



# UBCMJ

UNIVERSITY OF  
BRITISH COLUMBIA  
MEDICAL JOURNAL

Fall 2019 Volume 11 Issue 1

Exercise is Medicine:  
Treatment and Prevention  
of Chronic Disease

Advance Care Planning  
in Community-Dwelling  
Elders

Chronic Disease and  
Rheumatology: a Continuous  
Challenge, a Hopeful Future

Cannabidiol as a Potential  
Treatment for Patients with  
Chronic Anxiety Disorders

Considering the Role of  
Emotions in Persistent  
Post-Concussive  
Symptoms



# CHRONIC DISEASE



THE UNIVERSITY OF BRITISH COLUMBIA

# On the cover

The University of British Columbia Medical Journal (UBCMJ) is a peer-reviewed, student-driven academic journal with the goal of engaging students in medical dialogue and contributing meaningful discourse to the scientific community.



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## CHRONIC DISEASE



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The lasting impact of chronic disease is one experienced by many. However, if conditions do not improve over the long term, what of symptom management? In this issue, we take a closer look at several alternative treatments currently being used to alleviate the effects of chronic conditions, including prescribed exercise, as well as new treatment possibilities that are being explored, such as cannabinoids.

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# The Evolving Landscape of Chronic Diseases

Christine Wang<sup>1</sup>, Seo Am Hur<sup>1</sup>

Citation: UBCMJ. 2019; 11.1 (3-4)

A chronic disease, defined as one that is without a cure, encompasses a spectrum of conditions from well-managed illnesses to degenerative and debilitating conditions without effective treatments. The most common chronic diseases in Canada include cancer, diabetes, cardiovascular disease, and respiratory diseases such as chronic obstructive pulmonary disease or asthma.<sup>1</sup> Currently, more than one in five Canadians live with one of these common chronic conditions.<sup>1</sup> The burden of chronic disease on the healthcare system is substantial and is projected to become even greater due to the aging population. However, not all chronic diseases are associated with old age. There are many chronic diseases which can be diagnosed in childhood, such as asthma, neurological disorders, mental health conditions, and cystic fibrosis.<sup>2</sup> While advances in prevention and treatment of infectious diseases have decreased infant mortality, this increase in lifespan has led to a rise in childhood chronic diseases. However, the life expectancy for some of these chronic conditions has improved substantially. For example, childhood leukemia, one of the most common childhood malignancies, has had significant improvements in the treatment regimen and now carries a 95% five-year survival rate.<sup>3</sup> Furthermore, the Canadian Cystic Fibrosis Registry reported an increased median survival age from 31.9 years in 1990 to 49.7 years in 2012—an age that is projected to increase.<sup>4,5</sup> The increasing life expectancy associated with certain conditions is redefining the ever-growing pool of diseases that are now understood to be chronic rather than acutely fatal.

Chronic diseases are diverse and affect various body systems and age groups. For instance, chronic rheumatological conditions such as systemic lupus erythematosus and rheumatoid arthritis have a relatively young age of diagnosis that can affect middle-aged adults or even teenagers.<sup>6,7</sup> In our feature articles section, internal medicine resident Dr. Julia Tan and rheumatologist Dr. Natasha Dehghan share some of the challenges and rewards of managing chronic rheumatological diseases and the therapeutics available to patients for management of their conditions.

Chronic infectious diseases, such as HIV and hepatitis B/C, are another category of chronic diseases. Advances in anti-retroviral therapy have resulted in a life expectancy for people living with HIV that is near-comparable to the general population.<sup>8</sup> These diseases affect a small portion of the population but are growing in number. While the prevalence of perinatal HIV transmission between infected mothers and their children has declined due to prenatal testing and prevention strategies,<sup>9</sup> the overall rates for HIV infection in Canada are still rising, with a 17.1% increase in the Canadian national diagnosis rate between 2014 and 2017.<sup>10</sup> A commonality between these chronic diseases is that they tend to be further complicated with other comorbidities, which makes management more complex.

Despite the availability of pharmacological and non-pharmacological treatments, the mortality and morbidity arising from chronic diseases is still quite substantial: in 2016, 89% of deaths in

Canada were due to a chronic disease.<sup>11</sup> For the most common chronic diseases, 80% of Canadians have a modifiable risk factor, including physical inactivity, smoking, unhealthy eating, and harmful use of alcohol.<sup>11</sup> In one of our feature articles, Dr. Kathy Gaul highlights the indispensable role of exercise in chronic disease treatment and prevention. Yet, health disparities in society persist due to barriers to addressing modifiable risk factors such as physical inactivity and decreased access to healthy food, which are correlated with low socioeconomic status.<sup>12</sup>

In addition to prevention and treatment, there is a growing role of palliative medicine in managing chronic diseases. Palliative care is a multi-disciplinary approach that involves the physical, mental, social, and spiritual care of patients, as well as their loved ones.<sup>13</sup> The federal government of Canada has committed \$11 billion over the next ten years towards home, palliative, and mental care, which are important in the care of patients with chronic disease.<sup>14</sup> As we recognize the growing number of chronic diseases, the perception of palliative care as merely “end-of-life care” is changing. The importance of palliative care integration early on in chronic disease management is discussed in a feature written by palliative care physician Dr. Catriona Aparicio.

Ultimately, the landscape of chronic disease is vast. There is a chronic disease in nearly every medical specialty, and the burden of chronic disease management is only increasing. The Canadian Community Health Survey in 2011 and 2012 found that 16.8% of Canadian are living with two or more chronic diseases.<sup>15</sup> Chronic disease and pharmacological treatment also come with increased risks of polypharmacy such as potential drug interactions.<sup>16</sup> The path ahead in chronic diseases will be multi-faceted and challenging, but it is also one that is hopeful of the medical advances on the horizon.

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# Exercise is Medicine: Treatment and Prevention of Chronic Disease

Catherine A. Gaul<sup>1</sup>

Citation: UBCMJ. 2019; 11.1 (5-6)

## Introduction

Health-enhancing benefits of exercise have long been known—Hippocrates encouraged exercise for the maintenance of optimal health and for prevention and treatment of disease.<sup>1</sup> More recently, noncommunicable chronic diseases are now responsible for more than 68% of deaths globally, with 75% of deaths in low- and middle-income countries.<sup>2</sup> Many chronic diseases are influenced by physical inactivity (PIA). Worldwide, PIA is the fourth leading risk factor for all-cause mortality.<sup>3-5</sup> PIA, with its associated low cardiorespiratory fitness, increases the risk of dying at least as much as smoking, obesity, hypertension, and high cholesterol combined.<sup>6,7</sup>

The concept of exercise as medicine has evolved with the expanded understanding of exercise physiology and molecular biology. Exercise is a potent stimulus for important signaling pathways at the cellular and molecular level.<sup>8,9</sup> It can modify inflammatory processes, which are often associated with chronic disease, and can initiate anatomical remodelling resulting in improved function in both health and chronic disease.<sup>8,10-12</sup>

## Prescribing Exercise as a Medicine

Exercise is structured physical activity that improves health and fitness by stimulating physiological and morphological adaptations in the body. Similar to other medicines, the response to exercise is specific and predictable. The prescription of exercise includes a dosage generated from dose-response curves for optimal treatment. A single dose can often initiate small but measurable benefits, with greater impact attained with regular use. Like most medicines, exercise also has a half-life: its positive benefits will dissipate if exercise is not continued regularly.

Optimizing the therapeutic potential of an exercise prescription involves following the FITT principle of **F**requency (number of sessions per week), **I**ntensity (level of effort), **T**ime (duration per session), and **T**ype (mode of exercise) within the well-established principles of exercise training. These include exercise progression, specificity, overload, and rest. Prescribed properly, physical exercise is an essential, first-line form of prevention and treatment of over 30 chronic diseases.<sup>9</sup>

Canadian Physical Activity Guidelines of 150 minutes of moderate-to-vigorous physical activity (MVPA) plus two muscle- and bone-strengthening activities per week help to optimize exercise prescription for the greatest health benefit.<sup>13</sup> Evidence indicates that by achieving these guidelines, risk of all-cause mortality can be reduced by at least 30%, as can the risk for cardiovascular disease (30%), osteoporosis (25%), stroke (25%), hypertension (20%), diabetes (20%), colon cancer (20%), and breast cancer (14%).<sup>14</sup> Understanding how exercise protects against and/or provides treatment for specific chronic diseases is critical to the prescription of exercise as a medicine.

The following sections provide examples and evidence of how exercise imparts its effect on chronic disease.

## Type 2 Diabetes: Management and Treatment with Exercise

Type 2 diabetes (T2D) provides an excellent model of exercise as medicine. Skeletal muscle plays a critical role in glycemic control through the actions of glucose transporters (GLUT4) responsible for glucose uptake. A single bout of exercise enhances GLUT4 translocation to the sarcolemma, even in insulin-resistant skeletal muscle fibers.<sup>15,16</sup> Contraction-induced increases in the activity of calcium/calmodulin-dependent protein kinases, AMP-activated protein kinase, nitric oxide synthase, and reactive oxygen species have all been linked to enhanced GLUT4 translocation independent of insulin. Additionally, GLUT4 expression is elevated following exercise, providing enhanced glycemic control post-exercise.<sup>15</sup> Exercise also effectively reduces hemoglobin A1c (HbA1c).<sup>17-19</sup>

While aerobic and resistance training each independently improve glycemic control in T2D, improvements are greatest with combined aerobic and resistance training.<sup>9,20</sup> Notably, there is growing interest in high intensity interval training (HIIT) to reduce risk of chronic disease, particularly T2D. A benefit of HIIT is that it requires less time commitment, though greater exercise effort, than MVPA. Because adherence to exercise prescriptions is often poor, typically due to perceived lack of time, this time-efficient exercise intervention can result in excellent benefits.<sup>21,22</sup> HIIT exercise has been reported to effectively increase GLUT4 expression and reduce HbA1c.<sup>18-22</sup>

The distinct signalling pathways of insulin and muscle contraction characterize just how important exercise is to the management and treatment of T2D. However, like most medicines, there is potential for deleterious drug interactions when prescribing exercise to those dependent on exogenous insulin. With the enhanced insulin-like effect of exercise, a careful, informed manipulation of insulin dose is often required. If prescribed effectively, and with due caution, exercise may be as efficient as glucose-lowering medications.<sup>22</sup> There is good reason to believe that, with appropriate exercise prescription, T2D may be a reversible chronic disease.<sup>9</sup>

## Anti-Inflammatory Response of Exercise

Many chronic diseases are associated with persistent, low-grade inflammation. Inflammatory cytokines have been associated with insulin resistance, initiation and progression of tumours, atherosclerosis, and several neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, and depression.<sup>24,25</sup> The anti-inflammatory role of exercise exists due to the ability of contracting muscle to release the myokine interleukin-6 (IL-6).<sup>9,25-28</sup> Through a cascade of cellular events, IL-6 initiates the inhibition of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF- $\alpha$ ). Exercise-induced IL-6 response is proportional to contracting muscle mass, exercise intensity, and exercise duration.<sup>9,27</sup> As a result, the prescription of exercise may

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effectively reduce the risk and progression of many chronic diseases by attenuating inflammation.

### Exercise for Mental Health

Individuals who engage in regular exercise experience fewer days of poor mental health compared to those who are inactive.<sup>25,28</sup> The benefits of exercise on depression are comparable to the effects of cognitive behavioural therapy and occur with all types of exercise when performed regularly.<sup>25,29</sup> With mental illness comes a high risk of PIA, a factor identified as contributing to a 15-25 year difference in life expectancy relative to those with good mental health.<sup>30</sup> Exercise, therefore, should be considered when treating mental illness, as it has the potential to reduce this gap and increase quality of life of those experiencing mental health challenges.

### Summary

Evidence from epidemiological studies and clinical research demonstrates that exercise attenuates the risk of many health challenges. As a medicine, exercise has a role to play in the maintenance of optimal health, as well as in the prevention, management, and even adjuvant treatment of chronic diseases. Perhaps exercise should be viewed as a chronic disease vaccine.

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# The Importance of Palliative Care in Chronic Disease Management

Catriona Aparicio<sup>1</sup>

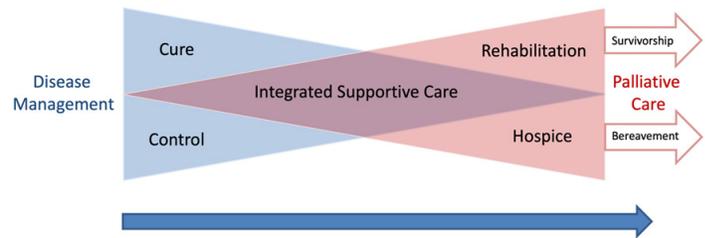
Citation: UBCMJ. 2019; 11.1 (7-8)

Palliative care is a subspecialty of various medical specialties with fellowship training and a specialty exam. However, a “palliative approach to care” is an important part of all disciplines dealing with chronic disease management. It is now included in the curricula of all Canadian medical schools, with a choice of different training program lengths for physicians.

CBC Radio One’s program “White Coat Black Art” presented by Dr. Brian Goldman, describes a conversation with a woman living with multiple sclerosis in the episode titled “A Meaningful Life.”<sup>1</sup> The woman with multiple sclerosis told the story about her disease and expressed her fears and hopes very eloquently. She experienced a life of increasing disability, cumulative functional and psychological losses, and the reality that she could die soon due to prolonged seizures. She considered circumstances where she would refuse emergency treatment because that intervention would significantly reduce her quality of life. She also considered medical assistance in dying, but found that her current quality of life was good because of the support she received. In particular, she emphasized the importance of palliative care in her care program, particularly in supporting conversations with her family about her goals of care.

Palliative care is an art as much as a science. The WHO definition of palliative care describes the biopsychosocial and spiritual aspects of palliative care, including care of the patient’s loved ones.<sup>2</sup> In past years, the practice of palliative care was a combination of physician experience, case histories of off-label prescribing of medications, and interventions based on intuition. As the specialty grows in importance and relevance, more rigorous scientific investigations are being carried out on the interventions used, as well as the range of pharmacological options such as medicinal cannabis and laxatives. Randomized controlled trials such as the Massachusetts General Hospital study in 2010 support the beneficial role of early palliative care consultation in oncology patient care.<sup>3</sup> A cohort of patients with newly diagnosed metastatic non-small-cell lung cancer were randomized to receive early palliative care consultation plus standard oncological care or standard oncological care alone, with referral to palliative care by their oncologist if necessary.<sup>3</sup> The patients receiving early palliative care consultation had better quality of life, less aggressive care at end of life, and longer survival. This was a key study in promoting the value of palliative care and demonstrating that rigorous scientific investigation can be carried out in patients with advanced diseases.

The ideology of early consultation with palliative care is described in the Bowtie Model of Palliative Care (Figure 1) by Dr. Pippa Hawley, UBC Head of the Division of Palliative Care.<sup>4</sup> It visualizes how palliative care and disease specialist care intersect. In the beginning, there is a larger involvement of disease management care, with some palliative care involvement. However, as the disease



**Figure 1** | The Bowtie Model of Palliative Care.

progresses towards end of life, the disease specialist care diminishes and the role of palliative care increases. This model illustrates the evolving role of palliative care in the care of people living with chronic disease, right from the point of diagnosis. Initially, palliative care may focus on symptom management, but it should also involve a “serious illness conversation” with the patient.<sup>5</sup> This conversation should be a progressive one, in which the meaning of the diagnosis and planned course of treatment are discussed and there is a focus on building a relationship between the physician and patient in the initial phase. This should be followed by further conversations at times of significant change in disease status, or at the request of the patient. These may include discussing the possibility that the patient may die, encouraging patients to express their goals and wishes, involving their loved ones, and naming a substitute decision-maker. In addition, physicians could consider asking themselves the “surprise” question each time they see the patient: “Would I be surprised if this patient died in the next year?” If the answer is no, this should prompt the physician to engage the patient in discussions about the patient’s wishes and goals of care.<sup>6</sup>

As the world’s population ages, physicians recognize that people with chronic diseases, and sometimes multiple comorbidities, often have prolonged suffering and a poor understanding of the nature and natural history of their diseases. As well, conditions such as Type 1 diabetes and certain cancers can now be considered a chronic disease due to advances in pharmacology and surgical techniques. As medicine advances, there is an increasing need for a palliative approach to care throughout hospitals, specialist clinics, family practice, long term care, and community nursing services. Specialist palliative care consultation should only be needed for the most complex cases.

Since the legalization of medical assistance in dying (MAiD), access to palliative care has become even more important. People with chronic diseases whose death is foreseeable are eligible if they have grievous and irremediable suffering. The Canadian Society of Palliative Care Physicians has campaigned in support of Bill C-277, “An Act Providing for the Development of a Framework on Palliative Care in Canada.”<sup>7</sup> Every patient requesting MAiD should be offered palliation of their suffering. In many cases, palliative care has led to a change in the patients’ quality of life, causing individuals to postpone or withdraw their request for MAiD, as demonstrated by the woman with multiple

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sclerosis interviewed by Dr. Goldman.

Palliative care is not about dying — in fact, it is about supporting people living with a life-threatening illness for as long as is needed. This support involves the management of a person's physical, psychological, emotional, and spiritual suffering. Palliative care is provided by a multidisciplinary care team including nurses, physicians, counsellors, social workers, physiotherapists, and other support services; and can be provided everywhere from the emergency room or hospital bed to the patient's home. Most importantly, palliative care is about supporting patients, their loved ones, and caregivers throughout the illness.

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# Chronic Disease and Rheumatology: a Continuous Challenge, a Hopeful Future

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Citation: UBCMJ. 2019; 11.1 (9-10)

Rheumatology is an internal medicine subspecialty which focuses on autoimmune diseases and inflammatory conditions affecting the musculoskeletal system. A majority of rheumatological conditions fall under the category of “chronic disease” and involve longitudinal patient care, which is often confounded by other biological and psychosocial comorbidities. Chronic diseases are defined as long-term medical conditions that can be treated, but not cured. According to the 2002 World Health Report “Reducing Risks, Promoting Health,” chronic diseases currently account for over 50% of all deaths and 43% of the global burden of disease.<sup>1</sup>

Many common rheumatological conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), are chronic, lifelong conditions with no known cure. The prevalence of RA is 0.5-1% of the population,<sup>2</sup> and the incidence of SLE is 0.1%, as cited in literature.<sup>3</sup> Compared to other chronic conditions such as coronary artery disease (CAD), diabetes, and certain malignancies, many rheumatological diseases are also diagnosed at a relatively younger age. One study, which identified 928 patients with SLE, found that the mean age at diagnosis was 35 years old.<sup>4</sup> In contrast, CAD tends to affect older individuals, primarily over the age of 55.<sup>5</sup> This younger age of diagnosis has implications on patients and further adds to the complexity of managing these chronic rheumatological conditions.

From the patient perspective, there are several physical and psychosocial consequences associated with having a chronic rheumatological condition. In a Finnish study which included 1095 patients with RA and 1530 healthy controls, the RA group was associated with a >7-fold increase in risk of disability compared to the general population.<sup>6</sup> Beyond the impaired physical function caused by these diseases, many of these patients are also at an increased risk of developing other comorbidities. For example, patients with psoriatic arthritis have a higher incidence of cardiovascular disease,<sup>7,8</sup> Sjogren’s syndrome confers a significantly increased risk of developing lymphoproliferative disorders,<sup>9</sup> and patients with RA have an increased incidence of chronic obstructive lung disease.<sup>10</sup> These chronic rheumatological conditions currently have no cure; therefore, these patients also have a life-long risk of developing various associated complications.

In addition to the significant impact that these diseases can have on an individual’s health, many chronic rheumatological conditions also lead to an earlier retirement and increased rates of disability leave. Young *et al.* followed RA patients over five years and found that up to one-third of individuals eventually stopped working owing to their disease.<sup>11</sup> The impact of this productivity loss is further compounded given that the diagnosis of these rheumatological diseases often occurs during an individual’s peak productivity and career. Unsurprisingly, there are significant societal and personal consequences for this patient

population. Patients may undergo shifts in their roles at home, which can contribute to economic and mental distress.

There are also profound psychological repercussions of having a chronic rheumatologic condition. Wolfe *et al.* published a study containing 11,704 patients with fibromyalgia (FM), SLE, RA, and non-inflammatory rheumatic disorders (NIRD). They found that depression was present in 15% of patients with RA or NIRD, 34% of patients with SLE, and 39% of patients with FM. This study also examined the EuroQol utility index (EQ-5D) score, a validated tool for assessing quality of life, in these patients and found significant impairments.<sup>12</sup>

For physicians, it can be challenging to manage a patient with a chronic rheumatological condition. Therapy often needs to be adjusted as patients age and go through various stages of life. With increased age, patients often develop further comorbidities that can preclude the use of certain medications. Moreover, many young females are often affected by rheumatological conditions during their child-bearing ages. A physician must collaborate with a patient to determine an optimal time for pregnancy, balancing a patient’s desire to have a family and controlling her disease activity. In SLE patients, for example, lupus nephritis can often flare with pregnancy and requires careful planning to ensure patient safety.<sup>13</sup> Furthermore, certain mainstay medications used in the treatment of rheumatological diseases, such as methotrexate, are contraindicated in pregnancy and breastfeeding, which also complicates management.<sup>14</sup>

Despite the challenges faced by both patients and physicians, rheumatology remains an exciting and rewarding field. The chronicity of these conditions allows for the development of long-term relationships between patients and their rheumatologists. Rheumatologists get to know their patients and have the privilege of seeing these individuals from their initial diagnosis, to tackling the challenges of creating a family, to growing into old age together. Patients and physicians alike derive comfort and meaning from a strong therapeutic alliance and the opportunities to build such a relationship are plentiful in rheumatology because of the longitudinal care.

