
<td>Kemet et al. (2020)</td>
<td>Case report</td>
<td>1 (1)</td>
<td>onabotulinumtoxin A (Myobloc®)</td>
<td>400 (100 every 3 mo. for 1 y)</td>
<td>Muscle trigger points (unspecified pattern)</td>
<td>RPL reduction (2 to 10 VAS)</td>
<td>Almost pain-free after 12 months; intraarticular morphine reduced to 40% initial dose; all pain treatments ceased</td>
</tr>
<tr>
<td>Polkun et al. (2016)</td>
<td>Case report</td>
<td>1 (1)</td>
<td>BTX-A (Unspecified)</td>
<td>100</td>
<td>Intradermal (1 cm² to 3 cm²)</td>
<td>RPL reduction as per patient reporting</td>
<td>PLP ceased within 4 weeks of BTX injection, up to 1 year at followup</td>
</tr>
<tr>
<td>Tycova et al. (2019)</td>
<td>Case report</td>
<td>1 (1)</td>
<td>BTX-A (Unspecified)</td>
<td>30</td>
<td>Surrounding the amputation</td>
<td>RPL reduction as per patient reporting</td>
<td>Reduced PLP severity up to 14 weeks from BTX injection</td>
</tr>
</tbody>
</table>

CGI = global clinical improvement based on a 0-3 scale (0 = no effect, 3 = marked improvement); VAS = visual analog scale; NRS = numeric rating scale; Amp = Amputations

Table 3. Summary of study subject characteristics.

<table>
<thead>
<tr>
<th>RLP</th>
<th>PLP</th>
<th>All Post-amputation Pain (RLP + PLP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies, No.</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Subjects, No.</td>
<td>52 LR (50 LR, 2 LR, unknown)</td>
<td>46 LR (37, 9, 1 unknown)</td>
</tr>
<tr>
<td>Amputations, No.</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Time post-amputation, mean (SD), y</td>
<td>4.4 (±1.3)</td>
<td>4.4 (±0.5)</td>
</tr>
<tr>
<td>Amputation level % (No.)</td>
<td>48.8%</td>
<td>30.2%</td>
</tr>
<tr>
<td>Amputation etiology % (No.)</td>
<td>48.8%</td>
<td>30.2%</td>
</tr>
</tbody>
</table>

Legend for Table 3: y = years; No. = number; SD = standard deviation; F = females; M = males; n = number of subjects for which respective data were known

Amputation level was known for 62 subjects (72 amputations) in RLP, and for 45 subjects (53 amputations) for PLP.

Amputation etiology was known for 55 subjects (63 amputations) in RLP, and for 41 subjects (49 amputations) for PLP.
Updates on chronic non-cancer pain management in face of the opioid crisis

Gayathri Sivakumar, Alexandra Budure, Elise Quint

ABSTRACT
Chronic pain not associated with malignancy is experienced by a significant proportion of the Canadian population. As the quality of life and physical functioning are markedly impaired in patients with chronic non-cancer pain, clinicians have commonly turned to opioid therapy for pain management. Since the 1990s, the steady increase in dispensing of prescription opioids has paralleled trends in opioid-related hospitalizations, overdoses, and fatalities. In fact, over-prescription and long-term opioid therapy are among the many root causes fueling Canada’s rise in opioid addiction and opioid-related deaths. Physicians and medical regulators have responded to this public health crisis by developing the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. The new evidence-based guideline aims to encourage safe prescribing practices, reduce and eliminate the use of opioid analgesics and promote non-opioid pharmacotherapy. While clear clinical guidelines will optimize physician prescribing patterns, it is imperative to recognize the need for non-pharmacological modalities for pain management, treatment, and care to holistically address the complex roots of opioid abuse.

INTRODUCTION
Chronic non-cancer pain (CNCP) is defined as any painful condition that persists for a minimum of three months and is not associated with malignancy. A Canadian population-based study using data gathered between 1994 and 2008 reported that 15-19% of adults experienced chronic non-cancer pain at any given time. CNCP has bearings on health and financial costs at an individual and population level. Suffering from chronic pain impedes activities of daily living, diminishes physical capacity and quality of life, and enhances disease burden. From an economy standpoint, CNCP is one of the foremost causes of healthcare resource consumption and disability among adults in the working-age group.

OPIOID THERAPY IN NON-MALIGNANT CHRONIC PAIN
In North America, physicians have commonly depended on opioids for acute, palliative and chronic pain management. When all indications for opioid therapy are included, Canada is the second-highest per capita consumer of opiate analgesics in the world, trailing behind the United States. High-dose dispensing of morphine, hydromorphone, oxycodone, and fentanyl have increased by 23% between 2006 and 2011 across Canada. Albeit there is evidence for the efficacy of opioids in treatment of severe, post-surgical or traumatic acute pain, little evidence supports long-term opioid therapy in the context of CNCP management. The sharp increase in prescription opioid analgesic use since the 1990s can be partly explained by aggressive pharmaceutical marketing strategies that encouraged primary care physicians to identify and treat chronic pain with opioids, despite a lack of evidence for using opioids for this indication.

In 2015, Canadian physicians prescribed opioids 53 times for every 100 people in Canada. In Vancouver, BC, a growing trend in the availability of prescription opioids in people who inject drugs is evident between 2010 and 2014. Nonmedical prescription opioid use (NMPOU) was significant among street youth and adults, and more than one-third of these individuals engaging in NMPOU had initiated the use of prescription opioids prior to illegal drug use. Use of opioid analgesics for CNCP may foster drug tolerance and lead to the prescription of higher-than-recommended doses, increased use of illicit opioids, iatrogenic addiction, accidental poisonings, and fatal overdoses. Hospital visits and treatment admission rates for opioid poisoning has increased by over 30% in the period between 2007 and 2015. In Ontario, the number of opioid-related deaths per year (excluding heroin-related fatality) has increased from 127 in 1991 to 540 in 2010, and this number continues to rise. Of the Ontarian patients under social assistance, 1 in 550 patients initiated long-term opioid therapy faced opioid-related mortality at a median of 2.6 years from the first opioid prescription. Nationally, the Public Health Agency of Canada reported 2,458 opioid-related fatalities in 2016.

CLINICAL GUIDELINES FOR CHRONIC NON-CANCER PAIN MANAGEMENT
The emergence of the opioid epidemic created a strong sense of urgency among clinicians and medical regulators to establish prescribing guidelines for CNCP. In 2010, recommendations proposed by the National Opioid Use Guideline Group for safe and effective opioid utilization was adopted. As the opioid crisis became more pronounced, critics argued that many of the prescribing recommendations from the 2010 Canadian Guideline were ambiguous, liberal with opioid use, and most importantly, eminence-based rather than evidence-based. Researchers from the McMaster G. DeGroote National Pain Centre have revised the 2010 Canadian Guideline and incorporated evidence-based findings to provide a focused framework for safe opioid prescribing practices for CNCP management.

The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain follows standards for trustworthy guidelines and is comprised of three categories of guidance: recommendations, good practice statements, and expert guidance. This guideline provides
Table 1. Summary of Canadian Guideline for Opioids for Chronic Non-Cancer Pain

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Strong evidence exists to support maximization of non-opioid pharmacotherapy and nonpharmacologic therapy, rather than a trial of opioid therapy.</td>
<td>Strong</td>
</tr>
<tr>
<td>2. For patients who have continual pain, despite optimization of non-opioid treatment, there is evidence to propose a trial of opioids and monitor for response. Opioid therapy should be terminated if there is no improvement in pain or function.</td>
<td>Weak</td>
</tr>
<tr>
<td>3. There is strong evidence against the prescription of opioids for patients with an active substance abuse disorder.</td>
<td>Strong</td>
</tr>
<tr>
<td>4. For patients with an active substance abuse disorder who experience pain even with optimized non-opioid therapy, the psychiatric disorder should be addressed before considering a trial of opioids.</td>
<td>Weak</td>
</tr>
<tr>
<td>5. For patients with a history of substance abuse disorder who experience pain despite maximization of non-opioid therapy, it is recommended to continue with the current therapy rather than a trial of opioids.</td>
<td>Weak</td>
</tr>
<tr>
<td>6. Prescribed opioid dosage is recommended to be less than 90 mg morphine equivalents daily (MED).</td>
<td>Strong</td>
</tr>
<tr>
<td>7. For patients beginning opioid therapy, evidence suggests limiting the first prescribed dose to less than 50 mg MED to reduce risk of nonfatal overdose or deaths.</td>
<td>Weak</td>
</tr>
<tr>
<td>8. There is evidence to suggest that cyclical prescription to other opioids may mediate dose reduction in patients who have persistent pain despite using opioids.</td>
<td>Weak</td>
</tr>
<tr>
<td>9. For those consuming more than 90 mg MED, there is evidence to support tapering opioids to the lowest effective dose with the aim of opioid cessation, if possible, rather than maintaining a consistent regimen.</td>
<td>Weak</td>
</tr>
<tr>
<td>10. There is strong evidence to suggest the use of a formal multidisciplinary program for opioid-consuming patients encountering serious challenges in tapering.</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Accompanying the recommendations in this clinical guideline, the good practice statements are supported by indirect evidence, represent common-sense practice, and are associated with assumed large net benefit. These include informed consent, monitoring and adjusting the opioid therapy, and understanding the potential contraindications to opioid prescription. Lastly, the expert guidance provides direction in an area for which there is little or no published evidence. The guidance statements also include strategies for mitigating risks including urine drug screening, treatment agreements, tamper-resistant formulations, fentanyl patch exchange and naloxone kits.

**MULTI-PRONGED STRATEGIES NEEDED IN COMBATING THE OPIOID CRISIS**

While these clinical guidelines are necessary to promote best-practice prescribing patterns, they are not sufficient. Other strategies must be implemented simultaneously in order to curb opioid abuse. Evidenced-based clinical guidelines are certainly necessary to optimize prescribing behaviours and mitigate opioid overuse, dependency, and addiction. Trends in opioid dispensing and associated adverse events must be closely monitored to evaluate the impact of public health and policy interventions. Medical colleges across Canada have committed to establishing a national narcotics monitoring network to identify prescribing practices among physicians, high-risk prescribing behaviours and at-risk patients. This information can then be reported back to regulatory bodies.20 The network will also allow physicians to compare their prescribing practices with peers, promote harm reduction measures, and optimize the use of opioids. However, there may be a downside to this increased monitoring. Physicians may be punished for prescribing higher volumes of opioids which could lead to undertreatment of pain. Additionally, the information gathered can help modify postoperative pain management practices, especially in surgical specialties, with long-term opioid therapy.20

Over-prescription of opioid analgesics by physicians is only one of many contributors to the growing opioid crisis. To curb opioid use and abuse, it is imperative to not only treat the physical symptoms of pain but also address upstream factors contributing to pain. Interdisciplinary pain treatment centres (IPTC) recognize pain in a collaborative approach with pain specialists, physical therapists, chiropractors, acupunturists, massage therapists, mental health providers and addiction specialists. This holistic approach, through a biopsychosocial lens, incorporates non-pharmacological modalities, such as cognitive behaviour therapy (CBT) and mindfulness meditation.18,20 A meta-analysis of 65 studies reported an additional 20% reduction in pain with IPTC in comparison to pharmacotherapy.22 Further supporting these findings, a systematic review with 3089 patient participants found a pain reduction of 37% in the CBT group vs 4% in the control.21 In a wide range of studies, IPTC therapy proves to positively impact the perception of pain and pain behavior, in addition to enhancing pain-coping skills, physical function, and psychosocial well-being.21,24,26 Moreover, there is evidence for increased return to
work in an IPTC vs a unimodal treatment model (68% vs 32%).

Interestingly, a study by Okifuji et al (1999) found a significant decline in the number of patients using opioids post-IPTC therapy in comparison to consumption at the time of program enrollment from 65% to 20%.

Multidisciplinary approach to pain management has been recommended as a treatment modality by the International Association for the Study of Pain in addition to several Canadian provincial Colleges of Physicians and Surgeons. Currently, multidisciplinary chronic pain centres are limited to urban areas, leaving sub-urban and rural areas with poor accessibility. In conjunction with holistic pain management practices, the issue of illicit use of opioids also needs to be addressed. Access to harm reduction services, including supervised consumption sites and overdose prevention programs, will be instrumental to improve unsafe injection practices, reduce overdose morbidity and mortality, and facilitate detoxification and addiction treatment.

