



FRINGE

Fall 2020 | Volume 12 | Issue 1

Fringe science embraces the unconventional, alternative, experimental, and innovative.



Chronic
antibody **Disease** Obstructive
Trends
Telehealth Sleep
Flavan Community
Facilitating **Indigenous** Vision
Restoring Novel **telesurgery** Conventional Healthcare
Strategies **robotic** Mental **Pain** Initiatives
BCS Integration **Transparency** Enterprise
Treatment **Mental** Student
Clinical **Pain** Rate
Perspectives Bioprosthetic



THE UNIVERSITY OF BRITISH COLUMBIA

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.

On the cover



In this issue we explore some of the most important and highly discussed topics in the 21st century. These topics that were once considered fringe have come to the forefront of our modern life. The cover art symbolizes Medicine as an ever-evolving field that reflects the changes in technology, culture and Knowledge.

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What the fringe?

Emma Finlayson-Trick¹, Olivia Tsai¹

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From outlandish and unsubstantiated musings to novel hypotheses, fringe science embraces ideas that are unconventional, alternative, experimental, and innovative.¹ Many approach fringe science with skepticism because musings can have negative consequences, especially when made by unqualified individuals. As a recent example, during a COVID-19 task force briefing, U.S. President Donald Trump suggested that injecting disinfectant might be a good approach for combating viral infection.² The following day, the New York City Poison Control Center reported 30 cases of possible exposure to disinfectant, more than double the cases experienced on the same day the previous year.³ Fortunately, most irrational musings remain in the outskirts of scientific thinking.

On the other end of the spectrum, novel fringe hypotheses have the potential to become accepted areas of research when exposed to rigorous experimentation. For instance, take Dr. Barry Marshall who spent years trying to convince the scientific community of the relationship between *Helicobacter pylori* infection and stomach ulcers, an idea ridiculed by his contemporaries. It was only after a dramatic proof of concept where Dr. Marshall drank *H. pylori* broth, developed gastritis, and self-dosed with antibiotics to treat himself that his idea was taken seriously.⁴ Now, the role of *H. pylori* in health and disease is an expanding area of mainstream research. Other examples of widely accepted theories that began in the fringes include the Big Bang theory, continental drift, and germ theory.

In this issue of the University of British Columbia (UBC) Medical Journal, we celebrate fringe with two feature articles that highlight innovative thinking. We begin with Dr. Hadi Mohammadi, a mechanical engineer who leads the Heart Valve Performance Laboratory at the UBC Okanagan campus. In his article, Dr. Mohammadi describes the process of developing and testing a novel synthetic material to mimic the properties of cardiac tissue. The material offers an exciting new model for young surgical residents eager to hone their skills. Moving from models to medical genetics, our next feature article is written by Dr. Chris Maxwell and a team of oncology and hematology researchers based out of B.C. Children's Hospital (BCCH). Since the first human genome was sequenced 17 years ago, rapid technological advances have helped to establish the field of precision medicine.⁵ Dr. Maxwell describes how BCCH is using precision medicine to improve the lives of children living with cancer and blood disorders. In doing so, he provides fascinating insight into the blossoming field of pharmacogenomics. It is our hope that these curated pieces, along with a number of student-written articles, such as Brendan McNeely's "Current trends in robotic surgery: A role for telesurgery in remote Canadian communities" and Wajid Khan's "The Current Evidence Behind Functional Medicine" demonstrate the potential for exciting results inherent in fringe science and encourage others to engage in fringe thinking.

As we produce this issue of the UBC Medical Journal, the world is grappling with the COVID-19 pandemic. We would like to acknowledge the students and faculty whose dedication to the journal enables us to continue production. During these uncertain times, the journal itself applied some fringe thinking and developed a blog as an alternative avenue to publish student writing. Hosted on the UBC Medical Journal website, the blog is a space for students to share their research interests, travel experiences, and opinions on medicine and medical education. During the pandemic, the blog has interviewed students who are pursuing research projects related to COVID-19 and has published an opinion piece about self-isolation. Since launching in early April, the blog has been visited more than 5000 times from viewers located around the world, such as in Canada, the United States, India, South Africa, Germany, and China. If you are interested in writing for the blog, please contact external.editor@ubcmj.com.

Conflict of interest

The authors have declared no conflict of interest.

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Simulation of cardiothoracic reconstructive surgery: A novel technology

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Introduction

Cardiac surgeons must maintain a high level of technical proficiency to ensure quality of care and patient safety. To hone their skills, students and experienced surgeons rely on educational tools such as artificial models.¹⁻³ Silicone-based models are used extensively as their mechanical properties resemble those of biological materials. The main issue with silicone-based models is that they are dry, unlike native tissues. In addition to silicone-based models, dead tissues harvested from animal or human cadavers are also used. However, a major problem with using tissue from animals or human cadavers is that they feel different than living human counterparts. Due to the inadequacies of these current models, creating a realistic but inexpensive model that mimics the mechanical and physical properties of human tissues is highly desirable. At the Heart Valve Performance Laboratory (HVPL) at the University of British Columbia, we have developed a synthetic model that can be used for the simulation of various cardiothoracic surgeries ranging from bypass surgery to heart valve implantation.

Our Synthetic Model: Polyvinyl alcohol with bacterial cellulose

Polyvinyl alcohol (PVA), a hydrophilic polymer, can crosslink to form a type of hydrogel with various tissue engineering applications.⁴ For instance, when combined with other materials, PVA-based hydrogels can assume qualities similar to skin tissue, cardiac tissue, and bone tissue, to name a few. At the HVPL, we combined PVA with bacterial cellulose to control the mechanical properties of our synthetic tissue.^{3,5-7} This tissue offered consistent physical and mechanical properties to that of human tissue.

We then enlisted four cardiac surgeons at the Kelowna General Hospital (Kelowna, British Columbia, Canada) to practice a mitral valve reconstructive surgery on our synthetic tissue. We collected their input on several areas of interest, such as needle control, pressure needed to sew, and suture managing. The surgeons reported that the synthetic tissue felt like real tissue, presented great suture retention, and presented great suture penetrating ability (which was determined by comparing different sutures such as polyglactin Vicryl and Prolene 6-0/7-0/5-0). Overall, the surgeons agreed that the synthetic tissue could be considered for use in cardiovascular surgical training.

While we are still in the prototyping phase of production, our synthetic valve model offers an exciting development in surgical training. For those who are interested in learning more about using this synthetic tissue in surgery, we have provided instructions for mitral valve prolapse reconstructive surgery. In this surgical description, we have included photos to better illustrate the use of our synthetic tissue.

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Instructions for Mitral Valve Prolapse Reconstructive Surgery

Mitral valve prolapse is when one or both flaps of the mitral valve do not close properly and instead bulge into the left atrium during heart contraction. Estimated to occur in 2–3% of the population, mitral valve prolapse may present as a heart murmur, which is caused by blood leaking backward through the valve.^{8,9} Other symptoms may include heart palpitations and chest pain. Depending on the severity of the mitral valve regurgitation, a prolapse may or may not require treatment.

If surgery is required, a surgeon may use the following technique as demonstrated using our synthetic tissue. Posterior leaflet prolapse is excised by a quadrilateral or a triangular excision in order to remove the bulge (Figure 1A). A specific type of suture referred to as “stay sutures” are positioned in the vicinity of the chordae to differentiate the prolapsed area (Figure 1B). The bulge segment is detached and removed by making a perpendicular incision with respect to the free edge towards the annulus. Then, sutures referred to as “plication sutures” are placed along the posterior annulus in the resected zone (Figure 1C). A few sutures known as “direct sutures” are placed on the remaining leaflet tissue which reinstates the mechanical integrity of the valve without tension (Figure 1D). Finally, an annuloplasty ring is imposed to the annulus to maintain the original and regular shape of the valve (Figure 1E).

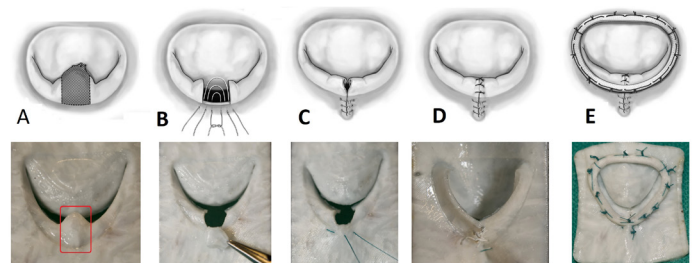


Figure 1 | Performing a quadrangular resection with annular plication using the proposed synthetic tissue phantoms.

Conclusion

Our synthetic tissue provides a realistic platform for practicing surgical procedures that is comparable to experiencing surgical operations with human patients. Advances in surgical training models may help surgeons better prepare for countless types of difficult cardiothoracic surgeries and allow them to achieve a high level of skill, confidence, and expertise.

Conflict of interest

The author has declared no conflict of interest.

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A BRAvE new world: The Hematology Oncology Personalized Enterprise (HOPE) at BC Children's Hospital

Chris Maxwell^{1,2}, Rebecca Deyell^{1,2}, S. Rod Rassekh^{1,2}, Gregor Reid^{1,2}, and Caron Strahlendorf^{1,3}
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Introduction

Cancer is the leading disease-related cause of death for children and adolescents (the leading overall cause is fatalities from accidents). In Canada, almost 1000 children under the age of 14 are diagnosed with cancer each year, the majority being less than five years old when the disease presents.¹ Overall, conventional therapy now achieves cure rates of >80%, but this remarkable accomplishment comes at considerable cost to the child; survivors are at greatly elevated risk of developing chronic health problems later in life, including life-threatening complications such as secondary cancers.² The large number of life years lost, combined with the emotional and financial toll of a cancer diagnosis on families, makes childhood cancer a major public health issue that demands more effective and less harmful therapies.

Cancer in children differs from cancer in adults in important ways, such as the tissues affected, mechanisms of disease, and responses to therapy. Pediatric cancers are less genetically complex than adult cancers, on average presenting with mutation rates 14-fold lower;³ this is likely due to earlier presentation in life. Therefore, simply applying the lessons learned from adult malignancy is not necessarily an effective approach to pediatric cancer. This is especially true of precision oncology, an approach that targets the specific changes that arise in the cancer cells of each patient.⁴ While similar cell pathways are often affected in both adult and pediatric cancer, there are big differences in other characteristics of these cancers that can profoundly affect the response to a targeted drug. As precision medicine has enormous potential to achieve better efficacy with lower toxicity, research is urgently needed to optimize the application of these approaches to childhood cancer.

Precision Oncology at BC Children's Hospital (BCCH): BRAvE and PROFYLE

An explosion of new drugs and more rapid methods to predict tumor responses offers hope for the application of precision medicine to a child's relapsed tumor. Next generation sequencing-based pediatric cancer trials are underway in Europe, Australasia, and North America. These trials are laying the essential groundwork for the integration of precision medicine approaches into the standard of care for childhood cancer by establishing patient enrolment strategies, clinical protocols, and critical safety data. Most of these initiatives are reactive—enrolling patients with refractory and/or relapsed cancers—and early results both stimulate hope and highlight critical gaps. Over 55% of pediatric patients who undergo whole genome and transcriptome analysis (WGTA) of tumours and matched germline have actionable

molecular findings in categories of cancer predisposition, prognosis, diagnosis or therapeutics.⁵ However, despite frequent novel drug target identification using various omics approaches, very few pediatric patients (about 10%) are enrolled on precision oncology trials and receive interventions.⁵ This challenge is complex as many children may not be eligible for new therapies (no evidence of disease, lack of consent/assent, patient too unwell), while others may face barriers including lack of access to pediatric clinical trials or published pediatric safety data, lack of funding for off-label use of medications, or lack of suitable pediatric formulations.

Better Responses through Avatar-omics Evidence (BRAvE) at BCCH is a research initiative that addresses a serious challenge to effective precision medicine in pediatric cancer: how to identify and facilitate pre-clinical testing of personalized treatment protocols for each child in a timeframe that enables effective clinical intervention. Through the BRAvE program, a pediatric-specific cancer panel can be utilized to screen diagnostic samples from children with cancer in BC. This has the potential to identify actionable targets suitable for future therapy, if first-line therapy fails. However, cancer evolution—the gain of tumor variants at relapse or the loss of tumor variants present at diagnosis—is a major threat to a prospective precision oncology approach. For this reason, it is important to identify tumor variants that are most likely to persist through disease progression and tumor types that are most amenable to a prospective approach.

Clonal evolution does occur in pediatric leukemia, wherein a minor clone at diagnosis is often selected for outgrowth at relapse.^{6,7} While evolution often occurs in single nucleotide variants, such as through chemotherapy-related mutation,⁸ structural variants—aneuploidy, copy number variants (CNVs), or translocations—frequently persist with leukemia progression.^{6,7} For example, 78% of CNVs and 82% of structural variants detected at diagnosis were also detected at relapse in childhood leukemia samples.⁶ CNVs tend also to be retained in pediatric sarcoma metastases.⁹ Even in a heterogeneous disease like medulloblastoma, a tumor type that shows substantial genetic divergence at recurrence, half of the relapsed samples (44.4%, 4 of 9) retained putative drug targets identified at diagnosis.¹⁰ Thus, structural variants identified at diagnosis may persist in relapsed disease, and precision therapies targeting these structural variants may prove effective at disease relapse.

The prediction of pediatric cancer relapse is challenging, and many children who suffer a recurrence are not initially identified as high-risk at diagnosis. However, most children who subsequently relapse initially respond to standard therapy. The BRAvE approach with upfront panel testing can be accessible to a large number of patients at first diagnosis. This can enable early initiation of the precision medicine workflow which could gain crucial time for the identification, testing and selection of the best precision treatment protocols for the relapse. However, it is also critical to obtain clinically validated confirmation of persistence of the molecular target at the time of relapse prior to considering targeted therapy.

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Terry Fox PROFYLE (Precision Oncology for Young People) is a national pediatric precision oncology pipeline that offers WGTA and matched germline sequencing of very poor prognosis cancers from children, adolescents and young adult patients (<29 years old). Following the success of the Pediatric Personalized Oncogenomics program launched in BC in 2013, PROFYLE leverages the expertise of three pediatric sequencing programs (BC, Ontario, Quebec) so that patients at all pediatric cancer programs across Canada can access WGTA and proteomic analysis of their very poor prognosis tumours, either at diagnosis or relapse.

In PROFYLE, proteogenomic target identification is built on the collective expertise at the BC Cancer Research Institute, the Genome Sciences Centre, and the BCCH Research Institute working together with teams from across the country. Moreover, BC researchers help shape the biobanking and tumor modeling initiatives, with BCCH hosting the Western Canadian PROFYLE Biobank. One of the key components of PROFYLE is the Therapeutics Node, designed to facilitate access to molecularly targeted therapies. The Therapeutics Node is leveraging collaborations with international clinical trial networks, is planning a PROFYLE master targeted therapy protocol, and has facilitated access to therapies through Health Canada single patient protocols or innovative therapy compassionate access requests. A national Drug Access Navigator position has been established to facilitate targeted therapy access, and a patient and provider resource website is being developed to help provide information on clinical trial availability and patient/parent supports.

Together, the PROFYLE and BRAvE teams envision a change in personalized pediatric oncology, from an approach that is currently reactive at cancer relapse to one that is proactive at cancer diagnosis. The initiation of a precision medicine workflow when pediatric cancer is first diagnosed has the potential to benefit many children with cancer. In addition, having sequencing at multiple time points will allow for the study of cancer evolution over time, and provide insights into drug resistance and tumor heterogeneity.

SAFE at BCCH

The remarkable progress in cure rates achieved for childhood cancers was realized through the testing and implementation of aggressive treatments, including combinations of chemotherapy, radiation, and bone marrow transplantation. Many of these treatment regimens were developed in the 1950s to 1970s, allowing researchers to now investigate the chronic health effects in long-term follow-up studies of survivors. The findings have been stark: by age 50, survivors had experienced an average of 17 chronic health conditions of any grade, of which nearly five were of grade 3–5.² Future personalized approaches offer the hope of more targeted and less toxic therapies. However, tailoring therapies to each child’s personal predisposition, termed pharmacogenomics, and identifying biomarkers that predict adverse events offer immediate optimism for reducing the late effects of today’s treatment.