Furthermore, rheumatology is a rapidly progressing field with many active clinical trials examining new targets for therapy. Biologics such as tumor necrosis factor inhibitors and interleukin inhibitors, as well as small molecules such as Janus kinase inhibitors, have changed the trajectory of many rheumatological diseases. These advancements have also led to improvements in work presenteeism and reduced overall impact of disease. In a study which included 577 patients with axial spondyloarthritis, those treated with biologic therapies had significantly greater work productivity and reduced activity impairment.<sup>15</sup> Furthermore, with these new medications, many patients are now enjoying prolonged periods of symptom-free disease.<sup>16</sup> In fact, sustained remission in RA, off medications, is not uncommon. In a study that looked at 454 patients from the Leiden Early Arthritis Clinic and 895 patients from the British Early Rheumatoid Arthritis Study, 9-15% were able to achieve disease modifying anti-rheumatic

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drug-free remission.<sup>17</sup>

Another interesting and relatively recent development in rheumatology includes the introduction of biosimilars. There are currently 18 Food and Drug Administration approved biosimilars in the United States, with many more in active clinical trials.<sup>18</sup> These new molecules, which have been manufactured using existing biologics as a reference product, have implications on patient management, medication affordability, and generation of further competition among pharmaceutical companies. A myriad of research, including a recent systematic review of 113 journal articles and 149 abstracts published in January 2019, is being conducted to review the safety, efficacy, and risk of switching patients who were previously stable on biologicals to biosimilars.<sup>19</sup> This particular systematic review did not identify significant risks between a single switch from a reference biologic to a biosimilar; however, further data exploring this topic is required.<sup>19</sup>

Ultimately, although chronic rheumatological conditions can be a challenging diagnosis for patients and physicians, rheumatology remains an interesting and meaningful specialty. There continues to be a wealth of research in rheumatology, such that perhaps, someday, these diseases may no longer be chronic, but curable.

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# Chronic Exposure to Toxic Metals as a Risk Factor for Alzheimer's Disease: A Review

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Citation: UBCMJ. 2019; 11.1 (11-13)

## Abstract

Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by progressive memory loss, decline of cognitive functions, and, eventually, the inability to communicate or perform daily life tasks. Despite the fact that researchers have made significant progress regarding the etiology of AD in recent years, the environmental risk factors involved in the pathogenesis of the disease still remain unclear. One widely known hypothesis that deals with environmental risk factors is the biometal dyshomeostasis hypothesis, which claims that the accumulation of toxic metals in the body over time is positively associated with the stages of neurodegeneration observed in AD. While many studies have produced results in support of this hypothesis, others have found no significant relationship between exposure and disease outcomes. This review will focus on elucidating contentious areas in the existing body of knowledge surrounding AD by examining the evidence behind the biometal dyshomeostasis hypothesis.

## Introduction

In 2017, Alzheimer's Disease International estimated that roughly 50 million people worldwide were living with some form of dementia, and that roughly two-thirds of those cases had AD.<sup>1</sup> That year, AD was responsible for an estimated 1.54 million deaths worldwide, and AD-related mortality is predicted to increase significantly as the global population ages.<sup>1</sup> Currently, there is no known cure, and out of over a hundred clinically-tested drug treatments, only five have been approved for use as AD treatments in Canada.<sup>2</sup> These drugs may help in managing common symptoms, but they often have little to no effect on life expectancy, as the typical life expectancy after being diagnosed with AD ranges from four to eight years regardless of medications.<sup>3</sup> In Canada, the national prevalence of AD and other forms of dementia is rising, and the Alzheimer Society of Canada estimates that there are over 564,000 Canadians living with dementia today.<sup>2</sup> In addition to that, an excess of 25,000 new cases are being reported each year, and by 2031, the national prevalence of dementia is projected to rise up to 937,000 cases.<sup>2</sup> This increase in cases would put a significant strain on Canada's economy, as it would increase national dementia healthcare costs from \$10.4 billion per year to \$16.6 billion per year—an upsurge that Canada's health care system is ill-fit to handle.<sup>2</sup> Hence, it is imperative that Canada enacts primary prevention methods to decrease the incidence of dementia in the near future. The purpose of this review is to identify and explore the relationship between environmental exposures and the pathogenesis of AD. Once the relationship between exposure and disease is established, that information can be used to promote better health outcomes by guiding policy decisions related to environmental and occupational health and safety.

## The Biometal Dyshomeostasis Hypothesis

The biometal dyshomeostasis hypothesis attempts to explain environmental risk factors for neurodegenerative disorders based on the fact that toxic metals can promote aggregation of  $\beta$ -amyloid clusters in the brain, which is a biological hallmark of AD.<sup>4</sup> While there are a multitude of risk factors that may contribute to the pathogenesis of AD, the most prominent risk factors are aging, genetic predispositions, previous traumatic brain injuries, and environmental exposures.<sup>4</sup> Out

of those, the only factor we can actively change is the exposure to environmental hazards, with the main exposure of concern being toxic metals.

People are mainly exposed to toxic metals in the environment by soil and water contamination, as well as airborne pollutants generated by industrial waste from mining operations, mills, and battery factories.<sup>5</sup> For instance, lead, aluminum, mercury, and cadmium are heavy metals that are utilized extensively in industrial processes. While acute exposures may generate little to no risk, the bioaccumulation of these toxic metals over time can lead to effects such as permanent brain damage, which may be associated with the pathogenesis of AD.<sup>4,6</sup> Thus, workers in industrial facilities are at a high risk for developing AD later in life.<sup>7</sup> Of course, all people are at risk due to the ubiquitous nature of airborne pollutants and soil and water contamination, but occupational exposures tend to be far more significant.<sup>8</sup> Workers in battery factories are often exposed to much higher levels of heavy metals compared to the general population, and one meta-analysis showed that being chronically exposed to aluminum increased lifetime risk of developing AD by nearly 70%.<sup>8</sup> This phenomenon makes sense from a biological perspective, as the cellular damage inflicted by the bioaccumulation of toxic metals can result in a number of neurological impairments, including memory loss, tremors, and changes in sensory perception, all of which may be correlated with the development of neurodegenerative diseases such as AD.<sup>5,6</sup>

## Review of the Evidence

Multiple epidemiological studies have already linked chronic exposure to heavy metals with neurodegenerative effects such as memory loss and reduction of brain volume, which sets the foundation for the biometal dyshomeostasis hypothesis. Until the early 2000s, this hypothesis was highly contentious among researchers, for although the majority of studies had observed higher blood levels of heavy metals in AD patients compared to healthy patients, there were also studies with no statistically significant difference between groups.<sup>7,8</sup> For example, one cohort study observing the effects of aluminum exposure on workers in the automobile industry found that there was no significant difference in brain function compared to unexposed workers of the same age range, and two cross-sectional studies conducted in a similar occupational setting reached the same conclusions.<sup>9,10</sup>

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In recent years, however, findings from key studies have started to become more consistent, and researchers seem to be nearing an agreement about the potential risks of environmental and occupational exposure to heavy metals.<sup>11</sup> In 2018, a meta-analysis of 42 studies showed that blood levels of mercury, aluminum, and cadmium were significantly higher in AD cases than in controls.<sup>4</sup> Furthermore, a report from a hospital in Seoul revealed that blood levels of lead, copper, and mercury were significantly higher in patients who had AD compared to those with no neurodegenerative diseases, which suggests that not only may the same concept also hold true with other toxic metals, but there also may be synergistic effects associated with exposure to multiple metals.<sup>12</sup>

Many studies observing the development of AD narrowed their focus to a singular toxic metal. For instance, one post-mortem case-control study of a family in China that had been exposed to high levels of mercury throughout their lives showed that the accumulation of mercury in the brain can inflict significant neurological damage, as all members of the family had experienced a degree of neurodegeneration not typical of their age groups.<sup>13</sup> Another post-mortem case-control study in California analyzed the results of 99 MRI brain scans and found higher levels of iron and lower tissue integrity in the hippocampus of subjects who had died of AD.<sup>14</sup> Both of these examples illustrate the potential neurodegenerative effects of long-term exposure to toxic metals. Moreover, a meta-analysis of case-control studies observing lead as a risk factor for AD found that there was a significant difference in lead exposure between disease groups, though the researchers also recommended prospective studies to be conducted in the future.<sup>15</sup> While there are limited prospective studies involving human subjects, one retrospective cohort study conducted in Thailand showed that long-term exposure to arsenic in early stages of childhood development significantly impaired brain growth in a group of children, which led to them having lower brain weights at maturity.<sup>16</sup>

### Methodological Flaws in Past Studies

Many of the observational studies reviewed here focused on isolating one specific heavy metal to explore its neurotoxic effects, but restricting the scope of observation to individual exposures has some noteworthy limitations. Having a single-metal study design is not representative of reality, as people are often exposed to multiple different metals at the same time, and combining exposures may have synergistic or antagonistic effects on neurotoxicity. In fact, one rodent study reported that the administration of a mixture of metals decreased the rodents' neural functions much more than any single metal did.<sup>17</sup> That is likely because multiple metals enter the body through the same biological pathways and share the same ion transporters in circulation, which means that any change in the circulatory level of one metal may have unintended effects on the circulatory level of others.<sup>5</sup> By only specifying one toxic metal as an exposure of interest, many of the observational studies reviewed here failed to account for the effects of other toxic metals in the environment. Having this uncertainty present, there is a clear need for more comprehensive studies exploring the effects of chronic exposure to multiple metals in order to reveal their combined effects on the pathogenesis of AD.

Additionally, many studies found it challenging to account for all sources of bias. A few of the studies reviewed did not adjust their results for extraneous variables, which could have introduced confounding bias into their conclusions. Some potential confounding factors include variations in exposure time, variations in the concentrations of toxic

metals that individuals were exposed to, and genetic predisposition to AD. As well, there may have been information bias in some of the cohort studies, as participants did not always know their own exposures, so self-reported data on exposure status may have been inaccurate.

### Future Research Directions

In many of the papers reviewed here, researchers emphasized the need for longitudinal cohort studies to further support their conclusions, and they recognized that larger sample sizes would be needed in order to attain generalizable results.<sup>4,15</sup> These claims have substantial implications for future research, prescribing that in order to fully confirm the role of toxic metals in the pathogenesis of AD, future research should involve more prospective studies in order to track lifetime environmental exposures and to determine how different combinations of toxic metals in the brain can affect the severity of neurological damage. Theoretically, a prospective cohort study could observe lifetime toxic metal exposure and accumulation of toxic metals in the brain by having participants receive MRI scans on a yearly basis. That would decrease the potential bias associated with self-reporting exposure status, increasing the internal validity of the study. Knowing the true association between exposure to toxic metals and risk of developing AD will help decision-makers determine whether any environmental interventions are needed in order to mitigate health risks.

### Conclusion

Overall, there is already a fair amount of existing evidence to establish a positive relationship between exposure to toxic metals and the pathogenesis of AD, as the accumulation of toxic metals in the brain has been shown to lead to neurodegenerative effects.<sup>11</sup> However, more studies are needed in order to understand the complex interactions between exposures and how chronic exposure to multiple metals may affect one's lifetime risk of developing AD. Clearly, there is a gap in the research regarding how chronic exposure to mixed metals affects the development of AD. This is important as AD is both a disease that inflicts a heavy burden on individuals and their communities, and one where therapies to reverse the effects of neurodegeneration have been elusive. Providing long-term care for people with AD is an extremely costly expense for the Canadian healthcare system, and since there are no effective AD treatments on the market,<sup>1</sup> it is time to focus on research efforts that can inform environmental and occupational health and safety policies in order to mitigate the risk of AD.

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# The Prevalence and Management of Inflammatory Bowel Disease on Vancouver Island

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Citation: UBCMJ. 2019; 11.1 (14-15)

## Introduction

Inflammatory bowel disease (IBD) is a chronic, debilitating disease with a complex etiology which places a significant burden on both patients and healthcare resources. Canada has one of the highest prevalence rates of IBD in the world, at 0.7%.<sup>1,2</sup> In 2018, the direct and indirect costs of IBD totaled over \$2.6 billion, and it is expected that both prevalence and costs will continue to rise.<sup>1,3</sup> IBD management is complex and particularly challenging for those living in rural settings. It has been shown that IBD patients living farther from gastrointestinal (GI) services experience poorer outcomes.<sup>4,5</sup> Vancouver Island (VI) poses challenges to GI service access, with no gastroenterologists located outside the South Island region (see Appendix A for regional map).<sup>6</sup>

The epidemiological understanding of IBD on VI is lacking. Due to the distribution of GI services, there is potential for regional disparities in quality of IBD care. To date, there have been no studies of IBD on VI. As a result, there is a paucity of information surrounding prevalence and quality of care; this is important information, given the nationally high prevalence of IBD and large population living outside the South Island region.<sup>7</sup> This pilot study aimed to better understand the prevalence and management of IBD on VI and identify if regional disparities in access to and quality of care exist.

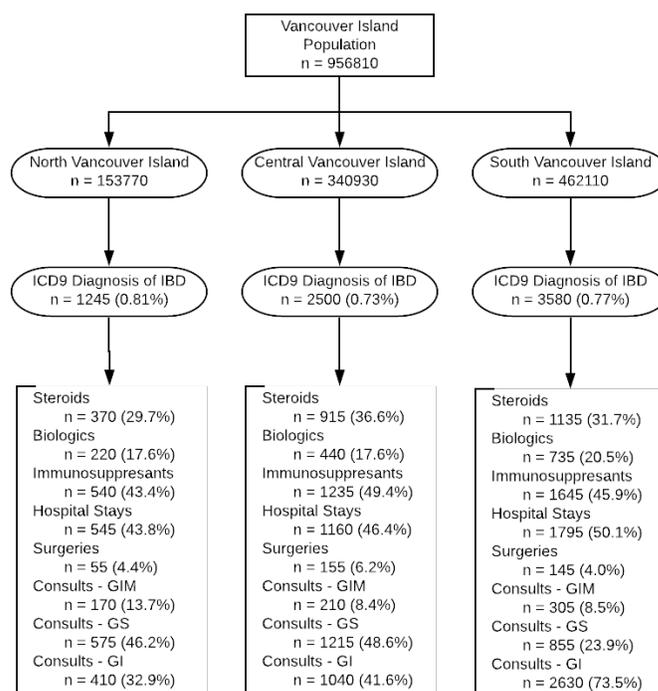
## Methods

We accessed data from BC Data Scout, a data feasibility service supported by Population Data BC, to gain estimates of prevalence and resource use statistics. The data submission separated VI into 3 geographic regions: North Island (NI), Central Island (CI), and South Island (SI). Patients were selected based on a diagnosis of IBD (diagnostic codes 555-556) using the ninth revision of the International Classification of Diseases (ICD9) because the BC Medical Services Plan utilizes the ICD9 diagnostic codes for billing purposes.<sup>8</sup> Eight cohorts were made for each region, categorizing patients by use of IBD medications, hospital stays, surgeries, and consults with specialist physicians (Figure 1). Appendix B outlines the specific interventions falling under each category. These cohorts overlap (patients may belong to more than one cohort), such that the total number of patients receiving any one intervention is accounted for in the cohort. Patients without an ICD9 diagnosis of IBD or without a primary residence on VI were not included. Resulting data were utilized to calculate prevalence and resource usage rates to compare IBD management between regions.

## Results

BC Data Scout outputs estimated the prevalence of IBD on VI to be 0.77%. Over half of IBD patients were from the NI or CI (Figure 1). There were no significant differences in IBD prevalence or demographics across regions (Figure 1). There were significantly lower rates of GI consultations (SI: 73.5%; CI: 41.6%; NI: 32.9%;  $p < 0.0001$ ) and higher rates of general surgery consultations in the NI and CI than in the SI (SI: 23.9%; CI: 48.65%; NI: 46.2%;  $p < 0.0001$ ). Compared to living in the SI, living in the CI was associated with a higher likelihood

of surgery (OR 1.96, 95% CI: 1.58-2.35,  $p < 0.0001$ ) and steroid use (OR 1.25, 95% CI: 1.12-1.38,  $p < 0.0001$ ). Both NI and CI residents had a lower likelihood of being prescribed a biologic than SI residents (OR 0.82, 95% CI: 0.7368-0.9307,  $p < 0.001$ ) (Figure 2).



**Figure 1** | Selected cohorts from BC Data Scout with the number of patients in each cohort for 2015-2017. GIM: General Internal Medicine; GS: General Surgery; GI: Gastroenterology.

## Discussion

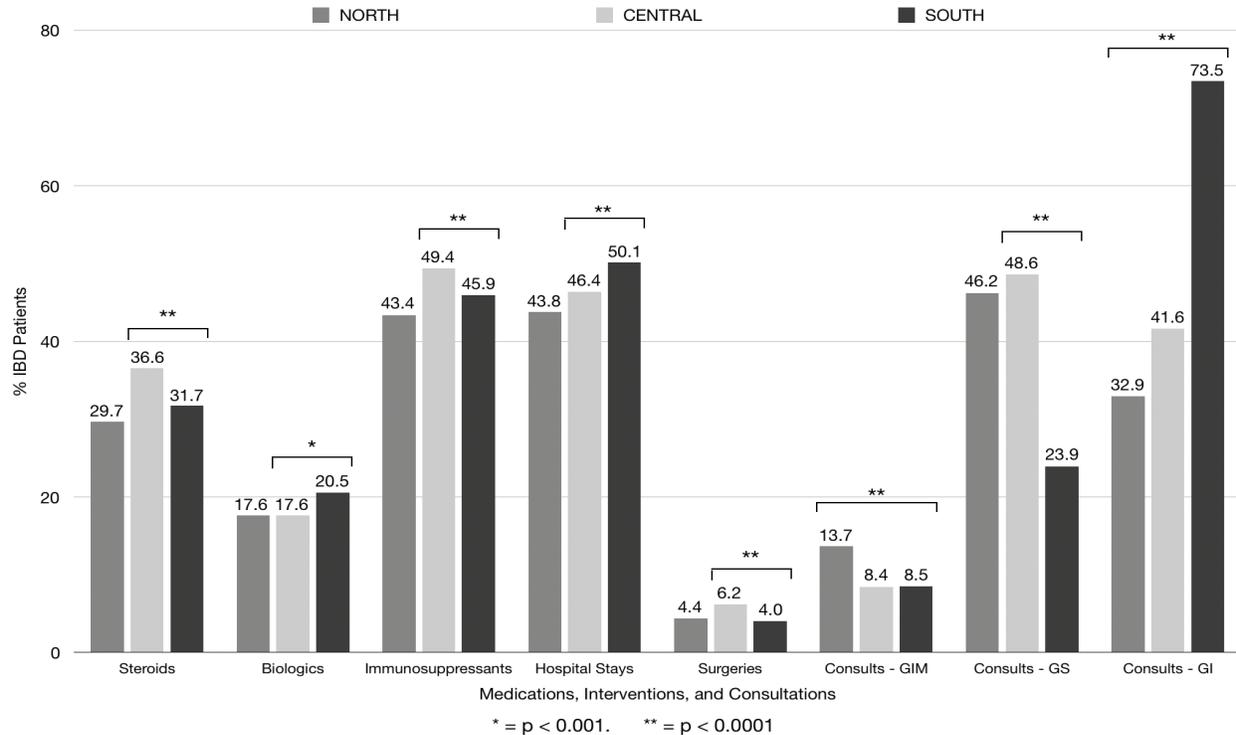
This preliminary evidence suggests a high prevalence of IBD and disparities in access to GI care and treatment approaches across VI. Patients living outside the SI, where all GI services are concentrated, received significantly fewer consultations with gastroenterologists (the specialists with the most expertise in IBD management) and significantly more consultations with both general surgery and internal medicine. Limited access to GI care is associated with poorer outcomes,<sup>9-11</sup> suggesting a potential area of concern for IBD patients living outside of the SI. Additionally, patients in the CI faced significantly higher rates of surgery and steroid use, which are associated with poorer outcomes, and patients in both the CI and the NI received fewer biologics, medications with extensive evidence supporting long-term efficacy.<sup>12-14</sup>

The primary limitation of this study is that BC Data Scout provides only summary statistics, limiting our ability to gain a detailed picture of the care received by patients in each region and to comprehensively identify confounding variables. Our future aim is to utilize more robust data sets, such as those from Island Health and the Ministry of Health, to further identify and quantify differences in IBD care.

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**Figure 2** | Percentage of IBD patients who received steroid, biologic, or immunosuppressant medications; surgical hospital stays; routine hospital stays; general internal medicine (GIM) consults; general surgery (GS) consults; or gastroenterology (GI) consults in the North, Central, or South Island from 2015-2017.

## Conclusion

VI has a high prevalence of IBD, yet these apparent disparities in the distribution of GI services exist. The results of this pilot study suggest that the barriers to care faced by IBD patients outside of the SI may lead to this population receiving less GI care, suboptimal medication regimens, and higher surgery rates. These apparent disparities have the potential to lead to poorer outcomes for patients living farther away from GI services. These results indicate the need to further investigate the impacts of these apparent disparities and to identify ways to increase access to GI services for IBD patients across VI.

## Acknowledgements

Data within this manuscript were generated from the BC Health Data Discovery Service, Jan 30th, 2019. Report IDs: 703065, 541910, 508582. All inferences, opinions, and conclusions drawn in this publication are those of the authors, and do not necessarily reflect the opinions or policies of the British Columbia Ministry of Health.

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# Using Video and Paper–Based Educational Resources to Teach Common Surgical Techniques to Pre–Clerkship Medical Students: Results from a Simulation–Based Training Workshop

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Citation: UBCMJ. 2019; 11.1 (16-18)

## Abstract

**Objective:** To evaluate how a one–time simulation–based workshop impacted the ability of pre–clerkship medical students to perform necessary technical skills required for surgical rotations, and to assess the effectiveness of paper and video educational resources.

**Methods:** This is a cohort pilot study that included 12 second–year medical students from the University of British Columbia. Participants were recruited via email and randomly assigned to either the video or paper–based educational resource. Students were educated on three common surgical techniques (Foley catheterization, sterility, and nasogastric tube insertion) and performed each task under supervision. Assessors were experienced clinicians who were blinded to the students' education resource group.