SUMMARY

As opioid-related morbidity and mortality increases in Canada, addressing this public health crisis will be paramount for individual and societal health. While clinical guidelines have been updated to advise best-practice prescribing behaviours, multi-pronged systemic approaches will be key to tackle the complex roots of the opioid epidemic. Interdisciplinary treatment modalities for pain management have provided considerable evidence not only for pain reduction, but also for improved physical functioning, psychosocial wellbeing, and quality of life. Harm reduction programs should also be established across the nation to mitigate adverse health outcomes of substance abuse and addiction. Physicians are at the front-line of the opioid crisis and as such, have an onus to their patients to advocate for such systemic changes to address pain management in a holistic, patient-centered approach and provide meaningful solutions to end Canada's epidemic of opioid abuse.

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Moving towards a molecular understanding of pain management

The future role of molecular medicine in pharmacologic treatment of patient pain

Logan Van Nynatten, Shafaz Veettil

ABSTRACT

The management of chronic pain remains a challenging area in the practise of medicine. As our population ages, the incidence and prevalence of those living with chronic pain continues to increase. Hence, there is need for methods that promote optimal pain management. One promising avenue is that of “personalized and molecular pain management”. Indeed, a variety of genetic and molecular factors have been shown to impact metabolism of narcotics, limiting drug effectiveness. Furthermore, the prominence of polypharmacy can complicate the action of pain medications. Additional laboratory and diagnostic tests may be of benefit for risk stratifying patients at high risk of abusing pain medications from those at lower risk. Combining this with physician worry of worsening the opioid addiction crisis in North America via prescribing narcotics, there remains great pressure on physicians to limit their use of narcotics. Unfortunately, this may result in patients who are suitable candidates for prescription opioids receiving inadequate pharmaceutical treatment to complement non-pharmacological interventions. Moving forward, the implementation of molecular medicine approaches to pain management may provide unique solutions to these challenges.

INTRODUCTION

The diagnosis and treatment plans for chronic pain – often defined as pain lasting greater than 3 months – remains a challenging topic within medicine. Although we have the means and knowledge to treat pain, many Canadians suffer from inadequate pain treatment. A Canadian survey in 2012 found 29% of adults reported continuous or intermittent pain lasting six months or longer. Of these individuals, 88% rated their pain as a 4 or higher on a ten-point scale. The prevalence of chronic pain was also shown to increase with age as 22% of those aged 18-34 and 39% of those aged 55 years or older reported chronic pain. Females also had a 4% higher prevalence than males. Other Canadian studies have found similar results. Indeed, pain is the most common reason patients seek healthcare, and accounts for approximately 78% of emergency department visits. However, large multicentre studies continue to demonstrate high pain intensity, and suboptimal pain management experienced by patients in Canada. Hence, the question becomes how do we adequately manage chronic pain in a responsible way as to prevent abuse of prescription narcotics? One promising avenue is that of “personalized and molecular pain management” to guide pharmacologic treatment within molecular medicine.

PERSONALIZED MEDICINE AND PAIN MANAGEMENT

Personalized medicine pain management refers to the concept of optimizing medication types and dosage based on individual patient genetic and molecular variation. The use of personalized medicine is already being implemented in a variety of other medical fields, such as oncology. It is possible to risk stratify tumors based on the pattern of protein expression and treat accordingly. For example, breast cancers expressing the HER2 ligand can be treated with trastuzumab, gastrointestinal tumors overexpressing CD117 are responsive to tyrosine kinase inhibitors, and non-small lung cancer expressing PD-L1 suppressing the anti-cancer immune response can be blocked with pembrolizumab. These are agents that work to specifically limit the molecular pathways conferring growth advantages to specific tumors in specific patients. Similarly, we should be able to apply molecular approaches to optimize treatment of acute and chronic pain. Ideally, we could identify pathways or protein polymorphisms that either enhance or limit the effectiveness of pain medications for individual patients. Although the implementation of using patient genetic polymorphisms and gene copy number of drug metabolizing enzymes is still a few years away in premise, the rapid expansion of genome wide association studies and molecular medicine puts personalized pain management well within reach.

METABOLIC FACTORS IMPACTING PAIN MANAGEMENT

Cytochrome P450 (CYP) enzymes provide over 80% of phase I drug metabolism. As one can imagine, gene polymorphisms, deletions, or duplications can result in significant qualitative and quantitative variation in CYP enzyme mRNA and protein expression impacting enzymatic function. In particular, CYP2D6 – of which there are greater than 50 allelic variants reported – metabolizes a variety of frequently used drugs including beta-blockers, antiarrhythmics, anti-depressants, neuroleptics, and critically, analgesics such as codeine, dihydrocodeine, hydrocodone, oxycodone and tramadol. As such, variation just in this enzyme alone can produce patients who are poor, intermediate, extensive and ultrarapid metabolizers of narcotics – something which is rarely considered in the office of a general medical practitioner. Furthermore, fluctuations in drug metabolism and the prevalence of such polymorphisms vary between ethnicities, with 3-5% of the European, 10-12% of Mediterranean, 21% of Saudi Arabian, and 29%
of the Ethiopian population being ultrarapid metabolizers of such narcotics. Such differences highlight how the impact of genetic variation on drug metabolism may be worthwhile considering in clinical practice.

There are multiple examples of other genetic variations potentially impacting drug metabolism and hence the patient’s experience living with chronic pain. NSAIDs, or non-steroidal anti-inflammatory drugs, are a common class of drugs used in the multimodal approach to pain management which are largely metabolized by CYP2C9 and CYP2C8 enzymes. At least 33 genetic variants have been reported for CYP2C9, again varying amongst ethnicities. Specifically, the two missense mutations more common in the Caucasian population, which include switching Arg44 to a cysteine and Ile359 to a leucine result in decreased enzymatic activity. Such polymorphisms could affect the metabolism of widely used drugs such as ibuprofen, naproxen, and celecoxib. The presence of the G129A polymorphism in Catechol-O-Methyltransferase impacts dopaminergic and adrenergic neurotransmission through a 3-4 fold decrease in the metabolism of catecholamine, having important consequences for drugs commonly prescribed for chronic cancer pain. The metabolism of many drugs is impacted by several CYPs, such as tricyclic antidepressants (TCAs) often used in treating neuropathic pain which are metabolized by both CYP2D6 and CYP2C19. Hence the serum plasma levels of TCAs can be impacted by polymorphisms in both enzymes. Cumulatively, these findings highlight how such subtle molecular variations can potentially impact the effectiveness of pharmacologic therapy, thereby impacting the degree to which pain relief may be experienced by patients. Incorporating such knowledge of genetic variations when developing treatment plans for patients may represent a great opportunity for optimizing treatment on an individual patient-to-patient basis.

POLYPHARMACY AND CHRONIC PAIN MANAGEMENT

Even taking into consideration the genetic factors impacting pain medication efficacy, metabolism, and duration of action, it is equally important to consider the other medications that the patient has been prescribed that could impact metabolism of narcotics, and hence the patient’s pain experience. Polypharmacy – the use of multiple drugs in the treatment of medical conditions – is quite prevalent in patient care today. It is not uncommon to see upwards of a dozen medications being taken by an individual chronically ill patient every day. The molecular targets of such drugs can alter cellular metabolism to both increase or decrease the efficacy of drugs prescribed for pain management. As an example, the ABCB1/MDR1 gene encodes an efflux transporter to remove certain substances from cells, and affects bioavailability of fentanyl, morphine, and related pain medication derivatives. There are common drugs that both induce (ex atorvastatin, cyclosporine, erythromycin, itraconazole, methadone, verapamil, tamoxifen) and inhibit (ex dexamethasone, morphine, retinoic acid) MDR1 activity. Prescription of drugs that have competing and synergistic effects on the bioavailability of drugs such as morphine and fentanyl are rarely considered and are likely a component as to why individuals may experience inadequate pain relief at doses physicians feel should be more than adequate to relieve pain. Combining this with the natural polymorphisms observed in MDR1, one can imagine how a high-throughput screening of drug interactions and patient genetic variation could be a useful tool to help specifically manage patients with chronic pain that are responding to treatment poorly.

Indeed, there is much work being done to try and develop such a high-throughput screening system, however it is not without its challenges. Most of these methods are based on either in vitro chemical reactions or in silico simulations of drug interactions. Of course, this does not fully account for the dynamic molecular interactions which occur in vivo impacting drug-drug interactions. Regardless, one main assay used to investigate drug-drug interactions in pre-clinical drug discovery, are in vitro high throughput fluorometric screening methods. Largely this works via multiwell plates containing CYP enzymes which metabolize a substrate into a fluorescent product, which can be detected. The addition of single or multiple drugs can be added to these wells, and their isolated or combined impact on CYP enzyme metabolism can be recorded based on fluorescence variation. At the in silico level, computer algorithms are in development that strive to predict drug-drug interactions based on molecular parameters. We propose that as these assays become more robust, the data collected from such high throughput analysis could be consolidated to generate a reference database where clinicians could refer to and make note of combinations of drugs that either maximise or limit the effect they are trying to achieve, for those patients who appear to show a lack of response to treatment.

MOVING TOWARDS A MOLECULAR UNDERSTANDING OF NARCOTIC ABUSE

Undeniably, there is an opioid abuse and addiction epidemic in London, Ontario, as well as across Canada. The Public Health Agency of Canada reported that at least 2458 Canadians died from opioid related addiction overdoses in 2016. Although opioid addiction is impacted by psychosocial and environmental factors, there may also be some additional genetic factors placing one at higher risk for addiction. It has been reported that polymorphisms of the mu-opioid receptor (A118G) and of the catechol-o-methyltransferase gene (V158M) may alter analgesic responsiveness and opioid abuse risk. Additionally, although the mu-opioid receptor (MOR) mediates most of the analgesic actions of opioids, the kappa-opioid receptor (KOR) has been suggested to be involved in limiting MOR analgesic tolerance, dependence, and withdrawal symptoms. Certain polymorphisms of the MOR gene (OPRM1) have demonstrated a significant association with populations of heroin addicts, and sequence variations in the MOR gene (OPRM1) have been found to be associated with heroin addiction in humans. Similar associations have been found with polymorphisms in the PYDN and ABCB1 gene families. It remains unclear as to whether such polymorphisms are predisposing factors for addiction or are the consequence of the development of drug resistance.
these and future associations become more clearly elucidated and understood, they may hold tremendous promise for the field of pain management. Indeed, the vast reason opioids are under-prescribed for chronic pain management in certain populations is physicians’ fear they will be stimulating opioid abuse and addiction.25 This is reasonable considering the majority of those who abuse opioids have their first exposure to the drugs from physicians. Currently, there is no effective laboratory test to risk stratify those patients who are at higher risk for addiction, abuse and opioid dependence from those who are not. Such a test would be useful to complement the widely utilized Opioid Risk Tool that currently exists as a survey screening method for determining risk of opioid abuse based on various patient psychosocial risk factors.26 Although addiction is in no way solely a genetic problem, using such personalized medicine approaches may help contribute to the generation of more effective criteria in prescription and dosing of narcotics.

CONCLUSIONS

In brief, a personalized medicine approach to pain management may be an effective tool to aid physicians in managing their patients’ pain. Ideally, such an approach would also help optimize which medications patients are taking to minimize adverse interactions limiting effective treatment of chronic pain. Furthermore, understanding the personal genetic variation of those enzymes critically involved in nutrient metabolism may help identify those patients who are at higher risk for abusing opioids, in consideration with other biopsychosocial factors. Considering uncontrolled pain compromises immune function, promotes tumor growth, and is associated with increased morbidity and mortality, personalized and molecular medicine pain management may offer a novel way to help to improve the quality of life for those who suffer from inappropriately managed pain.23

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Ethical examination of sham surgeries for relief of chronic pain in clinical practice

Katherine Fleshner, Jacek Orzylowski

ABSTRACT

Treatment of chronic pain is challenging for both patients and physicians alike. Interventional management of pain is often indicated for patients who are not helped by pharmacotherapy, and can include procedures such as neurectomy and vertebroplasty. However, randomized controlled trials of these procedures often demonstrate a significant improvement in symptomatology among patients in the control arm who have instead undergone a sham surgery, which eliminates the perceived surgical steps required for benefit but mimics the surgery in every other way. We examine whether an ethical framework might exist for sham surgeries to hypothetically be performed for clinical benefit of chronic pain. Once all evidence-based options are exhausted, performing sham surgeries may be justified under beneficence and non-maleficence since sham procedures are often equally efficacious but considerably safer than their true intervention counterparts. Physicians must only recommend such procedures with the intent of ameliorating patient suffering. Some degree of disclosure of a possible placebo effect prior to a sham surgery may satisfy the principle of autonomy while still maintaining the placebo response.

