UOJM JMUO

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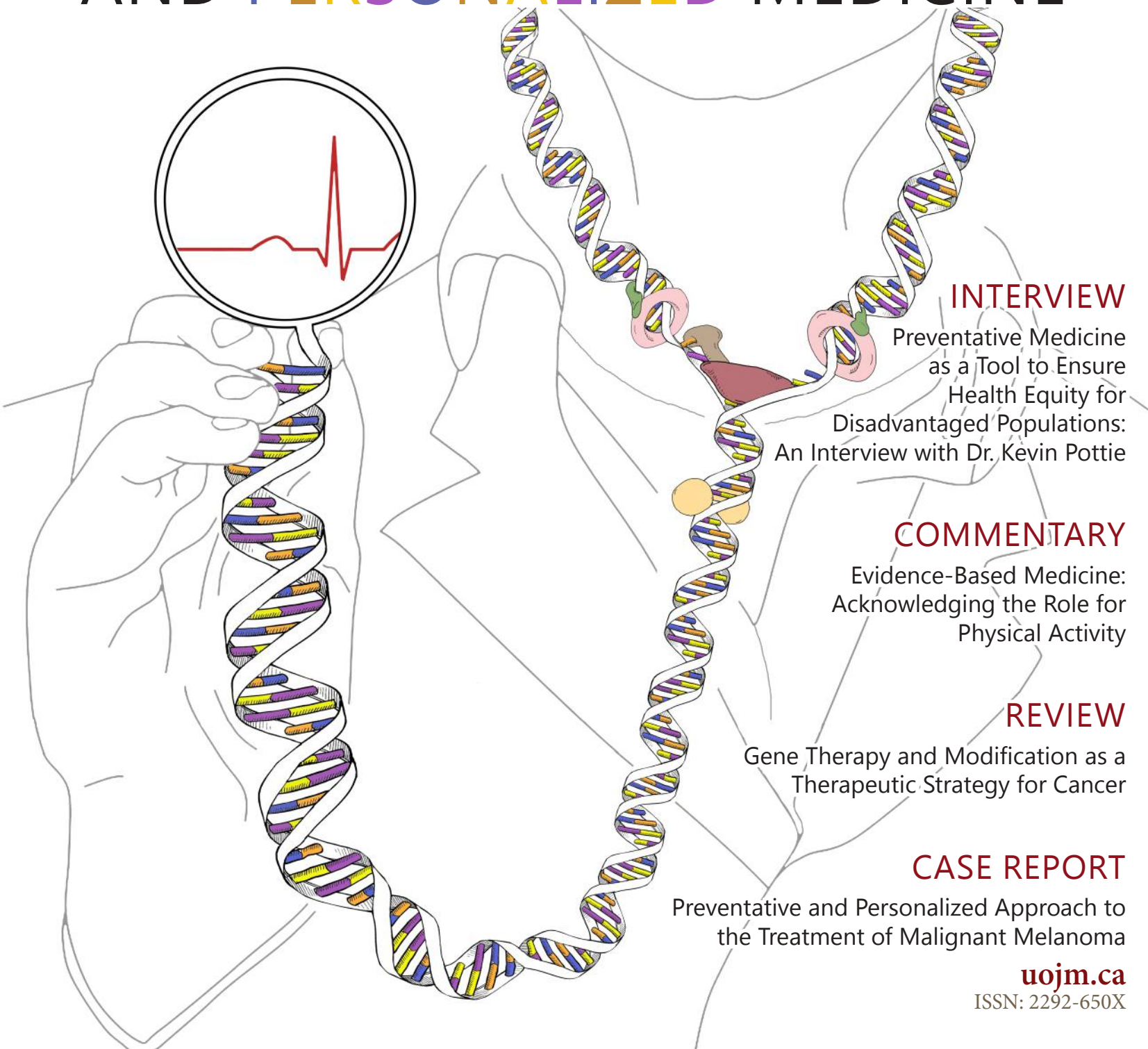
UNIVERSITY OF OTTAWA JOURNAL OF MEDICINE

JOURNAL MÉDICAL DE L'UNIVERSITÉ D'OTTAWA

PREVENTATIVE AND PERSONALIZED MEDICINE



INTERVIEW

Preventative Medicine as a Tool to Ensure Health Equity for Disadvantaged Populations: An Interview with Dr. Kevin Pottie

COMMENTARY

Evidence-Based Medicine: Acknowledging the Role for Physical Activity

REVIEW

Gene Therapy and Modification as a Therapeutic Strategy for Cancer

CASE REPORT

Preventative and Personalized Approach to the Treatment of Malignant Melanoma

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ABOUT US

UOJM is an international peer-reviewed journal led and published by the students of the Faculty of Medicine. We welcome submissions in a variety of areas in biomedical research and feature original research, review articles, news and commentaries, case reports and opinion pieces. Our articles are written in both English and French, and represent the only bilingual medical journal in Canada.

Le JMUO est un journal revu, édité et publié par les étudiants de la Faculté de médecine. Nous encourageons les soumissions d'une variété de différents domaines en recherche biomédicale et publions des articles de recherche originale, des articles de revue, des nouvelles et commentaires, des rapports de cas et des pièces d'opinion. Nos articles sont écrits en français et en anglais et représentent le seul journal médical bilingue au Canada.

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TABLE OF CONTENTS

UOJM
UNIVERSITY OF OTTAWA JOURNAL OF MEDICINE

JMUO
JOURNAL MÉDICAL DE L'UNIVERSITÉ D'OTTAWA

UOJM: Preface

Now in its sixth cycle, the University of Ottawa Journal of Medicine (UOJM) has had another successful year. One of our goals for this year has been to further increase our outreach and encourage submissions from outside the University of Ottawa. We are pleased to feature several articles authored by students from across Canada who share their perspectives about medicine, research, and patient care in this issue. We also began a collaboration with the recently launched uOttawa student-driven H.E.A.L. (Humanities Education, Artistic Living) blog, a canvas where students are welcome to submit their creative, artistic, and humanities pieces which don't always demand peer review.

Throughout the year, we held informative training seminars in peer review (Dr. David Moher), the use of social media in medical education and research (Dr. Ali Jalali), and article writing (Dr. Diane Kelsall from the CMAJ), as well as talks on careers in research and medicine (Drs. Phil Wells, Viren Naik, and Alexander Sorisky, and MD2016 Hoang (Tano) Pham). We are grateful for the time these experts have volunteered to share their experiences with us and to help us gain valuable knowledge and skills we will use in our careers as future physicians and researchers.

The publication of UOJM online and in print would not be possible without the tremendous dedication and valued support of medical and graduate students at the University of Ottawa. This year, we were also honored to be able to work in collaboration with students at the Northern Ontario School of Medicine (NOSM). Members of the UOJM executive and editorial teams contribute not only as authors, editors, and reviewers, but also strive to promote the journal and accrue sponsorship, contributing significantly to the success of each issue. In addition, we would like to acknowledge our faculty advisors (Drs. Phil Wells, Melissa Forgie, and David Moher) for their continued support. Finally, we would like to sincerely thank our sponsors, without whom publication of UOJM would not be possible: the University of Ottawa (Faculty of Medicine, Office of the Vice-President Research, and Department of Cellular and Molecular Medicine), The Ottawa Hospital, the Children's Hospital of Eastern Ontario, and The Royal Ottawa Mental Health Centre.

Looking to the future, we are pleased to announce that the theme for our fall 2016 issue, UOJM 6.2, will be "Global Health." We look forward to remaining active throughout the summer and are already accepting submissions! For more information on how to submit, go to http://uojm.ca/submissions/. Stay tuned, as we will be relaunching the website over the summer as well!

Volume 6, Issue 1 includes articles about preventative and personalized medicine written by students and physicians from across Canada. The growing burden and escalating costs of treating largely preventable diseases have several health-based organizations calling for shifting investments "upstream" into health promotion and disease prevention services. Furthermore, advances in medical research are bringing the horizon of truly personalized medicine closer every day, and students are playing an important role in advocating for healthcare issues, as well as bringing discoveries from the bench to the bedside. In this issue, we feature articles on the topics of pharmacogenomics, prescription physical activity, physician assistants as chronic care coordinators, eHealth interventions in Indigenous communities, complex regional pain syndrome, 3D printing, gene therapy and modification, and malignant melanoma. In addition, this issue features interviews on health equity, cancer prevention, and smoking cessation, and also includes a report on an elective in Nepal, a humanities piece on formal training in fine arts for medical students, and an article on an exhibit about Dr. Jérôme Lejeune, discoverer of Trisomy 21. We hope you enjoy reading the Preventative and Personalized Medicine issue!

Editors-in-Chief
Paula Adler
Devon Johnstone

JMUO: Préface

Dans sa sixième série, le Journal Médical de l'Université d'Ottawa (JMUO) a connu une autre année remplie de succès en ayant comme but d'encourager des soumissions d'articles venant d'ailleurs. Dans la présente édition, nous sommes fiers de partager plusieurs articles rédigés par des étudiants partout au Canada qui nous présentent leur perspective au sujet de la médecine, de la recherche, et des soins aux patients. Le journal a également entrepris une collaboration avec le nouveau blogue H.E.A.L de l'Université d'Ottawa qui est géré par des étudiants. C'est un espace créatif où les étudiants peuvent soumettre leurs réflexions artistiques et humanitaires ne nécessitant pas une révision par les paires.

Au cours de l'année, nous avons organisé des séminaires informatifs dans les domaines de l'évaluation par les paires (Dr David Moher), de l'utilisation des médias sociaux dans l'éducation médicale et en recherche (Dr Ali Jalali), de la rédaction d'articles (Dre Diane Kelsall du JAMC) et une présentation sur les carrières en recherche et en médecine (Dr Phil Wells, Dr Viren Naik, Dr Alexander Sorisky, et MD2016 Hoang (Tano) Pham). Nous sommes très reconnaissants envers ces experts qui ont donné de leur temps précieux de façon bénévole. Leurs expériences enrichissantes nous aideront à acquérir des connaissances et des habiletés que nous utiliserons dans nos futures carrières en tant que médecins et chercheurs.

La publication du JMUO en ligne et la version papier ne seraient pas possibles sans le dévouement extraordinaire des étudiants de médecine et des étudiants aux études supérieures de l'Université d'Ottawa. Cette année, nous sommes également honorés de travailler en collaboration avec des étudiants de l'École de médecine du Nord de l'Ontario (EMNO). Les membres des équipes exécutive et éditoriale du JMUO contribuent non seulement comme auteurs, éditeurs et réviseurs, mais ils font aussi la promotion du journal en assurant une communication efficace avec nos commanditaires. De plus, nous aimerions remercier nos conseillers pédagogiques (Dr Phil Wells, Dre Melissa Forgie, et Dr David Moher) pour leurs précieux conseils et leur appui. Finalement, nous aimerions remercier nos commanditaires sans qui la publication du JMUO n'aurait pas été possible : Université d'Ottawa (Faculté de médecine, Cabinet de la vice-rectrice à la recherche, Département de médecine cellulaire et moléculaire), l'Hôpital d'Ottawa, le Centre hospitalier pour enfants de l'est de l'Ontario (CHEO), et le centre de santé mentale le Royal d'Ottawa.

Nous sommes heureux d'annoncer que le thème de notre édition de l'automne 2016, JMUO 6.2, sera « La santé mondiale ». Nous acceptons déjà des soumissions cet été pour la prochaine édition. Pour plus d'informations sur le processus de soumission, visitez le http://uojm.ca/submissions/. Nous prévoyons également des mises à jour sur notre site web cet été.