Researchers at BCCH are among the world leaders in the fields of pharmacogenomics and biomarker research for graft versus host disease (GvHD). Adverse drug reactions are now well-documented for many chemotherapies used to treat childhood cancers, including cisplatin-induced hearing loss and anthracycline-induced cardiotoxicity. Anthracyclines are one of the most common treatment options for childhood cancers and have significantly improved cure rates, but are also associated with cardiotoxicity in 57% of treated

patients.¹¹ These adverse events are associated with genetic factors¹² and, therefore, genetic testing has the potential to inform best practices in treatment and patient care decisions. Genetic factors are similarly associated with cisplatin-induced ototoxicity,¹³ which offers hope that pharmacogenomic approaches in combination with otoprotective agents¹⁴ will reduce the incidence and severity of these adverse events. Finally, adverse events such as GvHD are associated with blood and marrow transplantation. Identification of biomarkers predictive of GvHD is needed to improve the efficacy and safety of these treatments, which have improved outcomes for children with very high-risk leukemia.¹⁵

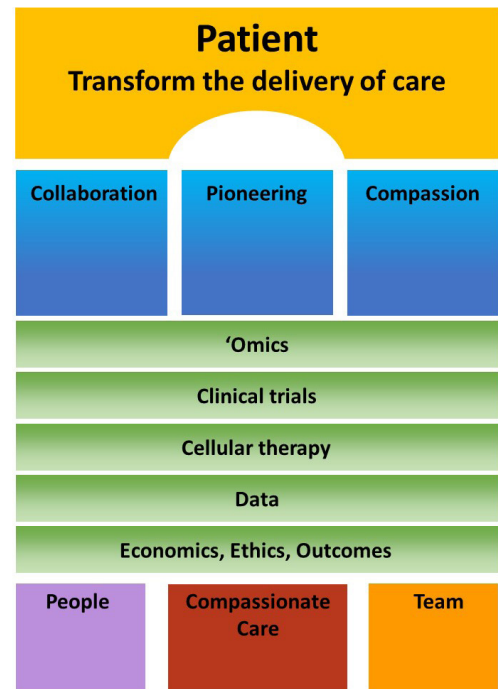


Figure 1 | BC Pediatric Hematology Oncology Personalized Enterprise (BC Peds HOPE)

HOPE at BCCH

BCCH is one of the leading pediatric cancer and blood disorder centres in Canada, and has the opportunity to transform delivery of care to some of our province’s most vulnerable patients.

BC Pediatric *Hematology Oncology Personalized Enterprise* (HOPE) is developing a personalized approach for each patient, from diagnosis to treatment to follow up, while recognizing that diagnostic uncertainty may still occur, germline predisposition may go unrecognized, susceptibility to drug-related toxicity may not be identified, and patient-reported outcomes may not be captured routinely.

BC Pediatric HOPE will be a comprehensive personalized cancer program founded on four pillars: omics, clinical trials, immunotherapy, and data (Figure 1), including health outcomes and economic impact outcomes embedded within the framework of the highest quality, ethically sound research and care. At BCCH, our obligation is to bring hope and compassionate care to patients and families, and to recognise and respond to vulnerability, suffering, and the importance of emotional connections.

BCCH has a history of providing compassionate and state-of-the-art clinical care. In addition, BCCH has a responsibility to develop, test, and implement new and better ways to diagnose and treat cancer and

blood disorders in children. For these reasons, childhood cancer and blood research at BCCH is transitioning towards more personalized research and treatment approaches for our children. As a team, we will implement innovative initiatives that will promote both the science as well as the humane aspects of healthcare for children with cancer, cancer survivors, their families, and their supportive communities.

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Conflict of interest

The authors have declared no conflict of interest.

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The rate and predictors of continuous positive airway pressure adherence in patients with obstructive sleep apnea presenting to a sleep clinic in British Columbia

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Abstract

Purpose: Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction while asleep that leads to sleep fragmentation and hypoxemia. OSA is associated with an increased rate of cardiovascular disease, stroke, motor vehicle crashes, and all-cause mortality. Continuous positive airway pressure (CPAP) reduces the risk of upper airway collapse, and its use is associated with reduced daytime sleepiness and decreased rates of cardiovascular disease and motor vehicle crashes. However, one of the major challenges associated with CPAP success is adherence. To date, there have been no studies on the rate or predictors of CPAP adherence in Canadians. We sought to determine the rate and predictors of CPAP adherence amongst a sample of patients presenting to the University of British Columbia Sleep Disorders Clinic (UBC SDC).

Methods: Patients referred for suspected OSA to the UBC SDC were recruited, underwent attended overnight polysomnography, and completed a health questionnaire. Patient charts were reviewed, and CPAP adherence was defined according to the recognized standard of CPAP use for ≥ 4 hours per night for $\geq 70\%$ of nights.

Results: In total, 1,250 patients were recruited. Of these, 844 were prescribed CPAP and 421 (49.9%) were adherent. The severity of OSA was the only significant predictor of CPAP adherence ($p < 0.01$). Adherent patients had a mean apnea hypopnea index of 34 events/hr compared to 27 events/hr in non-adherent patients.

Conclusion: CPAP adherence was 49.9% and OSA severity was its only significant predictor in this cohort.

Introduction

Obstructive sleep apnea (OSA) is the most prevalent respiratory sleep disorder. It is characterized by repetitive episodes of upper airway obstruction during sleep, which lead to sleep fragmentation and nocturnal hypoxemia.¹ Common symptoms of OSA include loud snoring, excessive daytime sleepiness, and frequent nocturnal awakening.² If OSA is not treated, it can potentially lead to increased rate of motor vehicle crashes, hypertension, heart failure, cardiac arrhythmia, stroke, and decreased neurocognitive performance.³ The global economic burden of OSA is in the billions of dollars per year, and the direct expenses associated with OSA in Canada alone were around 145 million dollars in 2008.⁴ These direct expenses include the health costs associated with managing OSA and its associated medical conditions, the financial costs of associated work-related injuries, motor vehicle crashes and lost productivity, and the non-financial costs derived from loss of quality of life and premature mortality.^[4]

OSA is commonly diagnosed by a polysomnogram (an overnight sleep study). This consists of an overnight stay in the hospital with collection of detailed physiologic data, including an electroencephalogram, airflow, and oxygen saturation. Disease severity is assessed by the apnea hypopnea index (AHI) which is the number of times per hour of sleep the airway closes (apneas) or narrows (hypopneas).

Continuous positive airway pressure (CPAP) is the first-line therapy for OSA.⁴⁻⁵ CPAP consists of a nasal or oronasal mask attached to an air compressor with tubing. The device establishes a positive pressure in the upper airway during sleep, preventing its collapse. It is efficacious in reducing and in many cases eliminating snoring, hypoxemia, and sleep fragmentation.⁶ CPAP significantly improves quality of life, alertness, and neurocognitive function.⁷ However, despite the high efficacy of this device, CPAP adherence ranges from 30–60%, and of those that use CPAP, an estimated 20–30% apply it insufficiently.⁹ CPAP adherence is commonly defined as using the device for ≥ 4 hours for $\geq 70\%$ of the nights monitored.⁸ According to a recent comprehensive systematic literature review that examined 66 studies (either randomized control trial or longitudinal) published between 1994–2015, the rate of adherence was 66%.⁹ Despite ample research from other contexts, to our knowledge there has yet to be a publication investigating CPAP adherence in the Canadian context. The aim of this retrospective study was to identify the rate and predictors of CPAP adherence amongst patients with OSA presenting to the UBC SDC.

We assessed whether previously hypothesized and demonstrated CPAP adherence predictors would be associated with CPAP adherence in this cohort. These included age, gender, AHI, Epworth sleepiness scale (ESS), body mass index (BMI), patient health questionnaire (PHQ-9), education, income, menopausal status, rate of car crashes, smoking status, marital status, bed partner status, snoring severity, occupational injury, restless leg syndrome, neck circumference, mood disorder, anxiety disorder, alcohol intake, stroke status, cardiac arrhythmia status, myocardial infarction status, periodic limb movement (PLM), hypertension, sleeping aid medication intake, and antidepressant medication.⁹

Materials and Methods

After obtaining Research Ethics Board approval from University of

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British Columbia, we reviewed the medical charts and health surveys of consenting patients that were referred to the UBC SDC between 2003–2009 for overnight attended polysomnography (PSG) for suspected OSA who were enrolled in a research cohort. Patients were required to: 1) be able to read and understand English; 2) be able to provide informed consent; and 3) not have used CPAP prior to their PSG. Additionally, patients referred to the UBC SDC for a PSG by sleep psychiatrists as opposed to a respiratory physician were excluded from the study. Lastly, those with serious medical conditions including active severe cardiopulmonary and psychiatric disease were also excluded from the study.

On the night of the PSG, patients were given a health questionnaire which was completed while they were at the UBC SDC. The survey obtained detailed information about medical and sleep history/complaints. This also included an ESS score to assess degree of subjective sleepiness. This is an eight-item validated survey that asks about the tendency of the patient to doze over the last month, and generates a score between 0–24. A score greater than 10 is considered indicative of subjective sleepiness.¹¹

OSA severity

PSG was performed using conventional instrumentation and was scored according to the recommendations on syndrome definition and measurement techniques published by the American Academy of Sleep Medicine.¹² Patients were categorized as having OSA if they had an AHI ≥ 5 /hr of sleep. OSA severity was further classified according to standard threshold values (AHI < 15 /hr for mild, 15–29/hr for moderate, ≥ 30 /hr for severe disease). Hypopneas were defined as a reduction in airflow associated with either a 3% desaturation or an arousal from sleep.

CPAP prescription and adherence

Patients prescribed CPAP in the clinic had a one-on-one education session with the CPAP coordinator that lasted 20–30 mins. This included general education about CPAP, sleep apnea, and potential issues that may arise (cleaning, mouth leak, and nasal congestion). They then took their prescription to a CPAP vendor who would fit them with an appropriate mask and provide the device. Patients then returned to the clinic for follow up to review their experience and adherence with the device.

Patients' medical charts were reviewed to obtain CPAP adherence information. Both objective and subjective (descriptive) data within the charts were collected when available. CPAP adherence was defined as using the device for at least 4 hours/night for at least 70% of the nights.¹⁰ Objective adherence data were obtained when possible from patients' downloaded data from their CPAP machine, which were obtained from CPAP providers who sent data downloads to the UBC SDC. Subjective adherence data were obtained by looking at the sleep physician's notes found in patient charts from the patient's most recent visit to the SDC. At the time of patient recruitment, the technology used to obtain objective CPAP data was less ubiquitous than it is today and thus many of the patients lacked objective data. Subjective data was used on its own when objective data was lacking. Only 21.3% of the patients that were prescribed CPAP had objective data available.

Patients were grouped into two groups, adherent and non-adherent. The non-adherent group of patients was made up of a combination of people who reported that they were not using the machine or were unable to adhere to CPAP, in addition to a group of people who failed to return for a follow-up. Patients who failed to return for follow-up were assumed by the sleep physicians at the UBC

SDC to have never purchased or used a machine.

Data sets and statistical analyses

We assessed whether a variety of factors were associated with CPAP adherence (Table 1), classifying adherence as a binary outcome (adherent versus non-adherent). In univariate analyses, we used t-tests for continuous variables and chi-square tests for categorical variables to determine whether there were significant differences between adherent and non-adherent patients. We used logistic regression to control for confounders in multivariate models.

A P value of < 0.05 was considered to be statistically significant. Statistical analysis was performed with SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

Table 1 | Potential predictors of CPAP adherence.

Patient characteristics	Age
	Gender
	Body mass index (BMI)
	Education
	Income
	Menopausal status
	Smoking status
	Marital status
	Bed partner status
	Neck circumference
Alcohol intake (eg. wine, beer, liquor)	
Sleep related	OSA severity measured by apnea hypopnea index
	Daytime sleepiness measured by Epworth Sleepiness Scale
	Number of car crashes
	Restless leg syndrome
	Periodic limb movement
	Sleeping aid medication intake
	Snoring severity
Cardiovascular related	Stroke status
	Cardiac arrhythmia status
	Myocardial infarction status
	Hypertension
Mental health related	Depression scale measure by patient health questionnaire (PHQ-9)
	Mood disorder
	Anxiety disorder
	Antidepressant medication
Other	Occupational injury

Results

The study population

1,250 patient charts were reviewed. 844 were prescribed CPAP by a sleep physician and 406 were not prescribed CPAP (Figure 1). Of those patients that were prescribed CPAP, 421 (49.9%) were adherent. Characteristics of patients according to adherence status is described in Table 2.

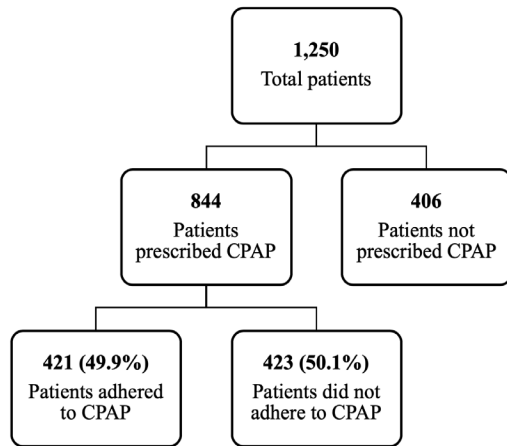


Figure 1 | Cohort sample size. Overall, 1,250 patients were identified, of which 844 patients were prescribed CPAP and 406 were not prescribed CPAP. Out of those that were prescribed CPAP, 421 patients adhered to CPAP and 423 patients did not adhere to CPAP.

Predictors of CPAP adherence

AHI was the only variable associated with CPAP adherence in this study ($p < 0.01$) (Table 2 and Table 3). The mean AHI in the adherent and non-adherent groups was 34 events/hour and 27 events/hour, respectively (Table 2). Patients were categorized into mild OSA (5–14, $n=172$), moderate OSA (15–29, $n=226$), and severe OSA (≥ 30 , $n=344$) (Figure 2). Amongst patients with severe OSA, 57% were adherent to CPAP compared to 50% of patients with moderate OSA and 32% of patients with mild OSA (Figure 2). A chi-square test was performed on the OSA groups by adherence status and the results were significant ($p=0.01$).

We found no other significant associations ($p < 0.05$) between CPAP adherence and five continuous variables (age, mean ESS, BMI, PHQ-9 score, and years of menopause for women) or 18 categorical variables (gender, antidepressant medication...etc.) (Table 3).

Discussion

CPAP is a highly efficacious therapy for OSA. However, one of the major challenges is low adherence. Despite numerous technological advancements such as quieter pumps, more comfortable masks, and improved portability, CPAP adherence remains a challenge for many OSA patients.⁹

Our study is the first to examine CPAP adherence in a large group of Canadian patients with OSA. Two major findings stand out. First, CPAP adherence was 49.9% in our cohort, a rate that is low but similar to previous studies in the literature.⁹ Second, OSA severity was the only significant predictor of CPAP adherence. This low CPAP adherence rate in our study and others is concerning to the care of patients with OSA. CPAP has a myriad of beneficial impacts including a reduction in daytime sleepiness, improved quality of life, increased alertness, improved cognitive function, and a reduction in motor vehicle crashes.¹³ Moreover, patients who use CPAP regularly have a reduced rate of cardiovascular events including strokes and myocardial infarction.¹⁴

There are many ways that CPAP adherence could be improved and supported.¹⁵ Positive initial experience with CPAP,¹⁶ behavioral interventions (such as cognitive behavioural therapy),¹⁷ patient education, and patient engagement tools may improve CPAP adherence and should be the focus of more intensive studies in the future.¹⁸ Nevertheless, we believe that CPAP adherence will remain

a significant challenge in the future given the nature of the therapy.

The relationship between OSA severity and CPAP adherence has been examined in previous studies in other contexts. In several studies, increased OSA severity, measured either using the AHI or oxygen desaturation index, was associated with CPAP adherence.^{11–15} The reason that more severe OSA might be related to greater adherence is open to speculation. One hypothesis is that increased symptoms associated with more severe OSA may be a greater motivator for patients to use CPAP. Stronger encouragement of CPAP use by healthcare providers towards patients with more severe OSA may be another possibility.

A variety of other variables were tested in this study for any association with CPAP adherence; however, none were identified to be significant predictors of CPAP adherence. Of note, factors such as age, gender, and sleepiness were predictors in some previous studies, but overall the literature is fairly inconsistent in this regard.¹⁰

There were a number of strengths to this study including its relatively large sample size and use of PSG to objectively diagnose OSA and assess severity. However, we acknowledge that there were many limitations. The most important limitation was the lack of objective CPAP adherence information in a large number of patients. Subjective or self-reported adherence tends to overestimate objective adherence. Additionally, CPAP adherence data were only collected at one time point (in general, a few months after prescription). Longitudinal data would have been ideal to more accurately assess CPAP adherence status over time. These data were from greater than ten years ago, and there have been significant improvements in terms of mask and device technologies since then. It is certainly possible that CPAP adherence rates today may be much greater. Finally, this was a single centre study and may not be generalizable to other jurisdictions. For example, in British Columbia, CPAP is in general not funded publicly and this lack of public funding may negatively affect CPAP adherence.

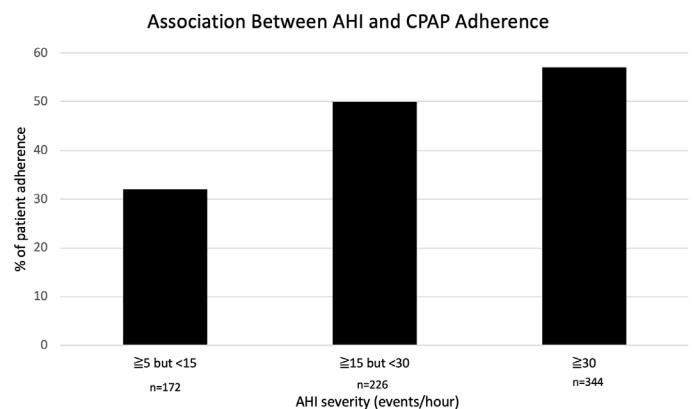


Figure 2 | Association between AHI and CPAP adherence. The more severe the OSA, the more patients adhered to CPAP. The resultant chi-square statistic performed on the variables was $p=0.01$.