INTRODUCTION

Chronic pain is a challenging condition. It is notoriously difficult to treat effectively and carries a large disease burden.¹ Unlike acute pain, chronic pain may or may not be associated with trauma and may be persistent. Chronic pain may also manifest with no clear etiology despite full clinical and radiological workup.¹

Current modalities of treatment for chronic pain include physical therapy, pharmacotherapy, and interventional therapy.² Pharmacotherapy is typically the first-line of treatment and includes non-steroidal anti-inflammatory drugs and opioids.² Intervventional therapy is a newer modality of therapy often reserved for drug-resistant chronic pain.² Interventions include implantable devices such as analgesic infusion pumps, spinal cord stimulation, and surgeries such as neurectomy and vertebroplasty.²

Novel surgical techniques are rarely rigorously evaluated before they are performed on patients.⁴ Nevertheless, surgical trials to evaluate the effectiveness of pain procedures will often utilize two patient groups: one group receives the active technique being studied and another receives a sham surgery.⁵ A sham surgery is defined as a surgery that mimics everything about the active procedure except for the steps considered necessary for benefit.⁵

Despite the lack of active intervention, pain procedure trials often report clinically significant improvements in pain in the sham surgery arm.⁵ Sham surgeries have also produced a marked improvement in disability and quality of life.⁵ Furthermore, evaluation of surgical trials with sham controls found improvement in the sham group in 74% of trials.⁶ For this reason, sham surgeries are an important component of research trials as they help to elucidate whether or not procedures provide any true benefit.

In spite of their importance in the research setting, sham surgeries are not routinely performed on patients in the clinical setting. In fact, surgical procedures found to have no measurable effect beyond placebo are often abandoned altogether due to a preference for evidence-based procedures.⁷ However, in a hypothetical scenario, might there be a way to perform sham procedures for clinical benefit while still maintaining ethical practice? The following article will examine this question under the medical ethical principles of beneficence, non-maleficence and autonomy.

THE PLACEBO EFFECT

The placebo effect is the symptomatic improvement with the administration of a medication or procedure that, perhaps unbeknownst to the patient, consists of no active ingredient or measure that can produce the anticipated change.⁸ In the era of medical paternalism, physicians regularly prescribed placebos when patients were terminally ill or when indicated therapies were likely to do more harm than good.⁹ Advocates of placebo administration also believed that it helped patients psychologically cope with the burden of illness.⁹

There are three dominant theories about how the placebo effect elicits analgesia. One theory is that placebo stimulates endogenous opioids in the body to produce pain relief, which is supported by the fact that placebo analgesia is reduced with administration of an opioid antagonist.¹⁰ Another theory postulates that operant conditioning of being treated by a physician causes the placebo effect.¹⁰ This theory can also explain the phenomenon of increased placebo response with increased surgical invasiveness.¹¹ Finally, the ‘meaning model’ of placebo effect suggests that the therapeutic interaction itself and the physician-patient relationship contribute to the placebo response.¹²

BENEFICENCE, NON-MALEFICENCE AND AUTONOMY

Medical ethics, as delineated by Beauchamp and Childress, consists of four principles: autonomy, beneficence, justice and non-maleficence.¹² Respect for patient autonomy requires that physicians honor patients’ right to self-determination with respect to medical decision-making.¹² Beneficence states that physicians must always act to promote the health of their patients, while non-maleficence states that the physician should do no harm to their
patients. Finally, the principle of justice is concerned with fairness and equality in the distribution of medical resources. In this paper, beneficence and non-maleficence will be applied to evaluate whether sham surgeries should be considered in clinical practice. The principle of autonomy will be applied to examine whether physicians should withhold information about the true nature of sham procedures.

The ethical tenet of non-maleficence stems from the Hippocratic Oath, in which the physician vows to do no harm to his or her patients. Simplistically, it can be argued that the benefits of a therapy must outweigh the risks or adverse effects, and no intervention that brings undue harm to a patient can be justified. With placebo pills, patients risk clinical deterioration but there are no risks associated with the placebo itself. A sham surgery mimics a true surgery, meaning that anesthesia must be administered and a superficial incision made, which are not risk-free. However, these risks might be offset by the fact that surgery-associated placebo is more potent than drug-associated placebo and thus can provide more benefit. Sham surgeries are also safer than their true intervention counterparts in RCTs, with far fewer adverse events reported from clinical trials. Finally, since there is no active intervention, local anesthesia or light sedation and minimally invasive surgical techniques could be employed to reduce the risks associated with anesthesia and the surgical wound.

Similar to non-maleficence, beneficence espouses that physicians should always promote health and act in the best interests of their patients. In this context, beneficence can be interpreted as the duty of the physician to prescribe therapies with demonstrable benefit. Treating chronic pain, however, is rarely so straightforward. Some pain does not respond to pharmacotherapy, and there is wide variation in analgesic response among patients. Also, many of the widely adopted procedures, when tested in RCTs, demonstrate minimal or no added benefit beyond that of a sham surgery. The evidence for various pain surgeries such as arthroscopy and vertebroplasty is, at best, mixed. If some pain procedures are no better than placebo, perhaps there can be a hypothetical role for a safer, less invasive placebo to be used.

However, even if sham surgeries are equally efficacious, can the ethical physician offer a placebo without violating beneficence? Is it still an act of deception if the physician does not lie about the nature of the surgery but withholds the fact that it’s placebo? Gold and Lichtenberg argue that the mindset of the physician must be considered. If a physician prescribes a placebo surgery because he or she does not believe in the validity of the patient complaint and/or just seeks to relieve him or herself of a demanding patient – this physician is not acting in the best interest of the patient and beneficence is thus violated. On the other hand, if the patient has exhausted other options and the physician truly, non-selfishly believes the sham surgery might provide some relief, the physician can still be in accordance with the beneficence principle.

Autonomy suggests that patients, as moral beings, have the right to self-determination in medical decision-making. Whether prescribing sham therapies can be done while preserving autonomy depends, to some extent, on the degree of disclosure considered necessary to fully respect patient autonomy. This can be difficult to navigate, as studies evaluating patient attitudes regarding physician recommendation of placebo have demonstrated that some patients deem it untrustworthy practice, while others feel it is acceptable. It is generally established, however, that the physician should disclose any information that a reasonable person would want to know and that might influence decision-making; however, there is debate over what exactly this constitutes. In the case of sham surgeries, the physician must communicate the potential risks, but is he or she obligated to explain exactly how the procedure works? To this point, Gold and Lichtenberg argue that patients generally seek care in order to feel better, not to be taught about how things work, rendering this type of information as peripheral.

What if the physician voluntarily discloses the nature of the placebo? If the patient consents to a sham surgery knowing their pain relief may be due to a placebo effect, then the principle of autonomy may be upheld. In fact, there is evidence that disclosure of the possibility of a placebo effect may not completely abolish the response. Physicians must, however, be savvy at communicating the evidence and risks for sham procedures as well as managing patient expectations of improvement so as not to promote false hope or give credence to other unscientific therapies. Bystad et al outline four points that physicians should communicate to patients when discussing placebo procedures. The physician should (1) describe the basic mechanisms of action, (2) provide information demonstrating the possibility of benefit if such information is accurate, (3) maintain a warm, empathic demeanor throughout the encounter, and (4) alleviate the patient’s stress as much as possible.

Education about the evidence surrounding sham procedures ensures that patients can make informed decisions about whether or not to proceed.

**CONCLUSION**

Chronic pain is difficult to treat. In a hypothetical situation, performing sham surgeries may be justified if the physician’s intent is to help the patient, other options have been exhausted and risks are minimized. Some degree of disclosure about the nature of the procedure may be appropriate to uphold patient autonomy and may not abolish the placebo response. The principles of beneficence, non-maleficence and autonomy can provide a hypothetical ethical framework for sham surgeries in clinical practice.

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Chronic pain management and the development of opioid use disorder

Improving opioid stewardship among Canadian prescribers

Lily Robinson, Richard Yu, Salonee Patel

ABSTRACT

Chronic pain is a common condition that impacts quality of life and often precipitates the need for medical attention. Despite evidence that long-term opioid use provides limited relief, prescription opioid therapy remains a cornerstone in the medical management of chronic non-cancer pain. Presently, 13% of Canadians are prescribed opioids for pain management, and physicians play a crucial role in preventing the development of opioid use disorders. However, Canadian physicians lack knowledge of and comfort with evidence-based principles of opioid stewardship. In this article, we aim to highlight ongoing Canadian efforts to address physician discomfort and improve clinical practice. We focus on 2017 Canadian guidelines that provide clinicians with evidence-based recommendations for opioid use in chronic non-cancer pain management. In addition, we call attention to provincial efforts to implement physician accountability measures. In reviewing the existing literature, we uncovered inadequacies in pain management curricula within the Canadian undergraduate and continuing medical education (CME) systems. We consulted the educational practices of the European Pain Federation and the Centers for Disease Control and Prevention to make recommendations for improvement to current Canadian pain curricula. Based on our findings, we recommend that (1) Canadian medical institutions expand upon current core pain curricula, (2) pain management education be made compulsory, (3) academic detailing be emphasized as a means of CME, and (4) multidisciplinary non-medical management of chronic pain be featured more extensively.

INTRODUCTION

In recent years, prescription opioid abuse has emerged as a growing epidemic across Canada. A leading cause of accidental death, substance use-related morbidity, and increased healthcare expenditure, prescription opioid abuse is inextricably linked to the management of chronic non-cancer pain. In Canada, chronic non-cancer pain plagues up to 19% of people, 25% of whom report having pain for greater than 20 years and 50% of whom report having pain for longer than a decade.

Within the context of Western medicine, prescription opioids have become a mainstay in the medical management of chronic pain. In Canada, prescription opioid consumption increased by 155% between 2000 and 2011, and the number of annual opioid related deaths – excluding those related to illicit opioid use – was 325% greater in 2010 compared to 1991. Additionally, one in every five hundred patients prescribed opioids for chronic pain died of opioid related causes at a median of 2.6 years after filling their initial prescription. The number of prescription opioid-related deaths rose to one in every thirty-two patients when more than 200 mg of morphine equivalent dose (MED) was prescribed daily.

Prescribers have a crucial role to play in preventing opioid related morbidity and mortality. However, Canadian physicians lack confidence in their knowledge of safe opioid prescribing practices, effective screening for addictive potential, and patient education regarding opioid abuse disorder. Herein, ongoing Canadian efforts to address deficiencies and improve opioid prescribing practices will be discussed. Additionally, we call upon strategies implemented in Europe and the United States to recommend improvements to Canadian medical education as it pertains to opioid use in chronic pain management.

CHRONIC PAIN MANAGEMENT AND PRESCRIPTION OPIOID ADDICTION IN CANADA

Opioid prescription practices underwent a paradigm shift at the turn of the 21st century. For many years, opioids were prescribed for acute pain, cancer-related pain, and terminally-ill patients. Beginning in 1996, however, Purdue Pharma falsely and aggressively marketed OxyContin to health care providers as low-risk, effective, and of low addictive potential in the treatment of moderate pain. Consequently, opioids emerged as a principal tool in the management of chronic non-cancer pain. Despite charges laid against Purdue Pharma in 2007 for misrepresentation of OxyContin, opioid prescription practices based on this misinformation remain prevalent today.