Le volume 6, édition 1 comprend des articles sur la médecine préventive et personnalisée rédigés par des étudiants et des médecins partout au Canada. Le coût relié au traitement des maladies augmente de façon importante et plusieurs organisations cherchent à investir dans la promotion de la santé, dans les services axés sur la prévention des maladies et dans une approche médicale plus personnalisée. Cette édition présente des articles sur la pharmacogénomique, la prescription d'activité physique, les assistants de médecins comme coordinateurs de soins de la douleur chronique, des interventions cybersanté dans les communautés autochtones, le syndrome de douleur régionale complexe, l'impression 3D, la thérapie génétique et le mélanome malin. De plus, cette édition comprend des entrevues sur la santé équitable, la prévention du cancer, et la cessation du tabac, ainsi qu'un compte rendu sur un stage au Népal, un article sur la formation dans les beaux-arts pour les étudiants en médecine, et un article sur Dr Jérôme Lejeune qui a découvert la trisomie 21. Nous espérons que vous profiterez de cette édition du journal sur la médecine préventive et personnalisée!

Rédacteurs en chef
Paula Adler
Devon Johnstone

Cancer Prevention as the Key to Long-Term Population Health: An Interview with Dr. Carolyn Gotay

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[1]Faculty of Medicine, University of British Columbia

ABSTRACT

Dr. Carolyn Gotay is Professor and Canadian Cancer Society Chair in Cancer Primary Prevention at the University of British Columbia (UBC). Her training began at Duke University and continued with a PhD in Psychology from the University of Maryland. During her first position at the University of Calgary, she became interested in the relationship between psychology and cancer, which would become the focus of her subsequent work. Dr. Gotay has held positions at Gettysburg College, the University of Calgary, and the National Cancer Institute (U.S.) where she acted as a Health Scientist Administrator. Following these positions, she began at the University of Hawaii, where she worked as the Director of the Cancer Prevention and Control Program. Throughout these various roles, her primary prevention interests were multi-faceted; they included a focus on clinical trials investigating quality of life as well as understanding end-of-life care and the psychosocial wellbeing of patients. Dr. Gotay joined UBC in 2008 where she continued her primary prevention research through the School of Population and Public Health and the B.C. Cancer Agency. Currently, Dr. Gotay is a leader in the Cancer Prevention Centre where she and her colleagues look at modifiable cancer risk factors and the application and assessment of interventions to modify these behaviours in the population.

RÉSUMÉ

Dre Carolyn Gotay est professeure et elle siège au sein de la Société canadienne du cancer dans le domaine de la prévention primaire du cancer à l'Université de la Colombie-Britannique. Son éducation universitaire a débuté à l'Université de Duke et elle a continué ses études doctorales en psychologie à l'Université de Maryland. Son premier poste fut à l'Université de Calgary et elle concentre ses recherches sur la relation entre la psychologie et le cancer. Dre Gotay a obtenu des postes à l'Université de Gettysburg, à l'Université de Calgary et à l'institut national du cancer (É.U.) où elle était administratrice scientifique de la santé. Par la suite, elle a travaillé à l'Université d'Hawaii, où elle a oeuvré en tant que directrice du programme de prévention et de contrôle du cancer. À travers son cheminement professionnel, Dre Gotay a étudié les soins primaires préventifs en lien avec la qualité de vie, les soins de fin de vie et le bien-être psychosocial des patients. En 2008, elle a eu la chance de continuer sa recherche en soins préventifs primaires à l'Université de la Colombie-Britannique dans le département de santé publique ainsi qu'à l'agence de cancer de la Colombie-Britannique. Dre Gotay demeure une leader au centre de prévention du cancer où elle travaille présentement avec ses collègues pour trouver des facteurs de risque modifiables du cancer et l'application d'interventions pour modifier ces comportements dans la population.

DR. GOTAY, CAN YOU PLEASE TELL US ABOUT YOUR BACKGROUND AND HOW YOU CAME TO WORK IN THE FIELD OF CANCER PREVENTION?

I am a psychologist by training, but I certainly did not start out with the intention of pursuing cancer prevention research. During the early part of my career in Calgary I was trying to find my role and research passion. I remember the Chair of my department asking me "if there was a link between cancer and psychology." At the time, the field of psycho-oncology was nowhere near a formally recognized discipline and there was not a lot of information written in the literature. I realized that the link between psychology and cancer existed across the entire continuum of cancer control—from prevention to end-of-life care and psycho-

Keywords: Cancer; Health; Prevention; Canada

social wellbeing. I moved through different institutions in the U.S. and spent the bulk of my early career learning about cancer control in the context of patient quality-of-life and clinical trials. When I moved to the University of British Columbia I took on a role in cancer prevention research, which was largely unfamiliar to me. Since arriving in Vancouver, I have learned a great deal. This research integrates fundamentals of psychology; primary cancer prevention involves the identification of modifiable risk factors and then building interventions to affect the behaviour of populations with regard to these factors. Perhaps you would call it happy circumstance, but cancer prevention has become my passion and has certainly re-invigorated my work.

WHAT EXCITES YOU ABOUT CANCER PREVENTION WORK?

I believe that no matter how well we preserve quality of life for our patients by managing their sequelae, the best outcome would not involve cancer in the first place. In fact, about half of cancers that are diagnosed among people in the population today are largely avoidable—with lung cancer as an example. I don't think we that will ever be able to prevent all cancers, but if we start to use the knowledge that we have to modify behaviour, I am certain that this will leave a more profound impact than any chemotherapeutic.

HOW HAS THE UNDERSTANDING AND CANCER PREVENTION EFFORT CHANGED OVER YOUR CAREER?

In my first position in 1980 at the University of Calgary, the building I was working in was called the *tumor centre*, because people we so scared of the word *cancer* and its association with terminal illness. Cancer awareness today has improved tremendously; the word itself is in the media every single day. Cancer has been demystified. As the baby boomers continue to age, the number of cancers is only going to increase. Over time, more cancer patients and survivors have become activists, with support groups, runs for the cure, etc. This new patient-driven light on cancer as an illness has been important for research funding and public education. However, cancer prevention consistently gets some of the least funding amongst all other realms of cancer research. Health promotion and disease prevention have not benefited as much from this cancer enlightenment. One could make the argument that we have an illness care system as opposed to a healthcare system. With that being said, a notable area where wonderful progress has been made involves smoking prevalence. In B.C. we are between 12–15% smoking prevalence, which is a huge positive change in comparison to the 25%+ prevalence seen a couple of decades ago.

ASIDE FROM FUNDING ISSUES WITH PRIMARY CANCER PREVENTION WORK, WHAT ARE SOME OF THE CHALLENGES THAT FACE THE FIELD?

One of the broadest problems that we face is the intrinsic human need for instant gratification to justify our immediate actions. This is particularly notable at the level of policy makers and politicians. It is a difficult situation for them because they need to show return on investment and effective terms of office for re-election. However, the solutions to problems that face the population involve long-term systemic changes that would really require a visionary. We like to see immediate results, and this is not how preventive medicine works. One of the strategies we are using to break through this issue of long-term payoff is to focus on short-term benefits for individuals that reduce risk factor exposure in their lives. For example, by focusing on improved sleep behaviours, people generally feel more rested and productive—whilst also gaining from the cancer risk reduction conferred by sleep optimization. Furthermore, the frustrating thing for the individual is that you can do everything right and still get cancer. Just like we save for our children's futures, we need to ensure that we take steps to make our future the healthiest one possible.

CAN YOU PLEASE DISCUSS SOME OF THE PROJECTS THAT ARE CURRENTLY BEING DEVELOPED BY THE CENTRE OF EXCELLENCE IN CANCER PREVENTION?

The Centre of Excellence in Cancer Prevention is a vehicle to bring researchers to UBC and build a critical mass of intellect from which we can develop multidisciplinary projects. Scientists within the centre are looking at everything from environmental causes such as arsenic and radon to nutritional epidemiology[1], as well as methods behind measuring nutritional exposure using biomarkers to track food intake. In the department of physiotherapy, studies are being done to look at the effects of physical activity on breast and colon cancer incidence all the way from the population level to the tissue metabolism level. There is a huge degree of liaising with the Cancer Society to understand the concerns from healthcare providers regarding current policy and gaps in care because they are truly the boots on the ground when it comes to day-to-day patient care. While I have several personal collaborations, I will discuss a few in more detail.

The first project I will discuss is the Worksite Wellness Program [1]. The Cancer Society has found that reaching people through worksites is a phenomenal way to access a large receptive audience—especially since the infrastructure of newsletters and social groups exists in most cases. Some of our interventions included setting up challenges between departments and tailored e-mail reminders to emphasize things like nutrition and wellness, as well as understand barriers at the individual level. This randomized control trial [1] showed a positive change in behaviour using both the e-mail intervention as well as the social support intervention. The wellness parameters included weight loss and increased fruit and vegetable consumption. These findings are

[1]Current efforts in nutritional epidemiology are focused on identifying methods in order to measure nutritional exposure using biomarkers and food intake tracking.

now being incorporated into worksites across British Columbia. However, one problem that arose was that we noticed that about 80% of our participants were women. We then started looking at male-dominated worksite wellness in rural B.C., Northwest Territories and the Yukon (especially in work camps and resource industry). This project is currently being implemented and we are seeing that our program is being accepted in a phenomenal way.

Another project looked at a sleep intervention for night shift workers[2] [2]. Being exposed to light at night has been demonstrated as a risk factor for breast cancer. When this news first came out, it was particularly concerning for women in healthcare, as much of their work was done during overnight shifts. We applied a telephone-delivered sleep intervention in 47 night shift workers delivered by the team at the UBC Hospital sleep clinic. This resulted in a statistically and clinically significant quality of sleep improvement that lasted 1 year post intervention. The next step will be to make this intervention more available to the larger population of night shift workers.

The final project I will discuss is a prostate cancer survivor study.[3] Prevention is key in cancer realms with a relatively long life expectancy, especially in the survivor population. Since prostate cancer is the most commonly diagnosed form of cancer in males (in Canada), we wanted to improve long-term outcomes post remission for patients. We identified nutrition as a key area for this demographic because many of the medications cause bone density changes, weight changes, muscle loss, and alteration in muscle activity. Our intervention was a cooking class for the men and their wives. This was led by a chef who taught the couples to do new things with old foods that they knew and loved, in order to improve the health profile of their meals. We are currently in the process of following their health and emotional status changes throughout the intervention and look forward to analyzing the results.

You can certainly see how it takes a creative, interdisciplinary approach to make an impact in the cancer prevention realm. Throughout all projects, our core mandate is sustainability, especially when we look forward after the period of funding is over.

HEALTHCARE IS CRITICISED FOR BEING REFLEXIVE; WE RESPOND TO ILLNESS AS IT PRESENTS IN THE POPULATION. WITHIN THE CONTEXT OF STRAINED HEALTH RESOURCES THAT WE FACE IN MANY AREAS OF CANADA, WHAT ROLE DOES PREVENTION PLAY FOR THE FUTURE OF CANADIAN HEALTHCARE? HOW DO THE STUDENTS OF HEALTHCARE ENGAGE WITH THE PREVENTIVE SIDE OF MEDICINE?

If we don't embrace preventive medicine, we are going to be far more overwhelmed in the future compared to today. The key is support from the leadership. Policy around billing for preventive counselling is an essential issue that must be addressed. The team-based approach to healthcare is most promising. No single part of the health team should take the full load of preventive medicine. As a learner and a student, it is your role to identify individuals in your teams who engage with preventive practices and learn from them. If you do not know the resources, that is totally alright, but it is absolutely your responsibility to be tapped into your network to know where to find those resources. Students need to look forward at the health system they will be inheriting, and as such it is really up to you to make preventive medicine a priority in your own practice.

ACKNOWLEDGEMENTS

The author would kindly like to thank Dr. Carolyn Gotay, PhD, for taking her time to answer these questions and explain her research field. For more information on the work conducted by Dr. Gotay and her colleagues, please visit https://cancerprevent.ca/.

REFERENCES

1. Monro M, Amick B, Bottorf J, et al. Be well at work: a randomized study of innovative workplace cancer prevention interventions. Poster session presented at: Semiahmoo 2014, the Annual Occupational, Environmental and Public Health Conference; 2014 Jan; Blaine, WA.
2. Gotay C, Shen H, Munoz C. The impact of an intervention to improve sleep quality in normal, overweight and obese female shift workers. Can J Diabetes. 2015;39(1):S68.