**Results:** All students agreed or strongly agreed that the simulation–based resources were useful for their learning. Participants from both groups reported increased confidence in performing all tasks after the workshop. The video resource group consistently performed better than the paper group according to the Adapted Global Rating Scale for Assessment of Technical Skills (Foley catheterization: 2.6 vs 2.0; nasogastric tube insertion: 3.6 vs 3.5; sterile techniques: 4.2 vs 3.9 for video and paper, respectively). More students were rated as “ready to perform independently” from the video group than from the paper group (67% vs 17%).

**Conclusions:** We found that simulation–based video resources were superior to paper resources in facilitating learning of practical surgical techniques. Further studies in this area are required to validate our findings.

## Introduction

The transition from classroom–based to clinically–based learning can be fraught with challenges and stress for students.<sup>1,4</sup> This transition requires students to adapt to new learning environments, develop a professional identity, acquire increasing amounts of medical knowledge, and work long hours while studying for examinations.<sup>1,4,6</sup> Amongst other challenges, learners are expected to perform technical procedures at the appropriate standard despite having little to no prior experience.

At the end of medical school, students are assumed to be proficient at performing various tasks and skills taught in clerkship rotations. However, it is challenging for students to observe and master all the required procedures due to a number of constraints. These include work hour limitations, a growing amount of new medical knowledge that students are expected to learn, and changes in patient safety standards leading to fewer teaching opportunities.<sup>7</sup> Furthermore, despite efforts to standardize learning, student experiences will inevitably vary depending on learner–specific traits, clinical preceptors, hospital settings, and patient cases.<sup>8</sup> This makes it difficult to ensure that all learners have observed and retained a standard set of basic surgical skills.

In response to the changing learning environment, simulation–based training (SBT) is emerging to be an effective training tool to teach skills uncoupled from a stressful clinical environment.<sup>7,9</sup> Current literature from nursing shows that SBT supports psychomotor development, improved student satisfaction and confidence, and increased knowledge acquisition compared to traditional teaching methods.<sup>10</sup> Specifically for surgical training, numerous studies with general surgery residents showed that technical skills transferred well from the simulated, low–pressure environment into clinical practice.<sup>9</sup> In recent years, there has been a shift to incorporate SBT into both

undergraduate medical education and residency training.<sup>7,11</sup> We propose that there is a role for SBT in teaching common surgical skills to undergraduate medical students.

The purpose of this pilot study was to provide pre–clerkship students with the opportunity to learn and practice three procedures required for surgical rotations. During this process, we also wanted to assess the effectiveness of our student–created simulation–based educational resources. Moreover, we wanted to assess the quality of our study protocol to inform future studies in this area. We hypothesized that all students would benefit from the workshop in terms of skill–building and confidence in performing tasks.

## Materials and Methods

### Learning Materials

In 2016, student investigators consulted with educators from the Department of Surgery at the University of British Columbia (UBC) to create a list of mandatory clinical skills that were not often seen or performed by medical students. In collaboration with the simulation lab at BC Children's Hospital and the input of numerous educators, students created educational videos and readings on five different procedures: nasogastric (NG) tube insertion, wound dressing, staples placement and removal, sterile technique, and Foley catheterization. These educational materials were created to instruct students with little to no experience on how to perform simple surgical tasks and were intended to be accompanied by hands–on practice with patient simulators.

Although paper–based resources provided more background information on the procedures, the instructional content on how to prepare and carry out the tasks between the paper– and video–based resources were identical. Illustrations embedded in paper–based resources were screenshots taken from the videos. All of these resources can be found at <https://ubcsimulationproject.wordpress.com/>.

Due to resource constraints—namely space limitations in the simulation lab, a lack of available assessors, time restraints, and a lack of funding—we focused on three procedures that had the greatest

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degree of complexity: male Foley catheterization, NG tube insertion, and sterile technique.

#### Recruitment

Medical students who completed their first or second year of medical school at UBC were invited to participate. Invitations were sent via an online registration form, and enrolment occurred on a first-come-first-serve basis. Assessors were clinicians (a general surgeon, a surgical fellow, and a nurse) recruited from BC Children's Hospital. All participants provided written consent for their participation.

In June 2017, a total of 12 students participated in this study (Table 1). It was deemed by the BC Children's Hospital's ethics board that this educational evaluation project did not require ethics approval.

**Table 1** | Student Demographics (n=12).

Year of Training	Completed 1 <sup>st</sup> year	100% (12)
Interest in Surgery	No	8% (1)
	Yes	25% (3)
	Maybe	67% (8)
Prior Experience in Performing task	Male Foley	0%
	NG	0%
	Sterile Techniques	25% (3)

#### Study Methodology

Students were blinded to the hypothesis and randomly assigned to the paper or video group. Due to time constraints, participants were allotted ten minutes to review the resource material and ten minutes to perform the task under supervision. Simulators were used so that students could obtain hands-on practice with Foley catheterization and NG tube insertion while they were evaluated by assessors. After completing each task, participants obtained immediate feedback from a clinician and subsequently provided their own written evaluation of the learning experience. This cycle was repeated until all participants had a chance to review and perform the three procedures.

#### Assessment

Student participants completed the Student Feedback Form (Appendix A) after performing each task. This feedback form included questions about participant demographics (Table 1), a series of statements ranked on a five-point Likert scale, and two open-ended questions.

Assessors were experienced clinicians who were familiar with the techniques. They were aware that two groups existed but were blinded to the students' allocation. Each assessor completed a written Assessor Feedback Form (Appendix B) immediately after the student performed the task. This feedback form consisted of a checklist of the main steps involved in each procedure and an adapted Global Rating Scale for Assessment of Technical Skills.<sup>12</sup> The Global Rating Scale was originally created to assess residents' performance in the operating room and was modified to omit sections on team communication and laparoscopic procedures.

#### Analysis

All quantitative analyses were carried out on Microsoft Excel. We obtained the mean and standard deviation for all numerical data. Further statistical analysis was omitted due to sample size limitations.

Qualitative analysis was conducted based on open coding and thematic analysis. Data collected from students' written feedback were independently coded by two investigators in order to increase inter-rater reliability. The initial codebooks revealed 63% agreement in themes. The investigators subsequently discussed discrepancies in the qualitative themes until consensus was reached.

## Results

All participants were students who had completed their first year of medical school (Table 1). The majority of participants (92%) were

definitely or possibly considering surgery as a future career choice. None of the students had any experience with Foley catheterization and NG tube insertion, while only one student in the paper group and two students in the video group had prior experience with operating room sterility.

#### Quantitative Results

Eleven participants (92%) reported increased confidence in performing all three tasks after the workshop. Table 2 shows students' self-reported assessment from pooled data collected on all three procedural techniques; although both groups agreed that the simulation workshop was a valuable educational experience, video resources were better received on all aspects. Subgroup analysis showed that lower ratings for paper resources were often attributed to lower scores given to the male Foley catheterization station. Students found this handout to be too lengthy for the ten-minute time restriction and less valuable of an experience compared to the other tasks.

Assessors rated students from both groups similarly in terms of technical skill but felt that more individuals in the video group could perform tasks independently compared to participants in the paper group (67% vs 17%, Table 3).

**Table 2** | Students' Feedback on Educational Resources (Pooled Data from All Tasks).

1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree and 5 = Strongly Agree

	Paper Group (6) Mean	Video Group (6) Mean
<b>Content</b>		
I was confident in performing the task <b>before</b> being exposed to the educational resource	1.2 SD 0.43	1.3 SD 0.59
I was confident in performing the task <b>after</b> being exposed to the educational resource	3.3 SD 0.96	3.4 SD 0.86
The module was an effective educational tool	3.5 SD 1.15	4.2 SD 0.71
The content was at an appropriate level	3.9 SD 0.83	4.4 SD 0.62
The content was relevant to my training	4.3 SD 0.59	4.6 SD 0.51
<b>Study Material</b>		
The study material effectively informed me about the subject	3.6 SD 0.98	3.9 SD 0.80
The material was presented in an acceptable manner	3.6 SD 0.92	4.2 SD 0.71
This material was too simple	1.9 SD 0.73	2.0 SD 0.49
This material will prove useful to my cohort	4.2 SD 0.62	4.6 SD 0.51
The study material was of a reasonable length	3.8 SD 1.22	4.6 SD 0.51
<b>Overall</b>		
Overall, this simulation module was a valuable educational experience	4.2 SD 0.73	4.6 SD 0.51

#### Qualitative Results

Overall, students in the paper group stated that paper handouts for all three tasks were presented in a clear and organized manner. However, students wanted more images or an accompanying video to better visualize the procedures. Some participants were unable to complete the readings in ten minutes while other students commented that the

material was of an appropriate length for the time provided.

Students in the video group stated that the material was concise, organized, informative, and presented in a clear fashion. For the most part, students did not feel that improvements were needed. Some participants from the video group commented that they wanted more background information and further explanation about how different procedures would be applied to clinical practice.

**Table 3 | Assessor Feedback of Students Based on Resource Group (Pooled Data from All Tasks).**

\*From NG and Male Catheter tasks only.

	Paper Group	Video Group
Global Scale (/5)	3.1	3.5
Readiness to Perform Independently*	17%	67%
Procedural technique	81%	87%

## Discussion

Overall, students seemed to benefit from a single exposure to an SBT workshop on common surgical techniques, and most students (92%) became more confident in performing all three tasks. The majority of our participants agreed that the learning resources included appropriate and relevant topics that were of a reasonable length. Student feedback also revealed the importance of a visual component as participants consistently rated video resources to be more effective than paper resources (Table 2). Furthermore, students assigned to the paper group frequently commented that they would prefer having more pictures or an accompanying video in order to enhance their learning. Since the instructional content of both resources was identical, our findings suggest that the video format was more effective at teaching procedural skills compared to the paper format. However, we acknowledge that students' learning styles may have affected this finding.

There has been an increased movement towards the integration of electronic resources into undergraduate medical education, including the use of computer-based clinical examinations, mobile technology in cadaver labs, and multimedia resources in teaching clinical skills.<sup>13-15</sup> However, there is conflicting evidence on the efficacy of video-based educational resources compared to conventional paper- or lecture-based training. For example, Todd *et al.* showed that video self-instruction for cardiopulmonary resuscitation was superior to a standard American Heart Association Heartsaver course,<sup>16</sup> whereas Rogers *et al.* found no difference in medical students' ability to learn and perform surgical knots between video-based teaching and a lecture-and-feedback seminar.<sup>17</sup> It is difficult to synthesize the evidence given heterogeneous interventions and varying degrees of participant skill.

In this study, more students from the video group were objectively rated "ready to perform independently" compared to the paper group (67% vs 17%) despite similar ratings in technical skill. This implied that students from the video group were perceived to be more confident in performing newly taught skills than those from the paper group. One possible explanation is that students from the video group may have been faster or less hesitant because they had the benefit of visualizing the procedures.

## Limitations

A major limitation is our small sample size, which restricted our ability to prove statistical significance between groups. Student participants who volunteered for this study were also more surgically inclined, thus we did not have a representative sample of pre-clerkship students. However, this student population is more likely to participate in SBT workshops and would be the target audience for these training sessions.

Additionally, we did not evaluate student performance in the

clinical setting to determine if skills were efficiently transferred. Assessors recruited for our study were also aware that two study groups existed; however, allocation concealment mitigated their potential biases when evaluating students. Lastly, the effectiveness of both formats as learning resources may be hindered by the arbitrary ten-minute limit that students were given to review the learning resource.

## Future Considerations

We were unable to have a control group with no exposure to simulation-based educational materials, nor did we have a combined resource group with access to both video and paper resources. We recommend incorporating these groups into future studies if a larger sample can be obtained. Alternatively, we recommend using a cross-over design where participants rotate through both video and paper resource stations in order to mitigate the effect of learner-specific traits. We also suggest that future studies should follow student participants into their clerkship years in order to evaluate if similar workshops affect student confidence and competency in clinical practice.

We recognize that SBT is very resource intensive. At the moment, UBC's medical school does not have SBT sessions for common procedural techniques. For sustainability, we suggest that SBT would be best incorporated into the undergraduate curriculum.

## Conclusion

To our knowledge, this is the first study to examine and trial simulation-based educational resources for common technical skills on pre-clerkship medical students. Despite the flaws in our research design, we believe our study is the first step in filling this research gap.

We found that simulation-based educational resources could be an effective way to teach mandatory clinical skills to pre-clerkship students. The majority of students reported improved confidence in performing new skills, and experienced clinicians rated up to 67% of participants as being able to perform independently after a single SBT workshop. Our findings also suggest that video format was more effective than paper format. Further research on the effect of SBT in pre-clerkship students and on the optimal modality for SBT materials is needed.

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# Initiating Advance Care Planning Discussions in Community–Dwelling Elders: Barriers and Facilitating Factors Influencing Family Physicians

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Citation: UBCMJ. 2019; 11.1 (19-22)

## Abstract

**Objective:** Advance care planning (ACP) allows patients to communicate their goals for future care. This is ideally completed when patients are still competent enough to make their own decisions, such as in the primary care setting. We aimed to explore common facilitating factors and barriers influencing family physicians (FPs) in initiating ACP discussions with community–dwelling elders.

**Methods:** Semi–structured interviews were conducted with a convenience sample of 13 FPs practicing in Vancouver, Canada. Interviews were analyzed using thematic analysis.

**Results:** FPs were more comfortable initiating ACP if they had a close relationship with the patient, if they were familiar with ACP terminology, and if the patient or family was willing to talk about death and dying. Most physicians felt impending death facilitated discussion, whereas a few physicians found that it made discussions more difficult. FPs often found it difficult to communicate the content of ACP discussions from office–based community practices to the hospital setting. A lack of time and of a concise framework hindered ACP initiation. We noticed that numerous ACP resources exist but may be unknown or inaccessible to physicians. FPs also commented on a lack of effective non–English ACP patient handouts.

**Conclusions:** The self–identified barriers and facilitating factors influencing FPs' decisions to initiate ACP were remarkably diverse and occasionally contradictory. There is a need for improved communication between healthcare providers, greater public awareness of end–of–life issues, and increased accessibility and awareness of ACP resources, especially in non–English languages.

## Introduction

Advance care planning (ACP) allows patients to communicate their healthcare wishes to providers in the event that they are unable to make decisions for themselves. Numerous studies have shown the benefits of ACP in a variety of chronic diseases including dementia, HIV, cancer, and congestive heart failure.<sup>1–3</sup> Among these, ACP may have the greatest potential to influence the care of the elderly, a population accounting for 80% of total deaths in Canada.<sup>4</sup>

Current literature supports early initiation of ACP among the elderly as they are at risk of sudden functional decline.<sup>5,6</sup> Although most elders engage in end–of–life care planning upon admission to a long–term care facility, data show that less than 36% of nursing home residents have the capacity to engage in these discussions.<sup>3,7</sup> It is important to initiate ACP with elders prior to entering residential care and while they can still actively participate in future care planning.

Family physicians (FP) are optimally placed to initiate early ACP discussions due to their longitudinal relationships with patients. They have been identified as patients' preferred person to discuss ACP topics such as resuscitation.<sup>8</sup> Furthermore, the most effective interventions to increase the completion of living wills involve direct patient–physician interaction over multiple visits, which can easily be accomplished in the office setting.<sup>9</sup> However, only 17.5% of older adults engaged in ACP activities have involved their FP.<sup>10</sup>

The purpose of this study is to identify barriers and facilitating factors that FPs face when initiating ACP discussions with their elderly patients. We hypothesized that the lack of ACP resources may be a potential barrier, and thus wanted to research current and ideal educational materials FPs would want to access. For the purposes of this paper, the terms Advance Care Planning (ACP) and End–of–Life

(EOL) Planning will be used interchangeably.

## Methods

### Design

We conducted semi–structured interviews using a standard interview guide (Table 1) with local FPs working in the Greater Vancouver Region, Canada. Interviews were recorded, transcribed, coded, and analyzed for themes. This paper focuses on the data collected from the barriers and resources aspect of the interviews.

**Table 1 | Interview Guide.**

<b>Who / Where</b>	<ul style="list-style-type: none"> <li>• What role do you think FPs should have in ACP in elderly patients?</li> <li>• How comfortable are you with discussing ACP with elderly patients?</li> </ul>
<b>What / How</b>	<ul style="list-style-type: none"> <li>• What does ACP for elderly patients (&gt;65 years old) look like in your practice?</li> <li>• What topics do you talk about?</li> <li>• How frequently do you follow up with the ACP decisions over time, if at all?</li> </ul>
<b>When</b>	<ul style="list-style-type: none"> <li>• When do you decide to have ACP discussions with your elderly patients?</li> </ul>
<b>Why</b>	<ul style="list-style-type: none"> <li>• What effect did ACP have on your patients?</li> </ul>
<b>Barriers / Resources</b>	<ul style="list-style-type: none"> <li>• What kind of influences help or hinder your decision to talk about ACP with elderly patients?</li> <li>• Are there any resources/educational materials you find useful?</li> <li>• What would you want to know to help facilitate discussions on ACP?</li> </ul>

Ethics approval was obtained from the University of British Columbia's Behavior Research Ethics Board (H16-00044).

### Sample Selection

A convenience sample of FPs practicing in the Greater Vancouver Region was recruited from family practice rounds at a local hospital, as well as from a list of 48 FPs participating as first–year medical student preceptors.

### Data Collection

All participants provided written consent for their participation. Interviews were conducted between May and June 2017. Nine interviews were held in person and four interviews were carried out by telephone. All interviews were conducted by the same investigator (IJ) using the standardized interview guide. Twelve of thirteen participants consented to voice recording. For the remaining participant, the investigator took

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notes throughout to ensure main discussion points were captured.

To analyze the accessibility of ACP resources, physicians were asked about specific tools they used to educate patients on ACP. We attempted to locate less common ACP resources, defined as any resource excluding My Voice, Medical Orders for Scope of Treatment (MOST), and Do Not Resuscitate (DNR) forms, within the first five pages of the Google search engine. My Voice is a 56–page ACP booklet created by the BC Ministry of Health and is often used by FPs to educate patients and families.<sup>11</sup> MOST is a form indicating the level of care the patient wishes to receive with regards to CPR and intubation. DNR is a form indicating patient refusal of resuscitation in the event of a pulmonary or cardiac arrest.

### Data Analysis

The recorded interviews were transcribed, checked for accuracy, and inductively coded. Two researchers (IJ and JH) independently analyzed the transcripts using open coding. Comparable codes with similar content were grouped into themes and the researchers discussed differences until consensus was reached. Data consolidation was supported by NVivo 11 qualitative data analysis software (QSR International Pty Ltd). Two other investigators (JK and MM) reviewed the final analysis and verified the themes.

**Table 2 | Participant Demographics (n = 13).**

\*Two doctors provided a range of 40–45 years old for their age category, and the average of 43 years was used in the median calculation.

Gender	Male: 9 (69%) Female: 4 (31%)
Mean age*	47 years (SD 10; range 30–61)
Ethnicity	Caucasian: 9 Chinese: 2 Korean: 1 Japanese: 1
Years in practice	17 (SD 11; range 3–36)
Type of practice	FP office: 12 Nursing home: 5 Hospital: 5 Community health center: 2 Rural practice: 1
Estimated % elderly in their practice	23 (SD 17; range 5–50%)
Education about EOL care	None: 8 One-time workshop: 4 >One-time workshop: 1
Self-rated comfort level with discussing ACP with elderly patients	Very comfortable: 7 Relatively comfortable: 5 A little more comfortable than start of career: 1

## Results

A total of 13 family physicians were recruited into this study (Table 2); twelve were recruited via email from a first-year medical student preceptor list at the University of British Columbia and one from family practice hospital rounds at Vancouver General Hospital. The participants' mean age was 47 years old and 77% of participants practiced in more than one setting. Twelve participants were fee-for-service and two participants had hospital privileges. There was a greater proportion of Caucasian (69%) and male (69%) participants. Although the study was not designed for ongoing sampling, saturation point was reached with a sample of 13 participants. The average interview duration was 20 minutes (range 7 to 38 minutes).

Factors identified fell under four themes: patient/family specific traits; physician comfort level; system-level restraints; and ACP resources (Table 3). All themes where participants showed conflicting opinions are presented in Table 4.

### A) Patient/Family Specific Traits

FPs had a difficult time initiating ACP if the patient or family was uncomfortable or not receptive with the topic, even if they were well versed in holding this conversation. This is illustrated in the following quotations:

“I tend to shy away from [following up with ACP discussions] if my patients are uncomfortable with it. I try to float it out there in a comfortable normal way the first visit but if they don't want to talk about it I tend not to bring it up in subsequent visits.” (Interview 1)

“I see a lot of barriers from family members with sick loved ones who are very firm and say ‘No, you have to do everything for Mom.’” (Interview 11)

**Table 3 | Frequency of Themes Mentioned in Interviews.**

Factor	Theme	Interview Mentioned
Patient/family specific traits	Barrier: patient/family not receptive	1, 2, 3, 4, 9, 10, 11, 13
	Facilitating factor: patients initiating the ACP conversation	1, 2, 11, 12
	Barrier: non-English speaking	11
Physician comfort level	Barrier: cognitive impairment	11, 12
	Barrier: weak patient-physician relationship	9
	Facilitating factor: strong patient-physician relationship	3, 4, 9, 12
	Barrier: ACP terminology	11
	Barrier: increased risk of death (e.g., older age, deteriorating health status)	7, 9
System-level barriers	Facilitating factor: increased risk of death (e.g., older age, deteriorating health status)	1, 3, 4, 5, 6, 10, 12, 13
	Barrier: lack of time	1, 7, 8, 9, 10, 11, 12
	Barrier: information transfer	7, 8, 9, 10, 11
ACP resources	Barrier: lack of effective ACP resources	9, 10, 11
	Facilitating factor: effective ACP resources	1, 7, 10

**Table 4 | Examples of Conflicting Perspectives.**

Influencing Factor	Interview Illustrations
Older age of patient	<b>Easier Conversation</b> It is more routine in older patients because we feel more comfortable and they feel more comfortable talking about end of life. (Interview 1)
	<b>Difficult Conversation</b> It's hard to bring it up. I think the older they are, the harder...Once they are past 85, it's hard to bring up because they know it's imminent. (9)
Deteriorating health status	<b>Easier Conversation</b> If they are dying they need to know. They need to get things prepared and things in order. (3)
	For people who don't have these co-morbidities or they're not frail...it becomes a hard discussion to have. (6)
My Voice as an effective resource	<b>Difficult Conversation</b> [If] they're healthy and well, it's sort of an easier conversation. But if they're actually sort of on the slippery slope of decline, I find it more difficult to initiate actually. (7)
	<b>Useful</b> I use the My Voice brochure, I use it all the time. If I'm going to have a conversation, I will direct them to that. (7)
	My Voice gives good background information and gives them a chance to do some homework. (10)
	<b>Difficult to Use</b> My Voice is daunting, it's too big, it's too long. It's got good information in it but I don't know if they could somewhat revamp it, differently, make it smaller. (12)
	The English version takes someone with a college degree to understand, like seriously, you and I would be reading the English version and you would have to concentrate to understand it. So fat chance that your average 65–70-year-old retiree will get through, not to mention there's a language barrier...You can't navigate it as a patient. (9)

Conversely, several physicians mentioned that they will definitely hold these discussions with patients who initiate the topic, even if it is with a demographic they do not normally approach. For example:

“If somebody brought it up to me, I would absolutely have the conversation with them.” (Interview 12)

Language barriers and cognitive impairment were also factors that hindered the ACP discussion (Table 3).