Although individual prescribing practices vary widely, physicians have collectively contributed to Canada’s growing opioid epidemic. Despite a lack of evidence for effective treatment of chronic non-cancer pain using long-term opioid prescription, 13% of Ontarians report use of prescription opioids for pain relief, 5.5% of whom are expected to be at risk of addiction. As well, high-dose opioid prescribing has continued to rise despite the evidence that risks of fatal and non-fatal overdose increase substantially with dose size. Risk to the public is further exacerbated by physicians’ failure to recognize double-doctoring and consequent drug diversion. In a 2015 study conducted in collaboration with the Center for Addiction and Mental Health (CAMH), 37% of patients admitted for prescription opioid dependence reported having
obtained opioids from physicians only, 26% used both prescribed and diverted opioids, and an additional 21% obtained prescription opioids from the street alone.\(^1\)

Consequences of poor opioid stewardship are numerous and often dire. Those who are prescribed opioids and develop opioid abuse disorder are at considerable risk of individual harms including motor vehicle collisions, fatal overdoses, opioid poisoning, and blood-borne infections among intravenous opioid users.\(^5\)\(^,\)\(^6\) Furthermore, destructive behaviours driven by addiction may lead to unemployment, fracturing of family units, housing instability, and incarceration. For these reasons as well as those related to health care expenditures, Canada has begun to invest in efforts to alter policy and empower physicians to improve prescribing practices.

**ONGOING CANADIAN MITIGATION EFFORTS**

In 2016, coordinated efforts between the Ministry of Health and Long-Term Care and nine provincial and territorial health ministers gave rise to a Joint Statement of Action to Address the Opioid Crisis, which emphasizes accountability and encourages improvement of clinical practice through programming.\(^7\) For example, 8,200 physicians in British Columbia were provided with reports comparing individual opioid prescribing practices to those of peers and best-practice guidelines. Sixty-six percent of targeted physicians found these reports helpful, and 50% intended to make changes to their practice. As well, Newfoundland and Labrador developed a safe prescribing program, which is now mandatory for completion by all license-seeking physicians and recommended for physicians currently in practice.

Evolution of Canadian prescribing practices began in 2007, when the Federation of Medical Regulatory Authorities of Canada formed the National Opioid Use Guideline Group (NOUGG) for development of clinical guidelines pertaining to opioid prescribing in chronic non-cancer pain.\(^1\) The NOUGG guidelines have been criticized as non-specific and permissive, facilitating only a minor reduction in prescribing rates and failing to prevent an increase in high-dose opioid prescribing. Consequently, the Michael G. DeGroote National Pain Centre (NPC) was enlisted to revamp Canada’s clinical guidelines, and recently published the 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain.

Several evidence-based amendments are reflected in the 2017 guidelines. First, it is now recommended that non-opioid therapy be optimized before instituting opioid use for chronic pain.\(^1\) Second, more stringent limitations have been placed on eligibility for opioid therapy. Patients with concurrent or prior substance use disorder should not receive opioids despite persistent pain, and psychiatric patients must be stabilized before initiation of opioid therapy. When prescribed to the appropriate patient, it is now suggested that opioid dose be limited to less than 90 mg MED daily, and patients should be tapered to the lowest effective dose. Finally, to mitigate risks, NPC guidelines emphasize drug screening, continued use of treatment agreements, implementation of tamper-resistant formulations, fentanyl patch exchange, and co-prescription with naloxone.

**EDUCATION STRATEGIES TO IMPROVE OPIOID STEWARDSHIP**

Despite federal and provincial efforts to reduce opioid prescribing and mitigate prescription opioid abuse, Canada ranks second only to the United States in per-capita prescription of opioids, worldwide.\(^7\) In order to adequately resolve this multifaceted issue, Canada must improve in its undergraduate and continuing medical education (CME).

Canadian medical education on the topic of opioid stewardship is currently inadequate. In a 2009 survey of pain curricula across nine Canadian medical schools, it was found that, on average, undergraduate medical students received only 16 hours of mandatory pain content, while veterinary students received 87 hours.\(^8\) In 2013, the European Pain Federation (EFIC) found that 82% of medical schools across 15 European countries did not have mandatory pain management education for undergraduate students.\(^9\) To address this, the EFIC published the Pain Management Core Curriculum for European Medical Schools and now offers a Diploma of Pain Management.\(^9\) We, therefore, suggest that Canadian medical schools respond to current inadequacies in undergraduate medical education by expanding upon current core curricula in pain management, while simultaneously instituting policies that will ensure proper dissemination and mandatory implementation nationwide.

In the realm of CME, a strategy referred to as academic detailing is leveraged extensively by the EFIC and various organizations throughout the United States.\(^10\) Proven to be a cost effective educational method, academic detailing involves synthesis and propagation of up-to-date clinical knowledge through one-on-one educational sessions with practicing physicians.\(^10\) In 2010 and 2013, respectively, the Dalhousie and BC Provincial Academic Detailing Services developed courses on opioid use in chronic non-cancer pain.\(^11\)\(^,\)\(^12\) In spite of individual provincial efforts, Canadian academic detailing on opioid use in chronic non-cancer pain does not appear to be widespread. We, therefore, recommend that licensed physicians in Canada who are currently prescribing opioids for chronic non-cancer pain be targeted for appropriate CME through academic detailing services.

Finally, we propose that future educational efforts emphasize multidisciplinary practices in the prevention of iatrogenic opioid addiction. The Centers for Disease Control and Prevention (CDC) has emphasized use of self-management skills, out-patient behavioural pain management programs, physical therapy, and counselling on expected course of pain before considering opioid therapy.\(^13\) In summary, expanding upon mandatory, tailored, and evidence-based pain content in undergraduate as well as post-graduate medical education is crucial to facilitating optimal opioid stewardship amongst prescribing physicians.

**CONCLUSION**

Despite the critical role of Canadian physicians in preventing opioid abuse, prescribers lack confidence and adequate training in opioid stewardship. The 2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain aim to (1) address prescription rates...
by emphasizing non-medical management of chronic pain and limiting eligibility for opioid prescribing, (2) prevent opioid abuse disorder by redefining optimal dosing, and (3) mitigate diversion and opioid related mortality by increasing drug monitoring efforts and promoting public health measures. To further address clinical deficiencies, undergraduate and continuing medical education on the topic of opioid stewardship must improve. Canadian medical institutions may wish to call upon European educational strategies when developing the pain curricula and implement policies to ensure ubiquity. Additionally, use of academic detailing for CME should be augmented and funds should be allocated for opioid related material development. To comprehensively address opioid abuse disorder, changes to clinical practice, public health policies, and funding allocation are surely required. Therefore, while improving prescribing practices alone is insufficient to mitigate opioid addiction, empowering physicians to prescribe appropriately will promote health and save lives.

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Cannabis for pain management: Pariah or panacea?
Historical perspectives and pharmacological mechanisms

Roger Hudson, Nirushan Puvanenthirarajah

ABSTRACT
Cannabis has been used in a medicinal context throughout recorded history and across diverse cultures to aid in the treatment of a wide array of ailments. Remarkably, clinical and preclinical investigations are only recently beginning to reveal the neurobiological mechanisms responsible for the clinically-relevant actions of cannabis that have been acknowledged by medical pharmacopeia for millennia. The therapeutic potential of cannabis-derived phytochemicals such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are currently being explored in several contexts. Experimental evidence suggests that modulation of signal transduction pathways underlying cellular excitability, as well as interactions with the endocannabinoid and serotonin systems, which modulate emotion and pain sensitivity under physiological conditions, are among the mechanisms responsible for its clinical efficacy. Interestingly, the diverse pharmacodynamic profile of CBD suggests a synergistic interaction with current first- and second-line medications used in the treatment of neuropathic pain to produce clinically meaningful therapeutic benefits. To advance understanding of the neurobiological mechanisms underlying therapeutic cannabis use in pain management and to integrate its use into modern clinical practices, it is important to understand medicinal cannabis use in historic and medical contexts. This review highlights the copious history of medical practices incorporating the use of cannabis, and discusses the potential pharmacological mechanisms responsible for its therapeutic efficacy in the management of neuropathic pain.

INTRODUCTION
For as long as humans have experienced pain, there have been efforts to identify its causes and to relieve suffering through the use of ritualistic or herbal remedies.1 In early human history, available treatments for pain were trifling, and included trepanning and ritualistic healing ceremonies.2 As collective understanding of pain progressed, the use of plant-derived extracts from the willow bark tree, opium poppy, and cannabis plant became common.3,4 In modern times, a comprehensive understanding of pain neurobiology and its various molecular and psychophysiological underpinnings are contributing to increasingly innovative and individualized therapies for those suffering from chronic pain and neuropathy.5 Advancements and discoveries within these areas have aided in the renaissance of cannabis as a pharmacotherapy for pain management, and stimulated research into the biological mechanisms underlying the therapeutic qualities of specific compounds derived from cannabis, also known as phytocannabinoids.6-8

Although cannabis has been used in various forms for millennia to aid in the treatment of an abundance of ailments, it is only relatively recently that we have begun to understand the phytochemical complexities differentiating cannabis plant strains, and the pharmacological mechanisms responsible for their therapeutic effects.4,7,9 The primary non-intoxicating phytocannabinoid in cannabis, cannabidiol (CBD), was initially isolated in 1940, but its pharmacology and therapeutic benefits were unknown until decades later.10-11 In contrast, the primary psychotropic compound in cannabis, delta-9-tetrahydrocannabinol (THC), was first isolated in 1964, and has remained the subject of the majority of cannabis-related scientific research.12 Insight into these chief phytocannabinoids within cannabis prompted subsequent research into the pharmacological mechanisms through which THC and CBD act, and led to the more recent discovery of the body’s own cannabis-like receptor system, the endocannabinoid system (ECS).13-16 Recent preclinical and clinical evidence suggests that the ECS plays an important role in modulating pain sensitivity under physiological conditions. This review highlights the copious history of medical practices incorporating the use of cannabis, and discusses the potential pharmacological mechanisms responsible for its therapeutic efficacy in the management of neuropathic pain.

BRIEF HISTORY OF CANNABIS USE IN PAIN MANAGEMENT
Extensive dialogue among physicians and researchers currently exists surrounding the recreational and medicinal use of cannabis and its various phytochemical derivatives. An often overlooked but critical source of information that may contribute to this exchange is the historical documentation from nearly 5000 years of human cannabis use in medicinal contexts.17 The utilization of cannabis seeds, leaves, tinctures and extracts have been identified across the globe, from ancient through to contemporary civilizations, and for numerous ailments that strikingly resemble the bases for its use in modern medicine.18

The earliest recorded evidence of medicinal cannabis use is documented in the ancient Chinese pharmacopeia ‘Shennong Bencaojing’ (Figure 1).19 It depicts the use of all parts of the cannabis plant including the seeds, leaves, female flowering heads, and stalks for over 100 ailments, including chronic rheumatic and gastrointestinal pains, inflammation, epilepsy, and acceleration of wound healing.20 The founder of Chinese surgery, Hua Tuo (140-208 AD) was renowned amongst generations of Chinese physicians who studied the Shennong Bencaojing, and championed cannabis as a potent analgesic.21 He was also the first to recognize its
anaesthetic qualities, and administered a boiled cannabis powder preparation laced with wine to patients prior to surgery. Notably, the prehistoric cultivation of cannabis, coupled with its extensive therapeutic applications and a large body of untranslated medical literature suggest the Chinese historical account to be a particularly rich source of practical information.

Cannabis use in ancient Egyptian medicine has been recorded in dynastic medical papyri since the Old Kingdom, and is among the earliest civilizations to utilize cannabis plant parts in medical treatments. Early indications that cannabis was prescribed medicinally in ancient Egypt are contained in the papyrus Ramessum III, dated to 1700 BCE, and references its application for the treatment of abscesses and inflammation of the eyes, a potential parallel to the modern equivalent of cannabis for the treatment of glaucoma. Physicians of the time showed meticulous understanding of the diverse pharmacological qualities of cannabis, as the anti-inflammatory, analgesic, antiemetic, and insecticidal properties of cannabis were illustrated in several ancient papyri dating back to 1550 BCE.

Cannabis is also well-documented throughout history as a critical component of ancient Indian, Greek and Arab medical practices dating back as early as 1000 BCE (Figure 1). Overwhelming evidence indicates that these groups were aware of its anti-inflammatory, analgesic, and sedative properties as it was often used for the relief of headaches, edema, fever, insomnia, dysentery and a variety of other gastrointestinal issues. Despite comparable exploitation of the anti-inflammatory and analgesic effects of cannabis throughout human history and across cultures, these and other medical applications were entirely unknown to Western medicine until the mid 1800s AD.