[2]The sleep intervention consisted of 12 telephone-delivered cognitive behavioral therapy sessions delivered by an experienced sleep counsellor. These sessions focused on changing unhealthy behavioral patterns by modifying thought processes.
[3]This study is currently in progress and therefore a formal citation is not provided. For more information, refer to http://spph.ubc.ca/cooking-class-study-seeks-to-increase-health-outcomes-for-prostate-cancer-survivors-and-their-partners/.

Preventative Medicine as a Tool to Ensure Health Equity for Disadvantaged Populations: An Interview with Dr. Kevin Pottie

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ABSTRACT

"An ounce of prevention is worth a pound of cure." —Benjamin Franklin. In this article, we interview Dr. Kevin Pottie, MD. Dr. Pottie is well known for his clinical and research work on preventative medicine, health equity and evidence-based guidelines, particularly as they relate to disadvantaged populations. We discuss with Dr. Pottie his career as a clinician investigator. He guides us through his journey and shares with us important advice on caring for newly arriving Syrian refugees based on recent published guidelines.

RÉSUMÉ

« Mieux vaut prévenir que guérir. » —Benjamin Franklin. Dans cet article, nous interviewons Dr Kevin Pottie, MD. Dr Pottie est reconnu pour sa recherche clinique en médecine préventive et en santé équitable particulièrement dans le domaine des populations désavantagées. Dans cette entrevue, Dr Pottie discutera de sa carrière en tant que chercheur clinique et nous partagera des conseils importants sur les soins à donner aux réfugiés syriens nouvellement arrivés au Canada. Ses conseils sont fondés sur des lignes directrices nouvellement publiées.

CAN YOU TELL US ABOUT YOUR EDUCATION, TRAINING, AND CURRENT POSITIONS?

I completed my undergraduate degree in Psychology, followed by medical school—both at Dalhousie University. I went on to do my training in Family Medicine at the University of Ottawa. Later on, I completed a Master's of Clinical Science in Family Medicine and Refugee Health at Western University.

I am a clinician investigator with a 30:70 division for clinical duties and research. I am an associate professor in the departments of Family Medicine and Epidemiology and Community Medicine at the University of Ottawa, a Principal Scientist at the Bruyère Research Institute, a member of the Canadian Task Force on Preventive Health Care (CTFPHC), and the Chair of the Canadian Collaboration for Immigrant and Refugee Health (CCIRH). The main focus of my research is on developing evidence-based guidelines to improve primary health care for disadvantaged populations.

HOW DID YOU BECOME INTERESTED IN PREVENTATIVE MEDICINE?

As a young medical student at Dalhousie, I was influenced by one of my mentors, Dr. Joni Guptill. I was completely intrigued by Dr. Guptill's stories from a recent mission with Médecins Sans Frontières (MSF). Soon after, I started to get involved in this field. My first mission with MSF was to address the Abkhazia Region diphtheria epidemic in the Republic of Georgia in 1995. My global health relief work took me to war- and epidemic-inflicted regions all around the world. Currently, the main focus of my work is health equity; of which preventative medicine is a component. Health equity focuses on addressing disparities in health care access and targeting the social determinants of health, such as housing, education, and employment. Preventative medicine and working with disadvantaged populations appealed to me as a medical student because I could appreciate the effect of my work in terms of saving lives and reducing suffering.

Keywords: Preventative medicine; Health equity; Refugee health

WHAT IS A TYPICAL WEEK LIKE FOR YOU? HOW DO YOU MAINTAIN BALANCE BETWEEN RESEARCH, CLINICAL WORK, AND PERSONAL LIFE?

As a researcher, I do not really have a typical week. I usually spend three half-days in clinic, which includes teaching family medicine residents and medical students. The rest of my time is devoted to research, which includes conception of projects (usually leading to grants or ethics applications), refining of methods and design, data collection, data analysis and interpretation, and preparation of publications. At any time, I usually have five to ten ongoing research projects plus graduate students' projects. As you advance in your research, you tend to spend most of the research time on conception of projects and data analysis and interpretation and less on data collection, but I continue to do that too. My work necessitates traveling for conferences, as well as team meetings since I collaborate with professionals from all around the world. For instance, I am heading to Saskatoon, Saskatchewan tomorrow to participate in the Refugee Healthcare Conference. The lack of a routine schedule can be challenging at times, but it keeps my job exciting.

Maintaining balance can be rather difficult. My clinical work schedule is usually pre-determined; however, it is research that has no limit and can extend into clinical and even personal life. I have definitely done research work while on vacations, so it is easy to be consumed in your research. However, it is essential to set boundaries and to realize the importance and joy of family and personal life. This in turn will give you energy and motivation to keep going in your clinical and professional endeavours.

CAN YOU TELL US ABOUT ONE OF YOUR INTERESTING PROJECTS?

In the period between 2005 and 2011, I co-chaired a team to develop the Canadian evidence-based clinical guidelines [1] for immigrants and refugees published in the Canadian Medical Association Journal (CMAJ). This internationally unique set of guidelines for migrant health involved the collaboration of over twenty interdisciplinary teams of clinicians, researchers, and other experts in the field. We subsequently developed a set of preventative checklists for practitioners providing primary care for immigrants and refugees [2]. It allows practitioners the ability to personalize clinical preventative care to patients, based on their region or country of origin and migration history, accounting for factors that impact their health. For example, certain factors such as forced migration, low income and limited proficiency in English and French increase the risk of decline in health and are important factors for consideration in the delivery of preventative care for such populations [2].

YOU HAVE BEEN INVOLVED IN SEVERAL PROJECTS IN PREVENTATIVE MEDICINE FROM THE WORLD HEALTH ORGANIZATION TO THE CTFPHC. WHAT IS YOUR TAKE ON THE CURRENT APPROACH TO PREVENTATIVE MEDICINE?

Preventative medicine is an exciting area as there continues to be a lot to learn. The government continues to invest in preventative medicine as it realizes the potential for cost savings and improved health outcomes. It is an exciting time to be involved in preventative medicine. For example, the use of genetics and personalized medicine is revolutionizing medicine overall, especially in the case of preventative medicine, as it allows for the identification of risk factors in one's own genome and to tailor preventative measures and interventions accordingly.

The greatest success in preventative medicine, as regarded by many, is the development of vaccinations. However, one of the challenges facing today's preventative medicine (and all areas of medicine for that matter) is access to care; and this is where my interest in health equity fits. I believe that regardless of the advancements we make in medicine, it would not have an impact if we are unable to reach the target populations. Ensuring equitable access to health care services and addressing social determinants of health are important components of the field of preventative medicine.

One mistake we all fall for is the belief that preventative medicine means we need to always do more. The pendulum in preventative medicine seems to have shifted too far towards overscreening, which is a challenge in this field. Overscreening is not without its drawbacks. It can lead to extensive tests, worried patients, and increased costs. It is important that preventative measures are guided by evidence; sometimes it is wiser to not screen. For instance, regular screening for post-traumatic stress disorder (PTSD) among refugees used to be recommended. However, we now know that overscreening for PTSD can re-traumatize vulnerable patients and attach an unnecessary label to them [1]. Our current guidelines advise against routine screening for PTSD, but rather recommend remaining alert [1]. Another example is screening for diabetes. Current guidelines from the Canadian Diabetes Association recommend screening for type 2 diabetes for everyone starting at the age of 40 [3]. However, guidelines from the CTFPHC on screening for type 2 diabetes suggest that there is actually no evidence that this approach reduces the incidence, mortality, or complications of diabetes among adults with low to moderate risk [4]. We were not able to identify randomized trials or observational studies demonstrating that regular screening for type 2 diabetes was associated with improved intermediate (i.e., frequency of diagnosis) or final (i.e., mortality) outcomes among patients with low to moderate risk [4]. All that to say, often it feels advantageous to do more, when it may not be driven by evidence.

GIVEN THE RECENT ARRIVAL OF SYRIAN REFUGEES IN CANADA, DO YOU HAVE ANY ADVICE FOR CARING FOR THIS PATIENT POPULATION?

With the recent humanitarian crisis in Syria, Canada was among the leaders in accepting a considerable number of refugees. These refugees arrive with a unique set of emotional, psychological, and physical needs, which present a challenge for primary health care providers. We have recently published a study in the CMAJ with updated recommendations to specifically address this issue [5]. The study discusses the CCIRH guidelines and the evidence-based preventative checklists as they relate to Syrian refugees, and provides an update of the literature. Feedback from practitioners caring for Syrian refugees from around Canada is helping to inform the guidelines. For example, the guideline recommends screening for hepatitis C, since its prevalence is uncertain among Syrian refugees. However, we are learning that hepatitis C is indeed rare among this group.

DO YOU HAVE ANY ADVICE FOR YOUNG LEARNERS WHO ARE INTERESTED IN PREVENTATIVE MEDICINE?

First, my advice for young learners is to identify an area of interest within preventative medicine (e.g., refugee health, women's health, chronic disease prevention, etc.). I can speak only to preventative medicine as it relates to primary care, but it really applies to all fields of medicine. Second, the role of mentorship is paramount. A mentor can guide the student, create opportunities, and provide connections to important resources. As a mentor, I expect students to have the passion for preventative medicine and to demonstrate continued long-term commitment. Third, I recommend getting involved as early as possible to build knowledge and acquire skills; this can be through research projects, advocacy groups, or international placements. Finally, each person needs to set priorities; for me, my biggest project is the one at home, with my children.

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REFERENCES

1. Pottie K, Greenaway C, Feightner J, et al. Overview: evidence-based clinical guidelines for immigrants and refugees. CMAJ. 2011;183(12):E824–E830.
2. Pottie K, Warmington R, Miller K, Raza D. Evidence-Based Preventative Care Checklist for New Immigrants and Refugees [Internet]. Ottawa (ON): Canadian Collaboration for Immigrant and Refugee Health; 2012 [cited 2016 Mar 06]. Available from: http://www.ccirhken.ca/ccirh/checklist_website/index.html.
3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada [Internet]. Can J Diabetes; 2013 [cited 2016 Mar 06]. Available from: http://guidelines.diabetes.ca/fullguidelines.
4. Pottie K, Jaramillo A, Lewin G, et al. Recommendations on screening for type 2 diabetes in adults. CMAJ. 2012;184(15):1687–1696.
5. Pottie K, Greenaway C, Hassan G, Hui C, Kirmayer LJ. Caring for a newly arrived Syrian refugee family. CMAJ. 2016;188(3):207–211.

Taking on Tobacco: A Discussion with Dr. Andrew Pipe About His Career and the Ottawa Model for Smoking Cessation

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ABSTRACT

Dr. Andrew Pipe is chief of the division of Prevention and Rehabilitation at the University of Ottawa Heart Institute and Professor in the Faculty of Medicine at the University of Ottawa. He completed his medical training at Queen's University, and interned at The Ottawa Hospital, beginning a career path which combined his interests in sports medicine, health promotion, and advocacy. He has been a physician for athletes at the international level, served on several sporting and anti-doping organizations, and is recognized as a leading expert on cardiovascular disease prevention, physical activity, and smoking cessation.

RÉSUMÉ

Dr Andrew Pipe est professeur à la Faculté de médecine à l'Université d'Ottawa et il est également responsable de la division de prévention et de réhabilitation à l'Institut de cardiologie de l'Université d'Ottawa. Dr Pipe a terminé son éducation à l'Université de Queen's et son entrainement à l'Hôpital d'Ottawa où il a commencé sa carrière dans un domaine incluant la médecine sportive, la promotion de la santé et la défense des droits. Il a été médecin pour les athlètes au niveau international et il est reconnu comme un expert sur la prévention de maladies cardiovasculaires, sur l'activité physique, et sur la cessation du tabagisme.

TELL US A BIT ABOUT YOURSELF, YOUR BACKGROUND IN HEALTHCARE, AND HOW YOU CAME TO BE IN YOUR CURRENT POSITION AS A CLINICIAN.

I grew up in England, and emigrated to rural Ontario with my family when I was 12. I went to Queen's University and began life as a student in honours politics. Halfway through, I became interested in medicine; I remember saying to myself that you can always be involved in politics as a physician, but you could never become involved in medicine as a political scientist.