Conclusions

In this large cohort of Canadian patients with OSA, CPAP adherence was low (49.9%). Sleep apnea severity was the only significant predictor of adherence. Future studies should focus on whether CPAP adherence is associated with clinical outcomes and whether other interventions (e.g., telemedicine, education, technological and behavioral) can improve adherence in Canadians. Doing so may enhance patient care and quality of life within the Canadian population and eventually lower the burden of OSA.

Table 2 | Correlation between continuous variables and CPAP adherence in adherent and non-adherent groups.

Variables	Adherent patients	Non-adherent patients	Standard deviation (Adherent)	Standard deviation (non-Adherent)	t-test P
AHI (apneic events/hour)	34	27	25	21	<0.0001
Age (years)	51	51	11	11	0.80
ESS (points)	11	11	4.6	4.4	0.63
BMI (kg/m ²)	33	32	6.8	7.2	0.38
PHQ-9 (points)	16	16	5.6	5.7	0.68
Menopausal status (years)	3.6	3.4	6.0	4.5	0.78

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; PHQ-9 = patient health questionnaire. Results presented as mean unless otherwise indicated. Significance level for p-value: <0.05. Patients were classified as CPAP adherent if they used CPAP for ≥ 4 hours per night for $\geq 70\%$ of nights

Table 3 | Frequency of categorical variables by adherent and non-adherent groups.

Variables	Chi-Squared P	Number and (%) of Adherent patients	Number and (%) of Non-adherent patients
Antidepressant medication (≥ 1 night/week)	0.57	21 (5)	17 (4)
Gender (male)	0.97	307 (73)	309 (73)
Smoking status (current smoker)	0.91	67 (16)	68 (16)
Marital status (living with spouse)	0.21	282 (67)	300 (71)
Snoring severity (\geq once/week)	0.52	400 (95)	398 (94)
Occupational injury (yes)	0.16	40 (9.5)	55 (13)
Neck circumference (≥ 17 inches)	0.97	312 (74)	313 (74)
Self-reported mood disorder (yes)	0.17	93 (22)	76 (18)
Anxiety disorder (yes)	0.84	30 (7.1)	32 (7.5)
Periodic limb movement (yes)	0.44	3 (0.6)	5 (1.2)
Hypertension (yes)	0.05	105 (25)	80 (19)
Myocardial infraction (yes)	0.78	18 (4.2)	16 (3.8)
Cardiac arrhythmia (yes)	0.75	28 (6.6)	30 (7.2)
Stroke (yes)	0.29	8 (1.8)	4 (0.9)
Income level ($> \$40,000$)	0.19	294 (70)	317 (75)
Alcohol consumption (≥ 1 drink/day)	0.13	391 (93)	380 (90)
Education (\geq college degree)	0.15	265 (63)	241 (57)
Sleep aid medication (use < 1 night/week)	0.30	370 (88)	360 (85)

Results presented as mean unless otherwise indicated. Significance level for p-value: <0.05. Patients were classified as CPAP adherent if they used CPAP for ≥ 4 hours per night for $\geq 70\%$ of nights.

Authors' contributions

This paper is the original intellectual product of the author, M. Mehrdash, who was responsible for the collection and analysis of data. N. Ayas was involved in the early stages of developing the concept and the design of the study. He also supported concept development throughout the duration of the research and contributed manuscript edits. N. Fox was in charge of ordering the medical charts, recruiting patients and managing the study. B. Peres and A. Hirsch Allen recruited patients, cleaned the data from the medical charts and the health questionnaire, and helped write and edit the manuscript.

Ethical approval: All procedures performed in studies involving

human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Conflict of interest

The authors have declared no conflict of interest.

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Saccades: A window to the brain in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the most common neurodegenerative movement disorder that is becoming more prevalent as the population ages. Currently, the diagnosis is made clinically with a sensitivity of 70–80% and a positive predictive value of 26% in the first three years of disease duration. It can be difficult to differentiate PD from other movement disorders, and evaluating therapeutic response is unreliable. Thus, new clinical tools are needed to aid in the diagnosis and monitoring of disease progression in PD. The complex circuits involved in generating saccades leads to saccadic dysfunction in several neurological disorders, such as PD. This makes saccades a potential biomarker for PD diagnosis and monitoring therapeutic response. PD patients experience low amplitude saccades with increased latency. Voluntary saccades are affected to a larger degree than visually driven saccades. PD patients also have an increased proportion of involuntary reflexive saccades. These saccade parameters relate to motor function, cognition, and change during treatment. Saccades also differ in other movement disorders, helping with disease discrimination. This review focuses on how saccades are normally generated, how they are affected in PD, and how these changes allow us to use saccades as a clinical tool in PD.

Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is becoming more prevalent as the population ages.¹ Currently, the diagnosis is made clinically with a sensitivity of 70–80%² and a positive predictive value of 26% in the first three years of disease.³ It is difficult to differentiate PD from other neurological movement disorders, such as essential tremor (ET), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CDB).^{2,4,5} Objectively characterizing PD progression and therapeutic response is not reliable.⁴ Thus, there is a need to develop reliable and objective tools to diagnose and monitor PD.^{2,6}

Saccades are eye movements that shift our gaze.⁷ Choosing a target to execute a saccade to, while inhibiting reflexive saccades to competing visual stimuli, is important to produce functional eye movements. The complex network allowing us to make purposeful saccades is vulnerable in neurological disorders such as PD.⁸ Saccades are easy, reliable, and cheap to measure using saccadometry, which measures the amplitude, latency, and velocity of saccades.⁷ This review will outline the mechanism of generation of saccades, saccade metric changes in PD, and how saccadometry may be integrated with the diagnosis and evaluation of treatment in PD.

Generation of Saccades

The purpose of saccades is to move the eyes quickly to shift the fovea, the area of the retina with the highest visual acuity, to a visual target at speeds up to 800 °/s (degrees per second).⁷ Reflexive saccades, movements made to visual stimuli, are controlled by cortical areas including the parietal eye field (PEF),⁹ the frontal eye field (FEF),¹⁰ and the supplementary eye field (SEF).¹¹ The PEF creates a saliency map to draw attention to salient visual stimuli and is a prominent region in generating reflexive saccades.⁹ The FEF creates the motor plan,¹² while the SEF modulates the switch from fixating to making a saccade.¹³ Prosaccade tasks, where saccades are made towards a visual stimulus at random locations, are used to study reflexive saccades.¹⁴ Prior to making the saccade, participants look at a fixation point from which they look away with or without a delay.¹⁴ Adding the delay assesses the ability to inhibit reflexive saccades.¹⁴

Voluntary saccades, goal-oriented saccades made without the presence of a visual stimulus,¹⁵ also utilize PEF, SEF, and FEF.¹⁶ In addition, the dorsolateral prefrontal cortex (DLPFC) inhibits unwanted eye movements, and the anterior cingulate gyrus controls motivation and attention.¹⁷ Two tasks used to study voluntary saccades are antisaccades and memory guided saccades. Antisaccade tasks require participants to saccade away from visual stimuli, and assess the ability to make voluntary saccades while inhibiting reflexive saccades towards the stimulus.¹⁸ Memory guided saccades require participants to saccade to remembered target locations and are a good test of memory and executive function.¹⁹

The integration center for reflexive and voluntary saccades is the superior colliculus (SC). To prevent unwanted saccades, the SC is gated by inhibitory neurons of substantia nigra pars reticulata (SNr).⁷ Voluntary saccades require direct communication of cortical brain regions with the striatum of the basal ganglia (BG) once a target is selected. Via the direct pathway, dopamine from substantia nigra pars compacta (SNc) acts on striatal D1 receptors resulting in SNr inhibition. Inhibiting SNr removes inhibition of the SC, allowing a saccade.⁷ Reflexive saccades bypass the BG due to direct PEF connections to SC, summarized in Figure 1.²⁰

Parkinson's Disease: Neurodegenerative and Related Changes

The classical parkinsonian motor symptoms include bradykinesia, muscular rigidity, resting tremor, and postural and gait abnormalities.²¹ There are also non-motor implications of PD, including cognitive and olfactory dysfunctions, psychiatric symptoms, sleep disorders, autonomic dysfunction, and fatigue.²²

The pathological hallmark of PD is the degeneration of dopaminergic cells in the SNc, which is associated with the formation of intraneuronal alpha synuclein aggregates known as Lewy bodies.²³ Depletion of SNc dopamine results in decreased inhibition of the internal globus pallidus (GPi) and SNr. Increased GPi activity increases thalamic inhibition, contributing to motor deficits such as bradykinesia. Increased SNr activity contributes to the saccadic changes in PD through increased SC inhibition. Non-motor symptoms are likely a result of Lewy bodies in the frontal cortex and brainstem nuclei, including the raphe nucleus and locus ceruleus.²⁴ Because the generation of saccades uses similar cortical and subcortical regions involved in both the motor and non-motor symptoms of PD, they are useful in the study of PD.²⁵

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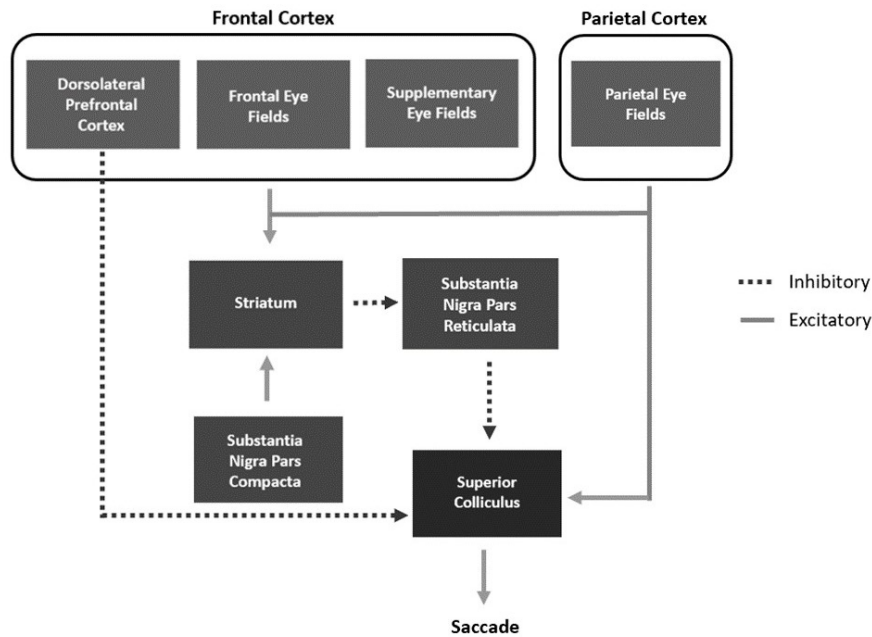


Figure 1 | Neural Generation of Saccades. The generation of saccades requires cortical input from frontal and parietal cortices onto the striatum and directly onto the superior colliculus. For voluntary saccades, the striatum receives excitatory signals from the cortex and substantia nigra pars compacta. The substantia nigra pars reticulata is inhibited, releasing inhibition of the superior colliculus. The dorsolateral prefrontal cortex inhibits the superior colliculus to prevent unwanted saccades. For reflexive saccades, the parietal eye fields have direct excitatory input onto the superior colliculus.

Saccadic Deficits in Parkinson's Disease

There are main observations made in the literature about the control of saccadic eye movements in PD patients:

- Decreased amplitude of saccades;^{14,46}
- Increased reflexive saccades;^{18,32,33,34}
- Increased latency of voluntary saccades;^{14,18,32}
- Impaired memory guided saccades;^{17,18,32} and
- Voluntary saccades are more impaired than reflexive saccades.^{14,18}

Hypometria, or reduced saccadic amplitude, is the most prominent eye movement abnormality.^{14,26} As a result, PD patients make multiple stepwise saccades to reach their target of interest.^{27,28,29} Increased stepwise saccades are likely a consequence of decreased inhibition of the SNr despite cortical input during voluntary tasks and the subsequent increase in SC inhibition.¹⁴ As a result, voluntary saccades are affected earlier in the disease process than reflexive saccades.^{14,30} Saccade amplitude decreases as the disease progresses, and as SC inhibition increases.³¹

PD patients make more reflexive saccades than controls.^{18,32,33,34} In a prosaccade task, PD patients are unable to delay their saccade until the fixation target disappears.^{18,34} In antisaccade tasks, direction errors in the direction of the stimulus are made more often in PD than controls, indicating that reflexive saccades are not suppressed.³³ The lack of reflexive saccade suppression is likely a reflection of impaired inhibition of saccades by the DLPFC as a result of dopaminergic depletion in the prefrontal cortex occurring later in the disease.³⁵ This theory is supported by functional magnetic resonance imaging (fMRI) data showing frontal under activation in PD.³⁶ In addition, fMRI data suggest that parietal overactivation in PD may be a compensatory mechanism resulting in increased reflexive saccades.³⁶ Together, these results explain the increased reflexive saccades, especially later in the disease process.³⁷

Voluntary saccades are impaired more and earlier than reflexive saccades.^{14,18} In tasks requiring PD patients to look away from a target

either immediately or following a delay, they demonstrate longer saccade latencies, more hypometric saccades, and more direction errors than controls.^{14,18,32} They have increased latency and decreased accuracy of memory guided saccades compared to controls.^{17,18,32} This finding is likely because reflexive saccades can largely bypass the BG, whereas voluntary saccades rely on the dopaminergic neurons of the SNc to allow the release of inhibition.¹⁴ A summary of these changes is found in Figure 2.

Clinical Implications

Currently, the diagnosis of PD is clinical and based on the presence of parkinsonian motor features in the absence of features suggestive of another cause.²² The presence of SNc neuronal loss and Lewy bodies in the absence of other pathological evidence satisfies a diagnosis, but can only be determined on autopsy.³⁹ Given the characteristic changes in saccades, they have potential as a biomarker for the diagnosis and treatment evaluation of PD, and may also be a target of treatment.

The amplitude of saccades reflects the motor burden in PD.⁴⁰ Reduced saccadic amplitude is present in both mild and moderate PD,¹⁴ and decreases with worsening motor symptoms.⁴⁰ PD associated changes in saccade amplitude are differentiated from healthy controls with a specificity of 90%, but a sensitivity of only 68%.⁴⁰ Evaluating saccade amplitude may fit the criteria as an ideal test because it correlates well with the Unified Parkinson's Disease Rating Scale (UPDRS) part III, which evaluates motor features.^{40,41}

Saccades can evaluate cognitive deficits related to PD. Intact frontal function is essential to inhibit unwanted saccades.^{14,18,42} Frontal lobe decline seen at the onset of dementia is correlated with saccade dysfunction.^{42,18} Those with PD dementia have more impairment in antisaccade tasks, are less able to correct direction errors, and have increased reflexive saccades than those without dementia.⁴³ Impaired reflexive saccades predict declines in cognitive outcomes over 54 months in PD.⁴⁵ Thus, saccadometry both objectively characterizes cognitive decline and predicts those at risk.⁴⁵

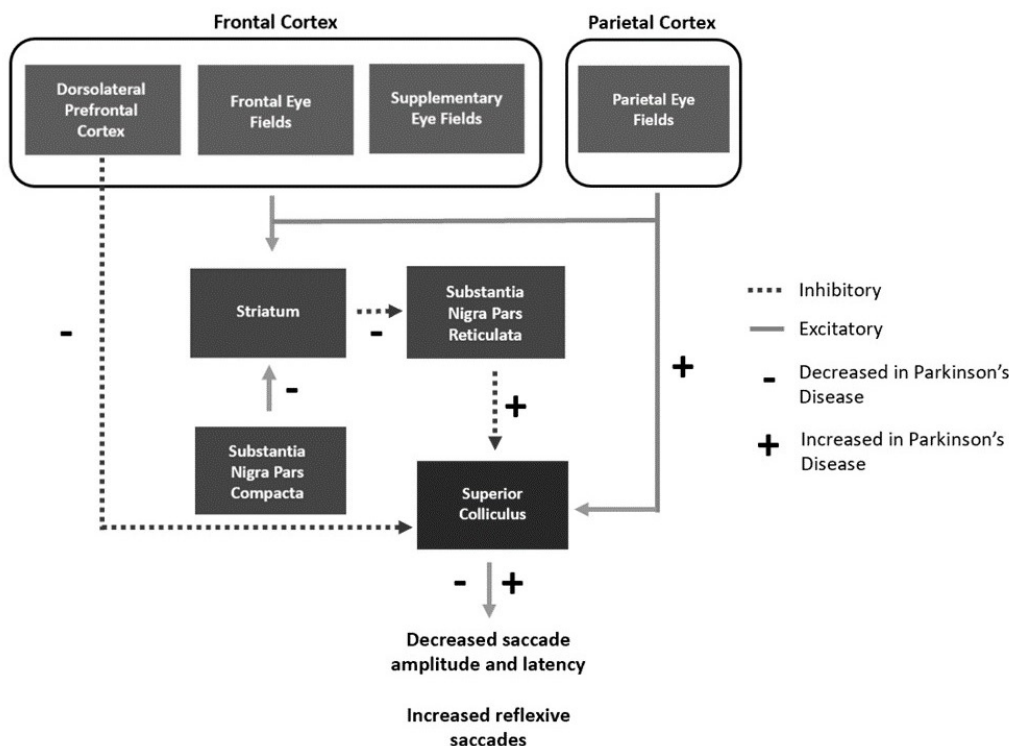


Figure 2 | Changes to Saccades in Parkinson's Disease. In Parkinson's Disease, decreased dopamine from the substantia nigra pars compacta decreases the inhibition on the substantia nigra pars reticulata from the striatum. This increases inhibition of the superior colliculus, causing hypometric saccades with increased latency. Decreased frontal cortex activity, including the dorsolateral prefrontal cortex, decreases inhibition of unwanted saccades. Increased parietal eye field activity increases reflexive saccades.