While employed as a member of the Medical and Physical Society of Calcutta in India in 1836 AD, the Irish physician Dr William O’Shaughnessy validated various folk claims and subjective reports on the therapeutic value of cannabis through experimentation. Dr O’Shaughnessy discovered multiple new applications for cannabis, and ultimately recommended its use for an array of therapeutic purposes. Through the administration of component extracts and tinctures, he effectively relieved tetanus-induced spasticity, reduced pain and suffering provoked by rheumatism, and calmed convulsions in children caused by epilepsy. Following his seminal publication on the medical applications of cannabis in 1839 entitled ‘On the preparations of Indian hemp, or gunjah’, the availability of cannabis extracts in over-the-counter medications, as well as its use in Western medicine increased rapidly. By 1850, cannabis extract had entered the United States Pharmacopoeia and was listed as a treatment for nearly 100 afflictions, including acute or chronic pain, opiate addiction, and convulsive disorders, and was readily available in over-the-counter formulations. However, following the development of analgesics such as synthetic opiates in the mid 19th century, which were viewed as a substitute therapy to wean patients off of opium, as well as chloral hydrate and non-steroidal anti-inflammatory drugs (NSAIDS) in the early 20th century, the prevalence of cannabis as a medicine and its necessity as an analgesic and adjunctive therapy in addiction began to decline. In recent years, experimental evidence has started to reveal the pharmacological mechanisms through which cannabis exerts its therapeutic effects. In fact, the precise mechanisms of action largely substantiate claims made to the therapeutic qualities of cannabis throughout recorded history.

### Figure 1. Select chronological history of the use of medical cannabis in various cultures throughout human history

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Relevant Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>4000 BCE</td>
<td>- Earliest evidence of cannabis cultivation. - Pollen deposits localized to ancient Chinese village Pan p’o.</td>
</tr>
<tr>
<td>2700-1500 BCE</td>
<td>- Earliest written record of cannabis used as medicine. - Pen-ts’ao Ching - oldest known pharmacopeia. - Recommends cannabis for over 100 ailments.</td>
</tr>
<tr>
<td>2350-1350 BCE</td>
<td>- Medicinal use of cannabis recorded in ancient Egypt. - Describes active use since pharaonic times; inscribed into papyri as 'shemshemat', dated to 1350 BCE.</td>
</tr>
<tr>
<td>1000 BCE</td>
<td>- Recreational and medical cannabis used extensively throughout India.</td>
</tr>
<tr>
<td>500 BCE</td>
<td>- Cannabis extracts used to treat inflammation, pain and severe headaches.</td>
</tr>
<tr>
<td>700-1700 AD</td>
<td>- Persian physicians used cannabis as treatment for variety of ailments. - Arab traders brought cannabis from India to Africa to treat malaria, dysentery, fever, inflammation; used as anti-emetic, analgesic.</td>
</tr>
<tr>
<td>1839 AD</td>
<td>- O’Shaughnessy published ‘On the preparations of Indian hemp, or gunjah’; cannabis use spreads rapidly throughout western medicine. - Medical use peaks in late 1800s: recognized in USA Pharmacopoeia.</td>
</tr>
</tbody>
</table>
POTENTIAL PHARMACOLOGICAL MECHANISMS OF CANNABIS IN PAIN MANAGEMENT

Pain is an evolutionarily conserved and highly complex process regulated by diverse psychophysiological mechanisms in the nervous system at the molecular and cellular scales. In particular, neuropathic pain is often treatment-resistant and idiopathic, thus presenting a major issue for physicians seeking to relieve patients' suffering. Compounds that activate the ECS, including cannabis and specific phytocannabinoids, are currently being investigated as independent and adjunct pharmacotherapies to treat persistent neuropathic pain. The ECS is centrally active in regions regulating pain including the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), and its activation inversely regulates cellular processes related to pain transmission, such as neuronal hyper-excitability.

Neuropathic pain is a chronic pain syndrome associated with drug-induced, traumatic, or disease-induced damage of nerve fibers involved in the transmission of pain. It can originate from a large number of ailments, and affects nearly 3% of the population worldwide, including roughly 900,000 Canadians. Phytocannabinoids such as THC and CBD have received a large amount of attention in the context of pain management due to their interactions with nociceptive transmitters and numerous neurotransmitter systems, including the endocannabinoid and serotonin systems.

By activating ECS receptors, endogenous cannabinoids contribute to the body’s natural ability to relieve pain and reduce inflammation. Upon activation of ECS receptors, intracellular potassium efflux increases while calcium and sodium influx decrease, thus contributing to a reduction in neuronal hyper-excitability. In terms of phytocannabinoids, THC is a potent partial agonist of the Cannabinoid type 1 Receptor (CB1R), but its therapeutic range is restricted by its intoxicating qualities. In contrast, CBD does not directly interact with CB1Rs, and produces no intoxicating effects, but instead increases endogenous cannabinoid signaling, and up-regulates CB1Rs following chronic exposure.

CONCLUSIONS

Modern clinical and preclinical investigations are just recently beginning to reveal the neurobiological mechanisms responsible for the clinically-relevant actions of specific phytocannabinoids, many of which have been acknowledged by medical pharmacopeia for nearly 5000 years. Despite the medicinal use of cannabis since antiquity, research revealing the clinical efficacy for medicinal cannabis in a variety of contexts is still in its infancy with much to be explored. Increasing understanding of the biological processes underlying pain, including neuronal hyperexcitability and the influence of innate inflammatory responses have shed light on how the endocannabinoid system and various phytocannabinoids interact with and modulate these organic systems. Further research is needed to clarify the distinct clinical voids that cannabis and its specific phytocannabinoids such as THC and CBD fill, either alone or in adjunct with other pharmacotherapies. Thus, for now, historical indices of medicinal cannabis use may be some of the richest sources of knowledge still yet to be fully explored.
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Biased mu-opioid receptor agonists confer analgesia with reduced side effects

Chloe Gui, Sean Wong

ABSTRACT

Opioids are considered mainstay treatments for acute and terminal pain. In recent decades, however, overprescription and the increasing prevalence of illicit opioids has propelled North America into a state of “opioid crisis.” Along with the analgesic benefits, opioid use also commonly induces a number of side effects. Respiratory depression is an especially dangerous and potentially lethal example. The development of painkillers with improved safety profiles is thus a priority. Downstream to the mu-opioid receptor, which is responsible for the analgesic effects of opioids, β-arrestin-2 signaling has been suggested to be important for the manifestation of side effects, including respiratory depression. Two novel mu-opioid receptor agonists, TRV130 and PMZ21, have recently been reported to preferentially promote G protein-coupling over β-arrestin-2 signaling, thereby promoting analgesia with reduced side effects. TRV130 has been found in clinical trials to be more potent than morphine but safer in the setting of acute moderate-to-severe pain and is currently under New Drug Application review in the U.S. PMZ21 has shown promising and unique pain-relieving effects in mouse models, but further investigation is warranted to examine whether its therapeutic effects and safety profile are translatable to humans.

INTRODUCTION

Opioids are compounds that bind opioid receptors and include: morphine and codeine, which are derived from poppy seeds (Papaver somniferum); semi-synthetic compounds such as heroin and oxycodone; and synthetic compounds including methadone, fentanyl, and propoxyphene.1 Opioid receptors are transmembrane G protein-coupled receptors (GPCRs) that are classified into mu, delta, kappa, and nociception subtypes.1 The analgesic and reinforcing effects of opioids are primarily mediated by mu-opioid receptors (MORs), which are widely-expressed in the central and peripheral nervous systems and in the gastrointestinal tract.2,3 Medically, opioids are used for pain relief, but chronic use and abuse can lead to physical dependence. One of the biggest challenges in treating chronic pain with opioids is providing sufficient symptom relief while minimizing the risk of dependency and other side effects. Here, we examine promising novel opioids that are simultaneously biased towards analgesic signaling pathways and against pathways conferring side effects, thereby providing pain relief with fewer adverse events (AEs). We will also briefly discuss a computational structure-based approach for novel opioid discovery.

CURRENT LIMITATIONS OF OPIOIDS

Though opioid addiction has been described as early as the sixteenth century in Europe, in recent years, the prevalence of opioid drug abuse in both Canada and the United States has increased, leading to an increase in opioid-related hospitalizations and deaths.4,5 This epidemic has been attributed to multiple factors including over-prescription, the rise in illicit heroin and fentanyl, and aggressive marketing by pharmaceutical companies.6,7 Chronic use of opioids can lead to physical dependence, and abrupt abstinence can trigger withdrawal symptoms that include drug cravings, anxiety, diaphoresis, tachycardia, and gastrointestinal distress.8 Side effects of these medications also include sedation, dizziness, gastrointestinal distress, tolerance and respiratory depression.9 The latter is particularly dangerous and is the primary cause of opioid-related overdose and death.10 Furthermore, patients on opioids must be tapered off slowly to avoid withdrawal.10 MOR signaling is responsible for both the analgesic and side effects of opioids. Hence, side effects of MOR agonists are considered to be “on target” effects and have traditionally been regarded as inevitable disadvantages of MOR-targeting opioids. These AEs also limit the maximum dosage of morphine and other opioids.2

G PROTEIN-BASED OPIOIDS AND TRV-130

In recent years, it has been demonstrated that different intracellular pathways can be induced by activation of a single GPCR receptor. Different agonists may demonstrate activation bias towards one particular downstream pathway over another.11,12 In the case of MORs, studies have shown that some agonists exhibit G protein-coupling bias while others exhibit bias towards alternative pathways such as β-arrestin signaling.13,14 This signaling preference results in distinctive functional selectivity despite having a common receptor.13,14 Studies examining MOR signaling have identified β-arrestins to be key modulators of opioid effects. For instance, β-arrestin-2 contributes to opioid tolerance by binding to and desensitizing MORs to ligands and β-arrestin-1 has been shown to promote ubiquitin-proteasomal degradation of the receptor.15 In mice lacking β-arrestin-2, chronic morphine treatment did not induce tolerance, suggesting that β-arrestin-2 is also necessary for opioid tolerance development.15 Furthermore, morphine-treated β-arrestin-2 knockout mice also exhibited less physical dependence, constipation, and respiratory depression than their wild-type littermates, although this effect disappeared at higher doses of morphine.15 The analgesic effects of morphine were present and, in fact, enhanced in the β-arrestin-2 knockout mice. Thus, the β-arrestin-2 pathway is implicated in major dose-limiting AEs but not in analgesia. Respiratory depression associated
with morphine use persists even after the analgesic response ends, further suggesting that unique signaling pathways are responsible for the therapeutic effects and side effects of opioids. In this line with this conclusion, β-arrestin recruitment is associated with a narrower therapeutic window due to increased risk of AEs. For example, fentanyl exhibits preference for β-arrestin signaling over G protein signaling and has been shown to cause respiratory depression even at low analgesic doses. Taken together, an opioid biased towards G protein signaling and against β-arrestin-2-recruitment could potentially provide pain relief with lessened risks of dependence and respiratory depression.

In 2013, DeWire et al of Trevana Inc reported the discovery of TRV130, a novel G protein-biased MOR-targeting compound exhibiting minimal β-arrestin-2 recruitment. To find this compound, the investigators experimentally screened the internal chemical library at Trevana, seeking a compound with high G protein but low β-arrestin-2 signaling. TRV130, later named Oliceridine or OLINV0, was found to activate G protein-coupling to a similar extent compared to morphine but was 86% less efficient in recruiting β-arrestin-2. TRV130 is also notably more potent than morphine and structurally different from known MOR agonists. In a recent phase IIb clinical trial, TRV130 was reported to provide effective pain relief for patients who had undergone abdominoplasty. Pain relief achieved was significantly greater than that provided by placebo, and TRV130 was found to be significantly more potent than morphine as well. Patients treated with TRV130 were less likely to experience side effects, including nausea, vomiting, and respiratory dysfunction; in other words, TRV130 has a wider therapeutic window and may be safer than morphine. A press release dated November 7, 2017 announced that phase III trials of intravenous TRV130 for moderate-to-severe acute pain have shown promising results, and a New Drug Application has been submitted to the U.S. Food and Drug Administration (FDA).