As an athlete, I decided that I wanted to maintain a relationship with sport over my career, and I came under the influence of people in Ottawa during my internship at the Civic Hospital who cemented that. Following my internship, I practised medicine in a small mining community in Northern Ontario for three years. While there, the track at Laurentian University was one of only two synthetic tracks in Canada, and it became the site for all kinds of invitational track meets prior to the Montreal Olympics. The local medical society recommended me to be the physician for meets, so I was able to maintain a relation with sport at a fairly high level.

I then decided to travel to Australia and Papua New Guinea for a couple of years. I kept letters of introduction from various sport organizations in my back pocket, and I used my interest in exercise physiology as an opportunity to combine my travels with medical practice.

Upon my return to Canada, I became involved with the Canadian Men's basketball team at the world championships in Manila, and I also served as the physician for the Canadian cross-country ski team in Scandinavia. I then began an orthopedic residency in Ottawa, because the conventional wisdom at the time was that if you had an interest in sport and wanted to practise medicine, orthopedics was the way to go. However, after a year I realized that this wasn't the career path I wanted to follow.

Keywords: Smoking cessation; Preventative medicine; Tobacco

I was getting prepared to go back overseas to a third world country, when Willy Keon, who was the creator and head of the Heart Institute at the time, called me up and recruited me. During this time, I became involved in some anti-tobacco activities, as I was already sensitized to anti-tobacco issues as they related to sports sponsorship and so on.

One day, Willy called me up and asked me to finish cardiac surgery training, telling me that they'd arrange for me to get a fellowship elsewhere and then return to Ottawa. I thought about it for a couple of weeks and told him, "I'm probably the only guy in the world that would say this, but I don't think this would be right for me or for you, and I expect that you'd like me to probably pack my bags." To my surprise, he expected this, and offered me an academic appointment to keep up my work on physical activity, sport issues, and particularly the anti-tobacco stuff because of its consistency with the values of the Heart Institute.

Over the course of my 35 or so years at the Heart Institute, I've had an amazing array of involvements and opportunities: I ran the artificial valve clinic, catalyzed issues related to community health promotion and physical activity issues, and others. About 13 years ago, I was asked if I could take over as the chief of division of Prevention and Rehabilitation.

I look back and sometimes I have to pinch myself. I will be going to my 12th Olympics in Rio, for example. I've been involved in a whole array of anti-doping issues internationally and served on several international sport organizations in a consulting role on issues that relate to sports medicine, or anti-doping programs. I've also had a wonderful series of clinical adventures, but probably the most important work that I've done has been to do with issues that relate to tobacco control and smoking cessation.

WHAT TRIGGERED YOUR INVOLVEMENT WITH SMOKING CESSATION ADVOCACY?

As a medical student I remember thinking that, given what we knew about the consequences of tobacco, it made no sense that smoking and tobacco products were dealt with in our community the way they were. As a jock, I thought that smoking was a crazy behavior that interfered with physical performance. I remember that people's eyebrows would raise when I said that my apartment in the intern's residence was going to be smoke free, because nobody did that sort of thing at the time. When I was in general practice, I immediately became aware of the problems posed on a daily basis by patients who were smokers and, as we now know, addicted to nicotine. I think I was always kind of aghast and disappointed that the medical community and, in particular, many of the major health organizations in those days had done nothing to address this problem.

I had this one very significant experience; I got asked by one of my patients to see her husband. He was a contract driller, which meant he was off in the middle of the bush, drilling for sometimes a couple of months at a time. She got a message that he'd had this bad cold and was on antibiotics, and wasn't getting any better. He had a couple of episodes of hemoptysis, we did a chest X-ray, and blatant was this lung tumour. I made the appropriate referrals, but long story short, inoperable, palliative care.

One day I said to his wife, "We both realize the nature of the situation in terms of your husband's condition, and I think it's important, and please forgive me for asking this, but do you have a will?" The answer was no, and I explained, "Well, in the absence of a will, and particularly if he dies suddenly, there are going to be some challenges, so I really think it's important that you get one." A few days later, she had the will, and asked me to witness it for her. I said, "A physician should not be witnessing the wills for the patients they're caring for, for various obvious reasons, but I'll see if I can get someone to help you." I asked the nurse if she could help and I assured her that I would personally back her, and that there would be boxcars of lawyers that would come to her defense if necessary. She agreed to witness, and soon after I went back into the room. The children were there, the wife was there, and I bet you it wasn't ten minutes later, the patient vomited. His tumour must have eroded into his pulmonary artery, and he exsanguinated before our eyes into his bed. It was just the most horrific thing that one could ever see or experience and a horrible thing for family and children to have to see. I remember thinking, "Those bastards in the tobacco industry are responsible for this, and somebody should do something about that." Those words came to resonate often in the years to come, because whenever you find yourself thinking, "They should do something about it," it immediately removes yourself from consideration as being part of a solution to a problem. Here's where I think my political science background came in; I became determined that if there were opportunities for advocacy, I would act upon them. That lead me into a bunch of adventures both in sport and other areas of tobacco control.

COULD YOU TELL US A BIT ABOUT HOW THE OTTAWA MODEL FOR SMOKING CESSATION EVOLVED?

When I first took my current position, I began to look at what we were doing for smoking cessation at the Heart Institute. One day, somebody said, "You know, on floors 2, 3 and 4, we see 2,500 patients a year who are smokers, what are we doing with them?" We were all over people that were hypertensive, or dyslipidemic, or dysglycemic, or had diminished renal function; lights would flash, we'd fire multiple medications, and everyone would pat themselves on the back about what wonderful jobs they were doing in terms of managing these harbingers of future cardiovascular disease. Nobody was paying the slightest bit of attention

to the fact that the monumental modifiable cardiovascular risk factor might be there.

So we set about developing a protocol that would very systematically identify and then provide assistance to patients who were smokers and then follow them up using some intriguing kinds of approaches. In association with Dr. Robert Reid and one of the nurses in particular, Bonnie Quinlan, we began to document what we were doing and were able to show very substantial increases in the number of patients who were stopping smoking. That created an opportunity to expand the program, first into general hospitals in the Champlain region, and eventually into 300 healthcare centres across Canada. We also have an adapted model which is being applied in family health teams and other primary care settings across Ontario. We're dealing with hundreds of physicians and thousands of smokers, so in some ways we've transformed smoking cessation practice in those settings. However, I think it's important to understand that there is still a huge reservoir of smokers out there in the community, which underscores the importance of the continued development of public policies and regulations.

WHAT ARE THE KEY ASPECTS OF THE MODEL THAT MAKE IT UNIQUE OR SUCCESSFUL?

Systemization has been very important. We emphasize the same protocol-driven approach to smoking cessation that we would use to address other clinical problems; we don't leave anything to chance. Everybody gets their blood pressure taken when they come to the hospital, and that affords an opportunity to identify hypertension. The protocol specifies that the smoking status of the patient must be identified, and we do that in two ways: asking people if they've used tobacco in the past seven days, or in the past 6 months. Only using those kinds of questions will give an accurate idea of a person's smoking status. Once documented, this triggers a cascade of other events according to the protocol, which is embedded in the hospital's care maps.

Equally important has been our ability to transform the knowledge of clinicians about smoking and its relationship to a whole array of other clinical situations, in order to move beyond "smoking is a habit and it's your fault." We really want to enhance clinicians' understanding of the processes that are responsible for the perpetuation of smoking behavior, for example, the interaction between smoking and those who have significant psychiatric illnesses. About 40% of all cigarettes today are consumed by individuals with psychiatric illnesses, and people used to assume that they didn't have the skills to manage this habit. They also assumed it was their only pleasure so if you messed with it, you'd mess with the management of their underlying illnesses. But these all turned out to be completely bogus concepts.

SPEAKING OF THE MENTAL HEALTH COMMUNITY, DOES THE PROGRAM ADAPT TO SPECIAL POPULATIONS?

Absolutely. We spend a lot of time talking to our primary care colleagues about how they can assist, and about these kinds of relationships, and the implications for the care that the physicians provide. For example, the rate at which a person metabolizes nicotine is an important determinant of how likely they are to become a smoker and whether they'll have difficulty stopping. If a woman becomes pregnant, her rate of nicotine metabolism may increase substantially, so now you begin to have reasons as to why those otherwise earnest and determined young women who said, "I'm going to stop smoking when I become pregnant," have difficulty quitting.

In terms of the mental health population, it's important to understand that hundreds of times a day, a smoker is administering small doses of monoamine oxidase inhibitor–like substances, which explains why so many people with a history of, or propensity for depression are smokers. Schizophrenics smoke so exceptionally aggressively because when you stimulate the alpha-7 nicotinic receptors in their brains, this has a gating effect, and dampens the intensity and frequency of the stimuli that constantly assail and destabilize those individuals. Most clinicians have no clue about these kinds of interrelations; even as prosaic as the fact that if you're a smoker, you dramatically accelerate the metabolism of a whole variety of medications, including anti-psychotic medications, or even caffeine. Clinicians are often blissfully unaware of these commonplace kinds of relationships, which are all the more tragic given the fact that tobacco is Canada's leading cause of preventable disease, disability, and death. You would think that as a profession, we would want to know everything we possibly could about these features, so that we can help our patients who are addicts.

Contrary to what many clinicians think, the management and stability of underlying psychiatric conditions can be dramatically improved with smoking cessation. There is clear evidence that people with psychiatric illnesses can in fact quit smoking, and do so at rates similar to that of general population. This may take more time, however, and may require a more careful follow-up. The other important reality is that the life expectancy of Canadians with significant psychiatric illnesses can be 20 years less than that of other Canadians, which is an astounding public health discrepancy. The majority of that difference is accounted for by high rates of smoking and development of tobacco-related diseases. As such, this is a population that will benefit from this type of thoughtful assistance.

In terms of Indigenous populations, I have not yet seen evidence of approaches that have been novel, effective, and innovative. We acknowledge that there is sacred and spiritual use of tobacco

in ways that do not reflect smoking as we know it, so that's an issue that's always raised when this topic comes up. The challenge, however, still remains. For example, there is a very large First Nations community just south of us in Akwesasne that has noted several issues relating to contraband tobacco and high rates of tobacco-related disease. To our embarrassment, we have not had success in developing innovative strategies with which to address these issues within the community.

Finally, the belief that you can't use nicotine with patients that have cardiac disease is a concept (although untrue) that continues to get in the way of clinicians being able to help patients stop smoking. As you can see, there's absolutely no reason why smoking cessation can't be adapted to meet the needs of specific high-risk populations. Along the way you can dispel all kinds of other deadly misconceptions that get in the way of helping people address a lethal condition.

WHAT IS THE ROLE OF PHARMACOTHERAPY IN SMOKING CESSATION?

The evidence shows that you can triple or quadruple the likelihood of smoking cessation success when you provide pharmacotherapy appropriately. What you're doing is stimulating nicotinic receptors and inducing in the brain the kinds of changes that are typically produced by smoking, using either nicotine or another agent. What that does is it forestalls the development of symptoms of craving and withdrawal. This makes a patient comfortable enough so that they can then go about their daily life free of discomfort while they acquire a whole repertoire of non-smoking behaviors. Underlying that is the concept that you must make sure that the doses of the agents you're providing are appropriate to provide adequate relief from withdrawal, and that those doses are maintained long enough. For example, in pregnant women, we have to be prepared to titrate doses during pharmacotherapy in order to ensure an appropriate response during long-term follow-up. We take pains to try to talk to our colleagues about the needs of specific populations.

WHAT IMPACT DO YOU THINK E-CIGARETTES COULD HAVE ON THE FUTURE OF HEALTHCARE, AND DO YOU THINK THEY HAVE ANY ROLE IN SMOKING CESSATION?

The e-cigarette question is very intriguing for a number of reasons. There's no question that aerosolized nicotine is infinitely safer than nicotine that is inhaled as a product of combustion, so from a harm reduction perspective, these devices offer some promise. The challenge, however, is that these products are totally unregulated in Canada. There can be an array of other substances added to these solutions, such as flavouring products. Furthermore, we have no way of knowing what dose of nicotine these devices are delivering. So first and foremost, we need these products to be regulated. In the current absence of federal government regulation, the provinces have moved to fill that void. Nova Scotia and Ontario have banned the use of these devices in places where people are not normally allowed to smoke, as well as the use of flavouring substances.