Abnormalities in saccades help differentiate PD from other movement disorders. For example, while hypometric saccades with increased latency are observed in PD, PSP also has slowed saccade velocity.⁵ The key feature differentiating PSP is that vertical gaze is affected to a larger extent than horizontal gaze.⁴⁵ In CBD, there is increased latency and slow saccade velocity with normal amplitude.⁴⁵ MSA shows both hypermetric and hypometric saccades.⁴⁶ ET is characterized by normal reflexive and antisaccades, but impaired smooth pursuit.⁴⁷ Numerous other eye movement features differ between these neurological disorders, but are beyond the scope of this review.

Saccades may be useful in evaluating PD treatment. Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective tool in improving motor symptoms of PD.⁴⁸ With STN-DBS, there is improved amplitude and accuracy in memory guided saccades and antisaccades, but not reflexive saccades.^{49,50,51} There is also a decreased latency in both voluntary and reflexive saccades.^{53,54} Overall, STN-DBS improves saccade performance, but further research is needed to fully understand the effects of STN-DBS on saccades.

The effects are less clear with carbidopa levodopa (L-dopa), specifically Sinemet, with differing effects on reflexive and voluntary saccades.^{55,56} Discrepancies may be due to L-dopa's effect on the fronto-striatal system⁵⁵ or directly on the SC.⁵⁷ Voluntary saccades benefit with reduced error of antisaccades and shortened latency of memory guided saccades.⁵⁵ However, prosaccades latency increases, showing impairment with reflexive saccades.^{55,56,57} Others report no change in antisaccade latency.^{56,57} Because antisaccade latency is not affected by medication, the correlation with UPDRS part III is significant both on and off medication, and may be of use in evaluating motor symptoms.⁵⁷

Finally, saccades may be a target of treatment in PD as they result in several functional impairments. For example, in tasks where participants search for a target, hypometric saccades lead to decreased search areas.³⁸ Hypometric saccades may interfere with mobility, leading to increased falls, as visual scanning is impaired.⁵⁸ They may also contribute to reading difficulty.^{59,60} Ongoing research is developing saccade training to improve amplitude and latency of saccades and freezing of gait.⁶¹

Conclusions

Saccadic function in PD is compromised such that patients experience hypometric saccades with increased latency and decreased inhibition of unwanted saccades. Voluntary saccades are affected more than reflexive saccades. Saccades show promise in the diagnosis and evaluation of clinical disease, but less is understood about how treatments affect saccades. Limitations to the clinical studies include different saccade task parameters and differential individual responses to treatment. If saccadometry is implemented clinically, further studies must investigate the changes in saccades during different stages of the disease and the response to treatment. Ultimately, the saccadometry shows promise in the evaluation of PD and its treatment, and possibly for other neurological conditions, including Alzheimer's, PSP, MSA, ET, and CBD.^{5,8,62}

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Conflict of interest

The author has declared no conflict of interest.

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Congenital absence of inferior vena cava in a 33-year-old with antiphospholipid antibody syndrome: A case report

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Abstract

Background: Agenesis of the inferior vena cava (AIVC) is a rare disorder that, when combined with co-morbid hypercoagulable disease such as antiphospholipid antibody syndrome (APAS), increases the risk of chronic deep vein thrombosis (DVT). We report a 33-year-old female with a past medical history of recurrent DVTs and antiphospholipid antibody syndrome (APAS) who at the age of 33, was incidentally found to have AIVC while assessing clot burden, which likely contributed to her recurrent DVT episodes earlier in life.

Management: The combination of AIVC and antiphospholipid antibody syndrome is rare and can lead to recurrent DVTs in young patients. Prolonged anticoagulation is the preferred treatment when used in conjunction with the prescription of compression stockings, modification of risk factors, and treatment of further complications.

In this paper we provide a case discussion and up-to-date information on diagnosis and management of a patient with both AIVC and APAS.

Introduction

Congenital anomalies of the inferior vena cava (IVC) in asymptomatic adults are estimated to be present in 0.3% to 0.5% of the population; agenesis of the inferior vena cava (AIVC), one of the many congenital anomalies of the IVC, has an incidence from 0.0005% to 1% in the general population.¹⁻³

In AIVC, the inferior vena cava fails to develop in utero. Poor venous return to the right atrium contributes to the combination of inadequate venous flow, venous hypertension, and thrombophilia, which increases risk of deep vein thrombosis (DVT)⁴⁻⁵ Research suggests that an estimated 5% of patients <30 years of age with an unprovoked DVT also had AIVC.⁴

Patients with AIVC can present with abdominal and lumbar pain, abdominal wall venous dilation, lower extremity swelling with chronic venous insufficiency, and recurrent DVTs.⁶⁻⁸ However, most cases of AIVC are an incidental imaging finding and present in patients with DVTs, thromboembolism, and/or thrombophlebitis.⁹

Thrombophilias are an important underlying etiology of DVTs. One of the well-known thrombophilias is antiphospholipid antibody syndrome (APAS). APAS is an autoimmune condition caused by the presence of antibodies directed towards phospholipids. It is characterized by multiple thromboembolic events, recurrent pregnancy loss, and persistent antiphospholipid antibodies (aPL) on blood testing.¹⁰ In addition, patients with APAS may present with cutaneous manifestations (i.e. livedo reticularis), thrombocytopenia, or transient ischemic attacks.¹¹ Managing APAS involves the treatment and prevention of acute thromboembolic events. Heparin is the preferred therapy in the setting of an acute thromboembolic event. Heparin is then bridged to lifelong warfarin therapy for secondary thrombosis prevention.¹²

Research suggests an interplay between AIVC and thrombophilia in the development of DVTs.¹³ Lambert *et al.* reported the following co-morbid thrombophilias with AIVC in decreasing order: factor V

Leiden heterozygosity (18.6%), heterozygous prothrombin mutation (12.5%), antiphospholipid antibodies (4.8%), and antithrombin (3.8%).¹⁴

We present a case of a young female with long standing APAS and recurrent DVTs who, years later, was diagnosed with AIVC after an acute lower extremity DVT.

Clinical Case

A 33-year-old, non-smoking Caucasian woman with a past medical history of recurrent bilateral lower limb DVTs and antiphospholipid antibody syndrome (APAS) was referred to vascular surgery after an incidental finding of an absent IVC on axial imaging. Her past medical history was also notable for Hirschsprung's disease with colectomy and ileostomy, polycystic ovarian syndrome, psoriasis, and congenital adrenal hyperplasia.

In 2017, the patient suffered an episode of acute left leg swelling and was diagnosed with DVT on doppler ultrasound. At this time, she was taking warfarin for previous DVTs but her INR (international normalized ratio) was not therapeutic. Following the ultrasound, she underwent magnetic resonance imaging (MRI) to characterize the thrombus and investigate the underlying etiology, as the presentation of a young female with recurrent bilateral DVTs was unique. The MRI showed a left common femoral vein and right mid superficial femoral vein thrombosis, and suggested findings of AIVC with extensive venous collateralization. Follow-up computed tomography (CT) of the abdomen and pelvis with contrast showed AIVC with collateralization via the lumbar, azygous, and hemiazygous veins (Fig 1A-C). Enlarged renal veins drained into prominent lumbar veins, which then drained into hepatic veins that converged to form a small length of IVC to the right atrium (Fig. 1C, D). The incidental finding of the infrahepatic AIVC on MRI led to the referral to vascular surgery.

At her vascular surgery consultation, the bilateral leg edema was well managed; she had not had any recent DVTs and her warfarin therapy achieved the therapeutic INR range. On physical exam, she had noticeable collateral pelvic and abdominal veins, but no skin changes of chronic venous insufficiency. Vascular surgery recommended the following: 1) continued long term anticoagulation; 2) no surgical intervention; and 3) return for re-assessment should she develop significant skin changes or debilitating symptoms from leg swelling.

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Discussion

The diagnosis of AIVC is often an incidental finding with imaging or other more invasive procedures such as surgery.¹⁵ In this case presentation, the diagnosis of AIVC was made via axial imaging years after recurrent bilateral DVTs.

The true etiology of AIVC is currently unknown, though there are some theories. In our patient with an infrahepatic AIVC, the underlying etiology is thought to arise from either embryonic dysgenesis at six to eight weeks gestation during the formation of the IVC, and/or intrauterine or perinatal thrombosis.^{3,16–17} There is also an association with renal aplasia, where the IVC may not develop properly due to renal vein thrombosis.^{2,18} The anatomy compensates by increasing collateral venous flow, but this is often not sufficient to prevent chronic venous insufficiency and recurrent DVT.

Imaging is an important tool in the diagnosis of vascular abnormalities. To diagnose DVTs, ultrasound is the gold standard. However, it can be inconsistent in the diagnosis of abdominal vascular abnormalities because the technique is operator dependent and can be affected by increased bowel gas and obesity.¹⁹ In cases where clinical suspicion of an abdominal vascular abnormality is high, CT or MRI is preferred, as seen in our case.¹⁵

When it comes to the management of AIVC and DVT, there are no long-term follow-up studies. Prolonged anticoagulation is the preferred treatment when used in conjunction with the prescription of compression stockings, modification of risk factors (i.e. discontinue oral contraceptive pill, reduce immobilisation, and limit excessive physical exertion), and treatment of further complications. Research suggests limited DVT recurrence with 6–24 months of anticoagulation treatment, but there are reports of recurrence after one and two years of treatment.^{4–5,20} There is no consensus for the duration of anticoagulation therapy, but a minimum of three to six months of anticoagulation should be implemented.¹¹

Surgical therapy can involve venous reconstruction by either prosthetic or autologous tissue bypass, catheter directed thrombolysis, and surgical thrombectomy.¹⁵ For definitive treatment, surgical reconstruction is indicated in patients with persistent severe symptoms and extreme venous insufficiency that is refractory to medical therapy.¹⁵

Our patient had both a known hypercoagulable disease, APAS, and an anatomical variant (AIVC), increasing the overall likelihood of thrombosis. The diagnosis of AIVC was not made earlier despite recurrent bilateral DVTs, presumably due to APAS being considered the original etiology of the DVTs. Given that the patient had extensive collateral blood flow from the azygous and hemiazygous vasculature, as well as adequate medical control of her chronic venous insufficiency, the patient was discharged on long-term anticoagulation and compression stockings.

Conclusions

We report a case of a young female with recurrent DVTs that were caused by a combination of AIVC and APAS. The APAS was diagnosed early, and no further imaging was performed to explain her recurrent DVTs. There is currently no evidence to support the need for lifelong anticoagulation in AIVC. Further studies are needed to determine the need for prolonged anticoagulation for patients with AIVC who develop DVT. Prolonged anticoagulation is the preferred treatment, while surgical reconstruction is indicated in patients with persistent severe symptoms refractory to medical therapy.

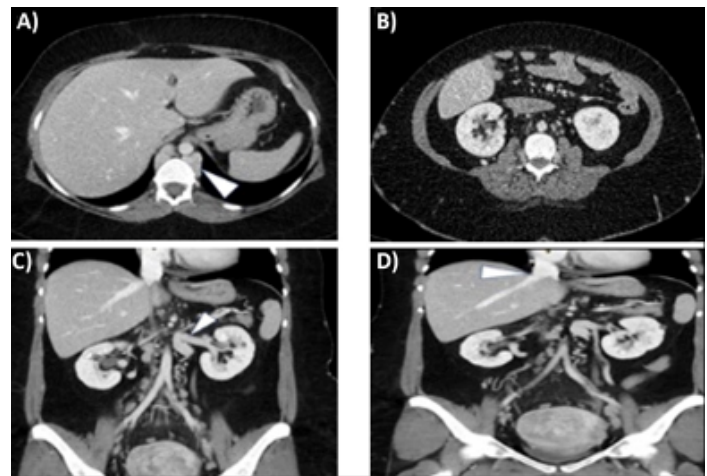


Figure 1 | Abdominal computed tomography (CT) with contrast (A) Axial CT scan demonstrating the dilated azygous and hemiazygos veins (arrowhead). (B) Axial CT scan demonstrating the AIVC. (C) Coronal CT scan demonstrating the renal veins draining into the lumbar veins (arrowhead). (D) Coronal CT scan showing the hepatic veins converging to form a short portion of the suprahepatic IVC entering the right atrium (arrowhead).

Conflict of interest

The authors have declared no conflict of interest.

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A method of facilitating medical student engagement with local Indigenous communities

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Abstract

In order to mutually benefit both the Indigenous population and medical students, the Indigenous Health Representatives of the UBC Island Medical Program designed and implemented a series of monthly workshops on two topics (diabetes health and adolescent health) for the Victoria Native Friendship Centre (VNFC). Workshops were student-led in conjunction with the VNFC staff and other local healthcare professionals, including nurses, physicians, and nutritionists. Specifically, the diabetes workshops entailed a group discussion around various topics related to diabetes, such as nutrition, footcare, wound care, and pathophysiology to name a few. Additionally, community members accompanied by a medical student would sequentially visit a footcare nurse to receive footcare. The youth health workshops focused on group engagement on topics related to sexual health, alcohol, marijuana, healthy teen habits, stress management, healthy relationships, and self-compassion. This method of engagement was deemed beneficial to community members by providing education and resources that were in need. In summary, we offer our model that engages medical students with a local Indigenous community in hopes of guiding other programs that support medical students in building relationships in their community.

Introduction

There are multiple synonyms used for the term Indigenous Health Representative (IHR) throughout Canadian medical schools, such as Indigenous Health Officer or Local Officer of Indigenous Health.¹ Fundamentally, the purpose of this role is to facilitate programs engaging medical students with Indigenous communities, thereby bringing reconciliation to healthcare. Recognizing the history of colonialism, it is prudent to specify that the IHR position is granted to one student per class who has shown a strong history of working with Indigenous community members and a commitment to improving the health for Indigenous people. By acknowledging the Truth and Reconciliation Commission of Canada (TRC) of 2015, the University of British Columbia (UBC) recognizes the importance of selecting candidates who have Indigenous ancestry, highlighting the importance of Indigenous voices representing the Indigenous population. The objectives of this role are not often explicitly defined, offering an innovative opportunity for those who hold the position. Here, we share our efforts as IHRs as they apply to medical schools nationwide. The purpose of this commentary is to illustrate one possible methodology that medical students can use while attempting to engage with their local Indigenous community.

The 94 Calls to Action created by the TRC recognize the significance of Indigenous people in healthcare leadership positions and the need to advocate for change within healthcare for Indigenous people. Richmond and Cook state accurately in their report: “systematic change cannot be achieved by a group of advocates; it is a shared responsibility that will require the collaboration and integration of various actors and knowledges.”² Inspired by this statement, the IHRs from the UBC Island Medical Program (IMP) undertook an initiative to foster engagement between medical students and the local urban Indigenous community. The Victoria Native Friendship Centre (VNFC) is one of 118 nationwide Friendship Centres.³ Friendship

Centres began in the 1950s and serve as an urban-based resource for urban Indigenous people to access various services and supports, as well as to create connections with community.³ This initiative involved the development and delivery of footcare and diabetes workshops within the adult population and youth health workshops at the youth drop-in program. This community-driven program is an IMP student-led initiative that started with an inspiration from students wanting to engage with the community to enhance learning, while giving back to the community. Since all UBC extracurricular activities must be supervised by a UBC Faculty of Medicine staff member, the IHRs sought out an Indigenous staff member who works closely with the health of Indigenous people and communities.