STRUCTURE-BASED DISCOVERY OF BIASED OPIOID AGONIST PZM21

Alongside to traditional experimental screening, virtual screening has become a successful tool for drug discovery. Molecular docking is a computational method that has been used to study ligand-receptor interaction since its invention in 1980. In molecular docking, algorithms predict conformations of the ligand-receptor complex and subsequently rank these by a score that represents how well the ligand and receptor bind. Subsequently, the rankings of ligands and their conformations allow researchers to shortlist potential candidates for further investigation. Improvements in computational power, improved screening software, and the increased availability of structural data have allowed researchers to approach drug design from a structural perspective. Molecular docking is therefore a virtual screening technique that is cost-effective and potentially more efficient than experimental screening. Recently, Manglik et al employed this structure-based method of drug discovery to identify a novel G protein-biased opioid, PZM21.

In the pursuit of superior MOR ligands, Manglik et al studied the binding properties of 3 million compounds in 1.3 million configurations, each against inactive MOR. 2500 compounds with the best docking profiles were manually inspected for novelty and interaction with key residues, and of these, 23 molecules were selected for further testing. After optimizing compounds for affinity, the most potent compound, PZM21, exhibited strong G protein-coupled activity with no detectable β-arrestin-2 recruitment. PZM21 was revealed to be highly specific for MOR, showing no kappa- or nociception-opioid receptor activity and only weak delta-opioid receptor activation. In mouse studies, PZM21 conferred analgesia in a hotplate assay, which assesses higher-level central nervous system and spinal nociceptive circuits, but no pain relief in the tail-flick assay, which assesses spinal reflexes. These experiments suggest that PZM21 selectively blocks the affective component of pain, a distinction novel among opioids. Furthermore, mice treated with PZM21 did not exhibit respiratory depression whereas morphine at equi-analgesic doses suppressed respiration. Mice given PZM21 also did not display a phenotype consistent with reward circuit activation, which is linked to reinforcing behaviours and addiction. On the other hand, mice given morphine demonstrated acute hyperlocomotive responses and preferred to spend time in locations associated with morphine administration, both markers of reward circuit activation. Overall, PZM21 is a novel biased opioid agonist demonstrating strong G protein signaling preference over β-arrestin-2 recruitment, resulting in potent analgesic benefits with reduced AEs.

FUTURE DIRECTIONS AND SUMMARY

Both TRV130 and PZM21 are promising G protein-biased MOR ligands with fewer side effects compared to other opioids. The mechanisms of these drugs suggest that robust activation of the G protein signaling pathway and avoidance of β-arrestin-2 recruitment broadens the therapeutic window and increases the safety of opioid compounds. Interestingly, TRV130 and PZM21 exhibit unique signaling despite sharing a bias for G protein-coupling. Notably, PZM21 induces less respiratory depression than TRV130, which causes significant depression, though to a lesser extent than morphine. PZM21 also has little effect on the reflexive pain circuit and provides primarily afferent pain relief. Thus, structure-based drug discovery, as demonstrated by the discovery of PZM21, may be useful for identifying novel ligands and elucidating novel pathways. PZM21 remains to be clinically validated as a painkiller, however, and its side effects and risks need to be further investigated at analgesic dose. Currently, TRV130 is awaiting FDA New Drug approval in the U.S. Its wider therapeutic window, lessened AEs, and demonstrated effectiveness in treating moderate-to-severe acute pain making it an attractive alternative to current opioid medications in some clinical settings.

REFERENCES


The Schullich Pain Medicine residency
An interview with Dr Geoff Bellingham

Dino D’Andrea, Emily N Dzongowski

INTRODUCTION
Dr Bellingham completed his medical school and anesthesiology residency at Western University. He followed this with a fellowship in Chronic Pain Management at the University of Toronto, with a focus on interventional pain management using fluoroscopy and ultrasound guided techniques. Dr Bellingham returned to Western University to work in the Department of Anesthesia and Perioperative Medicine in his capacity as an anesthetist and as a chronic pain specialist. Here at Western, he directs the Pain Clinic at St. Joseph’s Health Care and also played a key role in the development of Canada’s first Pain Medicine residency program.
We had an opportunity to chat with Dr Bellingham and discuss a wide range of topics including his choice of career path, the Pain Medicine residency program, and other pain medicine topics in the context of the current opioid epidemic.

UWOMJ: Why anesthesiology?
I didn’t know I wanted anesthesiology until my third year of medical school when I did my clerkship rotations. Ultimately, what it came down to was that I really enjoyed the people I got to work with in anesthesiology. Based on my experience, what I like to tell medical students looking for career advice is that sometimes a specialty chooses you, rather than you choose the specialty. As an anesthesiologist, you must be comfortable in acute situations and have a certain ease with managing the airways, circulation, breathing and all that kind of resuscitation stuff. I was very happy that I was able to develop that skill set. As a resident, I took pride in the fact that I would always run to the code blues and be comfortable in trying to help the situation. I enjoyed the operating room environment and seeing all the different types of operations, but also liked that anesthesiology could be an avenue to do other things like chronic pain obviously for myself, or intensive care, regional anesthesia, cardiac, simulation, education, and more.

Why chronic pain?
My interest was sparked early in pre-clerkship while I was in Tobermory doing my rural family medicine experience with Dr George Harper, a local family physician. He was phenomenally knowledgeable and took care of all sorts of stuff there in the community. I was with him for a house call once to see an elderly patient with pain and Dr Harper decided to try this medication called amitriptyline. I remember being surprised that we were attempting to treat pain with an antidepressant! I found this fascinating and thought to myself that pain is such a big issue, and if I can know what this guy knows, then that’s a really valuable skill. With that distinct experience in the back of my mind, and then after getting to spend some time in the pain clinic as an anesthesiology resident, I gravitated toward the chronic pain pathway. In chronic pain clinic, you get to see all sorts of really interesting cases, like very unusual pain syndromes. For example, you can have someone with complex regional pain syndrome, a devastating condition where even light touch to the limb can be intensely painful. We still don’t understand it well, and I find the mystery around it intriguing.

How is your time divided?
I’m currently the program director of the Pain Medicine residency program, and in addition I’ve also served as the Pain Clinic medical director for the past year. I see patients in clinic, do some research and then of course education with our residents where I’m a pretty active teacher. For my average week, I spend Mondays and Tuesdays seeing pain patients in clinic, and on Friday I have time with our fluoroscopy unit where we can do some interventions about the spine. Wednesday is my academic day where I’m performing office based work related to administration of the residency program and Pain Clinic. That leaves Thursday my one day in the operating room. So as you can see, my time is pretty heavily weighted towards pain these days.

What are the pros and cons of anesthesia and pain medicine?
The operating room environment is what I love about anesthesia. Seeing all my colleagues, those who I had an affinity towards that got me into anesthesia in the first place, is truly a joy. I like keeping my skills sharp for airway management and cardiovascular support, and seeing all the different types of emerging technologies and all the interesting patient cases that come through the door. For chronic pain practice, I like how it’s a point of pride that people ask for you by name. You have a singular identity as an expert in this particular field that somebody wants your opinion on. In addition, you get the opportunity to develop a relationship with patients and hopefully take them from a place that’s not so great to a place that’s a little bit better and more manageable. With operating room anesthesia, you are not able to develop similar patient-doctor relationships as those developed in the pain clinic. The drawback of pain practice is having to become involved in legal or insurance related matters that require report writing, form filling, and other administrative issues that can be very frustrating for both doctors and patients. With pain practice, you’ve entered into this more administrative realm that you just don’t have in the operating room.

How was the Pain Medicine residency started?
The person who championed this in Canada was Dr Pat Morley-Forster, the previous Pain Clinic lead and fellowship
director here at Western. Over the course of ten years, she and other pain specialists in Canada lobbied and were successful in developing a Pain Medicine residency program. Dr Morley-Forster did all the ground work with the other founding members, and once that was established there was this template from which to build a residency program. I was the fellowship director at the time, and became involved with the residency program's development and getting it accredited by the Royal College. It was a tremendous amount of work, but everyone here at Western was very supportive and enthusiastic about it. Ultimately, Western was the first centre in Canada to roll out a Pain Medicine residency program in 2014, and many other centres in Canada soon followed.

Who enters into the Pain Medicine residency program, and how is it structured?

You enter into the program after a five-year residency in areas like anesthesia, neurology, physical medicine, emergency medicine, or internal medicine. Other specialties can also be eligible but require approval by the specialty committee of the Royal College. Currently, I have four residents: two anesthetists, one physiatrist, and one neurosurgeon. The program itself is a full two years consisting of twenty-six blocks. Although, it doesn't have to be a full two years because you can get credit from previous rotations, so realistically about a year and a half is reasonable.

What is the difference between a pain residency and a pain fellowship?

Pain fellowship programs are not required to provide their trainees with any particular set of clinical experiences. Some programs may offer more interventional opportunities, while others could be more clinic based. My fellowship in Toronto provided me with a mix of interventional and office-based outpatient experience. However, there was no set curriculum. For example, I had to advocate for my own addiction medicine clinical experience since my supervisor did not plan for it. In contrast, a Royal College accredited Pain Medicine residency has a much greater breadth of clinical experience, which program directors are held accountable for providing. There are 13 blocks of pain clinic experience, in addition to mandatory rotations in addiction medicine, psychiatry, neurology, acute pain service, cancer pain, pediatric pain, and musculoskeletal/rheumatology clinics. Selective experiences can also include rotations such as sleep medicine, something very relevant for the patients of a practicing pain physician. Residents can also obtain fluoroscopic or ultrasound-based interventional skills. Ultimately, the residency program is designed to train physicians to be leaders in pain management whether it be administrative, research or education.

Why is a breadth of experience so important in pain medicine?

It’s especially important since you learn to tie all of the components of good pain management together, no matter what specialty you come from. For example, an anesthetist would not have the training to manage anxiety and depression, while a psychiatrist would not how to do a nerve block, and a physiatrist would not know how to appropriately dose a patient controlled analgesic pump for acute postoperative pain. Pain management is more than simply learning to put needles into people. You must have some literacy in knowing who you’re treating with that needle. For example, if you have someone coming into your clinic after a motor vehicle accident that you think can benefit with some sort of facet joint injection for their whiplash, but at the same time they have this litigation going on, they’re suing some person for the crash, they feel wronged, are angry they can’t work, and so on. Do you think that your injection is going to be as effective as it could be under these circumstances? The answer is no because you can’t inject away injustice. So, what to do about a person like with pain who feels hard done by? Well that’s for our pain psychologists to help with, but as the person doing the injection, at least I have a much better sense of who I’m dealing with, and all the multi-faceted issues that need to be dealt with.

What is the role of a pain medicine specialist in combating the current opioid epidemic?

We want to help physicians become more comfortable with managing patients on opioids, which includes placing recommendations for our colleagues who may not be so comfortable. There is no secret to good opioid management. We don’t have any secrets we keep only in the Pain Clinic, it’s all out there in the Canadian National Opioid Use Guidelines. It’s about physicians doing their due diligence to have a rational pharmacotherapeutic plan, good responsible prescribing practice, clear education with patients, clear expectations with patients about what opioids can and can’t do, and cognisance of long-term effects. This is also what we train our residents to do. It’s also important to be aware that a pain medicine specialist isn’t synonymous with an addiction medicine specialist. I mean, that’s a very distinct category with its own nuances. I think what we need to do in pain medicine is be able to correctly identify an issue or aberrant drug use, stabilize people, make recommendations, and go on to more appropriate treatment.

Do you see graduates of the Pain Medicine residency making an impact on the opioid problem?

It’s early to tell since we’ve only graduated two or three nationwide, but it’s the unique perspective on pain that our residents leave with that I hope gets out there. Injections alone will not take the pain away, nothing could be further from the truth. Injections can help, but only for a short period of time. If you’re 42 years old and you want an injection for your back pain, sure it will help, but you can’t do that every three months for the rest of your life! Sustainability, talking about other surrounding issues, pacing, multi-disciplinary care, maybe injections here and there to wean opioids, these are all just pieces of a puzzle on how to tackle the problem.

What would you most like to see improved in the field of pain management?

There needs to be more multi-professional and interdisciplinary
care. There are lots of different types of pain clinics out there, and just like any other field of medicine, you have a spectrum of really good ones, and others that are not so great. We need to promote education, self-management, multi-disciplinary care. There are some clinics with a heavy focus on injections as the answer to pain, with a lack of patient engagement. If we can turn this around, specifically in Ontario, we can start to turn that ship around and realize that an injection does not address the opioid crisis, and it never will. If someone has an issue with an opioid, you can't inject that away. You have to sit down with them and understand their pain, social circumstances, and many other factors potentially at play. We need more of this. That's really where we need to steer the ship. And that was part of the impetus for the Pain Medicine residency program.