**B) Physician Comfort Level**

Physician comfort level in conducting ACP discussions was influenced by the depth of the patient–physician relationship. Multiple participants stated that they felt more comfortable initiating difficult conversations with patients whom they had a strong relationship with. This is best illustrated in the following quotation:

“My practice is bimodal because half of my practice followed me from my old clinic and I have some patients who joined me recently, so I don’t know them as well. It’s the same demographic in terms of age and ethnicity, so I find it much harder to bring it up with my newer patients.” (Interview 9)

Physicians’ familiarity with ACP terminology and paperwork also influenced their willingness to broach the topic. One participant mentioned that different terminology used between different health authorities led to substantial confusion. Lastly, some physicians found it easier to initiate ACP when death was more imminent, whereas other physicians found it difficult for the same reasons (Table 4).

**C) System–Level Barriers**

Lack of time was commonly cited as a prominent barrier, especially in a fee–for–service environment. This is illustrated in the following quotations:

“At one point, I tried to have this discussion with everyone regardless of age; for all of my patients greater than 65 years old, I’m going to try to have an advance directive on file, so I just started doing that. But it was just so time consuming that I gave up.” (Interview 7)

“I guess remuneration is an issue, we don’t get paid to have these conversations. If we have a separate billing to do this, we would do it.” (Interview 12)

Physicians were also unsure about the impact of ACP due to issues with implementation. This was largely due to ineffective information transfer between office–based community practices and hospital environments, as seen in the following quotation:

“I don’t find the documentation part gets translated or used appropriately...Certain hospitals, upon admission, will send a one–page fax asking for any and everything you have...and you have a feeling that the information you carefully compiled for them is actually not going to get looked at.” (Interview 9)

**D) ACP Resources**

FPs frequently used MOST and DNR forms (85%) as well as the My Voice document (54%) to initiate ACP discussions. We found varying opinions regarding the utility of the My Voice document due to its length and complicated language (Table 4). We also realized that there is a lack of effective non–English resources, as all resources existed solely in English with the exception of My Voice, which appeared to be poorly translated, as illustrated in the following quotation:

“The Chinese version of My Voice, it was very awkwardly translated, it’s horrible. I mean I’m fluent in Chinese and I read

it, and I have to read it three times to know what they’re [saying].” (Interview 9)

Some physicians also cited the lack of an effective and concise ACP discussion guide as a barrier to discussion. This is illustrated in the following quotation:

“I think it would also be nice if there was a template that could help direct this conversation, to keep the conversation concise and focused because sometimes the conversations get side–tracked just because of the breadth and depth of it.” (Interview 7)

The investigators also collected information on resources other than those mentioned above, including resources physicians used to initiate ACP discussions (Table 5) and the types of resources they felt were missing from practice (Table 6).

**Table 5 | List of Current Resources Specific to ACP Mentioned by Physicians.**

Resource mentioned	Interview #	Ability to locate within 5 search pages
Vancouver Coastal Health pamphlet on Cardiopulmonary Resuscitation	1	Yes
Dementia roadmap	1	Yes
North Shore Palliative group	10	Yes
Fraser Health Options of Care pamphlet	11	No
Dr. R. Gallagher’s YouTube video on ACP and death and dying from Pathways BC website	11	No
The GP Services Committee video on role-playing with RNs for difficult EOL conversations	12	No

**Table 6 | List of Ideal Resources Specific to ACP Mentioned by Physicians.**

- One–page ACP framework/template about critical questions to ask (Interviews 5, 7, 8)
- Printable shared decision aids (Interview 11)
- Knowing what other colleagues do (Interviews 1, 5, 6, 7)
- Tools for cultural literacy (Interview 1)
- List of programs and resources, including affordable nursing homes and home support (Interviews 2, 4)

**Discussion**

This study revealed that a remarkably diverse and occasionally contradictory number of factors influenced ACP initiation among a convenience sample of FPs, most of whom lacked formal ACP training.

All participants found it easier to initiate EOL care discussions with patients or families who were open to talking about death and dying. FPs also indicated that they would discuss ACP with patients they would not normally approach if patients brought up the topic themselves. This is consistent with other findings, and highlights how delivering quality palliative care requires engaging in a broader discussion about cultural taboos on death and dying.<sup>12,13</sup> Although only one of the participants mentioned cognitive impairment and lack of English proficiency to be barriers, these factors have been established in the literature to be significant obstacles to ACP.<sup>14–16</sup>

While all participants were moderately comfortable with initiating ACP discussions, several factors influenced their willingness to approach this topic. Factors that decreased FPs’ comfort levels included differences in ACP terminology across health authorities and the lack of a strong connection with the patient. Interestingly, there were conflicting responses to whether impending death, as indicated by older age or deteriorating health status, facilitated or hindered the ACP conversation. This suggests that individual practitioner traits have a significant impact on perceived barriers.

Time constraints and ineffective communication between office–based community practices and hospital environments were

significant systemic barriers.<sup>12,13,17,18</sup> The majority of our participants were compensated on a fee-for-service basis, and commented that it became difficult to address ACP in a single visit due to the breadth of the discussion and other priorities of care. While literature has shown that ACP has multiple benefits for the elderly population—including improved quality of dying, decreased family stress and anxiety, and reduced hospital admissions and length of stay—participants doubted the utility of ACP.<sup>19,21</sup> Office-based FPs often did not have a clear understanding of how ACP affected patient care due to transfer of patient care near end of life.<sup>13</sup> In contrast, they were often aware of situations where mutually established advance directives were not implemented due to issues with information transfer. There is a lack of a standardized method to transfer ACP information from office-based community practices to hospitals, and patients are assumed to be full code unless legal documentation can be provided. From our interviews, FPs often conveyed patients' documented wishes through phone communication with the hospital physicians or through fax, but practices varied widely depending on the physician responsible and on hospital policy.

In response to difficulties with communicating patients' EOL wishes to hospitals, physicians proposed two solutions: increase accessibility to forms via creation of a central data storage system, and/or focus on educating the patient and family. The latter approach calls for patients and their families to take charge of essential documents and to voice goals of care to other providers. In lieu of a centralized system, proper patient and familial education is an important solution to communication issues at this time.

This study also addressed available and ideal ACP resources. Although My Voice is a commonly used ACP resource, some physicians found the length, reading level, and non-English translations inappropriate for most audiences. Given the significant diversity of urban populations, virtually all FPs in Canadian urban settings will encounter patients with alternative first languages. Our study showed a need for culturally competent, multilingual ACP resources.

We found that numerous ACP resources exist but were not well known or accessible.<sup>22</sup> For example, several physicians expressed interest in resources illustrating how other health care providers conduct ACP discussions, which do currently exist. Furthermore, multiple FPs were unaware that advance care directives were available online at [advancecareplanning.ca](http://advancecareplanning.ca), despite this website being a central nation-wide resource. This has implications for new and current ACP resources, such the ACP framework developed by Dhillon et al., which may have poor uptake.<sup>23</sup>

### Strengths and Limitations

This study provides an updated perspective on the perceived barriers and facilitating factors influencing FPs in their role in ACP. Strengths of this study include holding one-on-one interviews with participants and a focus on community-dwelling elders.

Our major limitation is our small convenience sample size of Canadian urban-based physicians, most of whom are involved in undergraduate medical education and do not have formal ACP training. Physicians who had prior interest or participation in ACP discussions may have had increased willingness to participate, potentially limiting the generalizability of our findings. Participants also frequently worked in more than one setting, and thus, study findings may not reflect the opinions of FPs working solely in the clinic setting.

### Future Directions

Given the findings of our study, we have a few suggestions for future projects on ACP in the primary care population. To improve patient and family receptivity, there is a need for increased public awareness on palliative care and its benefits. This can be accomplished through a variety of modalities, including public conferences and outreach programs. Given the important role of families in communicating

patients' EOL goals across care settings, it would be beneficial to explore family members' understanding of advance care plans when a patient presents to hospital. This can be conducted through surveys or focus groups and will help identify important teaching points to increase implementation of advance care plans. Lastly, we recommend the creation of succinct, non-English patient information resources and a handout outlining the different ACP terminology used across various health authorities.

### Conclusion

We found that FPs' self-identified barriers and facilitating factors influencing their decision to initiate ACP were remarkably diverse and occasionally contradictory. We identified common barriers hindering ACP, including patient and family unwillingness, lack of familiarity with ACP terminology, time constraints, and difficulty with information transfer. Our research highlights a need for improved communication between healthcare providers and for increased public awareness on EOL issues. There is also a need for increased accessibility and awareness of ACP resources, especially in non-English languages.

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# Associations Between Physical Activity and Inflammatory Bowel Disease: Results from a Canadian National Survey

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Citation: UBCMJ. 2019; 11.1 (23-26)

## Abstract

**Objective:** Inflammatory bowel disease (IBD) is increasing in prevalence and incidence worldwide, particularly in Canada. Crohn's disease (CD) and ulcerative colitis (UC), the two most common forms of IBD, are characterized by inflammation of the gut. Physical activity is known to reduce chronic inflammation, but its potential preventive effect on IBD remains inconclusive. This study investigated the relationship between physical activity and IBD in the Canadian population.

**Methods:** The sample of 111,647 respondents were drawn from the Canadian Community Health Survey (2013-2014). Multinomial logistic regression was used to analyze the association between physical activity levels and IBD status (CD, UC, and no IBD), adjusting for the potential confounders of age, sex, body mass index, and type of smoker.

**Results:** The highest proportion of inactivity was found in the disease groups of CD (52.4%) and UC (45.0%), followed by no IBD (42.6%). The adjusted odds ratio of having CD were 1.42 (95% CI 0.99-2.03) and 1.59 (95% CI 1.14-2.23) for moderately active and inactive respondents, respectively, relative to active respondents. There was a trend in the UC group with the highest odds ratio of having UC observed in the moderately active respondents (OR 1.27, 95% CI 0.85-1.89) compared to active respondents, but this did not reach statistical significance.

**Conclusion:** Moderate activity and inactivity, relative to activity, were associated with higher odds of having CD and UC, with a stepwise trend observed in the CD group. Physical activity may offer a potential avenue for preventing IBD and informing future public health interventions if future studies demonstrate causality.

## Introduction

Inflammatory bowel disease (IBD) is a chronic, multifactorial condition, characterized by inflammation of the gastrointestinal (GI) tract and an increased risk of comorbidities and colorectal cancer.<sup>1-3</sup> Crohn's disease (CD) and ulcerative colitis (UC) are two of the most common forms of IBD with important clinical distinctions.<sup>4</sup> CD affects the entire GI tract from the oral cavity to the anus, and spreads to all layers of the gut.<sup>1,2</sup> In contrast, UC targets the colon and the rectum and is limited to the innermost mucosal layer.<sup>1,2,5</sup> Since the middle of the twentieth century, IBD has been increasing in prevalence worldwide, now affecting over 3.5 million people in North America and Europe.<sup>6,7</sup> North America has the second highest prevalence worldwide, at 319 and 249 cases per 100,000 population for CD and UC, respectively.<sup>8</sup> IBD is not only a common condition in North America, but also one that is being increasingly diagnosed; Canada has one of the highest incidences of IBD in the world, at 13.4 and 11.8 cases per 100,000 population for CD and UC, respectively, across all age groups.<sup>6,9</sup> These high rates of incidence and prevalence in Canada are projected to continue increasing over the next decade.

The rise in IBD parallels the worldwide epidemiological transition to an increased prevalence of chronic diseases associated with lifestyle and environmental risk factors such as increased stress, smoking, poor diet, and physical inactivity.<sup>2,3,10-12</sup> Regular physical activity has been shown to reduce inflammation through downregulation of pro-inflammatory mediators, induction of anti-inflammatory mediators, and alleviation of stress.<sup>13,14</sup> In rats, physical activity prior to induction of UC significantly reduces inflammatory markers, lesions, and mucosal damage, and increases the expression of anti-inflammatory cytokine interleukin-10.<sup>15</sup> However, much of the research to date has focused on physical activity's effect on general inflammation and is inconclusive regarding its preventive impacts on specific inflammatory diseases such as CD and UC.<sup>14-16</sup> These inconclusive findings have been attributed to methodological inconsistencies including variations in the type, intensity, and duration of physical activity, lack of control groups, and

unclear distinctions between pre- and post-onset of IBD.<sup>14-17</sup>

The effect of physical activity on the development of CD and UC remains unclear. This study investigates the relationship between decreased physical activity and higher odds of IBD, in a multivariable model adjusted for potential confounders. The data used to investigate this relationship are from the 2013-2014 Canadian Community Health Survey (CCHS), a population-based national survey that is specific to the Canadian demographic. In the context of an increasing prevalence of IBD, physical activity offers a population health avenue worthy of further investigation.

## Methods

### Study Design

The CCHS is a cross-sectional, national survey conducted in 2013 and 2014.<sup>18</sup> Every CCHS iteration gathers information on health and disease status, healthcare utilization, social relationships, and healthcare determinants from the Canadian population aged 12 and older. The survey includes all provinces and territories, representing more than 98% of the population. Those excluded are persons living on reserves and Aboriginal settlements, full-time Canadian Forces members, institutionalized individuals, children aged 12 to 17 years in care, and persons living in select remote Quebec health regions. Details of sampling and interview methods can be found on the Statistics Canada website.<sup>18</sup> Ethical approval for the use of these data is covered under The University of British Columbia's publicly available data clause in Policy #89 for research involving human subjects.<sup>19</sup>

### Analytic Sample

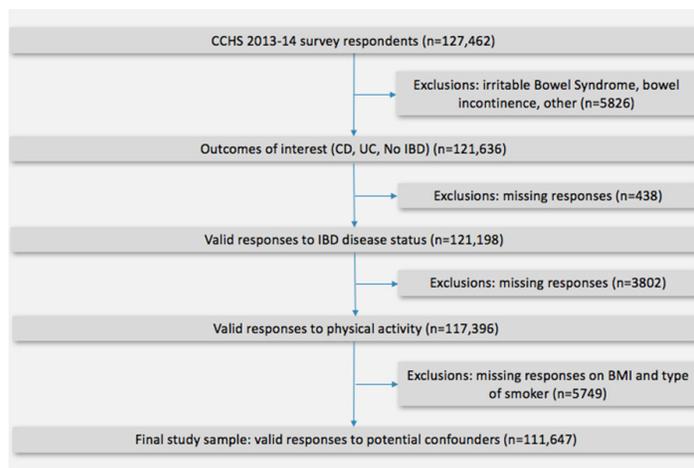
To investigate the relationship between physical activity and IBD, this analysis included all individuals who provided valid responses to physical activity and IBD status, as well as to the potential confounders of age, sex, body mass index (BMI), and type of smoker.

Figure 1 shows the inclusion and exclusion process for the analytic sample drawn from 127,462 respondents to the CCHS 2013-2014 survey. Of the total respondents, 5826 were excluded for other types of bowel disorders such as irritable bowel syndrome and bowel incontinence. Of the remaining 121,636 eligible respondents, 438 provided invalid responses (Other, Not Applicable, Don't Know, Refusal, Not Stated) to

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the type of bowel disorder, 3802 to physical activity level, 5055 to BMI, and 694 to type of smoker. These respondents were excluded from the sample. The final analytic sample consisted of 111,647 respondents (88% of the CCHS 2013-2014 sample).



**Figure 1** | Inclusion and exclusion process to generate the final analytic sample to investigate the relationship between physical activity and IBD.

### Study Variables

The categorical outcome variable for IBD (CD, UC, or No IBD) was obtained from responses to two consecutive questions in the CCHS survey. All respondents were asked, “Do you have a bowel disorder such as Crohn’s disease, ulcerative colitis, irritable bowel syndrome, or bowel incontinence?” Respondents who answered “Yes,” “Don’t Know,” or “Refusal” were subsequently asked, “What kind of bowel disease do you have?” Those who answered “Yes” to CD or UC were assigned to the respective categories, and those who answered “No” to the first question were assigned to the reference group. The survey prompted respondents that chronic health conditions such as IBD are expected to last or have already lasted six months or more and are diagnosed by a health professional.

The categorical explanatory variable for physical activity was generated by Statistics Canada. Survey participants provided the frequency and number of minutes they spent on transportation or leisure-time physical activities in the past three months, such as walking or biking to school or work and sporting activities. Based on the reported frequency and duration of activities, Statistics Canada calculated the energy expenditure (EE) and metabolic equivalent of exercise as compared to when the body is at rest. Statistics Canada categorized the respondents as active (EE >3 kcal/kg/day), moderately active (EE = 1.5-3.0 kcal/kg/day), or inactive (EE <1.5 kcal/kg/day), based on daily EE for transportation and leisure-time physical activities.

Potential confounders of the relationship of interest included age (four groupings to reflect risk groups),<sup>2,20</sup> sex (female or male), BMI (neither overweight nor obese, overweight, or obese), and type of smoker (daily smoker, former or occasional smoker, or never smoked). These potential confounders were selected based on the literature and conceptual understanding of IBD.<sup>14,20,21</sup> BMI was a derived variable calculated by CCHS, based on weight and height.

### Analysis Plan

Analyses were conducted using SAS University Edition (SAS Institute Inc., Cary, NC) and probability weights provided by Statistics Canada were applied to account for uneven probabilities of selection and to calculate estimates of variance. The CCHS Public Use Microdata File is covered under the Statistics Act that applies confidentiality rules for the use of the data and prevents the disclosure of confidential

information.<sup>18</sup>

Initial descriptive statistics were generated to explore the data and characteristics of the study sample were compared using the chi-squared test. A multinomial, logistic regression model was created to investigate the relationship between physical activity and IBD.<sup>22</sup> The model was subsequently adjusted for confounding by age, sex, BMI, and type of smoker. A secondary analysis used a continuous BMI measure in place of the categorical BMI classes in the multinomial model.

## Results

As shown in Table 1, the analytic sample of 111,647 respondents was equally distributed among sexes and variably distributed among age categories, with the smallest proportion of respondents aged 50 to 59 years (17.9%). Most of the sample were considered neither overweight nor obese (48.6%) and had never smoked (43.5%). Notable differences in IBD status were found in different age categories and type of smoker. The rates of CD and UC were lowest in the youngest age group and the “never smoked” group for CD, compared to the overall sample. The overall sample’s IBD status differed significantly by levels of physical activity, sex, age, and type of smoker.

For the main study variables of IBD status and physical activity, nearly all of the study sample reported no IBD (99.1%), with the rest reporting CD (0.4%) or UC (0.5%). The largest proportion of respondents were classified as inactive (42.6%), followed by active (31.6%) and moderately active (25.8%). The highest prevalence of inactive respondents was found in the CD group (52.4%), followed by UC (45.0%) and no IBD (42.6%).

**Table 1** | Descriptive statistics of study sample investigating the relationship between physical activity level and IBD, from CCHS (2013-2014).

<sup>a</sup>Chi-squared tests with overall sample were significant at P <0.05

Variable	Overall (weighted %) (N = 111,647)	IBD status (weighted %)		
		Crohn’s disease (N = 586)	Ulcerative colitis (N = 673)	No IBD (N = 110,388)
<b>Physical activity level<sup>a</sup></b>				
Active	34,211 (31.6)	131 (20.9)	155 (25.1)	33,925 (31.6)
Moderately active	28,803 (25.8)	159 (26.7)	160 (30.0)	28,484 (25.8)
Inactive	48,633 (42.6)	296 (52.4)	358 (45.0)	47,979 (42.6)
<b>Sex<sup>a</sup></b>				
Male	52,073 (51.2)	221 (45.6)	238 (41.2)	51,614 (51.3)
Female	59,574 (48.8)	365 (54.4)	435 (58.8)	58,774 (48.7)
<b>Age<sup>a</sup></b>				
12-29 years	23,269 (26.2)	75 (13.1)	37 (8.8)	23,157 (26.3)
30-49 years	25,303 (31.9)	175 (43.7)	140 (35.6)	24,988 (31.8)
50-59 years	19,406 (17.9)	122 (19.4)	138 (21.5)	19,146 (17.9)
60 years or more	43,669 (24.1)	214 (23.7)	358 (34.2)	43,097 (24.0)
<b>BMI</b>				
Neither overweight nor obese	50,523 (48.6)	282 (45.6)	305 (46.5)	49,936 (48.7)
Overweight	37,784 (33.0)	182 (33.7)	211 (32.5)	37,391 (33.0)
Obese	23,340 (18.3)	122 (20.7)	157 (21.0)	23,061 (18.3)
<b>Type of smoker<sup>a</sup></b>				
Never smoked	42,874 (43.5)	155 (29.4)	186 (31.1)	42,533 (43.6)
Former or occasional	52,303 (42.5)	309 (47.5)	388 (51.1)	51,606 (42.4)
Daily	16,470 (14.0)	122 (23.0)	99 (17.8)	16,249 (14.0)

The bi-variable analyses showed a negative association between amount of physical activity and having either CD or UC. The odds of having CD and UC were increased for those who were moderately active and inactive, compared to active respondents. For respondents with CD, as the level of physical activity decreased from active to moderately active to inactive, the odds ratios (ORs) increased from 1.0 to 1.57 (95% confidence interval [CI] 1.10-2.26) and 1.87 (95% CI 1.35-2.58), respectively, indicating a stepwise association between less physical activity and the odds of having CD. This stepwise trend was not reflected for UC patients, even though the odds of having UC were

higher for those with less activity. The odds of having UC were in fact higher for moderately active respondents (OR 1.47, 95% CI 0.98-2.20) compared to inactive respondents (OR 1.33, 95% CI 0.98-1.81). The confidence intervals for the association of physical activity and UC included the OR estimate of 1.0. In contrast, the CIs for CD patients did not cross 1.0. Based on these results, increasing inactivity showed a step-wise association with CD and possible, but non-significant, association with UC.