To highlight the importance of sharing our methodology of engagement with community, we turn to the TRC that created 94 Calls to Action to properly address the reconciliation process in Canada. The TRC recognizes the significance of Indigenous people in healthcare leadership positions and the need to advocate for change within healthcare for Indigenous people. Richmond and Cook state accurately in their report: “systematic change can not be achieved by a group of advocates; it is a shared responsibility that will require the collaboration and integration of various actors and knowledges.”³

The decisions that directed the path of both of our initiatives were guided by the needs within the community observed by the VNFC healthcare team members. In our experience, there was an expressed need for footcare in the context of diabetes and a desire for health-related education within the youth drop-in centre, a need also expressed extensively in the literature. In Canada, the prevalence of Type 2 Diabetes is exceedingly greater in the Indigenous population compared to the non-Indigenous population.⁴⁻⁶ To illustrate this disproportion, the rate of diabetes for on-reserve First Nation members is approximately 17.2%, for off-reserve First Nation members is 10.3%, and for Metis is 7.3%. This is compared to a 5% rate for non-Indigenous people in Canada.⁷ For those living with diabetes, 14–24% must manage the burden of complications from foot ulcers and lower leg amputations.⁸⁻⁹ It is recommended that those with diabetes should have their feet examined at least once per year.¹⁰⁻¹¹

The programming delivered to the youth department also helped address a gap in services for Indigenous youth. Expressed in the TRC,

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there is a need for more resources for the health and well-being of Indigenous youth across Canada. Challenges that many Indigenous youth face are in areas of mental health, physical health, health-related behaviours, and education.¹² In Canada, more than 25% of Indigenous youth report at least a two-week period of depressive symptoms in a single year and 10% of Indigenous youth had thoughts of suicide by age 12 which then increased to 30% by age 17. Additionally, less than half (45%) of Indigenous youth are obtaining the recommended 30 minutes of moderate to vigorous activity most days of the week and two-thirds (66.5%) are not acquiring a well-rounded nutritious diet.¹² Supporting youth to participate in cultural activities and physical activity is important in improving their overall health and well-being. Furthermore, youth resilience is strengthened when cultural awareness and having a positive self-identity are encouraged.^{12,13}

A Method of Engagement

The main goal of our work with the community was to first build and foster a mutually beneficial relationship between students at the IMP and the health team at the VNFC, which would allow students to learn Indigenous perspectives while contributing to a much-needed service in the community. Scientific research was not an objective of this initiative; rather, we wanted to provide support for improved programming at the VNFC, as well as share our methods to help guide future medical students who want to pursue similar initiatives.

The model used to launch our workshops series primarily relied on collaborations between medical students and VNFC staff to facilitate community-driven decision-making (Figure 1). It is imperative that students who wish to engage with community understand what community-driven decision-making means. The IHR first reached out to the VNFC’s health team lead to voice their intention to work with the VNFC to address a gap in care that is decided by the community. To

facilitate this, a health team meeting was arranged that included social workers, health support workers, the physician supervising the medical students on the project, the youth health team lead, and the Aboriginal diabetes nurse educator for the community. The focus of the meetings was to hear the interests of the VNFC staff and provide space for them to make decisions on the direction of the workshops. Additionally, to get a wider community perspective, the healthcare support worker spoke with multiple community members to inquire about possible needs that were felt to be unmet by the community. Methods to do this included open discussion and anonymous survey completion led by the healthcare team. Ethics approval for this initiative was not required and, therefore, not acquired. Descriptions of the two workshops are outlined in Table 1.

Goals and objectives of the workshops were developed with community consultation, including the need for a budget. Timeline and frequency of workshops were determined based on community need and student availability. The details of the workshop content and curriculum were discussed by the community health team and the medical students; however, the ultimate decisions were determined by the community. For the footcare and diabetes workshops, the community’s nutritionist, diabetes nurse educator, and health support workers were all at the decision-making table for the direction of the workshops (e.g., diabetes education topics to discuss, length of footcare sessions per participant, number of participants per workshops, methods of advertisement, and items in the self-care take-home bags). For the youth health workshops, the youth team lead decided on all the topics to cover. Prior to both workshops, students would provide the health team leaders with a proposed outline and details of the workshop to be delivered in order to gain feedback or make revisions before the workshops.

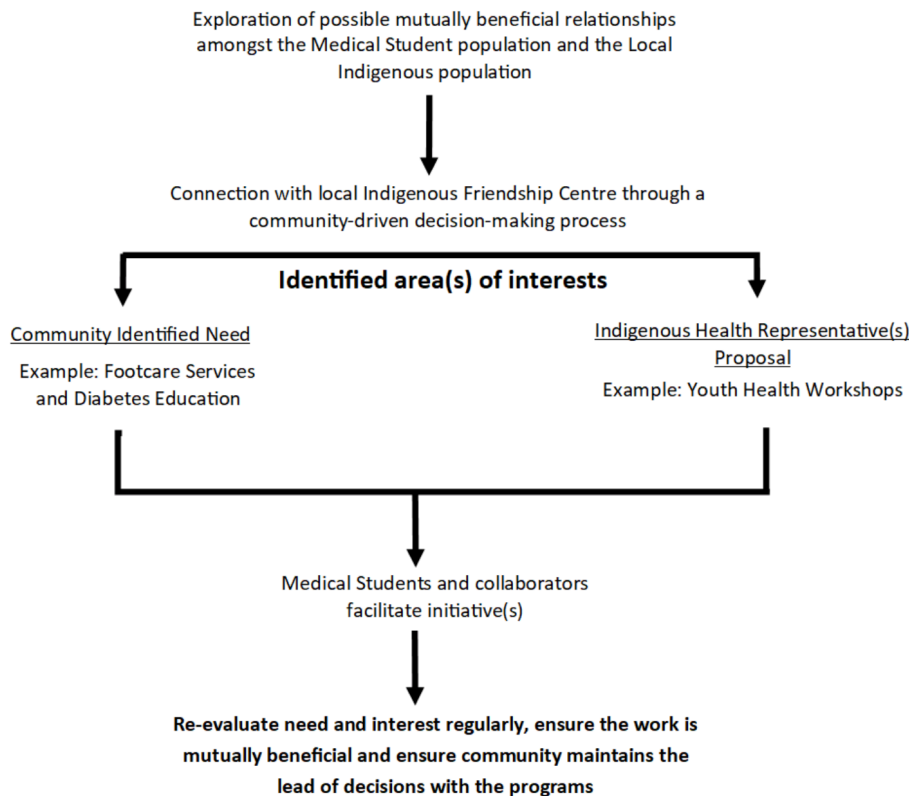


Figure 1 | A method to facilitate medical student and community engagement via a local Native Friendship Centre.

Given that footcare and diabetes education was a community-identified need, our team hosted monthly diabetic-focused workshops to provide footcare and education. In a similar manner, monthly youth health workshops were conducted with the VNFC afterschool program. Volunteer IMP students created and delivered the youth health workshops on topics chosen by the VNFC youth staff. The VNFC youth staff were engaged in the workshop by supervising and providing real-time input. This made it a collaborative process between the volunteer IMP students who brought medical information to the workshop, and the VNFC youth staff who shared related experiences and advice based on their understanding of what is most relevant and useful to the Indigenous youth. These two workshops fostered engagement between medical students and community members.

We also engaged the community by having the VNFC advertise on our behalf. This included advertisements via the VNFC's monthly newsletter, the drop-in monthly schedule, a paper advertisement at the health centre's main office, and through word-of-mouth when staff worked directly with community members. The advertisement posters were created by the IMP IHRs with input from the VNFC staff. This emphasizes how engagement with community is a team effort with both the IMP IHRs and the VNFC being advocates for the workshops.

Table 1 | Details of two workshops conducted at Victoria Native Friendship Centre in collaboration with Island Medical Program Indigenous Health Representatives.

	Adult Diabetes-focused Workshops	Youth Health & Wellness Workshops
Program Start–End Date	Sept 2018 – Present	Sept 2018 – Jan 2020
Workshop Frequency and Duration	6–8 workshops per year, 2 hour duration	5–6 workshops per year, 1 hour duration
Topics of Discussion	Footcare tools, prevention of ulcers, at-home footcare, diabetes nutrition, and blood sugar management	Sexual health, drugs & alcohol, healthy teen habits, coping with stress, healthy relationships, and self-compassion
Workshop Delivery Methods and Resources	Group circle discussions and individual 1:1 footcare treatment with footcare nurse	Icebreaker games, short video clips, handouts that highlighted key messages, interactive activities (e.g., Bingo with prizes), and PowerPoint presentations
Medical Student Involvement	Year 1 and 2 medical students joined in group discussion and accompanied community members during footcare	Each workshop was created with extensive research into the topic and subsequently delivered by 2–3 students
Funding	Covered costs of footcare and basic footcare supplies for participants to take home (e.g., lotions, socks)	Students covered costs of small snacks/treats for youth participation

Medical Student Experience

During the diabetes-focused workshops, medical students accompanied community members while they received their clinical footcare. In this setting, they were able to engage with Indigenous people living with diabetes and learn about complications from the disease first-hand. The students appreciated the opportunity to directly connect with Indigenous community members and resources such as the VNFC. In total, approximately a quarter of two IMP cohorts (Class of 2021 and 2022) attended at least one workshop.

Youth health workshops offered volunteer IMP students the opportunity to create and deliver workshops on topics of importance to Indigenous youth and themselves. The IHRs instructed the VNFC youth drop-in coordinators to ask their youth what health topics they wanted workshops on and to report this information back to the IHRs. The IHRs presented the list of topics to the IMP students who selected a topic on the list that interested them the most, and thus learned about that topic further by creating and delivering a workshop about it. Medical students also gained valuable information about the resources available for Indigenous youth in the community from the youth drop-in coordinators. One challenge that some workshop providers reported was difficulty keeping the youth engaged for the full workshop duration. This challenge was addressed by shortening the workshops to 45–60 minutes down from the original 120 minutes. Additionally, allowing for an open-structure natural flow workshop that included breaks and time for free discussion improved engagement. Overall, based on verbal feedback, all the medical students involved had a positive experience.

Community Member Experience: Diabetes-focused Workshops

The community members expressed appreciation for the workshops. Of all the community members who attended a workshop, half returned for another session. Furthermore, this new service attracted members of the local Indigenous community who had never used VNFC services before. These new members were introduced to the plethora of additional community and healthcare services available that were previously unknown to them. This outcome demonstrates the positive impact of holding workshops at community centres where the health team can promote awareness of other services offered to participants. Challenges we faced included securing consistent turnout for community members, students, and nurses.

Youth Experience: Youth Health Workshops

Observationally, the youth were actively and enthusiastically engaged to discuss the health topics presented at the different workshops. The active engagement included sharing stories and asking questions. The Youth Drop-In Coordinator has welcomed IMP students back for another year of monthly workshops on similar topics.

Conclusion

Friendship Centres offer a well-rounded community connection for IHRs as they geographically co-exist with nearly every Canadian medical school and host a variety of health-related programs. Student-led workshops are a feasible and mutually beneficial opportunity to facilitate community engagement and aid in supporting the TRC's Calls to Action. The diabetes-focused workshops even drew new members to the VNFC, enabling them to learn about other services that are freely available. The summary of the program and this report was discussed and shared with the VNFC Healthcare team.

Recommendations

During workshop development, consider the following:

1. Communicate closely with the Indigenous community to identify topics of interest and need;
2. Consider factors that may affect participant turnout—these factors are best learned by asking the healthcare team in the community;
3. Identify funding sources if needed; and
4. Identify a feasible, flexible and dynamic workshop format with feedback from the community healthcare team.

When conducting workshops, we recommend focusing on relationship building that encompasses trust, continuity, respect, and patience.

Acknowledgements

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Conflict of interest

The authors have declared no conflict of interest.

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Considering the integration of cannabis into conventional chronic pain management strategies

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Abstract

Opioids are commonly used as analgesics. However, with a recent surge in opioid related overdoses and deaths it is apparent that alternative chronic pain management strategies are required. Cannabis is a promising alternative therapy. Modifiable dosing paradigms have been proposed in which cannabis reduces the opioid dose required while maintaining the analgesic benefits when administered in combination with opioids; this is referred to as the “opioid-sparing effect.” However, even with detailed dosing regimens and promising results, cannabis has not been incorporated into preexisting pain management strategies. Moving forward, clinicians should be encouraged to integrate cannabis into their pain management paradigm.

Chronic pain afflicts 20% of Canadians, and half of these individuals have lived with chronic pain for ten or more years.¹ Millions of Canadians struggle with chronic pain every day and its effects are pervasive. It lowers one’s physical, social, and mental functioning, which adversely affects one’s quality of life^{2,3} and increases the risk of suicide.³ Although many interventions exist for pain management, opioids’ notorious use as analgesics has been under scrutiny in recent years. Due to its greater accessibility, a surge in opioid-related overdoses causing increased hospitalizations and mortalities has drawn media attention and widespread public outcry over the dangers of opioid use.¹ While opioids are very effective in treating severe acute and chronic pain, both short-term and long-term use can result in deleterious health effects^{4,5} in addition to hyperalgesia, addiction, tolerance,^{5,6} overdose, and even death.^{1,7} It is apparent that alternative strategies in managing chronic pain are desperately required. One therapy being explored is the use of cannabis for chronic pain management. Multiple sources of evidence support the analgesic efficacy of cannabis and suggest that chronic neuropathic⁸⁻¹⁰ and musculoskeletal pain¹¹ may be successfully managed with cannabis. Given its efficacious therapeutic results and a need for safer alternatives to opioids for pain management, cannabis can ameliorate the treatment of chronic pain and positively impact the lives of its sufferers.

Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two most abundant cannabinoids extracted from cannabis.¹² THC has been effective in alleviating pain, nausea, and symptoms of anxiety and depression.¹² However, THC is associated with many of the adverse effects of cannabis use, as THC is intoxicating, impairing, and addictive.¹² CBD provides similar benefits in addition to its anti-convulsant, anti-psychotic, anti-inflammatory, and neuroprotective properties.¹² Unlike THC, CBD is non-intoxicating and balances the effects of THC by lowering the risk of adverse effects caused by THC while increasing the maximum THC dose tolerated.¹² Additionally, there is a lower risk of adverse events with CBD.¹²

As chronic pain becomes the most prevalent motive for cannabis use in individuals with primary illnesses,¹³ a better understanding

of cannabis and its dosing procedures is required due to the relative lack of knowledge among clinicians towards cannabis dosing for patients.¹² Previous research indicates that cannabis dosing is unique to the individual,^{8,12} however, generalized dosing paradigms have been proposed and may be modified to better serve the unique requirements of the recipient. Researchers promote a “start-low, go-slow”¹⁴ approach and recommend administering 5–10 mg of CBD twice a day, increasing the dose weekly until the pain is relieved.¹⁴ Should CBD be unable to achieve this result alone, 1–2.5 mg of THC should be added to the dosing regimen and gradually increased until pain relief is achieved.¹⁴

Although the dangers of cannabis use are an area of ongoing research, short-term⁸⁻¹¹ and long-term¹⁵⁻¹⁷ risks have been documented. Short-term adverse events are usually mild to moderate in severity¹⁰ and are generally well tolerated by individuals.^{8,9,11} Common effects include dizziness, drowsiness, nausea, dry mouth, and euphoria.⁸⁻¹¹ However, research suggests that the risk of such unfavorable events can be reduced if daily THC dosages do not exceed 30 mg.¹² Long-term risks associated with cannabis usage are not comprehensively researched; most trials have been short in duration with small sample sizes and have exclusively outlined short-term consequences. Chronic long-term effects include cannabinoid hyperemesis syndrome (CHS). Symptoms of CHS include severe, cyclic nausea and vomiting that is accompanied by abdominal discomfort.¹⁵ Cannabis use disorder (CUD) characterized by dependency, respiratory issues, psychological and social distress is another concern.¹⁶ Additionally, there is inconclusive evidence on the correlation between prolonged cannabis usage and psychosis.¹⁷ Previous research has found that higher cannabis dosages do not result in greater pain alleviation.⁹ Furthermore, unlike opioids, the same dose of cannabis can be maintained without the development of tolerance to its medicinal benefits.¹⁸ This supports that the “start-low, go-slow” paradigm, involving the administration of CBD while maintaining minimal THC dosages, is a favorable approach to dosing, as it may reduce the incidence of some of the cannabis-associated risks.¹²

Before cannabis can be solely prescribed to target chronic pain, more thorough studies are required to gain better understandings of the long-term consequences and administration regimen. Currently, the preeminent pain management proposal suggests that cannabis can be administered in conjunction with opioids.¹⁴ When cannabis is administered concurrently with opioids, it reduces the opioid dose required while maintaining the analgesic benefits; this is referred to as

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the “opioid-sparing effect.”¹⁹ A meta-analysis investigating the effect of THC when simultaneously administered along opioids such as morphine (MS Contin) and codeine (Codeine Sulfate) found that on average, the opioid dose was reduced by 3.6 and 9.5 times respectively, and individuals still benefited from pain reduction.¹⁹ However, even with promising results and proposed dosing regimens, cannabis has not been integrated into preexisting chronic pain management strategies. One integrative approach is encouraging the liaison between physicians and pharmacists. Pharmacists possess specialized knowledge in pharmacology and drug interactions, which can be utilized to develop personalized and safe dispensing of cannabis to sufferers of chronic pain.²⁰ Undoubtedly, there is a critical need for safer alternatives to opioids for pain management. Moving forward, it will be essential for clinicians to be educated on the analgesic properties of cannabis, with support for collaboration between healthcare professionals to encourage integration.