The other challenge is that the tobacco industry is buying some of these companies, and they have no interest in marketing e-cigarettes as an alternative to conventional cigarettes. Rather, they will use these devices as line extensions of existing products. This opens the door to a larger number of e-cigarette users becoming dual users, as well as increased use by adolescent non-smokers who may then turn to conventional tobacco products. Finally, current evidence shows that e-cigarette users are approximately 40% less likely to stop smoking than those who use other methods of smoking cessation pharmacotherapy. Keep in mind that evidence is limited, but it is evolving and growing.

WHAT ADVICE DO YOU HAVE FOR STUDENTS WHO ARE INTERESTED IN GETTING INVOLVED IN ADVOCACY?

If you're intrigued by something, don't be afraid to follow and pursue those interests. Also, don't be afraid to be unconventional. I think there is very much a tendency, which is more marked today than it was during my training, that you have to follow a certain route. There is absolutely nothing wrong with thinking a little outside the box, particularly when it comes to advocacy matters. I think all of us in medicine, irrespective of our discipline, are going to encounter circumstances which cry out for some form of advocacy. I would encourage students to speak out thoughtfully, without hesitation, on issues that can only be helped by doing so. Becoming involved in those kinds of activities can be fascinating, in that they take you into territories you never dreamed possible and experiences that are beyond the conventional.

I think of some of the advocacy roles I got involved in with tobacco control, whether it was helping to get smoking out of airplanes, or the elimination of sponsorship of sports, public health bylaws and so on. I was suddenly in unfamiliar territory, but it was fascinating. At the end of the day, what I've done in tobacco control has probably been one of my greatest contributions to the overall health of the community, and in hindsight, I don't think I'd have done things any differently.

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Physician Assistants as Chronic Care Coordinators—An Interdisciplinary Patient-Centered Approach to Managing Diabetes

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ABSTRACT

With an aging population and an increasing number of people living with chronic disease, Canada's primary care system is in need of change. Healthcare must better incorporate prevention and patient education in the battle against chronic disease. This article explores the growing role of Physician Assistants (PAs) in enhancing access to appropriate care for the chronically ill, using an example of a PA working as part of a family physician practice in Northern Ontario to improve the care of its diabetic patients.

RÉSUMÉ

Avec une population vieillissante et un nombre croissant de personnes vivant avec une maladie chronique, le système de soins primaires canadien est en besoin de changement. Les soins de santé doivent mieux intégrer la prévention et l'éducation des patients dans la lutte contre les maladies chroniques. Cet article explore le rôle croissant des adjoints au médecin (AM) dans l'amélioration de l'accès aux soins appropriés pour les patients vivants avec des malades chroniques. Ceci sera illustré par le biais d'un exemple d'un AM travaillant dans une pratique de médecine familiale au Nord de l'Ontario pour améliorer les soins de ses patients diabétiques.

INTRODUCTION

The delivery of primary care is rapidly evolving in Canada as our healthcare system is overwhelmed by the challenges of an aging population and the increasing burden of chronic disease [1]. The advent of Physician Assistants (PA) is changing the human landscape of healthcare delivery, particularly in rural settings. These newer players may hold the key to improving not only timely access to primary care, but also the quality of care, by spending more time engaged in preventative care and managing chronic illness. PAs can assist in a supportive role, but also in more specialized functions such as managing subsets of a physician's practice. This commentary reviews the role of a PA as a diabetes care coordinator in a Northern Ontarian physician's office.

ADDRESSING CHALLENGES OF PRIMARY CARE AND CHRONIC ILLNESS

Implementation of timely access to healthcare has been a continuing challenge in primary care and medicine in general. With the shift in healthcare towards increasing emphasis on prevention and management of chronic disease, we must ensure that access is not only timely, but also appropriate [1]. PAs have been part of the non-military healthcare system in Ontario since 2007 [2]. In Ontario, both the University of Toronto and McMaster University offer two-year, Canadian Medical Association Accredited PA Programs [2]. PAs have been shown to be well-accepted by the public, as well as safe and effective primary care providers [3–5]. The involvement of PAs has also been shown to improve timely access to healthcare [4]. Physician Assistants are well positioned to improve not only access to care, but the quality in time spent managing and educating chronically ill patients. Time and time again, it has been shown that "chronic disease interventions that positively affect patient well-being necessarily include systematic efforts to increase patients' knowledge, skills, and confidence to manage their condition" [6]. This can be an important niche for PAs.

Physicians often do not have the time to engage in non-problem-based patient education and lengthy follow-ups required by complex chronic illnesses such as diabetes. For example, only 45% of diabetics in the U.S. receive the optimal care they need [7]. With poor glycemic control, we see increased serious comorbidities such as myocardial infarction, stroke, blindness, and kidney disease [8], which are burdensome for patients and for the medical system [9]. It is in everyone's interest to refocus efforts on preventative medicine and incorporate more thorough management of diabetes. We have an opportunity to offer more personalized care with greater access through the use of PAs to provide supplementary patient follow-ups and education. Physicians

Keywords: Primary care; Chronic illness; Physician assistants; Diabetes education

have in fact been asking for more support in the form of "non-physician providers to assist with chronic illness management" [10]. Though the exact role of PAs is not fully defined in relation to physicians [7], this may be one avenue where the use of PAs can fundamentally change the way we approach the delivery of care to the chronically ill; thus, evolving towards a more patient-centered approach with more prevention through increased access and education.

ROLE OF A PA AS DIABETES CARE COORDINATOR AT A FAMILY PRACTICE IN SUDBURY

The Northeastern Ontario Medical Offices (NEOMO) consists of a group of four family physicians whose practice includes over 2,000 diabetic patients. It recently secured Inter-Professional Health Provider (IHP) funding to hire a new Physician Assistant. The goal of this initiative is to "promote the building of small interdisciplinary and collaborative teams to enhance the access to and the delivery of quality primary care" [11]. Of the many responsibilities delegated to the new PA, what stands out as particularly effective and innovative is the PA's role as the "Diabetes Care Coordinator". This role addresses barriers to quality chronic care such as: "rushed practitioners not following established practical guidelines, lack of care coordination, lack of active follow-up to ensure best outcomes [and] patients inadequately trained to manage their illnesses" [12]. The PA's role did indeed provide for improved access and follow-ups, and enhanced patient education.

The PA was tasked with improving access and follow-up care by identifying high-risk diabetic patients who had sub-optimal control, and meeting with them on a monthly basis, as opposed to every three months, to help them get back on track. This provided more face-to-face support time with a primary care provider, with more time for activities such as foot exams and therapeutic counselling. The PA was also tasked with coordinating care with other health entities such as hospital discharge teams and working with hospital staff to enhance diabetic education.

The key piece in the battle against chronic disease is focusing on a patient-centered approach by educating patients in self-management. As stated by the Canadian Diabetes Association, "You are the most important member on your health-care team" [13]. To address this need, the new NEOMO PA was tasked with providing free in-house educational sessions for the practice's diabetic patients and their families. One class in a series of four tailor-made sessions is delivered once a week. The sessions are entitled: "Nutrition and Labels", "Blood Glucose Targets Monitoring and Hypoglycemia", "Complications and Exercise Education", and "Pharmacotherapy". They are held at the Northeastern Ontario Medical Offices, a setting that patients are familiar with.

The format is a town hall–style presentation, open to discussion and questions. This allows participants to benefit from group counselling and facilitates sharing of tips and recommendations amongst the participants and questions directed to the PA. Such group education sessions have been shown to significantly reduce HbA1c levels [14]. In fact, diabetic self-management education programs have also been found to significantly improve blood pressure, fasting glucose, lipid profile, physical activity, and the patient's knowledge of their own condition [15], as well as compliance with medication [16]. Many patients arrive with their own pre-prepared questions, which illustrates the interest and need for such interventions, and for more regular contact with primary care providers for the chronically ill. Such courses already exist in the community, but this one has the added benefit of being facilitated by the same primary care provider the diabetic patients see for their care. This strengthens the therapeutic alliance, provides continuity of care and adds a familiar face to both encounters.

As part of this education initiative, a Diabetes Passport was created and is being provided to all diabetic patients at the clinic. This tool was designed to serve as a reminder of the guidelines to be followed and to help patients track their progress. The PA uses this tool to promote self-management and encourages patients to bring it to the diabetes education sessions and visits to review with the PA. The Passport tracks target values and frequency of tests such as HbA1c, ACR, eGFR, BP, LDL-C and TG. It includes sections on foot self-exams, eye doctor visits, exercise recommendations, hypoglycemia and how to detect its early symptoms. Education materials and Passports specifically have been shown to aid with compliance and patient understanding, and to improve health [16–18]. This reinforces the proactive direction of having a PA as chronic care coordinator to dedicate time to essential aspects of patient care for the chronically ill, something that physicians are struggling to find time to do. It is not only a matter of having more boots on the ground in primary care, but of carving out specific complimentary roles among disciplines. Indeed, as the PA profession expands in Canada, it will be crucial to better define its role in relation to nurses and physicians.

CONCLUSION

The use of PAs in chronic care management is no silver bullet, but it represents a growing trend and promising new direction in Canadian primary care. With the increased focus on patient-centered care, increased access and patient education, this case has illustrated how PAs can serve to improve not only timely access to primary care, but also improve its quality of services for chronic care patients.

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REFERENCES

1. Vedel I, Monette M, Beland F, Monette J, Bergman H. Ten years of integrated care: backwards and forwards. The case of the province of Québec, Canada. Int J Integr Care. 2011;11 Spec Ed:e004.
2. Health Force Ontario. Ontario's Physician Assistant Initiative. Queen's Printer For Ontario, 2015. [Last Modified: March 10, 2015]. [Cited April 4, 2015]. Available from: http://www.healthforceontario.ca/en/M4/Ontario%27s_Physician_Assistant_Initiative.
3. Doan Q, Hooker RS, Wong H, et al. Canadian's willingness to receive care from physician assistants. Can Fam Physician. 2012;58(8):e459–e464.
4. Hooker RS, Everett CM. The contributions of physician assistants in primary care systems. Health Soc Care Community. 2012;20(1):20–31.
5. Doan Q, Sabhaney V, Kissoon N, Sheps S, Singer J. A systematic review: the role and impact of the physician assistant in emergency department. Emerg Med Australas. 2011;23(1):7–15.
6. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Affairs. 20, no.6 (2001):64–78.
7. Everett CM, Thorpe CT, Palta M, Carayon P, Gilchrist VJ, Smith MA. Division of primary care services between physicians, physician assistants, and nurse practitioners for older patients with diabetes. Med Care Res Rev. 2013;70(5):531–541.
8. Manns BJ, Tonelli M, Zhang J, et al. Enrolment in primary care networks: impact on outcomes and processes of care for patients with diabetes. CMAJ. 2012;184(2)E144–E151.
9. McBrien KA, Manns BJ, Chui B, et al. Health care costs in people with diabetes and their association with glycemic control and kidney function. Diabetes Care. 2013;36(5):1172–1180.
10. Reid RJ, Wagner EH. Strengthening primary care with better transfer of information. CMAJ. 2008;179(10):987–988.
11. Ministry of Health and Long Term Care, Ontario, Canada. Inter-Professional Health Provider Funding Application For Primary Health Care Patient Enrolment Model Groups. Queen's Printer for Ontario; 2009-2010 [updated 2013 Aug 19; cited 2015 Mar 10]. Available from: http://www.health.gov.on.ca/en/pro/programs/ihp/.
12. Improving Chronic Illness Care. The Chronic Care Model. "Copyright 1996-2015 The MacColl Center. The Improving Chronic Illness Care program is supported by The Robert Wood Johnson Foundation, with direction and technical assistance provided by Group Health's MacColl Center for Health Care Innovation". [cited 2015 Mar 10]. Available from: http://www.improvingchroniccare.org.
13. Canadian Diabetes Association. Living with Type 2 Diabetes. 2015. [cited 2015 Mar 10]. Available from: http://www.diabetes.ca/diabetes-and-you/living-with-type-2-diabetes.
14. Merakou K, Knithaki A, Karageorgos G, Theodoridis D, Barbouni A. Group patient education: effectiveness of a brief intervention in people with type 2 diabetes mellitus in primary health care in Greece: a clinically controlled trial. Health Educ Res 2015 Feb 26. pii: cyv001. [Epub ahead of print].
15. Molsted S, Tribler J, Poulsen PB, Snorgaard O. The effects and costs of a group-based education programme for self-management of patients with type 2 diabetes. A community-based study. Health Educ Res 2012;27(5):804–813.
16. Gold DT and McClung B. Approaches to patient education: emphasizing the long-term value of compliance and persistence. Am J Med. 2006;119(4 Suppl 1):S32–S37.
17. Dijkstra RF, Braspenning JC, Huijsmans Z, et al. Introduction of diabetes passports involving both patients and professionals to improve hospital outpatient diabetes care. Diabetes Res Clin Pract. 2005;68(2):126–134.
18. Dijkstra R, Braspenning J, Grol R. Implementing diabetes passports to focus practice reorganization on improving diabetes care. Int J Qual Health Care. 2008;20(1):72–77.