To explore confounding effects, the multivariable model showed that the main relationship between physical activity and IBD was attenuated but maintained the same trend as in the bi-variable model. The odds of CD were increased for those with increasing levels of inactivity, in a stepwise fashion (Table 2). The moderately active level had a CI crossing 1.0. The odds of having UC with increasing levels of inactivity did not reflect this stepwise trend. The OR of having UC for moderately active respondents and inactive respondents were 1.27 (95% CI 0.85-1.89) and 1.07 (95% CI 0.79-1.46) compared to active respondents, respectively. Taken together, the adjusted data in Table 2 suggested a stepwise, increased odds of having CD for increasing levels of inactivity, while the highest odds of having UC were associated with the moderately active respondents.

In both bi-variable and multivariable models, the potential confounders of sex, age, and type of smoker were associated with IBD disease status. Looking at age, respondents aged 30 to 49 years showed the highest odds for having CD, whereas respondents aged 60 years or older showed the highest odds for having UC. Respondents who were female or who smoked at a higher frequency also had increased odds of having CD or UC. Although the CI for the association between sex and CD included 1.0, the distribution of the CIs suggested increased odds of having CD for females. Conversely, the ORs for the association between BMI and IBD were close to 1.0 and the distribution of the 95% CIs included 1.0, indicating this was not a strong confounding relationship. These variables were included in the final model adjusted for confounding, based on their associations with IBD and confounders identified a priori in the study design. It is well demonstrated in previous research that smoking and BMI are associated respectively with physical activity and IBD, particularly CD,<sup>23,24</sup> and are thus important variables to include in multivariable analyses.

**Table 2 |** Unadjusted and adjusted logistic regression odds ratios (OR), investigating the relationship between physical activity level and IBD, from CCHS (2013-2014).  
\*CI, confidence interval

Variable	Crohn's disease		Ulcerative colitis	
	Unadjusted OR (95% CI <sup>a</sup> )	Adjusted OR (95% CI <sup>a</sup> )	Unadjusted OR (95% CI <sup>a</sup> )	Adjusted OR (95% CI <sup>a</sup> )
<b>Physical activity level</b>				
Active	1.0	1.0	1.0	1.0
Moderately active	1.57 (1.10, 2.26)	1.42 (0.99, 2.03)	1.47 (0.98, 2.20)	1.27 (0.85, 1.89)
Inactive	1.87 (1.35, 2.58)	1.59 (1.14, 2.23)	1.33 (0.98, 1.81)	1.07 (0.79, 1.46)
<b>Sex</b>				
Male	1.0	1.0	1.0	1.0
Female	1.25 (0.95, 1.65)	1.33 (0.99, 1.80)	1.50 (1.12, 2.01)	1.53 (1.16, 2.03)
<b>Age</b>				
12-29 years	1.0	1.0	1.0	1.0
30-49 years	2.75 (1.83, 4.14)	2.30 (1.50, 3.52)	3.36 (2.00, 5.64)	3.07 (1.86, 5.07)
50-59 years	2.18 (1.34, 3.54)	1.72 (1.07, 2.77)	3.62 (2.15, 6.10)	3.19 (1.91, 5.31)
60 years or more	1.98 (1.34, 2.92)	1.60 (1.06, 2.41)	4.27 (2.69, 6.78)	3.79 (2.40, 5.99)
<b>BMI</b>				
Neither overweight nor obese	1.0	1.0	1.0	1.0
Overweight	1.09 (0.79, 1.50)	1.00 (0.70, 1.41)	1.03 (0.74, 1.44)	0.91 (0.65, 1.25)
Obese	1.21 (0.86, 1.69)	1.01 (0.72, 1.42)	1.20 (0.85, 1.69)	1.01 (0.71, 1.42)
<b>Type of smoker</b>				
Never smoked	1.0	1.0	1.0	1.0
Former or occasional	1.66 (1.22, 2.26)	1.58 (1.16, 2.15)	1.69 (1.25, 2.28)	1.46 (1.09, 1.96)
Daily	2.44 (1.62, 3.67)	2.22 (1.44, 3.41)	1.79 (1.12, 2.84)	1.68 (1.05, 2.70)

A secondary analysis used a continuous measure of BMI along with other confounders, rather than categorical BMI classes. In the multivariable model adjusted for the continuous measure of BMI, the main relationship showed similar effects and trends as models adjusted for the categorical measure of BMI. Increasing levels of inactivity were associated with higher odds of having CD, with ORs of 1.42 (95% CI 0.99-2.04) and 1.60 (95% CI 1.14-2.25) for moderately active and inactive respondents, respectively, compared to active respondents. The ORs of having UC for moderately active and inactive respondents compared to active individuals were 1.27 (95% CI 0.85-1.89) and 1.07 (95% CI 0.79-1.46), respectively. This continuous measure of BMI showed ORs similarly close to 1.0 and CIs including 1.0, indicating a likely null association with IBD. Both measures of BMI did not appear to be strong confounders for IBD.

## Discussion

CD and UC are the two most common forms of IBD and are characterized by chronic inflammation of the GI tract.<sup>14</sup> Physical activity has been shown to reduce inflammatory pathologies by regulating inflammatory markers, cytokines, and mediators.<sup>13,14</sup> The purpose of this study was to investigate the effect of low levels of physical activity on the odds of having CD, UC, and no IBD condition. Quantitative analysis of the population-based CCHS data sample found that inactivity was associated with increased odds of having CD and UC. The effect of physical activity followed a dose-response pattern for CD patients, whereby the highest odds of having UC were found in moderately active respondents. These effect measures followed a similar pattern when adjusted for age, sex, BMI, and type of smoker, although UC CIs crossed the null and were not statistically significant. Importantly, causality may not be inferred from the statistical analyses performed, as the data come from a cross-sectional survey and do not distinguish the temporal relationship between reported physical activity levels and IBD status. The results described here only highlight associations between physical activity and IBD. As hypothesized, these findings suggest that physical activity is associated with lower odds of having CD. While the analyses did show an association of moderate physical activity with lower odds of having UC, the association remained non-significant.

The results from this study are consistent with previous research. Existing evidence in the literature, including a meta-analysis by Wang *et al.*, determined that increasing levels of physical activity showed an inverse association with IBD.<sup>14-17,21</sup> Importantly, studies that have investigated the effect of physical activity on CD and UC separately have found a similar, significant, inverse association with CD and a weaker, non-significant inverse association with UC.<sup>14,16,21</sup> The magnitude of the increased odds of CD and UC in this study are comparable to the associations in previous studies.<sup>14,16,21</sup> While this cross-sectional study could not explore the temporal relationship between physical activity and IBD, other previous case-control and cohort studies have shown similar associations using measures of sedentary activity, standing time, metabolic equivalent tasks (MET), and the Godin leisure time activity index.<sup>14,16,21</sup> Contrastingly, one case-control study by Hlavaty *et al.* showed nearly twofold higher ORs of having CD and UC in less physically active individuals compared to active individuals than the ORs seen in this study.<sup>15</sup> Their research, however, studied the frequency of childhood sporting activities, which may have had a cumulative effect and therefore magnified the inverse association.<sup>15</sup>

Consistent with evidence in the literature, despite the lack of a statistically significant inverse association between physical activity and UC, this study showed that physical activity of various forms may be associated with lower odds of having CD and UC. These results may be useful for informing public health interventions. The benefits of physical activity on IBD have been attributed to the regulation of pro- and anti-inflammatory markers and increased expression of

anti-inflammatory cytokines, mediated by myokines released during exercise.<sup>10,13,14</sup> Downstream effects of this regulation include stress reduction and decreased number of mucosal lesions associated with IBD.<sup>13,14</sup> Curiously, as shown in this study, UC may benefit more from moderate and low-intensity activities, in line with previous research that indicates that there is potential for inflammatory flare-ups resulting from intense exercise.<sup>17,25</sup> Strenuous periods of exercise may release pro-inflammatory cytokines and trigger a more intense or even systemic inflammation. A study by Bilski et al. found effects of moderate versus acute physical activity similar to the results of this current study, based on these mechanisms.<sup>10</sup>

This study is strengthened by the population-based, representative sample, providing adequate power to the statistical analysis. It does, however, have limitations that may affect the interpretation of the results. Firstly, the CCHS is cross-sectional and is subject to issues of temporality and reverse causality. It is not possible to discern from the survey data whether physical activity preceded the onset of CD or UC, which poses a bias since those with IBD may face difficulties of exercising and become sedentary as a result of disease status.<sup>26</sup> However, this study showed similar magnitudes of the preventive effect of exercise on IBD compared to other prospective cohort studies and studies that measured childhood physical activity.<sup>14,16,21</sup> Further longitudinal studies are warranted to elucidate the relationship between prior physical activity and subsequent onset of IBD.

Another limitation is the potential for reporting bias in surveys. However, self-reported IBD has been well validated in the literature and in other Internet-based surveys, showing high concordance with physician reports.<sup>27-29</sup> The categorical measure of physical activity may also be biased, as it relies on broad categories of activity level and does not use the gold standard of MET.<sup>14</sup> However, this is mitigated by the derivation by Statistics Canada, where the duration and frequency of various types of transportation and leisure activities were amalgamated to produce the physical activity index used in this study.

Finally, the interpretation of the results may be limited by the categorical measure of BMI and unmeasured confounders in CCHS. Literature suggests that many IBD individuals are overweight,<sup>30</sup> yet this higher-risk group was combined with the normal weight group in the categorical variable of BMI in the CCHS. This may have increased the odds of having CD and UC in the reference group, thus diluting the observed associations and biasing them towards the null. The true effect may be stronger with a better reference category for this confounder. Additionally, the risk, if any, of IBD for those at a high BMI may be a function of respondents being overweight and obese, rather than any one-unit increase along the categorical BMI index. These limitations were assessed in the secondary analysis, using a continuous BMI measure that may better capture the increased risk of disease and fully adjust for the potential confounding by BMI. The results of the secondary analysis did not differ from the main model using the categorical measure of BMI. Other potential confounders remain unexplored in the model in this study, such as family history, ethnicity, and disease severity. As the temporal relationship between physical activity and IBD was not explored in this study, and the severity of IBD may preclude individuals from physical activity, further studies are needed to illustrate the impact of severity on activity. As these variables were not captured fully in CCHS, the final model here did not account for their confounding effects, if any.

Further studies are warranted to elucidate the temporality of physical activity and IBD, as well as to use gold standard measures that are more robust to reporting biases. Nevertheless, this study has potential implications for public health interventions and guidelines for preventing IBD. These results add to the growing body of evidence for the preventive effects of physical activity, at various levels and in different forms. As IBD is rising in prevalence worldwide, and especially

in Canada, a thorough understanding of the preventive mechanism of physical activity on IBD offers strategies to prevent the disease and inform future public health interventions.

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# Immune Checkpoint Inhibitor Therapy Induced Acute Immunologic Hepatitis: A Case Report

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Citation: UBCMJ. 2019; 11.1 (27-29)

## Abstract

Immune checkpoint inhibitors (ICIs) have resulted in a paradigm shift in recent cancer therapy and are becoming widely used in the treatment for advanced malignancies. ICIs harness the body's immune response to help combat malignancy; however, patients receiving ICIs are at an increased risk of immune-related adverse events. We present a 67-year-old female with metastatic melanoma on combination ipilimumab (anti-CTLA-4)/nivolumab (anti-PD-1) therapy who developed elevated liver enzymes and fever. Her liver biopsy showed panlobular hepatitis and centrilobular inflammation, confluent necrosis, histiocytic aggregates, and absence of fibrosis, features consistent with ICI-induced hepatitis. After discontinuation of the combination therapy and a course of prednisone and mycophenolate, the patient's liver enzymes improved. Patients undergoing combination therapy should be monitored by serial liver function tests to screen for ICI-induced liver injury. Furthermore, a liver biopsy is helpful in confirming the diagnosis of ICI-induced hepatitis.

## Introduction

Immune checkpoint inhibitors (ICIs) are becoming widely used for treating advanced malignancies, including but not limited to metastatic melanoma, metastatic renal cell carcinoma, microsatellite unstable colorectal carcinoma, and non-small-cell lung carcinoma.<sup>1</sup> ICIs improve survival of patients with metastatic disease and show a promising future for cancer treatment.

Two commonly used ICIs are nivolumab (Opdivo) and ipilimumab (Yervoy). ICIs are monoclonal antibodies targeting downregulators of the body's anti-cancer immune response, such as programmed cell death protein 1 (PD-1), its ligand programmed death ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4), activating the patient's endogenous immune system. Nivolumab targets PD-1, found on T lymphocytes, and blocks its interaction with PD-L1 expressed on cancer cells.<sup>1</sup> Ipilimumab, on the other hand, targets CTLA-4 found on the surface of T lymphocytes and prevents deactivation of T lymphocytes.<sup>2</sup>

Given that ICIs inhibit negative immune regulation to help combat malignancy, patients are at an increased risk of immune-related adverse events. The gastrointestinal tract and liver are among the most commonly affected organs.<sup>3</sup> It is currently unclear why certain organ systems are preferentially affected over others; however, as more cases are reported, the pathophysiology of these adverse events may become better understood. In a safety review of 400 patients, when nivolumab and ipilimumab are combined, the risk for treatment-related grade 3-4 adverse events occurred in 55% of patients.<sup>4</sup> Furthermore, these effects can present earlier than when an anti-PD-1 or anti-PD-L1 antibody is used alone.

We present a case of severe drug-induced liver injury in a patient with metastatic melanoma treated with ipilimumab/nivolumab combination therapy. This is the first reported case at the Vancouver General Hospital. The purpose of this case is to illustrate the clinical and histopathologic presentation of liver injury in a patient on combination therapy and to briefly discuss its management.

## Case Presentation

A 67-year-old female with metastatic melanoma was treated with nivolumab and ipilimumab combination immunotherapy. After approximately three months of treatment, she developed a fever of 39 degrees Celsius. Although her symptoms resolved with low-dose acetaminophen, she developed elevated liver enzymes. The patient was admitted to the internal medicine unit for suspected immunotherapy-related hepatitis. The patient's serology for hepatitis A, B, and C, EBV, HIV, and CMV were negative. The patient's alpha-1 antitrypsin and ceruloplasmin were also negative. She was asymptomatic otherwise, and was discharged with a diagnosis of grade 3 immunotherapy-related hepatotoxicity. The patient was started on prednisone 80 mg daily, with subsequent improvement in her liver enzymes.

Four days following her discharge, the follow-up blood test revealed elevated liver enzymes—ALT of 990 U/L [ $< 50$  U/L], AST of 305 U/L [ $< 38$  U/L], and GGT of 96 U/L [ $< 55$  U/L]—although her serum bilirubin remained within normal limits. Despite being asymptomatic, she was advised to present to the emergency department by her oncologist. She was admitted to the internal medicine unit once again to investigate the etiology of her elevated liver enzymes while being treated with high-dose prednisone. Her past medical history was pertinent for biopsy-confirmed melanoma with metastasis to the breast and suspected lung metastases, hypertension, dyslipidemia, and type 2 diabetes. On examination, she denied having abdominal pain, fevers, chills, significant weight loss, or other gastrointestinal symptoms. She denied alcohol intake and her review of systems was non-contributory. Her combination immunotherapy was discontinued on admission and she was subsequently started on mycophenolate mofetil (Cellcept) in addition to continued prednisone.

On imaging, an abdominal ultrasound revealed no structural cause for elevated liver enzymes. Ultrasound-guided random core needle biopsies from the right hepatic lobe were taken for pathology assessment. Histologic sections demonstrated a panlobular hepatitis that was most severe in the centrilobular region (Figure 1A). Foci of confluent necrosis were seen in the central perivenular area (Figure 1B). Small histiocytic aggregates (Kupffer cell microgranulomas) were also present (Figure 1C). The inflammatory infiltrate consisted of lymphocytes with scattered plasma cells, neutrophils, and eosinophils,

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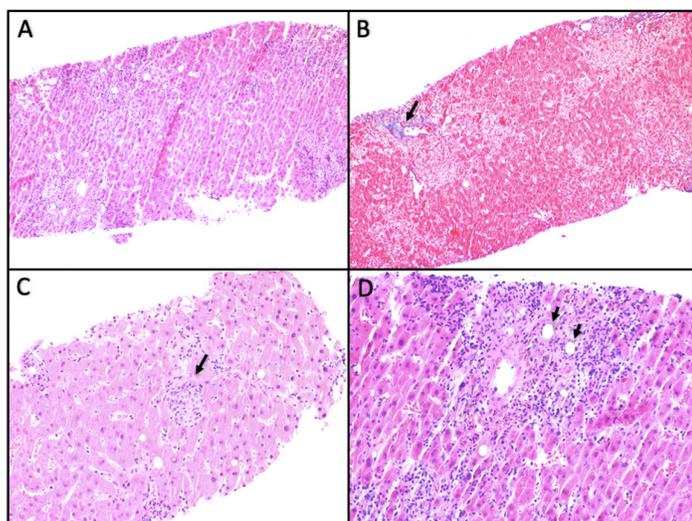
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some of which surrounded fat vacuoles (Figure 1D). A diagnosis of grade 4 ICI-induced hepatitis was established based on these histologic findings.

During the course of her admission, the patient's ALT, AST, and LDH (normally ranging from 60-100 U/L) increased to 1411, 373, and 350 U/L respectively. The patient was discharged in stable condition with a tapering course of prednisone and mycophenolate mofetil. Seventeen days after her discharge, her ALT and AST dropped to 472 and 114 U/L, respectively. Currently, she is asymptomatic with slowly improving liver biochemistry.



**Figure 1** | **A:** Panlobular hepatitis with inflammation was most pronounced in the centrilobular region. The lymphocytic infiltration is more pronounced around central vein regions (hematoxylin–eosin, original magnification x100). **B:** Confluent necrosis is outlined by pale red areas, but no increased fibrosis was noted. Arrow indicates reticulin fibers highlighted in blue (trichrome, original magnification X100). **C:** Arrow indicates a Kupffer cell microgranuloma predominantly consisting of small histiocytic aggregates and some lymphocytes (hematoxylin–eosin, original magnification x200). **D:** The inflammatory infiltrate is composed of predominantly lymphocytes and histiocytes with scattered plasma cells, neutrophils, and eosinophils. Arrows indicate fat vacuoles with surrounding inflammatory cells (hematoxylin–eosin, original magnification x200).

## Discussion

We describe a case of combination ICI-induced hepatitis in a patient with metastatic melanoma. Combination ICI therapy has been shown to be superior to monotherapy in a double-blind, phase 3, randomized controlled trial.<sup>5</sup> In a pooled analysis safety profile of combination therapy versus monotherapy, severe hepatic adverse events, defined by elevated liver enzymes and total bilirubin, were more common in combination therapy.<sup>4</sup> To our knowledge, there are only a few studies reporting combination ICI-induced hepatitis.<sup>4,5</sup>

The clinical symptoms of combination ICI-induced hepatitis can vary. In a study that followed four patients who developed combination ICI-induced hepatitis, clinical symptoms ranged from fever to jaundice (Table 1).<sup>6</sup> In our case, the patient developed a fever after 11 weeks of combination therapy with no other clinical symptoms.

Currently, there is no consensus on the histological diagnostic criteria of ICI-induced hepatitis. The histological differential diagnosis of ICI-induced hepatitis includes autoimmune hepatitis, acute viral hepatitis, drug-induced liver injury, and acute alcoholic liver disease.<sup>7</sup>

Furthermore, the definitive diagnosis of ICI-induced hepatitis requires a temporal relationship with ICI therapy.<sup>7</sup>

Although the histology of monotherapy ICI-induced liver injury is well documented, the histological findings of combination ICI-induced hepatitis have not been well described. De Martin *et al.* reported histological findings in four patients who developed combination ICI-induced liver injury (Table 1).<sup>6</sup> Recently, Everet *et al.* described fibrin ring granulomas in two patients treated with combination therapy.<sup>3</sup> Fibrin ring granulomas are characterized histologically by central lipid vacuoles surrounded by histiocytes and a fibrin ring with an outer histiocytic layer.<sup>7</sup> Fibrin ring granulomas are non-specific and can be found in granulomatous hepatitis caused by infectious agents (e.g., Q fever) or medications (e.g., allopurinol).<sup>8</sup> In our patient's liver biopsy, there were fat vacuoles with surrounding inflammatory cells. However, special stains (Martius Scarlet Blue and trichrome) failed to demonstrate any fibrin rings.

**Table 1** | Comparison of clinical and histological findings adapted from De Martin *et al.*<sup>6</sup> and this case.