**What advice do you have for medical students that are interested in anesthesia or pain medicine?**

The main thing is to just get as much experience as possible. For pain medicine specifically, you've GOT to get into the clinic. The interventions can be fun, but you've got to see the complex cases that require multidisciplinary management. You've got to see all the different pain issues – the psychological, the psychiatric, the addiction, the polypharmacy, the social dynamics, the expectation management, and the communication with the team. That's the difficult part. That's the part that you need a good understanding of because if you want to get into it, you have to know what you're getting into. And it's so important that you do that for pain medicine. If you just see the ultrasound or the fluoroscopy and you think “oh, that's pain medicine”, you're wrong. Pain medicine should be about teaching people to self-manage, guide them in good choices therapeutically, minimize harm, help to educate them, and along with your allied health colleagues teach them how to live a better life with chronic pain. If you're expecting to get into pain medicine and stomp out pain and cure it when you see it, you're going to be disappointed quickly. That is what you need to understand, and to do so you need to be involved. In short, spend substantial time in the clinic. For anesthesia, the advice is probably the same, get involved, and just get familiar with it as best possible.

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Analgesia for the critically ill patient

Jamie Riggs, Dominic Wang

CLINICAL NARRATIVE
You are the ICU fellow on call overnight at a tertiary care hospital. At approximately 2 AM, you receive a call from the emergency department (ED) with a consult. The ED resident gives you the following details: Mrs P is a 67 year old woman who presented recently with acute dyspnea and severe pain focused around an area of extensive erythema on her left arm. She has a pulse rate of 115, respiratory rate 45 breaths per minute, temperature 39°C, blood pressure 95/65 mm Hg, and O2 saturation 68% on room air. The resident also notes areas of dark and yellowish tissue surrounding her left elbow, which are suspected to be necrotic. She is currently receiving 100% O2 via a high flow mask and fluid resuscitation via two peripheral IVs. She is experiencing severe pain, which she rates as 10/10, but is otherwise stable. You agree to have this patient transferred to your care. While she is on the way up you remind yourself of the key components of pain management in the critically ill patient.

PAIN IN THE CRITICALLY ILL PATIENT
Pain is defined by the International Association for the Study of Pain as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”¹ Pain-related issues are a major cause of presentation to the ED, with estimates as high as 70% of patients.² A majority of patients will experience pain at some point during their stay in an intensive care unit (ICU) and identify pain as a major source of stress.³

The complications associated with poorly controlled pain in ICU patients must not be underestimated. Studies have shown that 82% of cardiac surgery ICU patients report pain as the most traumatic memory of their ICU stay.³ Other studies have reported that 18% of ICU patients are at high risk for developing posttraumatic stress disorder 6 months after their stay due to memories associated with pain.⁴ Poorly controlled pain has deleterious physiologic consequences; additionally, increased catecholamines associated with the stress response can impair tissue perfusion.⁵ Pain has also been shown to suppress critical immune-related processes such as natural killer cell, neutrophil, and T-cell activity.⁶,⁷ Therefore, appropriate pain management in all ICU patients must be considered an essential aspect of their care.

ASSESSMENT OF PAIN IN THE ICU
Assessment of the patient’s level of pain is a foundational element of treatment.¹ Numerous pain rating scales exist, such as the ubiquitous 1-10 rating scale often used in the ED, as well as in other settings.⁸ Assessing pain in the ICU presents additional challenges, as many patients will be hindered in their ability to self-report. Critically ill patients may have altered levels of consciousness, be mechanically ventilated, or be administered high doses of sedatives.⁹ However, the International Association for the Study of Pain notes that “the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of pain-relieving treatment”.¹⁰

Objective and reproducible assessment of pain should be the goal in all patients experiencing pain. Patient self-reported pain is considered the gold standard.¹ In patients who are not able to verbalize their responses, the use of visual scales has been shown to be the next best alternative,¹¹ though implementation is limited to patients with a suitable level of consciousness. Numerous scales based on observed patient behaviour have been devised, and their use has been shown to improve clinical outcomes and pain management when used consistently.¹² Most importantly, the assessment of pain must be carried out consistently throughout a patient’s stay in the ICU to ensure the most appropriate management.

TREATING PAIN IN THE ICU
Analgesic medications may be broadly classified as either opioid or non-opioid medications. Opioid medications (eg fentanyl, hydromorphone, morphine, methadone) are considered first-line medications for pain management in critically ill patients.¹ Choosing between the numerous opioid medications depends upon patient and medication characteristics. Patient factors include previous exposure to opioids, co-morbidities such as renal or hepatic disease, and hemodynamic stability. The rate of onset and elimination half-life of each medication also varies significantly and are important considerations. These properties are shown for select opioid medications in Table 1.

Non-opioid analgesics may be used as adjuncts in some circumstances.¹ They may be used to decrease the required dose of opioids, or to decrease opioid-related side effects (refer to Table 1). These have not been well studied in the ICU setting. Other non-pharmacological interventions have been proposed, including music and relaxation therapy. These interventions may reduce the required dose of opioids and are relatively low cost, safe, and easy to provide in appropriate patients. While limited evidence exists to support the effectiveness of these interventions, focus groups conducted with ICU patients and their caregivers have indicated that certain non-pharmacological interventions were found to be useful.¹³

What is the initial strategy with regards to pain management in the ED? What considerations must be taken into account in this case?
You ask the emergency physician whether any analgesia has already been provided and learn that a 0.5 μg/kg IV dose of fentanyl was given approximately 15 minutes ago. This is an excellent choice,
given that fentanyl has a rapid onset and has a relatively long half-life. Although morphine acts similarly, the patient is hypotensive, which could be exacerbated by morphine.

**Upon arrival in your unit, what are your first steps in addressing this patient’s pain?**

After Mrs P is transferred into your care in the ICU, reassessment of her pain should occur promptly. You reassess her pain, and she indicates “a 6 or 7,” suggesting that the initial dose of fentanyl has had an effect. At this point, it has been nearly 45 minutes since Mrs P received fentanyl, and so you must decide whether to push another dose or start her on an infusion. Your working diagnosis is necrotizing fasciitis of the elbow, with resulting septic shock. The plastic surgery and infectious disease teams are consulted.

**What agent will you choose for ongoing analgesia? What information would you want to make this decision?**

In deciding what agent to choose going forward, you reassess the patient’s blood pressure and find that it has increased to 105/75 mm Hg. She continues to receive fluid through peripheral IVs, and now has a central line inserted for invasive blood pressure monitoring. Considering that Mrs P is now in the more controlled ICU environment, you are comfortable that you will be able to closely monitor and appropriately manage any changes in blood pressure. Mrs P is still able to communicate, and indicates that she used opioids “for a few weeks after a knee operation” several years ago. She does not report any issues with addiction or dependence stemming from this use. At this point you decide to start Mrs P on a morphine infusion at a dose of 5 mg/h.

Mrs. P is treated with IV antibiotics and surgical debridement of her elbow. During the wound debridement, extensive tissue invasion was discovered and a substantial amount of necrotic muscle tissue was removed. She improves markedly with ongoing administration of fluids.

**What are the essential steps in the ongoing management of this patient?**

Mrs P must be regularly reassessed throughout her stay in the ICU, and have her morphine infusion titrated to achieve effective analgesia. Given that her management includes a surgical procedure to debride necrotic tissue, special care must be taken in the perioperative and postoperative periods to control her pain.

**DISCHARGE AND FOLLOW UP**

As Mrs P’s condition improves, preparations for discharge from the ICU are undertaken. Pain management is an essential component of follow-up care, as more than half of ICU patients report ongoing problems with pain many years after their discharge.44 Appropriate referral to rehabilitation services and practitioners who can provide ongoing support should be made. In some centres, specialized patient navigators work with each patient and their caregivers to facilitate care in the year following discharge.45 It remains to be seen whether these programs will significantly impact patient outcomes.

Patients, caregivers, and practitioners may be concerned that opioids administered in the ICU will lead to dependence on the drugs. A follow-up study of 2595 patients admitted to the ICU at a tertiary care hospital found that there was a decrease in opioid use at 48 months post-discharge, with only 1.8% of patients using opioids on most days, compared to 6.2% using opioids most days prior to admission.46 These findings suggest that post-ICU opioid dependence is rare.

Patients who remain on opioid medications post-discharge for chronic, non-cancer pain must be followed closely by an experienced practitioner. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain recommends a 5 to 10% dose reduction rate every 2 to 4 weeks for patients on high doses of morphine (>90 mg daily).47 Rotation between opioids as a potential strategy to taper dosage for gradual withdrawal was also suggested. This requires close monitoring, and regular follow-up visits must be scheduled.

Each session should discuss functional goals, psychosocial support, and plans for withdrawal symptoms and re-emerging pain.

**Table 1. Pharmacology of opioid and non-opioid analgesics.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Opioid</th>
<th>Route of Administration</th>
<th>Onset</th>
<th>Half-Life</th>
<th>Contraindications, Side Effects, and Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Opioid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>IV</td>
<td>5-10 min</td>
<td>2</td>
<td></td>
<td>May be contraindicated by significant hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketorolac</td>
<td>IV/IM</td>
<td>10 min</td>
<td>2.4-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibutrofen</td>
<td>IV</td>
<td>N/A</td>
<td>2.2-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>PO/PD</td>
<td>30-60 min</td>
<td>2.4</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>PO</td>
<td>N/A</td>
<td>5-7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: intravenous (IV), intramuscular (IM), PO (oral), PR (rectal).

Adapted from Barr et al (2013).
CONCLUSION

Pain among patients admitted to the ICU is common, and must be treated appropriately to avoid long-term complications. Frequent and objective reassessment of patients’ pain is the basis of appropriate care. Opioid therapy remains the standard of care in most cases, but non-opioid and non-pharmacological interventions may have some utility in selected cases. Patients who are discharged from the ICU should be referred to appropriate follow-up care, including ongoing pain management. In the long term, ongoing pain or traumatic memories associated with pain experienced during illness represent a significant burden on many patients, further emphasizing the importance of managing pain in all critically ill patients.

REFERENCES

The cost of pain
Economic implications of pain management practices

Adam Beswick, Caroline Piccininini

ABSTRACT
Prescription opioid use has historically been a regular component of the management of chronic nonmalignant pain in Canada. However, the economic implications of high rates of addiction and abuse have motivated consideration of more cost-effective management strategies. The economic burden imposed by prescription opioid use relates in part to lost workplace productivity, increased addiction treatment program costs, and increased overall healthcare expenditure for these patients. In this article, we present research on the economic implications of the current rates of opioid prescription, and report on the specific economic advantages realized in alternative therapeutic approaches to pain management.

INTRODUCTION
Pain management is ubiquitous across diverse medical specialties, and presents a unique challenge that extends far beyond the confines of a single patient-provider interaction. Although pain management is not a new component of practice for healthcare providers, the inappropriate prescribing of opioids has played a role in the current public health crisis of the opioid epidemic. Therefore, increased scrutiny of the way physicians treat pain is justified within the rapidly changing landscape of pain management in Canada.

Taken from a public health perspective, pain management in Canada imposes a considerable burden on the healthcare system. Chronic pain is estimated to affect 19% of Canadians, more than half of whom report that their pain has persisted for more than 10 years. Many patients and physicians have turned to opioid prescriptions to manage these chronic conditions, despite the potential addictive and destructive qualities of these drugs. A recent report from the CDC demonstrated that the probability of an individual patient becoming addicted to opioid drugs can be predicted by the length of the original prescription: a one-day opioid prescription carried a 2.9% risk of long term addiction, with this number rising to 30% for patients given month-long prescriptions. Globally, Canadians are the second largest consumers of pharmaceutical opioids. In 2016, there were 19 million opioid prescriptions filled in Canada, with the greatest prevalence of use found in Ontario, where 2 million Ontarians (14% of the population) filled opioid prescriptions in 2016.