Cannabis is challenging the traditional pain management paradigm that generally implicates opioids. Chronic pain afflicts millions of Canadians,¹ and as the dangers of opioid use become apparent, it is undeniable that alternative analgesic strategies are needed. Cannabis reduces the opioid dose required while maintaining the pain-alleviating benefits via the “opioid-sparing effect,”¹⁹ and viable cannabis dosing paradigms have been detailed.¹⁴ While currently-available research presents promising results,^{8–11} trials have been short in duration with small sample sizes. Further investigating the long-term analgesic efficacy and consequences of cannabis use is a worthwhile pursuit for researchers. Moving forward, long-term, blinded, randomized control trials with larger sample sizes should be conducted. With results indicating potential benefits, cannabis can improve the treatment of chronic pain and the outcomes of its sufferers.

Conflict of interest

The author has declared no conflict of interest.

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20/20 in 2020: Restoring vision by addressing the cataract backlog

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Abstract

Cataract is the leading cause of blindness in the world and remains a large issue for developing countries. With an aging and growing population, the number of individuals affected by cataracts is steadily increasing. Consequently, there is an ever-increasing backlog of untreated cataracts, particularly in developing countries, leaving millions blind. In order to address such a complex global health issue, it is imperative to take a multifaceted approach. In our commentary, we discuss major barriers, such as cost, transportation, lack of trained medical personnel, lack of infrastructure, and gaps in training. We also discuss strategies that can help reduce the backlog, such as utilizing cost-effective surgical techniques, increasing awareness, risk factor reduction, unique payment strategies, as well as highlighting models that have worked in the past. We believe with the right approach and support millions of people can have their vision restored.

Vision plays a paramount role in our everyday lives, as it not only allows us to perceive the external environment, but also greatly facilitates our ability to execute fundamental tasks. As such, the negative implications of vision loss are substantial, as it can adversely affect various domains, such as education, employment, and functional independence. There are currently 2.2 billion people that are visually impaired¹ and almost half of these cases could have been prevented or are yet to be addressed.² An estimated 90% of the world's visually impaired reside in developing countries.³⁻⁵ Cataract is the leading cause of blindness globally with over 20 million people bilaterally blind.⁶ A cataract is a clouding of the lens in the eye that progressively leads to decreased vision.⁷ With an aging and growing population, it is projected that the number of individuals affected by cataract will dramatically increase.⁸ As such, there is an ever-increasing backlog of untreated cataracts leaving millions blind, predominantly in developing countries. Tackling such a complex global health issue requires a comprehensive and multifaceted approach to address all areas of concern.

There are a number of barriers that prevent individuals in developing countries from receiving cataract surgery.^{9,10} Cost still remains at the forefront of this issue with many people not being able to afford surgery.^{9,10} There are also a number of nonsurgical costs, such as transportation to the hospital and receiving time off work. Strategies to mitigate this problem include decreasing the cost of surgery by reducing the cost of equipment and supplies, implementing unique pricing strategies so that low-income individuals can make smaller payments over time, and reducing non-surgical costs.^{9,12}

Choosing an appropriate surgical technique is another strategy to reduce overall cost. Techniques have evolved significantly from intracapsular cataract extraction (ICCE), which involves complete removal of the lens, as well as lens capsule and extracapsular cataract extraction (ECCE) in which the lens is removed but the capsule is preserved.¹³ Phacoemulsification was later introduced as an alternative to ECCE and is now considered the safest and preferred treatment in developed countries.¹³ Phacoemulsification uses an ultrasound-driven needle to emulsify the cataract and suction it through a much smaller incision in the eye.^{13,14} Although phacoemulsification is highly effective and the preferred surgery in the developed world, it accounts for only

10% of surgeries in developing countries, given the higher cost and steeper learning curve.^{15,16} In the developing world where a cheaper and more efficient procedure is needed, manual small incision cataract surgery (MSICS) is principally employed.¹⁷ MSICS is a sutureless procedure where a 6–6.5 mm scleral incision is made, followed by manual removal of the cataractous lens and insertion of a small (6 mm) rigid intraocular lens.¹⁸ In comparison to phacoemulsification, MSICS is a relatively safe and easy-to-learn procedure that is considerably faster (can be performed in 5 minutes), less expensive, and less dependent on technology.^{18,19} Although this technique has been demonstrated to be essentially as effective as phacoemulsification, it has been found to be associated with higher rates of astigmatism and worse uncorrected and best corrected visual acuity.^{19,20} Given the overall advantages of MSICS, it is imperative that surgeons are adequately trained in this procedure and that the necessary equipment and resources are available. A proposed intervention that could address the need for a comprehensive training system is the development and use of fully immersive, physics-based surgical training simulators that can be easily scaled for MSICS, similar to those that have been developed and evaluated for phacoemulsification.^{21,22}

Moreover, public health efforts need to be more focused towards human resource development. Currently, there is a clear discrepancy in the proportion of ophthalmologists per capita between developed and developing countries. For example, in Ethiopia there are five ophthalmologists per million individuals compared to approximately 111 per million individuals in France.¹² In 1999, the World Health Organization launched VISION 2020 which was a global initiative aimed at eliminating preventable and treatable blindness by the year 2020.²⁴ VISION 2020 assigned a target cataract surgical rate (CSR) of 2000–3000 surgeries per million individuals per year for countries in sub-Saharan Africa. However, with a limited number of personnel, many of these countries have failed to reach a CSR above 1000.¹³ Therefore, one critical step is to train more ophthalmologists, optometrists, technicians, and nurses in these areas which may be achieved through specifically targeted allocation of funds and resources. This could help increase the number of health professionals per capita, as well as increase the current CSR.

Beyond the crucial need for more eye care centers, another issue is the inefficient utilization of existing infrastructure and resources. For example, individual surgeon productivity in Sub-Saharan Africa is generally low, with a mean of 188 cataract surgeries per year, when realistically, a surgeon could comfortably perform up to 800 per year.^{26,27} This is also reflected in a study evaluating productivity in

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Southern Ethiopia, where cataract surgical resources were consistently underutilized at an average of 56% of capacity throughout the region.²⁸ This could be attributed to lack of funding, shortages in trained personnel and staff to run centers, as well as an unsteady supply of patients due to ineffective recruitment, awareness, and lack of transportation.^{28,29}

Preventative measures also need to be taken by increasing overall awareness of the issue and tackling cataract risk factors, such as cigarette smoking, ultraviolet light exposure, diabetes mellitus, and a high body mass index.⁶ Although many of the aforementioned strategies are quite costly, it is estimated that every dollar invested in eliminating avoidable blindness and visual impairment generates a fourfold return.³⁰ This reflects the increased number of people returning to the workforce, increased productivity, avoided comorbidities, and direct saving to the healthcare system.

The Aravind Eye Hospital in India is a great model that many developing countries could follow in order to tackle the cataract backlog.³¹ Their high-volume low-cost model is based on community involvement, screening eye camps, efficient utilization of medical staff, and patient education.^{31,32} A key strategy they use is efficient and comprehensive screening camps that are done directly in rural communities. With the help of volunteers, these camps are made to be efficient and can help mitigate any cost of travel while identifying patients in need. After screening, patients who require surgery are transported on the same day to the hospital to receive cataract surgery at no charge.

In our continual pursuit of addressing the causes and implications of global blindness, it is imperative to develop and focus on cost-effective interventions, particularly in developing nations. Many of the barriers these countries face pertain to resource development and allocation, funding, awareness, and inadequate use of existing infrastructure. Effectively addressing the cataract backlog has innumerable benefits, not only for afflicted individuals, but also for the communities and economies they are tied to. Ideally, this would involve developing resources and infrastructure with the objective of making MSICS accessible and affordable for all. India serves as a prime example of a country that has made strides in this concern and we hope that within the coming years, other developing countries adopt similar models and practices. We believe that every human deserves the right to sight. With the various strategies discussed along with increased government and non-government organization support, we can make great strides towards tackling the cataract backlog and restoring the vision of millions of people.

Conflict of interest

The authors have declared no conflict of interest.

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Pilot project: A peer-led basic life support training program for UBC medical students

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Abstract

Basic Life Support (BLS) training is mandatory for all medical students. Typically, students receive certification through private organizations, providing challenges with cost and availability. Peer-led BLS training is established in the literature as effective and beneficial to increase engagement and relevance. A peer-led BLS training program was established at the University of British Columbia (UBC), with the goals of decreasing course costs, increasing exposure to simulation labs, and providing a teaching opportunity for medical students. Two UBC medical students were certified as BLS instructors and taught courses for first- and second-year medical students at university-affiliated simulation centres. Both peer instructors and participants benefited from the program.

Background and Project Rationale

Basic Life Support (BLS) is the foundation for saving lives after cardiac arrest. All healthcare professionals, including medical students, are required to maintain up-to-date certification in BLS. Currently, medical students obtain their yearly certification through private organizations who charge \$60 to \$90 per course.¹⁻² This is a significant financial burden on medical students. However, in the hospital setting, this is mitigated by certifying staff members as BLS instructors to train and renew their colleagues' BLS certifications. This common practice in hospitals creates a sustainable and cost-effective way to maintain staff certification, while ensuring that staff are confident in their basic resuscitation skills.

The peer-led BLS training program at the University of British Columbia (UBC) was established with the desire to provide convenient low-cost BLS certification for medical students while providing an opportunity to support collegial learning. In the literature, peer-led BLS training programs have been implemented in medical schools in England, Japan, and Syria and compared to professional-led BLS training.³⁻⁵ Each study found that peer-led BLS was at least as effective as professional-led courses and have actually shown improved long-term knowledge retention. As well, students reported a safer and more relatable learning environment when taught by peers.⁵ Furthermore, the student instructors were provided a leadership role and an opportunity to strengthen their own BLS skills through teaching. We also strived to make the course more relevant for medical students by running sessions at university-affiliated simulation centres.

The peer-led BLS training initiative aimed to substantially reduce course costs, provide an evidence-based educational experience, increase exposure to simulation labs and scenarios, and provide students an opportunity to teach these skills to peers.

The Program

Two second-year medical students undertook the initiative, with guidance from an emergency medicine physician and UBC Faculty of Medicine member. In July 2019, the students completed a two-day Heart and Stroke Foundation (HSF) BLS Instructor Course plus course monitoring by a HSF-certified instructor. After completion and official certification, the students were qualified to carry out full and renewal BLS courses independently (Figure 1).

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The peer instructors volunteered to organize and teach full-length and renewal BLS courses for UBC medical students at the Vancouver-Fraser and Island Medical Program sites. The courses were run at university-affiliated simulation centres with high-fidelity manikins and common medical equipment used by students during clinical rotations. Each course consisted of video-based instruction, hands-on teaching, and skills practice, followed by a written and practical exam. A 'Code Blue' team-based simulation was incorporated into the course. Each student was charged \$10, which covered their HSF registration (\$3.50 per student) and instructor fees (\$75 annual fee). An anonymous post-course survey was developed and administered to students by email for quality improvement.

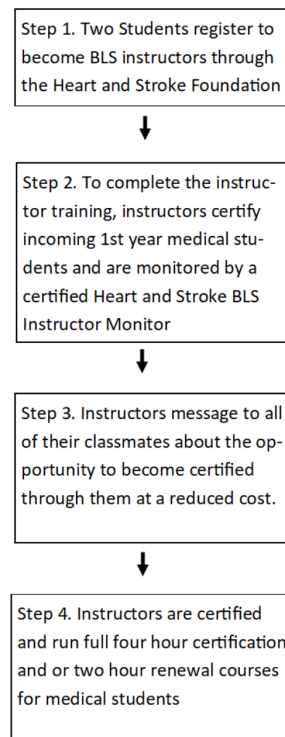


Figure 1 | Linear algorithm for launching a peer-led medical student BLS program.

Feasibility and Student Response

Overall, this pilot project showed proof-of-concept that a peer-led BLS program can be coordinated by peer instructors, implemented within months, and delivered to meet demand among medical students. Since July 2019, eight courses were taught, training 41 students total.

Students paid approximately 88% less than professional-led courses.¹⁻² When asked for feedback to compare to professional-led courses, students reported that peer instructors increased engagement levels and the use of high-fidelity manikins in a simulation room improved practicality. Furthermore, 93% of students who responded to the post-course survey indicated that they would recommend the course to a colleague and suggested expanding the initiative. Listed below are a few quotes from the student survey that identified the program's strengths:

"Extensive use of simulations is very helpful"

"Taught by peers for peers. Sustainable (hopefully). Cost-effective"

"Very engaging, specifically applicable to [medical] students"

"I also loved that it was a peer [leading the course] who understands our level of knowledge"

Overall, peer-led BLS certification for medical students is a cost-effective program that students found relevant and valuable.

Impact on Medical Students Being Certified

Early exposure in preclinical years to high-fidelity manikins and simulation has been shown to be effective at improving knowledge consolidation and growing confidence.⁶⁻⁷ However, prior to the BLS course, the majority of medical students in first- and second-year had no experience in a simulation lab. Using the high-fidelity manikins, students were able to feel for pulses, assess for chest rise, and practice performing on manikins lying on real hospital stretchers. The manikins contain feedback devices, which allowed students to monitor the rate and depth of their CPR, in addition to the time between shocks, breaths, and chest compressions. Real-time monitoring ensured students were performing quality CPR.⁸

Students were also provided a safe and personalized learning environment. Peer teaching creates a relaxed and accepting atmosphere, while giving the flexibility to customize the course to their peers' needs.

Impact on Medical Students as Peer Instructors

In addition to strengthening their own BLS skills, the peer instructors gained valuable teaching and facilitation skills. Teaching falls under the "Leader" CanMEDS competency and is expected to improve throughout residency.⁹ Each course involved a ratio of one teacher to six students, which required skills to teach a group and manage time effectively. Through teaching and evaluating the CPR and AED skills of their peers, the student instructors became more comfortable with the topic and performing BLS skills.

Barriers to Sustainability and Solutions

Although the program provided many benefits to students, there are barriers to creating a sustainable program and keeping costs low. Stability of the program is a concern because student instructors will inevitably graduate. Fortunately, a faculty physician is currently involved to oversee the project long-term. Furthermore, it costs \$550 to train each peer instructor plus a \$75 annual fee. These costs were covered by third-party organizations volunteering to train peer instructors and the \$10 course cost helped cover the annual fee. Additionally, peer instructors initially borrowed equipment to teach the BLS classes as a complete set of course equipment costs roughly \$3,000. However, the program has been successful in gaining funding from various initiative grants available to medical students and covered the cost to purchase a full set of BLS course equipment and train two new peer instructors. Future challenges will be to secure repeat funding as peer instructors continue to graduate. Access to simulation centres can also be a challenge. New peer instructors will need to build

experience using and accessing the simulation centre as the current instructors have. A solution could involve current peer instructors acting as mentors before they graduate so they can train replacements with simulation lab equipment.

Conclusions and Future Directions

It is essential that medical students are comfortable and confident in their BLS skills. The goal of this program is to reduce the financial burden of BLS certification and to foster a safe peer-to-peer learning environment to build students' skills and confidence in BLS for their careers. Recruitment efforts are underway to train current first-year students as peer instructors to continue the program. Compared to courses provided by private companies, students gain experience at high-fidelity simulation centres and student instructors gain important teaching skills. It is recommended that a sustainable model is created for peer instructors to continue training medical students in BLS.

Conflict of interest

The authors have declared no conflict of interest.

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First, do no planetary harm: Perspectives on medical waste and sustainability initiatives

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Abstract

Climate change is the greatest global health threat of modern times, and Canada is already falling behind. Our country is warming at roughly double the global rate, yet our healthcare sector produces the third-highest greenhouse gas emissions per capita worldwide. Our article first examines the history of this issue and the barriers to progress. We then explore how waste is produced and disposed of in hospitals and discuss the financial and environmental benefits of waste reduction. Finally, we highlight organizations that have championed aspects of healthcare sustainability and explore how medical students can contribute to medical sustainability.



Under the piercing fluorescent lights of the operating room, another case is coming to a close. The gowns and sterile drapes, all the same shade of industrial blue, are doffed into flimsy waste bins that fill in an instant. By the time the next patient is ready, they are gone without a trace.

Amid the noise and hustle of the emergency department, a physician carefully unwraps a clear plastic tray and picks out the three items she needs to insert the arterial line. The remaining unused items are left to join their packaging material in the trash.

In every corner of our medical system, we have become increasingly reliant on disposable equipment for safety and convenience. Recent studies place Canadian healthcare among the top three worst polluters per capita globally, producing 4.6% of Canada's total greenhouse gas emissions, a figure that is rising year by year.¹ Far from doing no harm, healthcare-associated pollution results in 23,000 disability-adjusted life years (a measure of premature mortality and disability) lost annually as a result of air pollution, wildfires, and heat-related illness, among other factors.¹⁻³ How did we get here and how do we improve?