Patient	Clinical Findings	Histological Findings
1	Fever 39.0°C	Granulomatous lobular hepatitis
2	Fever 39.3°C, rash	Granulomatous lobular hepatitis + fibrin deposits
3	None	Subacute hepatitis + focal confluent necrosis
4	Jaundice	Subacute hepatitis + periportal and lobular activity
This case	Fever 39°C	Panlobular hepatitis with confluent necrosis in centrilobular region and Kupffer cell microgranulomas

In patients treated with combination therapy, hepatic adverse events (transaminitis and/or elevated total bilirubin) are a relatively common occurrence.<sup>9</sup> In a pooled safety review consisting of over 400 patients treated with nivolumab and ipilimumab combination therapy, 17% of patients presented with treatment-related hepatic adverse events. All grade 3-4 liver injury patients required corticosteroids or mycophenolate, and symptoms resolved in 97% of these patients.<sup>9</sup> Furthermore, this safety review revealed that the peak incidence of hepatic events occurred at three months. In our case, the patient's onset of hepatic events occurred approximately three months after initiation of combination therapy.

The recommended workup for suspected ICI-induced hepatitis includes a complete blood count, a comprehensive metabolic panel, liver function tests, and serology to exclude infectious (e.g., viral hepatitis, cytomegalovirus, etc.) and autoimmune causes (e.g., anti-nuclear antibody, anti-smooth muscle antibody, etc.).<sup>10</sup> The American FDA-approved product labels recommend that patients should be evaluated for serum AST, ALT, and bilirubin before each dose, as well as after treatment completion.<sup>11</sup>

The management of ICI-induced hepatitis has been discussed by the Society for Immunotherapy of Cancer. Clinicians are advised to permanently discontinue ICI treatment in patients with grade 3 and 4 hepatitis (AST, ALT > 5x upper limit of normal, and/or bilirubin > 3x upper limit of normal).<sup>12</sup> Prednisone at 1-2 mg/kg/day can be tapered over a course of four weeks, and mycophenolate mofetil can be considered if symptoms are refractory after three days. If not already done, a liver biopsy is recommended to establish a diagnosis in patients with asymptomatic grade 3 or 4 hepatitis.<sup>12</sup>

In conclusion, we report a patient presenting with combination

ICI-induced hepatitis. This case illustrates the fact that patients treated with combination therapy may present with severe liver injury despite being asymptomatic, which warrants considerations to discontinue ICI therapy. Furthermore, a liver biopsy may be an essential aid in the diagnosis of ICI-induced hepatitis. Although discontinuation of ICI with the addition of potent immunosuppression (e.g., prednisone and mycophenolate mofetil) can be detrimental from an oncologic perspective, this must be balanced by the very real risk of possibly fatal acute liver failure and the fact that patients with metastatic cancer are not feasible candidates for liver transplantation.

### Statement of Ethics

Informed consent was obtained from the patient.

### Disclosure Statement

All authors state no conflicts of interest.

### Funding Sources

The authors have not received funding for this work.

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# An Effective Patient-Centered Approach to Chronic Pain: A Case Report

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Citation: UBCMJ. 2019; 11.1 (30-32)

## Abstract

**Background:** Chronic pain is a highly prevalent chronic condition in Canadians, which is arduous to treat and leads to a multitude of chronic comorbidities if treated sub-optimally. We aim to provide an example of evidence-based interdisciplinary care in a community-based clinic for a 28-year-old female with nine-year history of chronic neck and back pain whose symptoms were not controlled by multiple prior treatment modalities.

**Case:** The patient developed constant neck and back pain with debilitating headaches and a mood disorder after a motor vehicle accident. Treatment over 12 months included a wide variety of medical interventions, manual therapies, and counselling, with emergency room visits for managing pain flare-ups. The patient underwent myofascial trigger point injections targeting previously identified myofascial pain, then diagnostic ultrasound-guided medial branch blocks to assess facet joint involvement, followed by prolotherapy while awaiting referral to radiofrequency ablation of affected sites. Simultaneously, she joined in-clinic group education programs led by multiple health practitioners aimed at self-management of symptoms, including headache management, sleep improvement, behavioural modifications to cope with psychological responses to pain, diet planning, and functional movement rehabilitation.

**Results:** The patient noted progressive improvement within 12 months after her initial visit, with substantial self-reported improvements in pain severity and interference, ability and confidence in coping with pain, and depressive symptoms.

**Conclusions:** This case report documents a successfully managed case of chronic neck and back pain by combining multiple procedures with patient education and behavioural change programs that address other crucial components of pain control such as sleep, nutrition, and retraining movement.

## Background

The prevalence of chronic pain in Canada is estimated to be 16-29%, with back or neck pain alone constituting more than 10% of all visits to primary care physicians.<sup>1,2</sup> The complexities of chronic pain are compounded by comorbidities such as anxiety, depression, and decreased mental, physical, and social functioning.<sup>3-5</sup> The interplay of physiological, emotional, cognitive, and social elements of this disease highlights the need for a multidimensional approach for management, now dubbed the “biopsychosocial approach.”

Many current healthcare services are oriented towards acute care and reducing mortality risk rather than morbidity, leading to under-recognition and inadequate service for such chronic conditions.<sup>6</sup> Hence, a fundamental change in the way our services are delivered is needed to approach long-term, multifaceted illnesses like chronic pain. Interdisciplinary pain centres are the focus of this evidence-based care model.<sup>7</sup> At interdisciplinary clinics, treatment is based on goals for therapy and the proposed mechanism of the pain, supplemented with a variety of supportive strategies offered in-clinic. Such an example is the CHANGEpain clinic (CPC), located in Vancouver, BC, which is comprised of a team of pain specialists, general practitioners, and allied health professionals, and serves patients with a wide spectrum of pain disorders and socioeconomic circumstances.<sup>8</sup>

The CPC treats chronic pain with a layered approach: first targeting myofascial dysfunction with local saline injections, followed by imaging-guided local nerve blocks to identify affected nerves, then with longer-acting techniques to alter pain stimulation such as radiofrequency lesioning (RFL) or augmentation with prolotherapy. A

core component of the CPC's care plan introduces interactive pain neuroscience educational group workshops for all patients to learn self-management strategies, which include movement and exercise programs, relaxation techniques, sleep improvement, nutrition assessment, headache management, and behavioural approaches to cope with pain. Patients may choose to receive weekly 30-60-minute sessions, spanning 2-5 weeks, on the aforementioned topics led by a team of psychiatrists, certified pain management specialists, integrative medicine specialists, and yoga instructors. Each patient also receives a comprehensive list of free community resources for self-management of pain. The workshops are guided by growing evidence on the value of psychological services and self-management at an early presentation for chronic pain.<sup>9-11</sup> Education and self-management are cornerstones of the multidisciplinary care model, which enable behavioural interventions.<sup>12,13</sup> Behavioural strategies such as cognitive behavioural therapy and mindfulness meditation have shown significant benefit for pain outcomes, quality of life, and productivity, particularly in those with comorbid mental health conditions.<sup>12-15</sup> Functional movement rehabilitation services such as physiotherapy, chiropractic, kinesiology, yoga, and exercise physiology are a core component that enhances the sustained effectiveness of the medical services provided by the pain specialists.

With this case study, we aim to illustrate the clinical course of a chronic pain patient receiving treatment at a community-based interdisciplinary pain clinic to give healthcare practitioners insight into an interdisciplinary, mechanism-based care model for people suffering from chronic pain.

## Case

A 28-year-old woman was referred to CPC with a nine-year history of a persistent headache and constant, aching pain spanning her neck

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and upper back after a motor vehicle accident in July 2008. Immediately following the motor vehicle accident, computerized tomography imaging of the head and neck revealed no structural damage. She continued to experience headaches, pain in the neck and upper back, as well as depression, which interfered with regular activity such that she could no longer complete her university degree. Since the accident, she has received the following therapies: physiotherapy, kinesiology, massage therapy, cognitive behavioural therapy, group therapy, intramuscular stimulation, and multiple pain medications, including prescribed opioids. She visited the emergency room for pain flare-ups. She was diagnosed with myofascial pain, post-concussion syndrome, major depressive disorder, and post-traumatic stress disorder during this time.

At her initial visit to CPC in 2017, she characterized her pain as a constant dull ache in both sides of her neck rated as 7/10 on the numeric pain scale (NPS), upper back (8/10 NPS), and right lower back (4/10 NPS) with intermittent sharp pains worsened by prolonged postures and activity. She also experienced constant, nausea-inducing headaches bilaterally from her forehead to the occipital region. Physical exam revealed a forward-stooped posture and painful areas spanning diffusely from her left temporalis, spanning down along her vertebrae and paraspinal muscles to both iliotibial bands and right hamstring muscles. Active range of motion was limited for all cervical spine movements and extension of the lumbar spine. Neurological exam was normal.

Assessment of clinical findings suggested widespread myofascial pain and cervicogenic headache secondary to referred pain from cervical and thoracic spine structures. Her goal of therapy was to reduce pain and fatigue to a level where she could work from her office and attend social outings.

Immediate recommendations were to begin a series of myofascial trigger point injections (TPI) and enrolment into in-clinic group education programs and interactive workshops aimed at self-management of headaches and the behavioural response to pain, diet planning, and sleep improvement through pain neuroscience knowledge. She received five sessions of TPI that were spaced two weeks apart and done to assess the extent of myofascial dysfunction contributing to pain. When reassessed three months later, she reported increased range of motion and decreased headache.

As the initial therapies provided short relief lasting several hours to days of her back pain, she underwent four sessions of ultrasound-guided diagnostic and therapeutic medial branch blocks with a long-acting local anesthetic (ropivacaine) targeting spinal segments T8-11. She reported 90-100% pain relief in between the treatments, scheduled two weeks apart. She noted improved mood, increased activity levels, and discontinued all pain medications. Areas consistently providing the most pain relief were at T9-10, which prompted a referral for RFL, which involves insertion of an electrode that generates heat-emitting radio waves to create a lesion along a nerve that is causing pain of the affected area. While awaiting her appointment for RFL, which was only available at the hospital under fluoroscopy guidance, she was offered prolotherapy as an alternate therapy. Prolotherapy is a “regenerative” injection therapy purported to address chronic musculoskeletal pain through a mechanism involving treatment of ligamentous laxity and direct effects on nerve tissue.<sup>16</sup>

She elected to undergo four sessions of prolotherapy (1 mL glycerin 25%/dextrose 25%/phenol 2.34%, 3 mL lidocaine 1%, 2

mL 50% dextrose). These injections were spaced one month apart and targeted the bilateral levator scapulae and rhomboid attachments, spinous processes and laminae of C2-L1, bilateral facet joints of C3-T10, and the occiput/nuchal ridge. The cervical facets and laminae were injected under ultrasound guidance, while the other targets were injected with landmark guidance. Concurrently with the prolotherapy, she also received in-clinic strength and conditioning coaching from an exercise physiologist. She received a nutritional assessment performed by an integrative medicine specialist (MD with specialized training), a group therapy session led by a psychiatrist, two seminars on the causes and management of headaches, five sessions on pain management strategies, five sessions on improving sleep, and regular in-house Pilates classes. During her course of therapy at CPC, she saw a team of anesthesiologists, a rheumatologist, a physiatrist, specialized family physicians, a registered holistic nutritionist, a chiropractor with exercise physiology training, and Pilates instructors.

Twelve months after her initial consultation, she completed a comprehensive list of validated questionnaires that were compared to her baseline scores. Her results indicated substantial improvements in pain severity and interference, ability and confidence in coping with pain, and depressive symptoms (Table 1).

**Table 1 |** Scores for outcome questionnaires comparing the initial presentation and condition at 12 months.

<sup>a</sup>Brief Pain Inventory (Short Form): Higher scores represent greater interference of life activities.  
<sup>b</sup>Patient Health Questionnaire: 14-20 = moderately severe depression, 5-9 = mild depression.  
<sup>c</sup>Pain-related Self Statements Scale: CAT: <2.73 shows lower tendency to catastrophize; ACT: <2.73 shows lower tendency to use active coping strategies.  
<sup>d</sup>Patient Self Efficacy Questionnaire: <25 relates to low confidence in managing pain and low function; >40 shows higher confidence in managing pain and increased function.

	BPI <sup>a</sup>		PHQ-9 <sup>b</sup>	PRSS <sup>c</sup>		PSEQ <sup>d</sup>
	Pain Interference	Pain Severity		CAT	ACT	
1 <sup>st</sup> Visit	43/70	5/10	15/27	2.7/5	2.4/5	26/60
12 months	27/70	2.5/10	6/27	1.3/5	2.7/5	42/60

**Discussion**

This case of a recovering patient with chronic neck and back pain, as indicated by validated questionnaires for pain intensity and interference, depression, and coping capabilities, introduces the utility of a mechanism-based interdisciplinary model of care. Based on self-reported outcomes after 12 months of treatment, the patient experienced decreased pain severity and interference (Brief Pain Inventory),<sup>17</sup> increased functioning and confidence in pain management (Patient Self Efficacy Questionnaire),<sup>18</sup> and fewer depressive mood symptoms (Patient Health Questionnaire).<sup>19</sup>

Multi-disciplinary care is supported by high quality evidence as the standard for managing chronic pain,<sup>7</sup> and has shown significant improvements in many aspects of pain care, including improved pain outcomes, reduced wait times, work absence, and long-term disability, and favorable cost-benefit estimates.<sup>7,20-24</sup> However, multidisciplinary rehabilitation is difficult to study due to a wide range of healing philosophies, intervention components, and expertise of practitioners. There is a paucity of evidence on optimal content or timing of therapies,<sup>25</sup> and the implementation of multi-disciplinary care is constrained by resource and structural limitations involving such an array of healthcare practitioners. Here we provide an example of an effective multi-disciplinary care model delivered by the CPC. Due to the complexity of this approach, no single treatment can be highlighted as

more efficacious than the others. The patient felt that her commitment to active rehabilitation was a critical element of her engagement in the recovery program. A core aspect of this approach lies in the open and frequent communication between separate practitioners, and the integration of each opinion and plan into a common shared clinical record readily accessed by all team members. This is different than many multi-disciplinary approaches, where separate therapists operate in silos without an understanding of therapeutic responses seen by other practitioners.

Following the trajectory of this case, myofascial releasing needle treatments were provided first to address potential dysfunctional muscle, fascia, and biomechanics,<sup>26</sup> as indicated by the patient's prior diagnosis of myofascial pain. Partial responsiveness to the first layer of treatment warranted the examination and diagnostic testing of deeper structures such as the cervical and thoracic facet joints. Diagnosis of facet joint pathology cannot be made accurately with physical exam,<sup>27</sup> nor imaging.<sup>28</sup> However, there is strong evidence for the diagnostic value of nerve blocks providing at least 75% pain relief and restoration of activities.<sup>29</sup> Accurate testing requires ultrasound or fluoroscopy-guided nerve blocks using long-acting local anesthetic. Positive findings on diagnostic nerve blocks naturally progress to longer-term solutions like RFL, which have proven efficacy for pain control in patients refractory to other treatments.<sup>30,31</sup> In this case, prolotherapy was recommended to address the pain trigger of ligament laxity.<sup>32-35</sup> In patients responsive to prolotherapy, RFL provides longer term symptomatic relief as the root cause is addressed for the ongoing myofascial pain.

In summary, this case illustrates the complexity of chronic pain treatment, which requires a multi-faceted approach. To be effective long-term, pain procedures or physical therapies should be augmented with changes in behaviour, perception and movement patterns. Evidence-based pain neuroscience education equips a patient with the skills to adapt to common comorbid conditions that affect pain control, such as sleep improvement, nutrition assessment, and behaviour management.

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# The Nocebo Effect: Impact, Mitigation and Prevention.

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Citation: UBCMJ. 2019; 11.1 (33-34)

## Abstract

The nocebo effect is the induction of a symptom perceived as negative by sham treatment and/or by the suggestion of negative expectations. Recent evidence has mounted in support of the notion that the nocebo effect may be influenced by themes of language used by healthcare practitioners. The importance of the nocebo effect may be exaggerated in the chronic disease population, particularly in those at an advanced age. Using a clinical vignette to illustrate, this piece elucidates the nature of the nocebo effect in practice and explores potential areas of future consideration for physicians and physicians-in-training.

Consider the following scenario: patient GS, a 25-year-old male, receives a radiograph of the right hip and pelvis for sharp pain. The pain resolves without intervention shortly thereafter. The radiograph, however, captures the lumbar vertebrae and shows mild osteoarthritic-type changes in the L3-4 and L4-5 disc spaces. GS has no history of back pain and is active, well-muscled, and otherwise healthy.

In the interest of disclosure, his general practitioner explains that the radiograph demonstrated evidence of osteoarthritis, an irreversible, degenerative joint condition that causes pain and joint stiffness. GS, considerably more anxious than when he arrived, leaves without much further explanation. Two weeks later, when friends ask GS to go on a long hike—similar to ones they’ve done before—GS is hesitant and eventually turns down the invitation, fearing aggravation of the “joint problems” his doctor told him about. What has happened?

Amongst a host of other potential reasons for his refusal, the general practitioner’s language may have primed GS to experience the nocebo effect.

Closely related to its cousin the placebo effect, the nocebo effect is the induction of a symptom perceived as negative by sham treatment and/or by the suggestion of negative expectations.<sup>1</sup> In other words, patients may perceive what they expect to perceive, either positive (placebo) or negative (nocebo).<sup>2</sup> To illustrate, a 2010 study demonstrated that using gentler, more reassuring language to describe pain during local anesthetic administration (e.g., “We are going to give you a local anesthetic that will numb the area and you will be comfortable during the procedure”) was associated with significantly less patient-reported pain compared to the traditional preamble (e.g., “You are going to feel a big bee sting; this is the worst part of the procedure”).<sup>3</sup>

Given that language can palliate or potentiate the nocebo effect, it is reasonable to postulate that the words physicians and physicians-in-training use may have tangible effects on a patient’s behaviour, expectations, and subsequent clinical outcomes.<sup>4,5</sup> Building off of emerging evidence, physicians must ask themselves: how can we minimize nocebo-induced harm?

In the current evidence-based practice model, healthcare practitioners must be cognizant of potential biases in interpreting evidence. Certain study designs may not provide the insight required to deduce or predict an individual patient’s disease history.<sup>6</sup> Thus, projecting a biased interpretation of evidence may only serve to worsen patient experience, since individuals may exhibit disease without symptoms or symptoms without disease. This may prove especially

difficult for medical students, who are bred in a preclinical system of automatic association between symptom and disease.

Furthermore, it is essential to recognize that a patient’s disposition and situation may affect his or her interpretations of medical counseling. Is this patient generally anxious at baseline? Is the patient already living with a substantial disease burden? Did the patient lose a parent to the condition the physician is speaking about? For some patients, enumerating all potential adverse effects of a medication may be more harmful rather than informative. As the medical profession becomes increasingly patient-centered, physicians must reconcile their obligation to provide nonbiased information with an understanding that patients often present to physicians for their opinion and guidance above all else. Indeed, perceptions and expectations of pain and/or other symptomatology generally predict an increase in frequency and severity thereof.<sup>7,8</sup> To accept this may be to accept that ethical practices such as informed consent may need to be contextualized within the confines of an individual patient’s needs, rather than viewed as absolute and uniform for all patients, as highlighted by the questions above.<sup>9</sup>

Patients with chronic disease, particularly those at an advanced age, may be especially susceptible to the effect of “nocebogenic” language. While skipping a hike with friends may not precipitate any long-term sequelae for GS, a reluctance to engage in biweekly walks to the grocery store may be tremendously impactful for the otherwise sedentary, sarcopenic, 76-year-old woman with hypertension, chronic kidney disease, and diabetes, whose radiograph looks like that of GS. This clinical picture vividly illustrates the importance of encouraging patients to maintain self-efficacy and activity in light of a potentially morbid diagnosis. A physician’s language, thus, must foster and encourage a patient’s sense of self-efficacy and autonomy to optimize outcomes.<sup>10,11</sup>

The argument here is not that physicians should aim to withhold information about patients’ health conditions or taint patients’ perceptions with rose-coloured glasses. Rather, physicians should aim to present information so as not to disproportionately limit patients, thereby maximizing their potential and improving or maintaining quality of life reliably. Projection of negative expectations about a patient’s course may engender confirmation bias and subsequent behaviour modification that ultimately worsen the patient’s clinical outcome in accordance with the physician’s original and not entirely reasonable expectations. Prevention begins with the recognition that physicians can “nocebo” patients into symptoms that were previously absent.

Returning to the clinical encounter, one can recognize how the suggestion of negative expectations may have rendered GS unnecessarily fearful, anxious, and hypervigilant of osteoarthritic

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symptoms, causing a modification in behaviour that, unbeknownst to GS, may precipitate the symptoms that do not yet exist. By contrast, the same 10-minute office visit may have been better spent reassuring GS that the correlation between osteoarthritic symptomatology and radiographic evidence is imperfect and does not represent the constellation of patient experiences, and that weight-bearing exercise can reduce the symptom burden associated with osteoarthritis.<sup>12-14</sup> This dialogue is considerably less likely to “nocebo” GS into excessively cautious behaviours that will not improve his prognosis. Further, if GS’s condition did truly require lifestyle modifications, informing him of these would not constitute a nocebo.

While the cognitive processes affecting a patient’s decision-making are complex and multifactorial, the nocebo effect can play a key mediatory role. Mitigation of “nocebogenesis” requires subtle but significant modifications in the explanations physicians provide to their patients; focusing on self-efficacy, autonomy, and maintenance of existing healthy behaviours makes for a win-win for the patient and the physician. Nonetheless, the burden of action remains in the hands of the individual physician, be he or she a family practitioner or a general surgeon.

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# Community Service Learning in a Rural Indigenous Community

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Citation: UBCMJ. 2019; 11.1 (35-36)

## Abstract

Community Service Learning (CSL) activities provide medical students with unique learning opportunities via direct contributions to community initiatives set forth by the community itself. This can be a powerful and respectful method of educating medical trainees in rural, primarily Indigenous communities. As three medical students, the authors took part in a CSL project in Haida Gwaii. The project, its context, and lessons learned are discussed here as they apply to healthcare in British Columbia.