Integrating Pharmacogenomics into Clinical Practice

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ABSTRACT

Pharmacogenomics has the potential to improve patient-centered care and lead to an overall decrease in healthcare costs. This would be achieved through fewer hospitalizations due to adverse drug reactions, individualized and effective therapies, and decreased drug development costs with single nucleotide polymorphism pre-screening. Although challenges do exist in encouraging the use of pharmacogenomics—specifically in regards to resources, regulation, and impacts on the pharmaceutical industry—the benefits may outweigh the costs in terms of patient health and safety. In implementing pharmacogenomics, various clinical, ethical, legal, social and economical factors must be considered.

RÉSUMÉ

La pharmacogénomique aurait le potentiel de diminuer le coût des soins de santé et d'optimiser les soins primaires aux patients. Il serait possible d'y parvenir en réduisant les hospitalisations suite aux effets secondaires associés aux médicaments, en utilisant des thérapies individualisées plus efficaces et en diminuant le coût associé au développement de médicaments grâce au test de dépistage de polymorphisme d'un seul nucléotide. Malgré les défis associés à l'utilisation de la pharmacogénomique surtout sur le plan des ressources, de la régulation et de l'impact dans l'industrie pharmaceutique, les avantages en terme de santé et de sécurité sont à considérer. Plusieurs facteurs cliniques, éthiques, légaux, sociaux, et économiques doivent être pris en considération pour l'utilisation de la pharmacogénomique.

INTRODUCTION

Personalized medicine is an emerging practice that uses an individual's genetic profile to direct disease diagnosis, prognosis, and therapy [1]. In 2013, the Government of Canada granted $165 million to Genome Canada, the majority of which was applied to large-scale projects in the division of applied human health to develop personalized medicine [2]. Within the realm of personalized medicine are the fields of pharmacogenomics and pharmacogenetics.

Pharmacogenomics is an examination of common genetic variants within a population to determine associations with specific traits. In this field, genome-wide association studies are used to identify common single nucleotide polymorphisms (SNPs) in the human genome, which in turn may be used to identify genetic risk variants that could impact disease susceptibility and responses to certain therapies [3]. For instance, the pharmacogenomic association between the *apolipoprotein E4* allele and Alzheimer's disease has allowed clinicians to better identify patients at increased risk for developing this form of dementia [3]. Thus, physicians can educate high-risk patients and their families regarding ongoing monitoring and care. With increasing knowledge of genetic risk factors in relation to disease, researchers can continue to apply genome-wide association studies to obtain clinical risk assessments for various disorders [3].

Pharmacogenetics, on the other hand, studies both individual genetic profiles and possible responses to specific drug therapies in order to optimize treatments by maximizing drug efficacy and minimizing drug toxicity. The CPIC (Clinical Pharmacogenetics Implementation Consortium) has developed clinical guidelines for the dosing of multiple drugs based on pharmacogenetic studies of genetic variations among individual patients [4]. Most research done in the field of pharmacogenetics relates to the Cytochrome P450 (CYP450) family of enzymes, who together are capable of metabolizing over 30 classes of drugs [5–7]. Importantly, genetic variability (i.e., SNPs) within these enzymes may influence a patient's response to commonly prescribed drug classes [7]. A number of other successful applications have been recorded in recent years. In 2007, the U.S. Food and Drug Administration (FDA) used pharmacogenetics to recommend a change in warfa-

Keywords: Pharmacogenomics; Pharmacogenetics

rin usage [8,9]. Warfarin, a commonly prescribed anticoagulant, is difficult to dose due to its narrow therapeutic index and variability in dose-response [8,9]. These studies resulted in a new label for warfarin dosing, advising patients with genetic variations in either of the Vitamin K Epoxide Reductase Complex subunit 1 (VKORC1) or Cytochrome P450 2C9 (CYP2C9) genes to consume altered doses of warfarin to account for this unpredictability [8]. Recently, a prospective study carried out by Medco and the Mayo Clinic demonstrated that dose modifications based on genetic testing for CYP2C9 and VKORC1 variants decreased hospitalization rates by approximately one third [10]. Pharmacogenetics is also used to screen patients for thiopurine methyltransferase (TPMT) deficiency when prescribing 6-mercaptopurine (Purinethol) or azathiopurine (Imuran) [11–13]. This screening test is done to ensure that TPMT is active and able to metabolize thiopurines to prevent the formation of toxic metabolites, prior to initiating therapy [12,13,15]. Approximately 11% of the population has reduced TPMT activity and 0.3% of the population has a true TPMT deficiency [14]. In these patients, active 6-mercaptopurine accumulates and a larger proportion is converted to the cytotoxic 6-thioguanine nucleotide analogues, which can lead to bone marrow toxicity and myelosuppression [15].

Given the broad scope of personalized medicine, we have decided to focus our discussion on the role of pharmacogenomics in therapy, and more specifically to illustrate and evaluate the potential use of pharmacogenomics in personalized patient care. We aim to explore possible benefits to the community at large, and stimulate thought with respect to future considerations and challenges of implementing pharmacogenomics into clinical practice.

BENEFITS

The benefits of implementing pharmacogenomics may be substantial. Presently, pharmacogenomics has proven successful in identifying genetic variants associated with disease risk in many genome-wide association studies [16], and may one day replace "trial-and-error" prescriptions with therapy based on individualized genetic information [17]. Furthermore, increasingly rapid turnaround times are becoming realistic. Previously, most genetic testing for SNP analysis or copy number variant (CNV) testing would typically take days before results were received. Roberts et al. (2012), however, have described a point-of-care CYP2C19 genetic test for personalizing anti-platelet treatment with a three-hour turnaround time [18].

Pharmacogenomic testing may also be used to decrease adverse drug events [17]. A Canadian adverse events study reviewed 3,745 patient charts in 20 hospitals across Canada [19,20]. Of the 255 serious adverse events, 59 were related to medical management caused by drug therapy [19,20]. With 2.5 million hospital admissions annually, this suggests that approximately 40,000 serious, drug-related adverse events occur in Canadian acute care hospitals annually [19]. By decreasing adverse events through the application of pharmacogenomic technologies, trust in patient-physician relationships may be strengthened and stress on our healthcare system could be reduced. For example, a severe hypersensitivity reaction to the anti-HIV drug abacavir is characterized by a skin rash, as well as gastrointestinal and respiratory symptoms [21]. Mallal et al. (2002) initially demonstrated an association between abacavir hypersensitivity and haplotype *HLA-B*57:01* using a candidate gene approach [22]. This association was then replicated in other cohort studies [23,24]. Ultimately, these findings were confirmed in a large randomized controlled trial, which showed that cases of abacavir hypersensitivity could be reduced from 7.8% to 3.4% by excluding *HLA-B*5701*-positive patients from abacavir treatment [25]. This has since led to widespread adoption of genetic testing for *B*57:01* prior to the initiation of abacavir treatment.

Finally, SNP screening may allow pharmaceutical companies to exclude participants with variant forms of a gene from clinical trials who would react unsafely or ineffectively to the drug [17, 26]. Excluding these participants may eliminate the confounding of results due to genetic variation. This select participant exclusion could also decrease healthcare visits for patients who would have otherwise needed assistance for adverse events. As a result, drug efficacy will become easier to demonstrate within a specific population group, which in turn could help to expedite market availability [6,17]. Furthermore, improvements in efficiency will likely increase treatment options for illness, decrease drug development costs for pharmaceutical companies, and ultimately reduce purchasing costs for patients [6].

CONSIDERATIONS

Various challenges exist in incorporating pharmacogenomics into clinical practice. Primarily, we have a limited understanding of the complexities of the human genome. Studies are difficult to evaluate due to limited clinical phenotypes and multifactorial drug responses that may mask small genetic effects [16]. Millions of SNPs will therefore need to be assessed for their involvement with the pharmacokinetics and pharmacodynamics of common medications, a process which may be very time-consuming, complicated, and expensive [26]. Further research will be required, both to alleviate these uncertainties and to determine the most cost-effective approach for the integration of pharmacogenomics into clinical practice.

Secondly, pharmacogenomics may have an impact on the pharmaceutical industry. Pharmaceutical companies are driven by the prospect that the drugs they produce could serve more people than existing first-line therapies. As a result of competition and

restricted knowledge regarding which product will work best for the majority of the population, multiple drug alternatives may be created for a given condition. If pharmaceutical companies determine that their drug will only serve a small proportion of the population, they may not invest in further development [26]. Fewer drug alternatives will come to market for medical conditions, and more patients may go untreated if they do not respond to the limited number of available therapies [26].

Thirdly, private insurance companies may use the likelihood of response to certain drug therapies as criteria for insurance eligibility or premium rates. Safeguarding an individual's genetic profile, in terms of storage, control, access and information sharing, must therefore be considered [17,26–28]. Additionally, the consent, privacy and confidentiality concerning the genetic information would need to be reviewed with the patient before sequencing [17,26–28].

Finally, given the complexities of pharmacogenomics and its application to patient care, continuing education for healthcare providers will be of utmost importance. An inter-professional, team-based approach will likely be necessary in maximizing the potential benefits for patient care.

CONCLUSION

As pharmacogenomics becomes further entrenched in healthcare, a number of considerations must be taken into account. Although the clinical utility of pharmacogenomics has been discussed and demonstrated in certain contexts, the primary barrier for wider implementation is our limited knowledge within the field. Further research is needed to alleviate uncertainties and to determine the most cost-effective approach for implementation and integration of pharmacogenomics into clinical practice. A cautionary approach will need to be taken with respect to regulating access to genetic information and protecting patient confidentiality. Furthermore, depending on the technology used, genomic screening may take a significant amount of time. Finally, healthcare professionals will need appropriate training and education in using such information to make competent decisions. Despite these challenges, it is our opinion that the scope of medical management and patient care will be advanced by pharmacogenomics and personalized medicine. Further research will be required, however, before pharmacogenomics can be effectively integrated into our current healthcare system.