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Our current era is marked by an increased awareness of the negative impacts of industry and consumer habits on the health of planet Earth. Climate protests have been attended en masse in response to political reluctance towards cutting emissions.⁴ In the midst of this crisis, organizations of all sizes are finding ways to reduce their footprint. The City of Vancouver has implemented a ban on single-use Styrofoam, although hospitals are exempt from this ban;⁵ IKEA has installed solar panels to power its stores;⁶ Google has maintained a carbon-neutral status for over a decade.⁷

Unfortunately, the high upfront costs associated with sustainable modifications prevent many organizations from improving infrastructure and implementing environmentally sustainable practices. In addition to this barrier, the healthcare sector faces an overriding priority: the need to prevent or reduce healthcare-associated infections (HAIs). Over a century after Semmelweis published his work connecting handwashing to sepsis,⁸ the field of infection control gained significant ground. In particular, the 1980s were marked by a better understanding of bloodborne infections which prompted hospitals to shift from reusable to single-use devices.^{9,10} While patient safety is paramount and a handful of disposable items have been shown to reduce HAIs,^{10,11} modern trends of disposability in medicine do not always stem from evidence, but rather from an interplay of commercial, regulatory, and economic factors.¹²

Table 1 | A list of organizations working toward medical sustainability and examples of their recent achievements.

Organization	Role	Actions	Example of result
Canadian Association of Physicians for the Environment (CAPE)	Serves as the evidence-based and ethics-driven voice of Canadian medicine on environmental affairs.	Supports and guides physicians to advocate for healthier environments. Provides educational resources on environmental health issues.	Won a commitment from the federal government to phase out Canada's 14 coal-fired power plants by 2030.
The Canadian Coalition for Green Health Care	Acts as Canada's integrated resource network for environmentally friendly and sustainable healthcare service delivery.	Leads several sustainability and conservation initiatives. Provides educational resources such as the bi-weekly Green Digest.	Developed the Green Hospital Scorecard (GHS), a comprehensive benchmarking tool for hospital sustainability.
BC GreenCare - Energy and Environmental Sustainability Team	Leads energy and environmental sustainability work across the four Lower Mainland Health Care Organizations (Fraser Health, Providence Health Care, PHSA, and Vancouver Coastal Health).	Conducts research, develops programs, guidelines and policies. Oversees collaborative approaches relating to energy conservation and environmental sustainability.	Supported over 250 Green+Leaders working on healthcare sustainability projects across the Lower Mainland.
CFMS - Health and Environment Adaptive Response Task Force (HEART)	Committee of Canadian medical students under the Canadian Federation of Medical Students.	Coordinates advocacy and raises awareness of environmental health, climate change, and planetary health.	Developed planetary health curricular competencies for Canadian medical schools and published results in <i>Lancet Planetary Health</i> . ²¹
UBC EnviroMed Club	Club under the UBC Medical Undergraduate Society that brings together medical students passionate about addressing climate change.	Creates events and initiatives around the areas of community service, waste reduction, curricular change, and political advocacy.	Organized UBC medical student participation in two climate marches in 2019.
Health Care Without Harm	An international coalition of more than 1,100 institutions in 55 countries working towards sustainability and advocating for environmental health and justice.	Programs vary based on the region of the world and focus on a range of topics including: waste, chemicals, green building and energy, food, water, green purchasing, climate justice.	Secured commitments from over 200 healthcare institutions to reduce carbon footprint equivalent to taking 7.2 million cars off the road.
Greenhealth Exchange (U.S. B-Corp)	Combines billions of dollars in purchasing power of member hospitals to support sustainability and social responsibility goals.	Promotes green alternatives to disposable products and meets with vendors to investigate areas for improved sustainability.	Created a catalog of health products that are screened and sourced as high-quality green products.
MedShare	Reduces lifesaving unused or repairable medical equipment from being needlessly discarded.	Works with hospitals, distributors, and manufacturers to redistribute supplies to medically underserved communities.	Diverted over 13.5 million pounds of quality products from landfills and provided \$220+ millions of equipment to communities.

Yet challenges and opportunities can occupy the same niche. The avant-garde report by the 2015 Lancet Commission on Health and Climate described climate change as “the greatest global health threat of the 21st century.”¹³ After being concealed for so long, there is a growing awareness around the issue of medical waste. Physician-driven articles have appeared in some of Canada's leading news outlets, paving a path for medical professionals to question practices and improve sustainability.¹⁴⁻¹⁶

Waste reduction in Canadian surgical and critical care settings have demonstrated benefits to budgets and the environment.¹⁷⁻¹⁹ One study found that while operating rooms produce 33% of hospital waste, waste volume can be reduced by up to 93% with improvements to recycling practices, investment in reusable equipment, and optimization of supply management.²⁰ When waste cannot be reduced, proper waste separation systems can play a major role. Older evidence

demonstrates that the biohazardous waste stream may be comprised of incorrectly categorized nonhazardous waste,²¹ which costs nine times more to dispose of,²² and requires energy-intensive management with autoclave sterilization or incineration.

Furthermore, the development of a waste management plan that includes in-service training, waste auditing, and policy reform has been shown to reduce waste by more than 58% within a few months.²³ Improving purchase coordination can reduce the number of freight shipments, thereby cutting emissions from equipment transport. Further advancements can be made through urging medical equipment companies to develop sustainable supply chains and minimalist packaging.²⁴

Aside from medical waste, there are numerous other gaps in hospital sustainability that can be addressed. Tools like the Green Hospital Scorecard (GHS) have been developed for this exact reason.

The GHS is a comprehensive benchmarking tool for Canadian hospitals to measure and disseminate initiatives aimed at energy conservation, water conservation, waste management, corporate commitment, and pollution prevention.²⁵ Sustainability can also be incorporated into a hospital's construction or redevelopment, with initiatives to recapture harmful anesthetic gases or incorporate energy-efficient ventilation systems.^{26,27}

Within the realm of medical education, the Canadian Federation of Medical Students has been making strides toward incorporating and improving the quality of climate change education through a recent task force.^{28,29} Other organizations are working on multiple levels to intervene and improve healthcare sustainability. A nonexhaustive list of these organizations and examples of recent successes are presented in Table 1. By highlighting the links between planetary and human health, these organizations remind us of the very fact that you cannot have a healthy population without a healthy planet.

As medical students forging our own identities in this privileged profession, there has never been a more important time to set sustainability as a foundational pillar in our lives. We can further our understanding of medical sustainability by looking for opportunities to partner with hospital units or clinics to quantify and reduce their waste streams. We can join communities of activism such as the Canadian Association of Physicians for the Environment to advocate for systems change. And we can champion environmentalism from our positions of leadership on student and faculty governance committees, promoting sustainable principles in medical education, policy, and student activities.

Our long walk to an environmentally conscious healthcare system is only just beginning, and we can make huge contributions to its pace and direction. We must become a group of thoughtful clinicians who recognize the urgency of climate change and become early adopters for new sustainable best practices. In the blink of an eye, we will be the attendings that a new generation of medical students will look up to. Let us be the ones to create a system that cares for our patients of today and our planet of tomorrow.

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Current trends in robotic surgery: A role for telesurgery in remote Canadian communities

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Abstract

Telesurgery is the technique through which surgeons are able to use robotic surgical devices to perform operations without being physically present. Although telesurgery is a promising avenue for future surgical practice, several barriers, including cost, surgical training, and available technology, prevent its broad application. Emerging research has been aimed at overcoming such obstacles and ultimately may suggest a role for telesurgery to reduce surgical inequities of healthcare for people living in remote locations, particularly in Canada.

Over the past two decades, the utility of robotic surgery has been an emerging topic of conversation within the medical community. Currently, robotic surgery is used across a breadth of surgical specialties and includes various robotic systems, including the da Vinci Surgical System, the Navio Surgical System, and the Mako Robotic-Arm. Most commonly, robotic surgery has found utility in minimally invasive surgeries, including many gastrointestinal, gynecologic, and urologic surgeries.¹ In such surgeries, improved dexterity and visualization has allowed for robotic surgery to provide improved patient outcomes, faster recovery, and fewer complications.²⁻⁸ Robotic surgery has traditionally entailed the surgeon manipulating the robotic surgical machinery while remaining bedside in the operating room. However, recent advances in technology may allow for robotic surgery to include surgical procedures that take place with the surgeon physically distant. This physically distant robotic surgical technique is known as telesurgery.

Historically, telesurgery first gained popularity in 2001 when three New York surgeons performed separate cholecystectomies on six pigs in Strasbourg, France.⁹ Since that time, robots performing telesurgery have been approved by the Food and Drug Administration (FDA) in the United States and remain an important area of research in surgery.¹⁰ Telesurgery research in the United States has largely been targeted towards advancing technology for the purposes of medicine in areas of conflict (through the U.S. Army) and outer space (through NASA).²

In Canada, some medical experts believe that telesurgery can revolutionize healthcare delivery, especially in remote or isolated communities that lack specialized surgical services.¹¹ The Canadian population is distributed over a much broader area than the United States and as such, telesurgery has been suggested as an important and prospective avenue to the development of healthcare delivery in remote and isolated communities.¹² Telesurgery at remote sites, where a lack of transportation or weather can be significant obstacles, would allow for patients to receive the urgent care they need without traveling long distances. Previous trial surgeries through McMaster University have yielded positive outcomes. Patients were particularly pleased to have their operations performed locally, thereby staying with their families while also receiving the expertise of specialists and advanced procedures generally only available in larger hospitals.¹¹

In addition, by decreasing the need to transport and house patients in larger centers, there are potential reductions in healthcare costs, waitlists, and patient stress. Recent research has also suggested that robotic surgery may reduce the length of in-hospital stay and mitigate the necessity for more invasive open surgery, thus enabling broader use of telesurgery in patient management; however, this research area requires further scrutiny.¹³

Despite its promising potential to improve patient care, several limitations have prevented widespread implementation of telesurgery. First, the cost of implementation and regular use of telesurgery is significant. In 2014, the equipment and software costs to install a single telesurgery system was estimated to be approximately 1.2 million Canadian dollars.¹⁴ Moreover, the cost of yearly maintenance and disposables for each surgery have further reduced the economic viability of telesurgery in Canada. As such, telesurgery would likely not be an efficient use of healthcare resources in remote communities that could have specific and more urgent medical needs. Although the costs associated with telesurgery are high, as the prospective robotic surgery market is emerging, competition between companies developing robotic surgical devices may begin to decrease the cost of such systems.⁵

Telesurgery also presents challenges to ensuring the highest quality of patient care. During any surgery, technical equipment or emergent health issues may arise, requiring immediate troubleshooting at the bedside. In most robotic surgery centers, there are dedicated teams of nurses and surgical assistants that participate in the surgery; however, in the case of telesurgery, these individuals require additional specialized training.² It is also important to acknowledge that telesurgery creates a different type of surgeon-patient relationship, such that “telesurgeons” should take extra care to ensure their patients are well-informed and emotionally comfortable to continue appropriate patient-centered care.

From the surgeons’ perspective, telesurgery requires additional training and regular practice in order to maintain their surgical skills. In the past, regular telesurgery practice could not be replicated by local robotic surgery due to network-based delays in instrument feedback from the robotic surgical device.^{15,16} Emerging technology, specifically 5G infrastructure, is believed to mitigate these technical differences and greatly improve feedback between the surgeon and the robotic apparatus, thus making local robotic surgery and telesurgery more similar.^{17,18} However, the 5G network incurs an added cost to telesurgery and will likely take a substantial amount of time to reach the remote communities of Canada that would be best served by telesurgery.^{13,17}

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Altogether, the upfront costs to hospitals and health authorities, the potential need for bedside management, and the current limitations of computer and network systems have hindered the feasibility of telesurgery in surgical medicine. Although many obstacles remain to the broad implementation of telesurgery in remote Canada, it remains an interesting avenue of future medical practice as research emerges and technology continues to improve.⁴

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The author has declared no conflict of interest.

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The current evidence behind functional medicine

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Abstract

Functional medicine (FM) is a form of integrative medicine which attempts to manage chronic diseases by targeting their root cause. There are seven core clinical imbalances under which these root causes are categorized. Imbalances can be identified by combining a detailed history with comprehensive laboratory testing. Common causes of chronic disease in FM include intestinal dysfunction (or leaky gut syndrome) and heavy metal toxicity. These conditions have a solid scientific foundation, but further research is still needed to determine their responsiveness to FM therapeutics. While FM has shown success in some case studies, overall FM diagnoses and treatments are lacking in conclusive evidence and it remains to be seen whether FM will be a useful approach in the treatment of chronic disease.

Chronic disease places a significant burden on Canadians and the healthcare system. According to the Public Health Agency of Canada, 44% of Canadian adults over the age of 20 have at least one of the ten most common preventable chronic conditions.¹ Moreover, the annual cost of disease management accounts for 58% of the healthcare budget.² Proponents of an integrative approach, known as functional medicine (FM), claim it provides a superior model for handling chronic disease.³ FM proposes that addressing the underlying causes of chronic disease, rather than suppressing its symptoms, is key to its resolution. However, while certain root causes in FM are supported by scientific evidence, the diagnostic and treatment methods of FM remain a point of contention.

The identification and treatment of the root causes of chronic disease are the foundation of FM. They are categorized according to seven core clinical imbalances in:⁴

1. Assimilation: digestion, absorption, microbiota, respiration;
2. Defense and repair: immune system, inflammation, infection, microbiota;
3. Energy: energy regulation, mitochondrial function;
4. Biotransformation and elimination: toxicity, detoxification;
5. Transport: cardiovascular and lymphatic systems;
6. Communication: hormones, neurotransmitters, immune messengers;
7. Structural integrity: from subcellular membranes to musculoskeletal integrity.

A disease may result from the combined effect of multiple imbalances; alternatively, a single imbalance may lead to multiple disorders. Obesity, for example, can lead to hypertension, diabetes, and coronary heart disease; however, an unhealthy diet, sedentary lifestyle, and genetic factors can lead to obesity. FM organizes these relationships by combining a comprehensive patient history with extensive biochemical testing in order to narrow down the underlying causes of an illness.⁴ Once the cause is determined, it is generally managed with lifestyle changes, nutrition, vitamins, minerals, antioxidants, and supplements.

Imbalances related to the gastrointestinal (GI) tract are a common root cause of chronic diseases in FM. For instance, diseases such as Type 1 diabetes or inflammatory bowel disease (IBD) are associated with imbalances in GI mucosal barrier integrity and the

gut microbiome.^{5,6} This condition, known better as “leaky gut syndrome,” is a state of altered permeability of the intestinal lining, which leads to passage of microbial antigens causing an inflammatory or autoimmune response.⁷ Treatment of leaky gut-associated diseases excludes immunosuppressive medication and instead aims to restore the intestinal lining using nutrients, probiotics, and herbal remedies. Though management of leaky gut with these supplements have been shown to improve intestinal barrier function, their efficacy in resolving chronic diseases is currently unproven.⁸

Heavy metal toxicity is another common imbalance in FM implicated in several chronic diseases. Heavy metal exposure can occur through one’s diet, occupation, or the environment. For example, juvenile idiopathic arthritis has been associated with consumption of fish contaminated with trace aluminum during gestation or early childhood.⁹ Exposure to elevated levels of mercury can be neurotoxic, and has been associated with Parkinson’s disease and multiple sclerosis.^{10,11} FM also endorses the controversial notion that trace heavy metals found in childhood vaccines is a root cause factor in autism, though this has proven invalid in the literature.¹² A patient suspected of heavy metal toxicity may receive a comprehensive testing of hair, urine, sweat, saliva, etc. Critics argue, however, that it is impractical since trace heavy metal exposure is not clinically significant.¹³ In addition, the American College of Medical Toxicology (ACMT) warns that testing and treating indiscriminately is inadvisable as trace levels of heavy metals in the body is not abnormal.¹⁴ Moreover, detoxification measures such as diets, nutritional supplements, saunas, and chelating agents lack convincing scientific evidence, thus more research is needed in this area.¹³

Thus far, the strongest evidence for the FM methodology seems to be from cohort and case studies. A recent study comparing patient-reported health outcomes between cohorts treated at a functional medicine clinic versus at a family medicine clinic reported higher scores for health and wellbeing in patients who received FM care.¹⁵ Furthermore, in one case report, an 80-year-old patient diagnosed with stage III invasive ductal carcinoma of the breast received a combination of chemotherapy along with FM intervention.¹⁶ After evaluating nutritional status through laboratory testing, the patient was prescribed daily exercise, a sleep schedule, a nutritious diet, and intravenous vitamin C. The patient reported no significant complications over the course of treatment and entered remission a year later. However, it is difficult in this case to ascertain whether the FM intervention made a meaningful difference given that the five year survival rate for stage III invasive breast cancer is estimated to be 76%.¹⁷ Additionally, there is currently no high-quality evidence to

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suggest that vitamin C is an effective adjunct to chemotherapy.¹⁸

Another case report involved a 72-year-old man who was referred to an FM clinician after failing to respond to conventional therapy.¹⁹ His diagnoses included chronic depression, fatigue, and irritable bowel syndrome. The patient underwent comprehensive stool and nutritional/metabolic laboratory testing. He was then prescribed probiotics, vitamins, minerals, antioxidants, and a low carbohydrate diet. Several months later the patient reported significant improvement in GI symptoms, pain, fatigue, mood, and the ability to function normally. The authors believe that GI dysfunction, in this case, was a root cause for the other comorbidities, which resolved once the GI issues were addressed. While the outcome in this case report is optimistic, critics have cautioned that it lacks generalizability and the multitude of interventions, again, lack a scientific basis.²⁰

In relation to evidence-based medicine, FM seems to be undergoing an infancy period. This model of integrative medicine is still new and would benefit from an evaluation of its methodology using randomized controlled trials. Taking FM case studies into account, it can be concluded that its model of care has proven favorable among patients. However, this may be due to the additional time invested and attention given to each individual patient. Conditions such as leaky gut syndrome and heavy metal toxicity have been proven to play a part in chronic disease but treating these conditions with nutrients and supplements is an area that requires further investigation. Ordering a multitude of costly, unconventional laboratory tests is also an area of criticism and may benefit from an evidence-based approach. Moreover, conditions that have been proven false, such as vaccine-associated autism or stress-related “adrenal fatigue,” are still being diagnosed in FM, which harms its credibility.²¹ Ultimately, additional research is needed before FM can be considered an effective model to treat chronic disease.