ECONOMIC IMPACT OF OPIOID-BASED PAIN MANAGEMENT
In addition to the personal toll opioid addiction has on patients and their families, the economic consequences of this epidemic are substantial. Informed estimates posit that up to half of the total cost of opioid misuse is directly attributable to workplace economic loss (46%), largely driven by early death, disability, and reduced compensation due to job termination. Patients addicted to opioids also place a high economic burden on the criminal justice system and use 8 times the healthcare resources compared to non-addicted patients. A 2017 report by the American Federal Council of Economic Advisers estimated that the opioid crisis cost American taxpayers US$504 billion in total economic burden in 2015, representing 2.8 percent of the gross domestic profit; this figure represents a 6 fold increase in total economic impact compared to previous estimates as recent as 2013.

COST-EFFECTIVENESS OF ALTERNATIVE CHRONIC PAIN MANAGEMENT STRATEGIES
Meta-analyses of pain management with opioids have demonstrated that while opioids clearly provide strong analgesic benefit for a variety of pain etiologies (nociceptive, neuropathic, fibromyalgic, mixed), non-opioid pharmaceutical drugs can be equally as effective and, in many cases, more beneficial for patient functional outcomes. These differences have been attributed to the side effect profile of many opioid medications: patients have more severe side effects, higher rates of 30-day readmissions, higher costs of care, and 3.4 times greater risk of inpatient mortality. Similarly, one meta-analysis has shown that ‘weak’ opioids (e.g. tramadol, codeine) were not superior in cost-effectiveness to non-opioid drugs for post-operative pain management. Another study of post-surgical inpatients found that 13% of patients prescribed an opioid for pain management had an opioid-related adverse event; among this group of patients, the majority had a longer length of stay (55%), higher costs of care (47%), and an increased incidence of 30-day readmission to hospital. Overall, studies comparing postoperative pain management for surgical patients demonstrate that ‘opioid-sparing’ pain management techniques were more cost-effective compared to opioid-based pain management practices. Injectable NSAID analgesics such as ketorolac have been shown to be equally effective for pain management, with a similar median time to achieve relief and a significantly reduced likelihood of adverse side effects and withdrawal.

Multidisciplinary pain programs and other alternatives to pharmaceutical prescription may also have utility in the management of patients with chronic pain. For example, Kumar et al (2002) found that despite the high initial cost for spinal cord stimulation implantable devices, this technique was cost-effective in the long-term compared to opioid therapy for patients with failed...
back surgery syndrome. Although many studies have shown that certain alternatives can be cost-effective in comparison to opioids, the management of pain is highly dependent on the etiology of the pain complaint. Evaluation of alternative approaches is subject to variability in inclusion criteria, drug dosages, type of pain reported, underlying etiology, and outcome criteria. There is no single analgesic medication or alternative therapeutic approach that will universally outperform opioids. It is important to recognize, however, that a variety of alternative approaches to pain exist, and that some of these methods (eg spinal cord stimulation, implantable drug delivery systems, surgical pain relief procedures) have been proven cost-effective in select patient groups.

CONCLUSION

Physicians are uniquely responsible for making decisions that balance the need for effective pain relief with the need for judicious use of healthcare resources. This balance is difficult to manage in many opioid-based pain management treatment regimens. Indeed, the historical reliance on opioids has had negative consequences for both individual patients and the healthcare system. That being said, paid management is highly variable and dependent on a variety of patient factors; millions of Canadian patients will still depend on opioid-based pain management to treat chronic pain. Moving forward, we recommend that healthcare providers seek to supplement and, where possible, replace opioid-based management practices with more economically sustainable approaches that are based on evidence and judicious use of healthcare resources.

REFERENCES


A case of opioid-induced hyperalgesia
An overview of current evidence and recommendations
Herman Bami, Jordan Ho

ABSTRACT
This article presents a previously reported case of a 44-year-old woman receiving opioids for malignancy-related pain who presented with increasing pain symptoms. After a detailed examination of the patient's medical history, the pain was determined to be unrelated to her cancer and opioid-induced hyperalgesia (OIH) was diagnosed. The patient was eventually treated through a gradual tapering of opioids, in addition to complementary therapy and counseling. Following the case description, a concise review of the pertinent literature on OIH is conducted, emphasizing distinguishing factors between OIH and other similar syndromes as well as potential molecular targets. Finally, a brief summary of current recommendations is provided, although further research into this area is required to better evaluate the significance and treatment of OIH.

CASE PRESENTATION
A 44-year-old woman diagnosed in 2010 with a temporal glioma - which transformed into a high-grade glioma two years later - was referred to palliative care. She presented to an outpatient appointment at the Day Therapy Unit with sharp pain in the left arm, shoulder, and back that had developed over the past 5 weeks, alongside background dull pain ‘all over’ her body. The pain was noted by her husband to be worse following each rise in oxycodone dosage. She was subsequently admitted to the hospice for more effective pain management.

The patient had allodynia - central pain sensitization following normal, non-painful stimulation - whereby even light touch and contact produced burning pain. The constant pain in the patient’s left arm, shoulder, and back was found to be exacerbated by movement. Furthermore, she had been experiencing auditory and visual hallucinations, and had fallen recently, prompting concern over potential memory and central nervous system effects. Her other medical history was significant for headaches, seizures, and hypothyroidism.

For pain in the outpatient setting, the patient received long-acting oxycodone (55 mg twice daily), short-acting oxycodone (20 mg four times daily), codeine phosphate (60 mg three times daily), and paracetamol (1 g four times daily). Her other medications included: levothyroxine (25 µg), carbamazepine (600 mg twice daily) and levetiracetam (1.5 mg twice daily), moxicic (1 sachet three times daily), lansoprazole (15 mg twice daily), and metoclopramide (10 mg three times daily). These medications had not changed for the past three months.

In terms of social history, the patient lived downstairs in her family living room, and had become housebound due to her symptoms. Her relationship with her teenage children was fraught, and her husband was struggling with her increased care requirements. The resulting stress was reported to be affecting her mood.

Her physical examination was complicated by the presence of alodynia, but notable findings included bilateral tense masseter and temporalis muscles. Additionally, she was determined to have upper limb weakness (with a noted deficiency on the left side). Complete blood count, urea and electrolytes, calcium, and liver function tests were all normal, and a magnetic resonance imaging (MRI) scan of the brain showed that the glioma was static.

Differential diagnosis
While a wide array of potential diagnoses exist for increasing pain in patients with chronic diseases on strong opioids, a worsening in the primary condition must be carefully assessed. However, often pain caused by deterioration in the patient's primary condition will typically respond to increasing pain relief. Conversely, a patient with opioid-induced hyperalgesia (OIH) will generally not have their pain ameliorated by increases in opioid dosages, making the medical history - especially timing of increased pain and relation to opioid dosages - key to its diagnosis. Medical history factors that may confound diagnoses and must be further investigated include: low mood and anxiety influencing potential somatization of pain, drug interactions and metabolism, and pain of different aetiology (i.e. headaches, muscle pain).

CASE OUTCOME AND RESOLUTION
In this case, the patient’s oxycodone intake was decreased from 200 mg to 130 mg daily, distributed in regular doses every four hours. This was then further reduced by 5 mg per dose every 1-2 days. Complementary therapy and counselling were also employed to improve the patient’s mood and distract her from the pain. Lorazepam was prescribed to address the patient’s anxiety and muscle tension in the jaw. Eventually, the patient was stabilized on oxycodone (5 mg every 4 hours), with a dramatic decrease in her subjective pain description, thus supporting the diagnosis of OIH. The patient was followed up weekly, and remained on her new opioid dosage until four months later when an MRI indicated increased tumor size.

BRIEF REVIEW OF OPIOID INDUCED HYPERALGESIA
The use of opioids for chronic non-cancer pain has significantly increased in Canada, and it has precipitated a host of novel clinical considerations. Although first described in 1943, OIH has recently
been garnering attention. Though there is currently a lack of consensus on the definition of OIH, a recent review of the subject put forward the following operational definition: “worsening pain sensitivity without a new injury or exacerbation of an old injury, in a person chronically exposed to opioids”.2

Often compounding the difficulty of diagnosing and treating OIH are its similar symptom profile with opioid tolerance, allodynia, and withdrawal-associated hyperalgesia (WAH).3 Opioid tolerance occurs when increasing opioid dosages are required to produce the same effect; increasing dose would in this case improve pain relief.2 Alloynia is a phenomenon involving increased pain sensitization to a benign stimulus.3 It can often be treated effectively with opioids, non-opioid analgesics, and surgical interventions. Finally, WAH often involves a diffuse polyarthalgic pain occurring when detoxifying from opioid use; treatment often involves NSAIDs or monitored opioid dosing.2 Distinction between these syndromes involves a detailed and comprehensive review of medications and pain history.

Although the exact mechanism of OIH has yet to be elucidated, many theories have been proposed; these include sensitization of primary afferent neurons leading to enhanced release of glutamate, hyperexcitability of second order neurons to excitatory neurotransmitters, and up-regulation of nociceptive neuromodulators.4-6 In addition, several potential molecular targets have been found to be associated with the development of OIH including: the NMDA-glutamatergic system, K/Cl co-transporter and Cl homeostasis, transient receptor vanilloid 1, transient receptor potential member 8, 5HT-3 receptor, and the mammalian target of rapamycin.6

Due to the lack of clarity and consistency in the literature surrounding OIH, many recent reviews have been undertaken to better consolidate individual study results. In a review conducted by Fishbain et al (2009) on the subject, literature on OIH was examined in the context of better understanding the etiology of OIH in humans. The authors discovered that although there was a paucity of literature on the subject, there was sufficient evidence to support the presence of OIH in normal volunteers receiving opioid infusions.7 Furthermore, a recent systematic review examined OIH in post-operative patients, specifically looking at acute pain intensity at rest 24 hours after surgery.8 It was discovered that the group that had received high-dose intraoperative opioids had significantly increased pain scores at rest compared to the control group.9 This suggests that OIH can occur in otherwise healthy individuals, and thus re-emphasizes the need for further understanding in terms of clinical manifestations.

CURRENT RECOMMENDATIONS

Despite the insufficient amount of clear literature on the subject, certain treatments have been found to be effective in tackling OIH. Often, opioid tapering can be used to help alleviate symptoms and provide effective control.1 In order to successfully reduce dosages, clinicians can utilize and adjust existing frameworks, including the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain, Appendix B12: Opioid Tapering.9 Created by a group from McMaster University, these guidelines provide important precautions to consider when tapering, in addition to suggested dose reductions and time intervals for monitoring.9

In cases where reduction in opioid dosages are unacceptable to the patient, ketamine has been found to be successful in the treatment of OIH in outpatient case reports and clinical trials.3 However, there are limitations to the usage of ketamine, as currently it is only available in the US though injections.3 Trials are ongoing to further assess its use as well as other delivery models. In addition, gabapentin has also been shown to have a limited impact on reducing OIH in methadone-maintained individuals.3

Methadone has also been shown to be effective in reducing high-dose OIH, in part due to its incomplete cross-tolerance with opioid receptors and its NMDA receptor antagonism.4,10 However, methadone, at high doses, is also associated with disadvantages including toxicity and Torsades de Pointes.4 Other therapeutic agents that may prove efficacious include: dextromethorphan (a non-competitive NMDA-receptor antagonist), propofol, and COX-2 inhibitors.4 Other treatment strategies that may be effective include rational polypharmacy with non-opioid medications, minimizing opioid usage, and careful monitoring of withdrawal and OIH-associated adverse events.4

Furthermore, while there is limited supporting evidence, a recent review identified several strategies that should be considered to prevent OIH.11 These include: utilizing opioid combinations, limiting opioid dosage, administering co-analgesics and non-opioid analgesics, gradual withdrawal, utilizing regional/local anesthetics, and formal and documented dose equivalence calculations for chronic pain patients.9 While intuitive, these strategies may be effective in preventing the development of OIH, especially in chronic pain patients.

CONCLUSION

In this report, we examined a case of OIH in a patient receiving high-dose opioids for malignancy-related pain. The case highlights the importance of including OIH on the differential diagnosis for patients with escalating pain requirements. In addition, a brief review of the literature on the subject is conducted, specifically looking at syndromes with similar symptom profiles and potential etiology for OIH. Finally, a summary of current treatment recommendations is provided. Overall, there is a need for further study in this area, especially considering the current trends with regards to opioid usage and prescription in Canada.

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