REFERENCES

1. U.S. National Library of Medicine. Genetics Home Reference – Personalized Medicine [Internet]. March 28, 2016 [cited April 10, 2016]. Available from: https://ghr.nlm.nih.gov/glossary=personalizedmedicine.
2. Genome Canada. Annual Report 2013-2014 [Internet]. March 31, 2014 [cited 2016 Feb 6]. Available from: http://www.genomecanada.ca/sites/genomecanada/files/publications/febbe4e81e.pdf.
3. Norrgard K. Genetic variation and disease: GWAS. Nature Education. 2008;1(1):87.
4. Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. 2014;15(2):209–217.
5. Pirmohamed M. Pharmacogenetics and pharmacogenomics. Br J Clin Pharmacol. 2001;52(4):345–347.
6. Health Canada. Pharmacogenomics - Biotechnology - Science and Research [Internet]. [updated 2006 Jan 17; cited 2012 Oct 6]. Available from: http://www.hc-sc.gc.ca/sr-sr/biotech/about-apropos/pharma-eng.php.
7. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician. 2007;76(3):391–396.
8. Elias DJ, Topol EJ. Warfarin pharmacogenomics: a big step forward for individualized medicine: enlightened dosing of warfarin. Eur J Hum Genet. 2008;16(5):532–534.
9. Yin T, Miyata T. Warfarin dose and the pharmacogenomics of CYP2C9 and VKORC1 — Rationale and perspectives. Thrombosis Research. 2007;120(1):1–10.
10. Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduces hospitalization rates. Results from the MM–WES (Medco–Mayo Warfarin Effectiveness Study). J Am Coll Cardiol. 2010;55(25):2804–2812.
11. Wang L, Nguyen TV, McLaughlin RW, et al. Human thiopurine S-methyltransferase pharmacogenetics: variant allozyme misfolding and aggresome formation. PNAS. 2005;102(26):9394–9399.
12. Ford LT, Berg JD. Thiopurine S-methyltransferase (TPMT) assessment prior to starting thiopurine drug treatment; a pharmacogenomic test whose time has come. J Clin Pathol. 2010;63(4):288–295.
13. Salavaggione OE, Wiepert M, Weinshilboum RM. Thiopurine S-methyltransferase (TPMT) pharmacogenetics: variant allele functional genomics. Clin Pharmacol & Ther. 2004;75(2):19.
14. Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. Am J Hum Genet. 1980;32(5):651–662.
15. DiPiero J, Teng K, Hicks JK. Should thiopurine methyltransferase (TPMT) activity be determined before prescribing azathioprine, mercaptopurine, or thioguanine? Cleve Clin J Med. 2015;82(7):409–413.
16. Bailey KR, Cheng C. Conference Scene: The great debate: genome-wide association studies in pharmacogenetics research, good or bad? Pharmacogenomics. 2010;11(3):305–308.
17. Buchanan A, Califano A, Kahn J, McPherson E, Robertson J, Brody B. Pharmacogenetics: ethical issues and policy options. Kennedy Inst Ethics J. 2002;12(1):1–15.
18. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet. 2012;379(9827):1705–1711.
19. Baker GR, Norton PG, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ. 2004;170(11):1678–1686.
20. Cadario B. New appreciation of serious drug adverse reactions. BCMJ. 2005;47(1):14.
21. Daly AK. Pharmacogenomics of adverse drug reactions. Genome Med. 2013;5(1):5.
22. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. Lancet. 2002;359(9308):727–732.
23. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359(9312):1121–1122.
24. Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. Pharmacogenetics. 2004;14(6):335–342.
25. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358(6):568–579.
26. Gershon ES, Alliey-Rodriguez N, Grennan K. Ethical and public policy challenges for pharmacogenomics. Dialogues Clinic Neurosci. 2014;16(4):567–574.
27. Marx-Stölting L. Pharmacogenetics and ethical considerations: why care? Pharmacogenomics J. 2007;7(5):293–296.
28. Lipton P. Pharmacogenetics: the ethical issues. Pharmacogenomics J. 2003;3(1):14–16.

Evidence-Based Medicine: Acknowledging the Role for Physical Activity

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ABSTRACT

Modern technology and lifestyles have created an environment that predisposes our population to inactivity, resulting in fewer people meeting the Canadian Physical Activity Guidelines. There is a clear link between inactivity and the risk of developing chronic health conditions including hypertension, type 2 diabetes, and cancer; however, exercise prescription and counselling by physicians is lacking. This may in part be attributed to inadequate training of physicians during medical school. In this commentary, we outline the demand for awareness and training of physicians to prepare them to prescribe physical activity, and propose steps to increase exercise prescription for improved population health.

RÉSUMÉ

La technologie moderne ainsi que nos habitudes de vie actuelles nous prédisposent à l'inactivité ce qui mène moins de personnes à respecter les directives canadiennes en matière d'activité physique. Un lien direct existe entre l'inactivité et le risque de développer des problèmes de santé chroniques incluant l'hypertension, le diabète de type 2, et le cancer. Toutefois, l'exercice et le counseling prescrits par les médecins sont peu pratiqués par les patients qui pourraient en bénéficier. Dans cet article, nous soulignerons le besoin de formation des médecins afin de mieux les préparer à prescrire de l'activité physique à leur patients et leur proposer des étapes pour améliorer la santé physique de la population.

It is well established that physical inactivity increases the risk of developing chronic health conditions, including hypertension, type 2 diabetes, stroke, cancers, dyslipidemia, and osteoarthritis, along with various gynecological and respiratory problems [1]. Cardiorespiratory fitness is one of the strongest health predictors and is associated with lower all-cause and cardiovascular mortality [2]. Despite the substantial body of literature to support the numerous benefits of exercise in all individuals, both for primary prevention and treatment of many chronic health conditions [3], there is a very poor adherence to the recommended 150 minutes per week of moderate-to-vigorous exercise as per the Canadian Physical Activity Guidelines [4,5]. According to the 2012 and 2013 Canadian Health Measures Survey, which directly measured adult Canadian physical activity levels, only 24% of males and 21% of females met the guidelines [6]. These overwhelming levels of inactivity have extensive consequences on overall health such that the annual economic burden attributable to physical inactivity is estimated to be $10 billion [7]. The evidence supporting the widespread benefits of exercise on physical, mental, and emotional health has been recognized for decades, however modern technology and the built environment have nearly completely enabled society to function with a sedentary lifestyle [5,8]. Importantly, modern medicine has underutilized the potential of physical activity in primary prevention and the treatment of many common health conditions [9,10]. Therefore, physicians are missing a vital opportunity to educate Canadians about lifestyle factors that contribute to poor health outcomes and implement systematic changes to enhance the delivery of exercise as preventative and therapeutic medicine, such as referral to exercise specialists and fitness assessments [10,11].

Physicians are situated at the critical interface between the ever-growing body of knowledge within the medical community and their patients who rely on their dissemination of that evidence base. While physicians dedicate countless hours educating themselves on the best available therapies and diagnostic tools, there are certain areas of medicine that are under-recognized. The role of exercise to combat the negative health effects of a sedentary lifestyle is under-recognized due to its inadvertent exclusion from medical school curriculum, and a lack of confidence and time amongst physicians to appropriately prescribe exercise [12]. To this end, Stoutenberg and colleagues (2015) interviewed 58 medical school program directors from the United States regarding exposure to curriculum focusing on the benefits of physi-

Keywords: Exercise; Exercise prescription; Medical education

cal activity in preventative medicine over the duration of the four year programs and found that, on average, students were given a total of 8.1 hours of instruction on the topic [13]. This data is further substantiated by a survey of fourth year medical students at the University of British Columbia, which reported that 69% of students perceived exercise counseling to be highly relevant to clinical practice and 86% thought that they lacked adequate training in the area of exercise prescription [14]. With minimal exposure to the concept of complementing treatment paradigms with physical activity, it is not surprising that physicians do not feel confident in prescribing and counselling their patients about exercise. Given the evidence-based approach to western medicine, it is clear that the inclusion of physical activity into the medical curriculum is long overdue. Furthermore, the notion that physically active physicians are more likely to counsel and advise their patients about exercise indicates that these curriculum changes should also encourage medical students to lead physically active lives by example [15].

Exercise is Medicine Canada (EIMC) was launched in 2012 as a national initiative in conjunction with many Canadian universities, focusing on the promotion of physical activity and exercise prescription in healthcare settings. Specifically, the individual university partnerships with EIMC have been an important first step in engaging medical students and exposing them to the various benefits of exercise on chronic health conditions and as a preventative measure. These EIMC campus initiatives provide exposure to exercise prescription and help to supplement the current lack of physical activity counselling education in the medical curriculum. As physical activity advocates and members of the EIMC on Campus initiative at the University of Ottawa, it is our hope that medical students will continue to participate in EIMC events as well as promote the goals and vision of the initiative in order to demonstrate the need for the inclusion of mandatory physical activity and exercise prescription training within medical education. Moreover, we hope that medical students will continue to adopt strategies to incorporate physical activity into their own lives. While this will contribute to maintaining their own physical, mental, and emotional health, leading a physically active lifestyle will also provide personal insight into the plethora of perceived and actual barriers to exercise faced by their future patients. By endorsing physically active lifestyles, medical students will be primed to be relatable, compassionate, and energetic physicians with the requisite confidence to consistently prescribe exercise to their patients. Ultimately, the EIMC network could be a critical resource for patients to access educational resources about fitness as an important personal health metric, and for physicians to refer their patients to qualified exercise professionals.

Within the current healthcare setting, exercise continues to be under-prescribed; however, there are a few simple suggestions that we feel could, when employed, facilitate improved adherence to physical activity guidelines. First, if primary care physicians were to commit to keeping an exercise prescription pad in their office, then every appointment could be concluded with a brief discussion regarding a prescription for an accessible, cost-effective mode of exercise, such as walking 30 minutes per day, five times per week. In addition, it could be considered a standard practice to issue a follow-up visit 2–4 weeks after prescribing an exercise program, or making a referral to an exercise professional, to assess patient compliance and address any concerns in the same manner that prescription medications are followed to assess for efficacy and side effects.

In modern society, the perception of what exercise entails can be overwhelming and misconceived, especially in the context of the commercialized fitness industry where participating in exercise often falsely appears to require a “baseline” level of fitness [16]. Therefore, it should be the role of the physician together with exercise professionals to redefine exercise individually for each patient, and to encourage affordable and accessible options, including individual walking routines, free community-based fitness groups, and walking or running clubs.

As an initial step towards improving delivery of exercise counselling and prescriptions, medical students and physicians need to be adequately prepared with a physical activity arsenal. This begins with the inclusion of mandatory physical activity training in medical education, and promoting healthy, physically active physicians and medical trainees. Likewise, patients can also take on a leadership role in their overall health by engaging their physician in a dialogue about an appropriate exercise prescription or referral to an exercise professional. Together, physicians and patients need to recognize the efficacy and potency of exercise as a prescription for long-term health. If both parties agree on their specific definition of exercise and commit to meeting the Canadian Physical Activity Guidelines, routine exercise stands to be one of the largest returns on investment for health.

REFERENCES

1. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol. 2012;2(2):1143–1211.
2. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301(19):2024–2035.
3. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology (Bethesda). 2013;28(5):330–358.
4. Tremblay MS, Warburton DE, Janssen I, et al. New Canadian physical activity guidelines. Appl Physiol Nutr Metab. 2011;36(1):36–46; 47–58.
5. Warburton DER, Charlesworth S, Ivey A, Nettlefold L, Bredin SSD. A systematic review of the evidence for Canada’s Physical Activity Guidelines for Adults. Int J Behav Nutr Phys Act. 2010;7:39.
6. Statistics Canada. “Directly measured physical activity of Canadian adults, 2012 to 2013.” Health Fact Sheet. Statistics Canada Catalogue no. 82-625-X.
7. Krueger H, Turner D, Krueger J, Ready AE. The economic benefits of risk factor reduction in Canada: Tobacco smoking, excess weight and physical inactivity. Can J Public Health. 2014;105(1):69–78.
8. Tremblay MS, Esliger DW, Copeland JL, Barnes JD, Bassett DR. Moving forward by looking back: lessons learned from long-lost lifestyles. Appl Physiol

Nutr Metab. 2008;33(4):836–842.
9. Carroll JK, Antognoli E, Flocke SA. Evaluation of physical activity counseling in primary care using direct observation of the 5As. Ann Fam Med. 2011;9(5):416–422.
10. Petrella RJ, Lattanzio CN, Overend TJ. Physical activity counseling and prescription among canadian primary care physicians. Arch Intern Med. 2007;167(16):1774–1781.
11. Kennedy MF, Meeuwisse WH. Exercise counselling by family physicians in Canada. Prev Med. 2003;37(3):226–232.
12. Hébert ET, Caughy MO, Shuval K. Primary care providers' perceptions of physical activity counselling in a clinical setting: a systematic review. Br J Sports Med. 2012;46(9):625–631.
13. Stoutenberg M, Stasi S, Stamatakis E, et al. Physical activity training in US medical schools: preparing future physicians to engage in primary prevention. Phys Sportsmed. 2015;43(4):388–394.
14. Holtz KA, Kokotilo KJ, Fitzgerald BE, Frank E. Exercise behaviour and attitudes among fourth-year medical students at the University of British Columbia. Can Fam Physician. 2013;59(1):26–32.
15. Frank E, Segura C, Shen H, Oberg E. Predictors of Canadian physicians' prevention counseling practices. Can J Public Health. 2010;101(5):390–395.
16. Sequeira S, Cruz C, Pinto D, Santos L, Marques A. Prevalence of barriers for physical activity in adults according to gender and socioeconomic status. Br J Sports Med. 2011;45(15):A18–A19.