## Flexible and Enhanced Learning

Flexible and Enhanced Learning (FLEX), a longitudinal course that is featured in the renewed University of British Columbia (UBC) medical undergraduate curriculum, is designed to provide opportunities for medical students to pursue self-directed scholarly interests related to medicine. Projects range from clinical research, to electronic medical application design, to global health initiatives. Another example is a Community Service Learning (CSL) project, which is designed to facilitate learning through volunteerism, whereby students assist in providing health services based on needs and wishes identified by community representatives.

## The Community

Three medical students designed a CSL project focused on rural healthcare in the largely Indigenous community of Northern Haida Gwaii. This article discusses their project and their resultant insights.

Masset, British Columbia is a primarily Indigenous community with a population of 1300 located in Haida Gwaii, a remote archipelago in Northern British Columbia.<sup>1,2</sup> The area is comprised of the town of Masset and the village of Old Masset.

In precolonial times, thousands of Haida thrived in villages that were distributed widely throughout the archipelago.<sup>3</sup> However, 19th century European contact exposed the population to a smallpox epidemic that tragically decimated a substantial proportion of Haida.<sup>4</sup> The on-island Haida population declined from an estimated tens of thousands to less than six hundred by the end of the 19th century.<sup>5</sup> Furthermore, the intergenerational effects of the Canadian residential school system and other colonial pressures have led to a sharp decline of the Haida language, as current estimates and the 2016 Census data suggest that there are fewer than 30 fluent native Haida speakers.<sup>5-7</sup> Haida-led language initiatives including the Skidegate Haida Immersion Program and the Skidegate Haida Language House recognize that language is the cornerstone of Haida cultural stewardship.<sup>5,8</sup> These programs, alongside the important work of many others to reclaim Haida culture, are living testaments to the resilience of the people.

## Indigenous Healthcare in Canada

The colonial history of Western medicine in British Columbia has sadly contributed to the systematic mistreatment of West Coast Indigenous peoples. This legacy is punctuated by the actions of the government's Indian Health Services and the infamous "Indian Hospitals" of the

20th century.<sup>9,10</sup> Unfortunately, today there remains work to be done by the Canadian healthcare system in order to address the health gap between Indigenous and non-Indigenous Canadians. Indigenous people face a number of sociocultural barriers when accessing care and continue to report unsafe cultural practices when interacting with the healthcare system.<sup>11,12</sup>

Increasingly, there are efforts to deconstruct the colonial model of healthcare and return agency over healthcare services to Indigenous groups.<sup>12,13</sup> This supports access to traditional healing practices alongside Western healthcare services. Proponents of this healthcare model developed the First Nations Health Authority of British Columbia in 2013, as well as programs such as the First Nations Health Program in the Yukon and the Haida Health Centre in Northern Haida Gwaii.<sup>13</sup> At the forefront of this model are culturally competent practitioners.<sup>11</sup> UBC's Faculty of Medicine has made efforts to develop cultural safety in medical trainees by featuring mandatory Indigenous Cultural Safety modules, class visits to First Nations communities, and Indigenous Immersion programs.<sup>14</sup>

## Community Service Learning

To avoid a colonial approach, the students' *modus operandi* was to identify themselves as visitors to Northern Haida Gwaii and to engage solely in health-related activities at the request of community leaders. By forming a partnership with community members, the authors took the first steps as emerging medical professionals towards working respectfully with Indigenous groups. The literature has shown that both the participating community and researchers can benefit from the formation of suitable working principles agreed to by both parties.<sup>15-17</sup> By understanding the sociocultural context, acknowledging Indigenous health concerns, achieving cross-cultural understanding, and recognizing and utilizing Indigenous health resources, medical professionals and researchers may be able to work more effectively with Indigenous populations in delivering adequate and equitable health care.<sup>18</sup> Culturally safe healthcare research projects have been completed in Haida Gwaii previously, including the Haida Gwaii Diabetes Project and community-based needs assessments.<sup>15,16</sup>

The authors engaged in community health initiatives at Gudangaay Tlaats'gaa Nayy Secondary School, the Northern Haida Gwaii Hospital, and the Haida Health Centre. Activities included 1) volunteering for local health and wellness programs, such as health fairs, food security programs, mental health and wellness groups, exercise regimens for diabetic patients, and outdoor education programs for youths; 2) delivering presentations to high school students on topics chosen

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by student council, including nutrition, exercise, and chronic disease; 3) creating educational resources for community health programs, including pamphlets outlining resources for sufferers of domestic and intimate partner violence; 4) exploring funding resources for future community health programs; and 5) gaining clinical experiences with local physicians, nurses, and paramedics. The immersive nature of this project allowed the authors to gain an intimate understanding of the challenges in remote and Indigenous healthcare while supporting service providers. A detailed account of the community's healthcare needs will not be discussed here; however, a major concern identified by local individuals and practitioners was the relative lack of access to allied health services. Furthermore, existing health facilities are often at maximal capacity, threatening a healthcare crisis given the aging population. These circumstances are in keeping with the healthcare challenges faced by rural Indigenous communities across the country.<sup>19</sup>

## Conclusion

This manuscript highlights the importance of Indigenous cultural and historical awareness to care providers in the Canadian healthcare system. CSL projects serve as a practical method of developing Indigenous cultural competency through community immersion and service provision. By employing this model, medical trainees and professional colleagues can benefit from learning directly from these communities and their experiences in healthcare. As emerging leaders in healthcare, trainees will be presented with a tremendous opportunity to empower remote Indigenous communities by advocating for community control over healthcare provision, thereby facilitating the reclamation of cultural practices within this context.<sup>13</sup> It is therefore essential that trainees develop a requisite level of cultural competency, so that they are equipped to incorporate community involvement in health and wellness programs.

## Acknowledgements

We extend our most sincere thanks to our mentors at the Northern Haida Gwaii Hospital, our friends at the Gudangaay Tlaats'gaa Nay Secondary School, and the friendly, warm-hearted, and compassionate community members that we were so lucky to have worked with throughout our trips to Masset.

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# Considering the Role of Somatization in Persistent Post-Concussive Symptoms

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Citation: UBCMJ. 2019; 11.1 (37-38)

## Abstract

A substantial number of patients who sustain concussions develop persistent symptoms which last for months to years after their injury, leading to functional disability and reduced quality of life. Emotional distress may play a role in the persistence and severity of these symptoms through a process known as somatization. Identifying and treating somatization may help reduce the suffering and disability associated with persistent post-concussive symptoms. In order to do this, clinicians must be aware of the possible effects of somatization on physical symptoms and consider the role it may be playing in a patient's recovery.

Concussion, a form of mild traumatic brain injury, is a prevalent health concern, affecting roughly 42 million people worldwide each year.<sup>1</sup> Although concussion is usually considered to be an acute medical problem, between 10% and 50% of concussion patients develop persistent post-concussive symptoms, such as headache, fatigue, and dizziness, which last for months to years after the injury.<sup>2-4</sup> These symptoms can become chronic and debilitating, leading to high levels of functional disability and reduced quality of life.<sup>5,6</sup>

Despite extensive research into many physical, environmental, and injury-related factors, it is still unclear why certain patients develop chronic post-concussive symptoms while others do not. Factors one might intuitively expect to affect length of recovery, such as injury severity, are not good predictors of symptom persistence after the first few months.<sup>7</sup> Other factors, such as post-concussive amnesia, prior concussions, and initial post-concussive symptoms, predict symptom persistence inconsistently, with different authors reporting conflicting findings.<sup>8</sup> However, mental health concerns have been consistently associated with the development of persistent symptoms after concussion. Pre-injury mental health diagnoses and immediate post-injury measures of anxiety are some of the most robust predictors of persistent symptoms after a concussion.<sup>8</sup> While past research has focused on depression, anxiety, and post-traumatic stress disorder, recent evidence has suggested that another mental health concern known as somatization may also play a role in the course and severity of physical symptoms after a concussion.

Somatization is the process whereby emotional distress is manifested as unintentionally produced physical symptoms.<sup>9</sup> The physical symptoms of somatization are real and distressing and can occur either in the absence of organic pathology or as a component of a medical condition, prolonging and exacerbating pre-existing symptoms.<sup>10</sup> If somatization is affecting the symptoms of a medical condition, it can be identified clinically by symptom severity, distress, and functional impairment that are in excess of what would be expected based on that organic condition.<sup>10</sup> Somatization can result in high levels of functional disability,<sup>11</sup> and can lead patients to seek treatment for the exacerbated physical symptoms of their condition, instead of for the underlying emotional distress. This places a heavy burden on the healthcare system.<sup>12,13</sup> Somatization is associated with higher rates of other mental health concerns, such as anxiety and depression,<sup>14</sup> and

is known to affect a myriad of medical conditions, including irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, and chronic pain.<sup>15-17</sup> Recently, it has also been suggested as a possible modifiable factor contributing to persistent post-concussive symptoms.

In a prospective study of high school athletes, pre-injury scores on somatization inventories were the strongest pre-morbid predictor of length of concussion recovery time.<sup>18</sup> Similarly, in military personnel with combat-related concussions, pre-injury scores on somatization inventories predicted the development of persistent post-concussive symptoms.<sup>19</sup> In addition, soldiers with concussions had higher post-injury somatization scores than those with other non-concussive injuries.<sup>20</sup> These findings are not unique to adults. In pediatric populations, immediate post-injury scores on somatization inventories (taken within the first three days after injury) are related to delayed symptom resolution and concussion symptom severity over time.<sup>21,22</sup> The measures of somatization used in these studies are physical symptom inventories, which correlate well with physician diagnosis of somatization based on DSM-5 diagnostic criteria.<sup>23</sup> This evidence suggests that somatization may play a role in the experience of physical symptoms after concussion for some individuals.

How somatization might be interacting with physical symptoms after concussion has not been thoroughly investigated, as research in this field is still in its preliminary stages. However, the findings of prospective studies described above suggest that individuals predisposed to experiencing emotional distress as physical symptoms (i.e., those with higher pre-injury somatization scores) might be at a greater risk for experiencing exacerbated and prolonged concussion symptoms due to emotional distress via somatization.<sup>18,19</sup> If this is the case, symptoms would be produced by the injury and sustained by a combination of organic pathology and somatization. Stress surrounding recovery from a concussion could also be playing a role in somatization and physical symptoms. Concerns over recovery and beliefs about the long-term effects of a concussion could affect the amount of attention and worry patients give to their symptoms, which could, in turn, produce more emotional distress and amplify those symptoms.<sup>24</sup> These hypotheses provide preliminary insight into how somatization might contribute to persistent symptoms after a concussion. However, more research is needed on the interactions between injury, somatization, and persistent post-concussive symptoms in order to better understand and identify somatization after concussion.

Identifying somatization in patients with persistent post-concussive symptoms is instrumental to providing effective concussion care, as understanding the etiology of symptoms can help clinicians

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determine appropriate care trajectories. Although interventions for somatization have yet to be evaluated in populations with persistent post-concussive symptoms, mental health therapies, such as cognitive behavioural therapy, short-term psychodynamic therapy, and psychoeducational approaches, have been effective in reducing symptoms and improving functioning in other populations affected by somatization.<sup>25-27</sup> Clinicians must, therefore, understand and identify somatization (if present) in patients with persistent post-concussive symptoms in order to connect affected patients to such interventions and minimize suffering and functional impairment. Somatization inventories, such as the Patient Health Questionnaire somatization inventory (PHQ-15), may be effective tools to aid clinicians with this identification.<sup>28</sup> Such measures correlate well with the DSM-5 psychiatric diagnosis of somatic symptom disorder.<sup>23</sup> Unlike a clinician's assessment, however, they do not take into account emotional distress and functional impairment. Alternatively, screening for distress, functional impairment, and symptomology in excess of what would be expected from a concussion could also help clinicians in identifying somatization.<sup>10</sup> Ultimately, the most useful clinical tool for identifying somatization in this population would be a thorough understanding of the differences in clinical characteristics between patients with persistent post-concussive symptoms affected and unaffected by somatization. This has yet to be evaluated in the literature; therefore, in-depth empirical research evaluating these characteristics is needed to aid clinicians in effectively identifying somatization in patients with persistent post-concussive symptoms.

Evidence suggests that somatization plays a role in the persistence and severity of symptoms after a concussion for some patients. Identifying and treating somatization could help reduce the suffering and disability associated with persistent post-concussive symptoms. It is therefore imperative that healthcare professionals are aware of the possible contributions of somatization to post-concussive symptoms, so that they can take steps to identify and connect affected patients with suitable treatments for somatization in order to reduce symptoms and improve functioning in this population.

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# Cannabidiol as a Potential Treatment for Patients with Chronic Anxiety Disorders

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Citation: UBCMJ. 2019; 11.1 (39-40)

Anxiety disorders are common and debilitating chronic conditions with a high reported lifetime prevalence of approximately 32%.<sup>1</sup> Despite a multitude of pharmacological treatments currently available for anxiety disorders (e.g., serotonin–norepinephrine reuptake inhibitors, benzodiazepines, etc.), adverse effects, limited response rates, and residual symptoms are associated with these drug classes.<sup>2-5</sup> It is, therefore, evident that a substantial burden remains on individuals with anxiety disorders who cannot tolerate or do not benefit from current pharmacological options. This need for improved therapies highlights the anticipation surrounding cannabis as a potential anxiolytic pharmaceutical treatment.

Many Canadians purposefully target their anxiety by using medical cannabis.<sup>6,7</sup> In fact, a survey of Canadian cannabis consumers discovered that 63% of individuals sampled substituted prescription medications, such as benzodiazepines and antidepressants, for cannabis.<sup>7</sup> Despite this, arguments against the usage of medical cannabis for anxiety have been made, stating that a small positive correlation exists between anxiety disorders and cannabis use.<sup>8</sup> It is important to note, however, that the cannabis usage in these studies included  $\Delta 9$ -tetrahydrocannabinol (THC), the psychoactive constituent of cannabis. It should also be noted that certain individuals with anxiety and depressive symptoms achieve relief following low frequency cannabis use, yet symptoms were exacerbated following prolonged use.<sup>8,9</sup> Although the relationship between anxiety and cannabis is clearly complex and multifactorial, other side effects of cannabis use have been more consistently reported, including transient impairments in psychomotor and cognitive function, which impact working memory, attention, and some executive functions.<sup>10</sup>

Existing evidence from preclinical, clinical, and epidemiological studies involving the acute dosing of cannabidiol (CBD)—the phytocannabinoid constituent of *Cannabis sativa* lacking the psychoactive properties of THC—supports many Canadians' claims of CBD's anxiolytic properties against generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder (PTSD).<sup>11</sup> Regarding anxiety specifically, a systematic review by Walsh et al. included eight cross-sectional studies that reported anxiolytic effects from CBD.<sup>11</sup> It is also notable that one additional cross-sectional study reported a return of anxiety upon the cessation of cannabis use.<sup>12</sup> Further studies involving more long-term dosing of CBD must still be investigated, however, if CBD is to be accepted as a formal treatment for chronic anxiety disorders.

The use of cannabis for non-medical purposes in Canada was formally legalized on October 17th, 2018; this law is likely to promote further and much needed research into the benefits and harms of cannabis.<sup>13</sup> For instance, insufficient evidence exists for the use of

CBD on patients suffering from PTSD.<sup>14</sup> Studies have only begun to elucidate the neural circuit mechanisms behind the effects of CBD on anxiety and learned fear. In addition, as decades of psychiatry research have shown a large co-occurrence between anxiety-related and substance use disorders, many scientists and physicians have suggested researching the possibility of using CBD to treat both conditions concurrently.<sup>15</sup> Lastly, ongoing research seeks to determine how CBD should be administered, either as an isolated compound or in combination with other closely related molecules and metabolites. Researchers have shown that certain active chemical compounds found in cannabis have increased effects when combined with nonactive chemical groups or metabolites.<sup>16</sup> This synergistic phenomenon is titled the “entourage effect.” Therefore, precise formulations of both active and nonactive chemical metabolites must be combined and tested to optimize the anxiolytic properties of CBD.

Anxiety disorders are one of the most prevalent mental disorders worldwide. The high prevalence and morbidity of anxiety disorders as well as its accompanying economic, healthcare, and physical burdens strongly support the necessity for ongoing and future research.<sup>17</sup> The limited response rates of current anxiolytic pharmacological options combined with the recent legalization of non-medical cannabis magnify the excitement surrounding CBD as a potential anxiolytic. However, with competing evidence that cannabis has both anxiogenic and anxiolytic properties, more research is necessary to elucidate the optimum dosing, frequency, and combination of active and nonactive cannabis metabolites in order to maximize its anxiolytic properties while minimizing its potential adverse effects.

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# Practicing Proactive Medicine: Making Primary Prevention Our Primary Goal

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Citation: UBCMJ. 2019; 11.1 (41-42)

The importance of primary prevention has long been recognized by healthcare providers and patients alike. As the name suggests, primary prevention is concerned with the prevention of disease using a combination of healthy lifestyle measures, avoidance of risky behaviours (e.g., tobacco use, unsafe sexual practices), and the enactment of several system-level changes such as banning harmful substances and implementing publicly-funded routine vaccination programs for infants and children.<sup>1</sup> Despite the abundance of evidence in support of primary prevention, its vast importance often goes unnoticed as per the old proverb: “you never know what you’ve got till it’s gone.” Take the growing vaccine hesitancy movement for example, which has led to alarming global increases in measles cases by 30%, including a recent outbreak in Vancouver, British Columbia.<sup>2</sup> This is not to mention the estimated 1.5 million deaths that could be avoided each year with widespread vaccination, and the two to three million deaths that are currently prevented by vaccines.<sup>3</sup> Indeed, the advantages of certain primary prevention measures often must be taken away in order for society to truly feel the impact. Unfortunately, as demonstrated by ongoing vaccine hesitancy, such lessons often come at a significant cost.

Garnering far less media attention than the anti-vaccination movement is the equally worrisome global epidemic of so-called “lifestyle” or non-communicable diseases (NCD),<sup>4</sup> named as such for their strong associations with modifiable risk behaviours, including tobacco use, physical inactivity, harmful use of alcohol, psychological stress, and unhealthy diet.<sup>5</sup> Of these NCDs, cardiovascular disease (namely myocardial infarction and stroke) was the leading killer, claiming an estimated 17.5 million lives worldwide in 2012.<sup>5</sup> Regardless of the major impact these modifiable risk factors have on disease onset and progression, their importance is often underestimated by physicians and patients. Indeed, national U.S. survey data collected from 2000 to 2010 demonstrated that only 32% of patients seen by a clinician in the past year received physical activity counselling,<sup>6</sup> while other studies have similarly reported infrequent exercise, smoking, and diet counselling, and a lack of appropriate follow-up care by primary care physicians.<sup>7,8</sup> To explain why these statistics are low, physicians have reported barriers such as a lack of competence and training in lifestyle counselling,<sup>9,10</sup> reluctance to counsel patients who are unlikely to be motivated,<sup>11,12</sup> and limited appointment time.<sup>13</sup> Despite these barriers, evidence continues to demonstrate a measurable benefit from lifestyle counselling on the elimination of modifiable risk factors and subsequent improvements to health outcomes.<sup>14</sup> Given the large volume of clinical evidence linking these modifiable risk factors to adverse health outcomes, it is perhaps unsurprising to learn of ongoing initiatives to promote their uptake among the general public. One such example is Healthy Get-Together, a free monthly educational

workshop based out of Thunder Bay Regional Health Sciences Centre in Ontario that provides education on chronic disease prevention and healthy living strategies.<sup>15</sup> There is also substantial evidence to support the use of pharmacologic therapy for primary prevention, the most notable example being the use of statins for the prevention of cardiovascular disease.<sup>16</sup> However, as with lifestyle counselling, statins remain underutilized despite their efficacy and safety.<sup>15-17</sup>

More recently, studies have started to elucidate the downstream socioeconomic impacts of these NCDs, particularly with respect to the financial burden of disease. For example, according to a recent Canadian Medical Association Journal study, individuals who were hospitalized for acute myocardial infarction, cardiac arrest, or stroke were significantly more likely than non-hospitalized matched individuals to lose the ability to work and suffer consequential income deficits, with lower-income individuals being particularly susceptible.<sup>19</sup> Unfortunately, this relationship tends to be self-perpetuating, whereby adverse health events lead to physical disability and financial losses which themselves contribute to deleterious effects such as poor medication adherence and significant psychosocial stress,<sup>20,21</sup> thus worsening and creating new health problems.<sup>21,22</sup> Financial losses inevitably lead to heightened financial stress, particularly for lower-income individuals, demonstrating the bi-directionality of the social determinants of health. That is, although income and employment invariably contribute to the overall state of health and wellbeing of an individual, the inverse relationship (i.e., the impact of health on income and employment) is also of equal importance.

Effective primary prevention is paramount in preventing disease and the associated burdens on social wellbeing and financial stability. The exact understanding of this topic continues to evolve as researchers learn more about the complex socioeconomic impacts of disease. Indeed, socioeconomic outcomes are often equally or more devastating than the physical manifestations of the disease itself, particularly with respect to growing financial costs compounded with a reduced ability to work and earn income. In these scenarios, primary preventative measures should expand to focus on preventing these downstream socioeconomic impacts and the new or worsening health problems that might arise as a result. Clearly, the management of such burdens is complex and will undoubtedly require a multifaceted approach. Going forward, early priorities should involve the development of screening tools to improve our ability to detect patients at risk of these downstream outcomes. One such example can be found in the Toronto suburb of North York, where a group of family physicians led by Dr. Kimberly Wintemute has piloted a targeted poverty screening tool to help identify patients who are struggling financially in order to help them gain access to government social programs.<sup>23</sup> Initiatives such as this demonstrate the growing emphasis placed on primary prevention and the associated socioeconomic impacts of disease, though a sustained and nationwide effort will be required for larger-scale change. In the meantime, one thing is certain: by ensuring primary prevention does not take the back seat, physicians will ensure

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their patients do not either.