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Telehealth: Technology and healthcare

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Telehealth is a mode of healthcare delivery that allows physicians to communicate with patients using telecommunication technologies, such as computers and mobile devices, to deliver fast and reliable healthcare information. With the shortage of general practitioners in Canada, increases in wait times, and barriers in remote communities,¹ it is timely to review the benefits and limitations of telehealth. This analysis can inform the incorporation of telehealth into Canadian healthcare services.

With the increase in prevalence of chronic diseases,²⁻⁴ which require regular visits to a primary care physician, telehealth allows patients to easily access a primary physician in a timely manner. The earliest applications of telehealth were in acute care settings. One example is connecting bedside emergency care teams with experts in remote locations for care of conditions such as stroke and trauma, in order for timely interventions such as fibrinolytic therapy to be conducted.² Today, telehealth has expanded from consultations addressing acute care to helping patients manage lifelong chronic diseases such as chronic obstructive pulmonary disease (COPD), asthma, diabetes, and chronic heart failure.²⁻⁵ Telehealth allows patients easy access to effective and reliable primary care, particularly in remote areas where services are more difficult to obtain. Tasks that previously required an in-person visit to a physician can now be done via telehealth, including patient education, lab test reviewing, and medication safety checks. This is particularly relevant in today's setting where more than half of Canadians cannot schedule a same or next-day doctor's appointment, one in three Canadians wait six or more days to see their GP, and the only option for the majority of Canadians to see a doctor outside of regular work hours is the emergency department.¹ This accumulates to delayed access to care, which can result in increases in future hospital visits, increases in healthcare costs, and a demand for more doctors. Telehealth provides patients the opportunity to understand their symptoms, achieve effective glycemic and blood pressure control, and improve medication safety, from any location.⁶ In addition, advancements in hardware and image acquisition have allowed for early detection, with good diagnostic accuracy, of conditions such as diabetic retinopathy without an ophthalmologist visit.⁶ In terms of mental health, telehealth has enabled remote delivery of management techniques such as cognitive behavioral therapy (CBT), and created treatment options for patients suffering from post-traumatic stress disorder and alcohol, drug, and gambling conditions with satisfaction levels comparable to conventional methods.^{7,8} Pediatric care benefits from "telerehabilitation" methods, which use two-way interactive video conferencing to treat speech-language pathologies and motor learning and performance issues, and to diagnose Autism Spectrum Disorder in underserved regions where psychoeducational assessments are not readily available.⁹⁻¹² Following this current trend and the concurrent evolution of technology, it appears that telehealth has significant room to grow and expand in terms of the care and services it can provide.

However, telehealth is not without limitations in regards to providing optimal care to patients. Physician-patient interactions are typically noted to be more fragmented and disjointed, having the potential to lead to suboptimal practices, including excessive use of broad-spectrum antibiotics and over-prescription of narcotics.¹³ This over-prescription may be the result of pressure on physicians to practice conservatively when faced with limited diagnostic information, lack of access to full medical records, lack of an in-person patient-physician relationship, and other barriers that prevent appropriate workup.^{13,14}

Additionally, physical examinations where palpation and auscultations are required cannot be carried out through a video platform. The absence of touch can make it difficult to diagnose conditions such as appendicitis, or to detect features such as pedal edema that could be indicative of congestive heart failure or other conditions. While it remains unclear whether telehealth will ameliorate or exacerbate the rate of misdiagnosis, some studies have shown promise for addressing conditions that do not require in-person diagnosis, and where empiric therapy is reasonable. For example, the rate of misdiagnosis of urinary tract and sinus infections was not higher when conducted through virtual platforms in comparison to traditional office visits.¹⁵ It is also important to consider that geographic and social barriers, especially in remote locations, may prevent access to a stable internet connection, given the lack of incentive for internet providers to update their infrastructure in areas with smaller populations.¹³ In addition, differences in education, income, and digital knowledge can make it difficult for patients who are in the most need of healthcare services (e.g., elderly patients with chronic conditions) to obtain them, which can be seen as fundamentally contradictory to the purpose of telehealth.^{13,14,16,17}

On a grand scale, Medicare in the United States invested \$17.6 million towards telehealth in 2015.¹⁸ For some integrated health networks, this investment resulted in 52% of 110,000,000 total visits being conducted through online portals, such as virtual visits, with no measured increase in mismanagement and a decrease in malpractice claims.¹⁸ However, telehealth services in Canada have been significantly lagging behind in comparison. This is due to insufficient funding from provinces and lack of infrastructure for these online services, leading to increases in service fees for the companies that provide telehealth and limitations in what can be conducted and shared during a telehealth session.¹⁹ Additionally, some physicians have expressed their concerns about the use of for-profit telehealth services and how these go against the universality principle of the Canada Health Act.¹⁹ While provinces and physicians are hesitant to adopt new models of care that they are not fully familiar with, many Canadians are eager and interested in making use of virtual care.²⁰

With rapid advancement in the role of technology in medicine, it is worth discussing how telehealth can be used in today's digital age on a larger, more consistent, and more accessible basis across provinces and communities in Canada.

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The authors have declared no conflict of interest.

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Glasdegib: A breakthrough in the treatment of Acute Myeloid Leukemia (AML) for the elderly

Amardeep Singh Sekhon¹

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Brief introduction of glasdegib and overview of acute myeloid leukemia (AML)

On November 21st, 2018, the Food and Drug Administration (FDA) approved glasdegib—a potent breakthrough therapeutic indicated for the treatment of acute myeloid leukemia (AML) in geriatric patients that are ≥ 75 years of age or patients with multiple comorbidities that preclude the use of aggressive induction therapy.¹ Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells, characterized by the clonal expansion of myeloid progenitors (blasts) in the bone marrow and peripheral blood. Currently, AML is a rare disease afflicting approximately 3–4 patients per 100,000 individuals. The disease is far more common in the geriatric population, given the median age of diagnosis being 67.² Being previously incurable, AML is now cured in approximately 35–40% of patients younger than the age of 60. However, the prognosis is still guarded for individuals older than 65, with a 5-year-survival rate of less than 5%.³

Why are geriatric patients precluded from current chemotherapy regimens used for the treatment of AML?

The current chemotherapy regimen for AML is a combination of cytarabine and an anti-tumour antibiotic, such as daunorubicin, doxorubicin, idarubicin, or mitoxantrone. The usual approach to treatment involves the 7+3 protocol, where cytarabine is given continuously for seven days, followed by the anti-tumour agent administered daily for three days.⁴ However, the outcomes of the 7+3 regimen in patients diagnosed with AML over the age of 60 is often poor, with intensive induction chemotherapy in geriatric patients being associated with treatment-related mortality of greater than 10% and requiring prolonged hospitalization due to treatment-related disability.⁵ These could be due to the physiological changes of aging, the prevalence of co-morbidities, or tumour biology, which all have a substantial impact on the tolerance that geriatric patients have to intensive treatment modalities and their toxicities.⁵ Therefore, the current mainstay of AML treatment is low-dose cytarabine (LDAC) for geriatric patients not considered candidates for standard induction chemotherapy due to age and co-morbidities.⁶ Furthermore, research has also shown that AML in the geriatric population appears to be genetically different than in younger adults, making treatment to subdue cancer growth even more challenging.¹ Before the discovery of glasdegib, there was a marked requirement for AML treatment that addressed the needs of patients with co-morbidities and the needs of older patients who were not candidates for intensive induction chemotherapy.

The efficacy of glasdegib for use in chemotherapy regimens

Glasdegib is a potent and selective inhibitor of the Hedgehog Signaling Pathway (HSP), which is a signalling pathway that controls the

differentiation and proliferation of adult stem cells and is implicated in the development of some cancers such as AML.⁷ Glasdegib is used in conjunction with LDAC, a drug that inhibits DNA synthesis in cancerous cells. In preclinical studies, glasdegib combined with LDAC inhibited tumour growth and reduced the number of bone marrow blasts to a greater extent than either glasdegib or LDAC alone. In the BRIGHT AML 1003 clinical trial, glasdegib in combination with LDAC demonstrated a significant 54% reduction in mortality compared with LDAC alone, and an increased median survival from 4.3 months with LDAC alone to 8.3 months with glasdegib and LDAC.⁸ Although there was a substantial increase in overall survival observed in the BRIGHT trial, treatment-emergent adverse events (TEAEs) such as anemia, febrile neutropenia, thrombocytopenia, and pneumonia occurred at higher rates in the glasdegib plus LDAC treatment group compared to LDAC alone.⁹ Gastrointestinal symptoms (such as nausea and vomiting) were more frequent among patients receiving glasdegib in combination with LDAC, which was thought to be linked to the inhibition of the HSP in healthy tissue.¹⁰ Despite this, the use of glasdegib in AML treatment saw a substantial decrease in the rate of TEAEs when compared to standard induction chemotherapy, and was well tolerated among patients.¹⁰

Conclusion

With geriatric patient outcomes being unfavourable following a diagnosis of AML due to toxicity and the lack of tolerance to induction chemotherapy, glasdegib is a breakthrough innovation in the treatment of patients older than the age of 60. The approval gives clinicians another tool to use for the treatment of AML patients with distinct needs and offers a broader range of treatment options for geriatric patients with guarded AML prognoses.

Conflict of interest

The author has declared no conflict of interest.

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Jack of All Trades, Master of Some: Ever-changing roles of the Canadian family physician

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Abstract

Given the ever-growing tidal wave of medical knowledge, family physicians are managing more complex patients than ever before. Consequently, many new family medicine graduates, particularly those intending to practice in rural settings, often feel underprepared to handle such complexity. As a result, new family physician graduates are increasingly choosing to subspecialise their practice, often by pursuing enhanced skills training with nationally recognized Certificates of Added Competence (CACs). While some have argued against the subspecialization of a generalist specialty in the face of ongoing primary care shortages, others have used similar logic to justify the need for increased supports and formal training to help meet the needs of their patients and communities. Regardless of one's stance on the matter, the role of a family physician is evolving rapidly—for better or worse.

The term “old-time doc” brings to mind stereotypical images of a formally clad Victorian-era man donning a stethoscope and head mirror during a home-visit to an ill patient. Or, perhaps one might recall images of a 17th century plague doctor wearing their signature black robe and long, beak-like mask. One might also be reminded of a modern-day rural physician who performs caesarean sections, general anesthesia, and appendectomies, all the while running a medical clinic and picking up shifts in the local emergency department. Although modern day evidence-based medicine would be unrecognizable to an early 20th century physician, far less has changed with respect to the “do-it-all” approach embodied by modern-day rural family physicians. By providing “cradle to grave” care while shuffling between clinic, hospital, or home-visit, the rural family physician perhaps best demonstrates one of family medicine's core tenets—comprehensiveness.¹ The paucity of specialist physicians in these small communities has obligated family physicians to take on several of these roles themselves. However, the sheer breadth of knowledge and skill required by a rural family physician has unsurprisingly led to a considerable amount of discomfort among new graduates, many of whom feel ill-equipped to handle the acuity and complexity that often accompanies rural practice.²

To help these “do-it-all” rural family physicians more effectively meet the needs of their community, the College of Family Physicians of Canada (CFPC) offers nationally recognized enhanced skills training programs, officially called Certificates of Added Competence (CACs). In addition to pursuing fields such as hospitalist medicine, which often requires no additional formal training, family physicians can obtain formal CACs in addiction medicine, care of the elderly, emergency medicine, enhanced surgical skills, anesthesia, obstetrical surgical skills, palliative care, and sport and exercise medicine.³ CACs generally require six to twelve months of training at accredited residency training programs and designate physicians with post-nominal letters in their respective area of training (e.g., CCFP-EM for emergency medicine, CCFP-PC for palliative care). Alternatively, some CACs allow experienced providers to opt for the “practice eligible” route with past relevant clinical experience recognized in lieu of formal residency training.³

Since their introduction, CACs have been an attractive option for family physicians seeking to enhance their practice or transition entirely into their subspecialty of interest. The increased uptake of some of these training programs among urban family physicians has led to some debate, however.⁴ Initially designed for rural generalists seeking to gain additional competencies to supplement their practice, such programs have expanded to serve the interests of urban family physicians looking to specialize into a particular domain of family medicine. In fact, a recent report demonstrates that nearly 37% of Canadian family medicine residents plan on specializing their practice,⁵ a trend that has been steadily increasing in recent years.⁶⁻⁹ Aside from seat limitations in CAC programs, there are no formal regulations in place to prevent these large percentages of family physicians from specializing—meaning any eligible family medicine resident can apply during their final year of residency. Among some, this has led to a notion of family medicine training as a “stepping stone” for more specialized training.¹⁰ While critics have argued that such specialization occurs at the detriment to general family practice by failing to address the broader needs of the community,¹¹ few would debate the importance of enhanced skills training programs in improving the quality of essential care for patients who would otherwise go without. Patients in rural Canada requiring even simple procedural care, for example, are often forced to travel long distances due to the continued decline of rural surgical services over the past two decades, a change which has disproportionately affected some of the sickest and most vulnerable populations in the country.¹² When it comes to maternity care, studies have even demonstrated increased rates of adverse perinatal outcomes for women who must travel to access maternal services.^{13,14} With rigorous evidence supporting the safety and efficacy of enhanced skills as provided by family physicians in a variety of settings,¹⁵⁻¹⁷ enhanced skills-trained rural family physicians performing simple appendectomies and caesarean sections offer a demonstrable advantage over the timely, costly, and often dangerous journeys faced by patients leaving their rural communities to receive essential medical and surgical care.

While some CACs have faced little to no resistance, more controversy has surrounded the role of emergency medicine-trained family physicians (CCFP-EM) due to the large overlap in practice patterns between CCFP-EM and Royal College of Physicians and Surgeons (FRCPC)-trained emergency physicians (EPs)¹⁸. While the CCFP-EM training path was initially intended to improve emergency

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care provided by community-based family physicians, surveys have demonstrated that the vast majority (70–80%) of CCFP-EM graduates practise exclusively emergency medicine, with fewer than 10% describing their location as rural.^{19–21} While some have challenged the merits of two separate training routes, both paths continue to produce well-trained EPs to fill increasingly understaffed emergency departments across Canada. Indeed, with EP shortages estimated to be in excess of 1500 by 2025,¹⁹ both CCFP-EM and FRCPC-EM physicians are essential to adequately staffing emergency departments presently and in the years to come.

Although most recognize family medicine as the epitome of generalist medicine, the truth is that the roles of a family physician are in a state of flux owing to the increasing popularity of enhanced training programs and the continually expanding breadth of knowledge and skills required by the modern-day generalist family physician. Ultimately, a family physician's choice to subspecialize their practice or provide truly comprehensive “cradle to grave” medicine will come down to several factors including community need, remuneration, perceived lack of training in certain areas, and personal and career goals. In the end, while it is unclear whether family physicians of the distant future will continue to embody the idiom “jack of all trades”, they will most certainly continue to be the masters of some.

Conflict of interest

The author has declared no conflict of interest.

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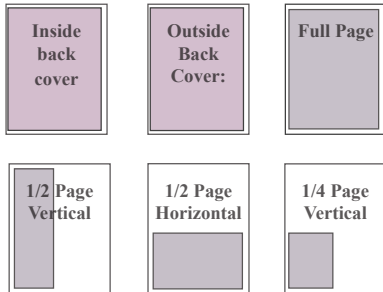
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