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# Patient–Clinician Relationships and Adherence to Antiretroviral Therapy in HIV/AIDS

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Citation: UBCMJ. 2019; 11.1 (43-44)

Only 25 years ago, contracting HIV was regarded as a death sentence. In 1996-1997, the life expectancy at age 20 for an individual infected with HIV was 19.1 years compared to 63.4 years for an HIV-uninfected person.<sup>1</sup> Now, HIV is considered a treatable chronic illness.<sup>2</sup> Patients in North America that are fully on antiretroviral therapy (ART) have life expectancies comparable to that of the general population.<sup>1</sup> Though HIV/AIDS treatment shares many common components of chronic disease care models with other chronic illnesses, people living with HIV/AIDS (PLHA) face unique and complex challenges in longitudinal care.<sup>2</sup>

One major challenge is ART adherence. Patient adherence to ART in British Columbia and worldwide has improved over the past decades, due to simplification of drug regimens, combination pills, and decreased toxicity and side effects of drugs. A study by the B.C. Centre for Excellence in HIV/AIDS (CFE) scored patients on their ART compliance between 2000 and 2009 using six indicators, showing that the percentage of patients with perfect compliance scores increased from <5% of those starting ART therapy in 2000, to >40% in 2009.<sup>3</sup> Despite the substantial progress, suboptimal adherence amongst patients is still quite common in British Columbia, with only approximately 40% of patients scoring perfect compliance scores in 2018.<sup>4</sup>

Research consistently shows that adherence alone is associated with slower progression to AIDS-related illness, fewer complications, lower mortality, and lower risk of HIV transmission.<sup>5</sup> The 2012 B.C. CFE study showed that those with poor compliance scores had mortality rates up to 22 times higher than those with perfect compliance scores.<sup>3</sup> As such, the issue of adherence remains a healthcare priority. However, this issue is quite complex since it relies not only on independent patient, clinician, and treatment factors, but also on the interaction between clinician and patient. This article aims to investigate the role of patient–clinician rapport in ART adherence and provide a summary of further suggestions for research and clinical practice.

## Impact of Patient–Clinician Relationships on ART Adherence

Patient–clinician interactions play a key role in the management of chronic illness; strong patient–clinician rapport has been shown to improve patient treatment adherence and lead to better clinical outcomes.<sup>6,7,8</sup> Though the patient–clinician relationship, by its subjective nature, is difficult to study in a standardized manner, research repeatedly demonstrates a positive association between good rapport and improved adherence. A study from the United Kingdom in 2007 showed that perceived respect for patients, the clinician's ability to initiate dialogue with the patient, and feelings of trust were all positively correlated with patients' self-reported adherence. Interestingly, patients' feelings of trust with the nurse showed

statistically significant correlation to adherence, whereas trust with the physician did not, likely due to more time and direct care provided by the nursing staff.<sup>9</sup> Another study by Schneider et al. dissected treatment adherence into six components and showed that quality of communication, trust, HIV-specific education, dialogue focused on adherence, and the patient's overall satisfaction with the clinician all independently increased self-reported adherence.<sup>10</sup> Other studies based in the United States support these findings.<sup>11,12</sup> These studies are often limited by their cross-sectional analysis and convenience sampling, as well as the subjective nature of questionnaires and self-reporting. However, they consistently suggest that trust, education, and two-way communication are important factors in ART adherence.

## Challenges in Patient–Clinician Relationships in HIV/AIDS

PLHA often face or anticipate discrimination while seeking care. They can experience stigma for contagion, sexual identity, mental illness, and substance abuse.<sup>7</sup> Even without direct signs of rejection, PLHA often face difficulty developing trust and rapport with their clinicians due to shame or expectation of discrimination.<sup>13</sup> Patients feel less encouraged to seek care if their clinicians do not foster empathetic, non-judgmental, and open discussions, especially due to the sensitive nature of sexual health, substance use, or sociocultural discussions often involved in care.<sup>14</sup> As HIV/AIDS can often coexist with lower education attainment, substance use, or mental health concerns, HIV-specific education and conversations of medication adherence can suffer if these areas are not addressed.<sup>14</sup> Physicians can also face their own challenges when caring for PLHA. They face a burden in not only keeping up with the ever-expanding body of HIV/AIDS research and guidelines, but also learning enough about their patients' lives within a 15-20 minute appointment to best guide them through the treatment. In addition, physicians may experience compassion burnout while managing low adherence rates, comorbidities, side effects of medications, and often insidious yet life-threatening complications of HIV/AIDS.<sup>15,16</sup>

## Further Suggestions for Research and Clinical Practice

Despite the efficacy of novel ART regimens and expanding knowledge on HIV/AIDS, patient adherence to treatment still remains a barrier to achieving desired clinical outcomes. Existing preliminary studies demonstrate a positive impact of strong clinician–patient relationships on treatment adherence. As such, further population-based, longitudinal studies with standardized questionnaires for measuring adherence and clinician rapport are needed. Furthermore, clinicians and clinicians-in-training, whether specialized in treatment of PLHA or not, would benefit from the following recommendations compiled from existing research and educational guidelines:<sup>16-18</sup>

1. Be aware of one's own attitudes towards HIV/AIDS, sociocultural differences, differences in sexuality, mental health, and drug use;
2. Provide appropriate reassurance and compassion towards dealing with a chronic illness and its implications on quality of life;

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3. Encourage questions and facilitate a discussion-based, rather than didactic, education, recognizing that education is an important part of treatment adherence;
4. Ask patients for their goals and preferences in treatment to develop a collaborative care plan and optimize treatment adherence; and
5. Take opportunities to learn and improve communication skills.

In summary, while HIV/AIDS treatment becomes more efficacious and accessible, patient-physician relationships remain a cornerstone in promoting better adherence so that every patient can benefit from the advances made in ART. Thus, physicians should employ evidence-based strategies to improve adherence for a historically challenging disease.

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# Spinraza & Spinal Muscular Atrophy: Moving Toward Treatment, But Not for Everyone

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Citation: UBCMJ. 2019; 11.1 (45-46)

In October 2018, the government of British Columbia announced that it will fund a life-saving pharmacotherapy called nusinersen (Spinraza), providing the first effective treatment to be approved for spinal muscular atrophy (SMA), a chronic neuromuscular degenerative condition.<sup>1</sup> SMA is categorized into three main subtypes: type 1 (severe), type 2 (intermediate), and type 3 (mild).<sup>2</sup> The age of onset for type 1, type 2, and type 3 SMA are 0-6 months, 7-18 months, and greater than 18 months, respectively. Moreover, the estimated age of mortality is approximately less than two years for type 1 patients, greater than two years for type 2 patients, and greater than eighteen years for type 3 patients. The incidence of the condition approaches one in 10,000 live births with type 1 accounting for 60% of cases.<sup>3</sup> SMA symptomatology includes muscle weakness, decreased muscle tone, limited mobility, delayed gross motor skills, spontaneous tongue movements, scoliosis, and problems with breathing, eating, and swallowing.<sup>2,4</sup>

SMA is caused by a homozygous deletion on the survival of motor neuron 1 (*SMN1*) gene, leading to a loss of SMN proteins and the eventual degradation of spinal motor neurons followed by paralysis.<sup>5</sup> Diagnosis is achieved through genetic testing, which is conducted to detect the absence of *SMN1*. However, the precise role of the loss of SMN proteins in driving SMA pathogenesis has not been characterized.

Adrian Krainer, professor and chair of the cancer and molecular biology program at Cold Spring Harbor Laboratory, spearheaded advancements in SMA treatment by shifting attention towards the role of *SMN2* as a possible therapeutic target.<sup>6</sup> The *SMN2* gene differs from the *SMN1* gene by a single base pair in one exon of the transcript product, leading to the production of mostly unstable, non-functional SMN protein. However, the *SMN2* gene also produces a small proportion of functional SMN protein, and a short antisense oligonucleotide developed by Krainer—nusinersen—augments this production and rescues the loss of *SMN1* function associated with SMA. Specifically, nusinersen attaches to a region of the *SMN2* transcript product, effectively blocking the splicing of exon 7 and preventing the frameshift mutation that would otherwise render the SMN protein from *SMN2* non-functional.

In the past, clinical trials that focused on developing pharmacotherapies for SMA included an investigation into the therapeutic potential of riluzole (Rilutek), a medication used to treat amyotrophic lateral sclerosis, and salbutamol (Ventolin), a  $\beta_2$  adrenergic agonist used to treat asthma and chronic obstructive pulmonary disease.<sup>7</sup> Although these drugs, among others, failed to demonstrate clinical efficacy in the treatment of SMA, researchers have continued to investigate other avenues for treatment, one of them being nusinersen. Namely, Phase 3 of the clinical trial “ENDEAR” demonstrated that SMA type 1 infants treated with nusinersen

displayed significant improvements in motor-milestones compared to infants that had not received nusinersen.<sup>8</sup> In particular, 51% of infants treated with nusinersen achieved the desired motor-milestone response compared to 0% of infants in the control group. Among the infants that received nusinersen treatment, 22% exhibited full head control, 10% demonstrated the ability to roll over, and 8% demonstrated the ability to sit independently. Relative to the control group, infants treated with nusinersen experienced fewer severe adverse events (56% vs. 80%), serious adverse events (76% vs. 95%), and mortality (16% vs. 39%). However, this trend was reversed for constipation (35% vs. 22%) and some respiratory events, including upper respiratory tract infection (24% vs. 9%) and pneumonia (23% vs. 7%).

With clinical trials producing encouraging results, nusinersen was approved as a treatment option for SMA by Health Canada in June 2017. While many are celebrating the drug’s availability, the prohibitive cost of nusinersen presents a significant limitation to patient access. In Canada, the cost of the first year of treatment is listed at \$708,000 followed by \$354,000 annually.<sup>9</sup> This cost perpetuates existing health disparities because public funding for nusinersen is generally limited to type 1 patients who are less than six months old (seven months in British Columbia), leaving type 2 and 3 patients of all ages without adequate access to treatment.<sup>10</sup> With many people questioning the government’s decision to restrict access to nusinersen, a recent report by the Canadian Agency for Drugs and Technologies in Health may provide some answers. This report made cost-effectiveness predictions using the data from three previous studies: the ENDEAR, CHERISH, and CS2+CS12 trials for SMA types 1, 2, and 3, respectively. Using this information, nusinersen was predicted to increase life expectancy of patients with SMA types 1 and 2, but not for type 3.<sup>9</sup> Additionally, the cost per quality-adjusted life years (an indicator of cost-effectiveness) for the treatment of SMA type 2 was significantly greater than that of type 1 (\$24.4 million vs. \$9.2 million), with type 3 lacking sufficient clinical data for an accurate estimate. Furthermore, research supporting the therapeutic value of nusinersen treatment for adult populations is currently lacking and requires further investigation.

Despite the aforementioned reasons, Canada should still strive towards increasing patient accessibility to nusinersen by adapting strategies from countries such as Germany, Portugal, and Romania among others that currently provide broader funding.<sup>11,12</sup> Additionally, Canada should endeavor to fund and support research initiatives that are centered around other therapeutic options. For example, vector-based gene replacement therapy is one initiative that has shown promise as a viable alternative to nusinersen that would expand the scope of SMA treatment, both in terms of patient population and clinical efficacy.<sup>13</sup> In conclusion, though the funding of nusinersen by the government of British Columbia (and Canada more broadly) presents promise for the treatment of SMA, its potential as a therapeutic agent is eclipsed by its limited accessibility for patients.

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# The Transgender Suicide Epidemic: What It Is and How Physicians Can Help

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Citation: UBCMJ. 2019; 11.1 (47-49)

**T**rans (Table 1) people have suicide rates that far exceed that of the cisgender population. The lifetime prevalence of suicide attempts in trans people across Canada, Europe, and the United States is estimated to be 22-43%, compared to 3.7% of all Canadians.<sup>1-8</sup> Despite these alarming statistics, the interplay between personal, socio-demographic, socio-cultural, and psychological factors behind trans suicide rates are only a recent area of study.<sup>9</sup> Emerging mental health research shows that modifiable risk factors such as lack of social and family support, unemployment, internalized transphobia (Table 1), invisibility in the community, and inaccessibility in healthcare settings increase depression and suicide rates amongst trans populations, whereas protective factors such as increased social and family support, legal document changes to represent preferred gender, and non-judgmental healthcare support are predicted to decrease suicide rates.<sup>9-13</sup> This demonstrates that multiple levels of public health domains—from individual health and physician-patient relationships to research and education, community support, and government policy—can collaborate to improve trans mental health.<sup>12</sup> This article explores factors involved in trans suicide and some of the ways that physicians can support their trans patients.

## Aggravating and Protective Factors for Trans Depression and Suicide

The disproportionately high trans suicide rate begs the question: is gender dysphoria an inherent risk factor for suicidal ideation, or is trans suicide driven by psychological distress caused by social disparities? Longitudinal studies show that suicide rates in the trans population remain higher than those of the cisgender population, even in those who have undergone hormonal treatment and/or sex reassignment surgery, suggesting that factors other than gender dysphoria are significant contributors to increasing suicide rates in trans populations.<sup>14,15</sup> The TransPULSE project in Ontario shows that the multiple facets of discrimination faced by the trans population are pertinent and modifiable risk factors for trans depression and suicide. These factors include, but are not limited to, transphobic violence and harassment, rejection by family and society, and employment adversities (lower income, difficulty finding employment, and workplace mistreatment).<sup>9-11</sup> A study of transsexual MTF (Male-to-Female) and FTM (Female-to-Male) populations (Table 1) demonstrated that for both MTF and FTM persons, transphobia in the community and lack of social and family identity support were significantly associated with increased prevalence of depression. In MTF persons, unemployment rates also played a substantial role in increasing depression prevalence, whereas in FTM persons, the inability to transition and wait to transition, either medically or surgically, increased depression rates.<sup>10,11</sup>

A more general study on trans adults in Ontario, which included those who did not medically or surgically transition, used a model-standardized risk ratio analysis to illustrate that strengthening

**Table 1** | Glossary (adapted from TransCare BC)<sup>25</sup>

Terms	Definitions
Transgender (Trans)	An umbrella term describing people whose gender and/or gender expression differ from their assigned biological sex at birth and/or the societal and cultural expectations of their assigned sex.
Transsexual	A broad term used to describe people whose gender identity is “opposite” from their assigned sex at birth. This term is perceived to be outdated, and most trans individuals choose not to identify with this term.
Transphobia	Attitudes such as ignorance, fear, dislike, and/or hatred of trans people, which may be expressed in verbal, nonverbal, social/political, and other forms.
Female-to-Male (FTM)	A person assigned female at birth whose gender is male.
Male-to-Female (MTF)	A person assigned male at birth whose gender is female.

protective factors can decrease suicidal ideation. These protective factors include gender support from parents, social inclusion (gender identity concordant government documents and support networks), protection from transphobia, and successful completion of medical transition. Most notably, those in the lowest tenth percentile of experienced transphobia had a 66% relative risk reduction of suicidal ideation in the past year, and a 76% relative risk reduction of suicide attempts. Based on current population estimates of 53,500 trans adults in Ontario, this translates to a potential prevention of 4601 trans suicide attempts per year.<sup>9</sup>

Evidence thus far suggests that transphobia, rejection from family and society, and unemployment are key risk factors for trans depression and suicide, whereas decreased transphobic experiences, parental and social support of gender identity, and successful medical transition for those who seek transition are important protective factors against trans suicide. Future longitudinal research projects with larger cohorts across varied racial, ethnic, cultural, religious, geographic, economic, and age groups may help better define and measure risk factors pertaining to unique trans populations. This can be the first step towards the development and implementation of more effective

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evidence-based recommendations for mental health interventions and suicide prevention strategies in individual, community, healthcare, and government domains.

### Challenges Faced by Trans Populations in the Healthcare System

In the healthcare setting, trans individuals face a discrimination that is unfamiliar to the cisgender population. In the context of existing sicknesses or disabilities that bring them to the hospital, they must also confront the possibility of transphobic judgement, harassment, erasure, or even refusal of treatment from their healthcare providers. Trans individuals consistently report greater hesitancy in seeking medical care and difficulty obtaining adequate care regardless of availability of care. The TransPULSE project reported that up to 38% of trans individuals experienced transphobia from their primary care physician.<sup>16</sup> Discrimination is especially prevalent in the emergency care setting, where over half of trans individuals have experienced harassment or refusal of care. Due to the expectation of such mistreatment, 21% of trans Ontarians have avoided going to the emergency department despite requiring urgent medical attention. The most common reason for avoiding care amongst Ontarian trans youth is being “afraid of what the doctor would say or do.”<sup>17</sup> Similar problems can be observed in the United States, with 26% of survey respondents in Philadelphia reporting being refused medical care, and 14% of respondents in Chicago reporting difficulty obtaining emergency care.<sup>18,19</sup>

The rejection that trans individuals face in healthcare settings has a negative impact on their general and mental health. Because many trans individuals are reluctant to seek care due to fear of discrimination, they suffer discontinuities in primary care and worsened depression. A study of trans adults in the Rocky Mountain region of the United States showed that trans patients who avoided care due to fear faced a 3.81 times greater odds of having attempted suicide in the past year, a devastating consequence of the failure of the healthcare system to welcome trans patients.<sup>20</sup>

Despite the universal basic health insurance in Canada, the discomfiting reality is that trans patients still face a non-inclusive healthcare environment. Due to trans-specific negative experiences such as verbal harassment, refusal of care, or erasure of their gender identity, trans patients are discouraged from seeking care even in emergency situations.<sup>16-20</sup> Physicians may also refuse to provide hormonal transition therapy due to perceptions that it is unsafe or difficult, or because treating trans individuals conflicts with their personal beliefs.<sup>21</sup> The lack of physicians educated on trans-related care and trans cultural humility is disheartening for trans populations.<sup>16</sup> In order to provide trans individuals the care they deserve, changes must be made to physician education and medical practice.

### How Physicians Can Help Their Trans Patients

With supportive physician care, especially from primary care doctors with whom trans patients interact most frequently for trans-related health concerns, the health and quality of life of trans individuals can vastly improve. Trans patients who choose to undergo medical transition are particularly in need of non-judgmental support from their physicians, especially during the emotional and physical changes that accompany the therapy period.<sup>22,23</sup> Below are some ways in which physicians can better care and advocate for their patients derived from existing research and TransCare BC Guidelines:<sup>10,12,16,17,20,21,24</sup>

- Respect the patient’s self-affirmed gender identity.
- Provide an inclusive environment. An effective way to do this is to

use appropriate language. Use correct names and pronouns when interacting with or charting on the patient. TransCare BC offers a glossary of terms intended for healthcare settings.<sup>25</sup>

- Recognize that trans patients are at increased risk for mental health concerns, especially during medical transition. Screen patients for depression and other mental health concerns when appropriate.
- Help patients stabilize mental or physical conditions that prevent them from accessing gender-affirming surgical or hormonal intervention.
- Learn about evidence-based guidelines and recommendations for hormone therapy and surgical interventions, and/or be prepared to refer the patient to a provider who can assist them. Education on trans-specific health concerns can make the patient feel safer, more understood, and more likely to seek care in the future.

### Conclusion

Trans populations face a disproportionate risk of suicidal ideation and suicide attempt. Distress caused by transphobic experiences, lack of support and acceptance from family and society, employment challenges, and barriers to medical transition are just some of the associated risk factors. In particular, trans discrimination in the healthcare setting is of major concern due to its negative impact on the physical and mental health of trans populations. With improved public education and awareness, social inclusivity, trans-sensitive medical support, and gender identity support from family and loved ones, trans populations can have reduced suicide rates and mental health issues. Individual physicians can care and advocate for their trans patients by learning more about trans-related health concerns and cultivating an inclusive environment in their practice.

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# **UBCMJ**

## **Volume 11 Issue 2**

### **Spring 2020**

## **Medicine and Media**

The UBC Medical Journal (UBCMJ) is warmly accepting submissions for our Spring 2020 issue on Medicine and Media. Medicine is a popular topic for discussion in the media. We can easily find articles about the latest health fad or a breakthrough discovery in treatment in newspapers, magazines, or scientific journals. On television, we are exposed to health channels and advertisements of health products that can influence our choices. The impact and reach of media have become even greater in recent decades due to the internet and the rise of social media.

The relationship between medicine and media can be a beneficial one used to educate the public and collect information. However, the influence of media on medicine can also be harmful. The scientific accuracy of the content shared with the public can greatly vary. Media can become a tool to spread misinformation and propagate false beliefs, as seen in the anti-vaccination movement today. In this coming issue, we invite authors to share their work on the role of media in medicine and how it may shape healthcare delivery, patient-physician relationship, and communication in the future.

To encourage and recognize high-quality writing, the UBCMJ Distinguished Writing Award (a \$250 honorarium) will be presented to the authors of the strongest article submitted in either the Fall 2019 or Spring 2020 issue.

**Submission Deadline: October 11, 2019**  
**Submit at: [ubcmj.med.ubc.ca/submissions/](http://ubcmj.med.ubc.ca/submissions/)**



# University of British Columbia Medical Journal

This issue of the UBCMJ could not have been possible without the support and guidance of the following individuals:

Linda Herbert  
Dr. Janette McMillan  
Dr. Michelle Wong  
Jennifer Fong

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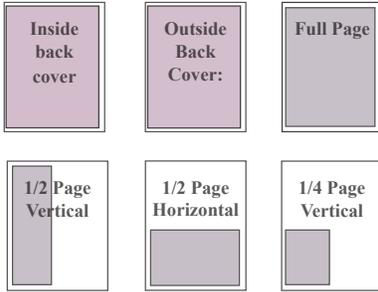
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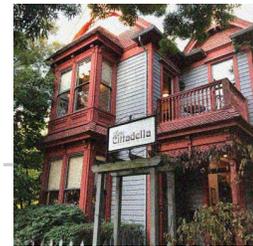
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