Towards a Framework for the Development, Implementation, and Sustainability of eHealth Interventions in Indigenous Communities

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ABSTRACT

eHealth technology, an umbrella term including telemedicine, telehealth, and mobile health interventions (among others), has recently begun expanding its reach into Indigenous communities. With this new "migration" comes the need for special consideration of the factors that contribute to "successful" adoption, integration, and sustainability of such eHealth technologies in Indigenous communities. While existing frameworks are typically helpful orientations to guide eHealth implementation, they commonly lack elements that give specific consideration to the important nuances and special considerations when piloting eHealth initiatives in these unique and diverse community and cultural contexts. There is thus a need to expand, adapt, or design new eHealth adoption and implementation frameworks that help guide the piloting and use of health technologies in respectful, ethical, and community-centered ways in Indigenous communities. This paper suggests subjective considerations for the preliminary development of a generic eHealth technology adoption and implementation framework in Indigenous communities. Considerations are divided into three main sections: Development and Adoption; Implementation; and Sustainability, with relevant discussion of the centrality of community engagement, inclusivity, and respect.

RÉSUMÉ

La cybersanté est une expression utilisée en médecine pour regrouper différentes technologies telles que la télémédecine, la télésanté, et les interventions de santé mobile. Avec une mise en œuvre graduelle de la cybersanté dans les communautés autochtones, il y a des considérations spéciales et des facteurs spécifiques à prendre en compte pour assurer une intégration efficace et durable de ces technologies. Certaines infrastructures existent déjà pour faciliter l'utilisation de la cybersanté. Toutefois, il est important que l'utilisation de ces technologies soit éthique, respectueuse des différences culturelles autochtones, et en fonction des besoins des communautés autochtones. Cet article suggère des éléments à considérer dans le développement préliminaire d'une approche médicale axée sur la cybersanté et dans la mise en oeuvre d'infrastructure dans les communautés autochtones. Les considérations sont divisées en trois sections : le développement et l'adoption; la mise en œuvre; et la durabilité, avec une discussion sur l'engagement communautaire, l'inclusion, et le respect mutuel.

INTRODUCTION

eHealth technology, an umbrella term including (but not limited to) telemedicine, telehealth, and mobile health interventions, has recently begun expanding its reach into Indigenous communities [1]. With its potential to support increased access to health services in rural, remote, and isolated communities, eHealth initiatives are occupying an increasingly relevant and important place in the spectrum of secondary and tertiary prevention services in Indigenous communities [1]. The diverse initiatives that have been implemented to date range from teleophthalmology-based retinal screening programs, to the use of health promoting short messaging services (SMS) for individuals living with hypertension [4].

With this relatively new "migration" of eHealth technologies into Indigenous contexts comes the need for special consideration of the factors that contribute to their "successful" adoption, integration, and sustainability in these community contexts. Existing frameworks of eHealth technology adoption and implementation tend to focus on best practices for piloting eHealth in urban communities, with an emphasis on quality, efficiency, and cost [2,5]. While these frameworks are typically helpful in guiding eHealth implementation, they commonly lack elements that

Keywords: Indigenous health; eHealth; Innovation; Sustainability; Community engagement

give specific consideration to context-specific nuances. There is thus a need to expand, adapt, or design new eHealth adoption and implementation frameworks that help guide the piloting and use of health technologies in respectful, ethical, and community-centered ways.

This commentary suggests subjective considerations in the preliminary development of a generic eHealth technology adoption and implementation framework in Indigenous communities. Considerations are divided into three main sections: Development and Adoption; Implementation; and Sustainability, with the themes of community engagement, respect, and equity cutting across all three considerations.

DEVELOPMENT AND ADOPTION

The importance of contextual inquiry

van Gemert-Pijnen et al. (2011) identify that introducing any eHealth technology into the healthcare system requires careful coordination and communication with health care professionals, patients, and technicians—a process they term "contextual inquiry" [2]. This process is an important but often overlooked consideration in developing and piloting eHealth technology. Specifically, contextual inquiry refers to the process of "information gathering" from the intended users and environment in which the technology will be implemented [2]. In an Indigenous context, there is an even more pronounced need to recognize that eHealth technology development and adoption is a participatory process.

The importance of contextual inquiry in the planning stages of eHealth innovation emphasizes the need for a process of "participatory development" grounded in community engagement [1]. Successful initiatives with Indigenous communities commonly come as the result of working in partnership with the members of the community to develop or provide an eHealth service that addresses a need that the community has identified for itself [3]. It is especially important that the values and opinions of all those involved are taken into consideration and respected throughout the process [3]. It is key to work in partnership with the community from the first day to ensure eHealth technology development begins (and remains) in line with community-directed needs and priorities.

One way to achieve these goals would be to conduct focus groups with community members and leaders to discuss the health needs of the community, and the ways in which eHealth might be able to effectively meet such needs [1]. In particular, those individuals identified as elders in the community should be approached for their input and perspectives on the project. It is of vital importance for the planning stages of programs (health-related or otherwise) in Indigenous communities to include, from the onset, real and meaningful engagement with elders and inclusion of their perspectives into the design of the project. One key strategy to assist in this relationship-building involves reframing communities as "co-researchers" with whom the health technology developers are actively working hand-in-hand, rather than seeing communities as "targeted populations" upon whom the technology will simply be passively implemented [3].

In this sense, contextual inquiry during the planning stages of an eHealth initiative moves well beyond a simple "needs assessment" and embraces the full spectrum of relationship-building, community engagement, and participatory action that is so fundamental to research and the development of relationships with Indigenous communities.

Community buy-in and obtaining ongoing permission

Achieving community buy-in is a crucial step in working to pilot or implement any health-related initiative in an Indigenous community [3]. The process of community engagement should include extensive community consultations and the willingness to work collaboratively with partners at the local level [3]. There is a strong need for frequent consultation and to obtain ongoing permission from both political and health leaders in the community [3]. Identifying locally-based individuals who will support the initiative ("local champions") is also critically important to the long-term success of the initiative [5]. With this permission comes the responsibility of generating awareness to ensure members of the larger community are fully aware and generally supportive of the methods and processes that will potentially be implemented in their community [1].

Recognizing existing technological infrastructure

Recognition of the existing technological infrastructure in the community is a critical consideration in rolling out an eHealth initiative [5]. Access to reliable, high-speed wireless signals or broadband may be limited in some communities, leading to the dilemma wherein communities that may perhaps be best suited for the eHealth initiative in question are not necessarily able to participate [5]. Engaging existing telemedicine providers or leaders in the region who have established connections with communities may allow for the use of existing resources, and can also provide a more locally-informed perspective on the resources and feasibility of implementing the initiative [5].

Engaging local health human resources

Evaluating a community's eHealth "readiness" must include positive and respectful engagement with local site coordinators and health workers who will play a central role in the daily function-

ing of the initiative [1,5]. Recognizing *who* will be involved at the frontlines of the project, *what* they believe about the project, and *how* they believe it can be made more relevant and useful to the community is an important step in the development stage that should not be overlooked. Preliminary considerations here might also include developing and delivering specific educational or training sessions for community health workers, and providing access to ongoing technical and financial support.

Identifying multiple funding avenues and contingency planning

The depth and longevity of eHealth initiatives are, in reality, often dictated by financial constraints [3,5]. It is crucial to be aware of the availability of long-term financial support for these projects during the planning stages. Ensuring that potential funding partners recognize and appreciate that the project itself may be required to adapt in response to changing community priorities (and that, as a result, the implementation process may potentially take longer than originally anticipated) is critical.

IMPLEMENTATION

Implementation includes the "enabling and reinforcing activities" as well as the mobilization of resources for the training, education, and use of the technology in daily practice [2]. In an Indigenous context, this might include ensuring ongoing financial and educational support for the community workers who are helping to roll out the initiative; maintaining the relationships that have been built with community members and leaders; and ensuring that there is fair and equitable access to the eHealth service itself.

Providing ongoing support for health workers

Once the initiative has been put in place in the community, it is important to ensure that there are established provisions for open channels of communication with frontline health workers involved in the daily functions of the initiative. This might include establishing and maintaining a dedicated forum for ensuring the perspectives and concerns of the frontline staff are heard.

Making provisions for equitable access

In line with the principles of justice and respect that guide Indigenous community-based health research, there is a need to ensure reasonable and equitable access to the eHealth service among members of the community, especially if the service being researched or piloted is already evidence-based [3]. In order to avoid the paternalistic approach that has marked research relationships with Indigenous communities in the past, implementing a new technology should be done while striving to ensure equitable access in the target population [3]. This provision should be made both out of respect for equity, and to avoid generating tension between members of the community, or animosity towards the intervention itself.

In the case of piloting evidence-based, health promotion eHealth initiatives, this could be as simple as ensuring the control group receives a lower level of intervention rather than no intervention at all [6]. While this approach may sacrifice internal validity, there are strong precedents for the use of such a method in Indigenous communities [6]. Researchers are encouraged to explore the possible use of the Pragmatic Randomized Control Trial, which trades internal validity for external validity and is commonly seen as flexible and community-supportive for Indigenous health research [6]. This approach is worth considering but is only one of numerous ways of ensuring research or piloting of technology in Indigenous communities is done with a particular emphasis on respect and equity of access.

SUSTAINABILITY

Recognizing the diversity of Indigenous communities

When implementing eHealth initiatives in Indigenous communities, it is crucial to recognize that no two communities are exactly alike. Communities even within the same geographic region may differ substantially in terms of health care resources, infrastructure, and community support for the initiative. A common saying in Indigenous health research circles bears repeating here: "If you have been to one Indigenous community, you have been to one Indigenous community."

Recognizing potential difficulties across "scaling-up"

It is important to understand that eHealth initiatives that are successful in theory (or even in practice) in the urban communities in which they are typically conceived may not necessarily enjoy the same success in diverse Indigenous communities. eHealth sustainability planning should recognize that successful research and development relationships with Indigenous communities require longer term commitments grounded in respect for the communities' approaches and timelines [1]. This underscores the particular attention that needs to be paid to consistent engagement with frontline healthcare providers, and to work with leaders to maintain support for the project, especially when there are changes in community governance (which can occur more frequently than in non-Indigenous communities).

Appreciating subjectivity in measures of result demonstrability

It is important to recognize that "success" in the eHealth initiative may be measured differently by the implementation team and the community itself. While pilot studies of the eHealth

initiative may not necessarily show statistical or strong clinical significance, it may have been perceived as successful from a subjective, qualitative perspective at the community level. Appreciating and making space for formal or informal qualitative evaluation of the perspectives of the community adopters, stakeholders, and patients is an important consideration in the evaluation of such eHealth initiatives [1,5]. With this evaluation should come the recognition that result demonstrability may be a more fluid concept in Indigenous communities.

An openness to ongoing community-directed change

Recognizing that in many cases the initiative may shift its original focus or goals in response to changing community needs or desires is an important consideration when planning for long-term sustainability. Setting up events and leading open and honest presentations that keep the community abreast of the program's updates and findings are both a form of respect and a necessity in ongoing community engagement. Frequent site visits from members of the non-locally based research team generally conveys respect for the community, and should take place on an ongoing basis.

CONCLUSION

eHealth technologies are well positioned to improve access to preventative medicine services in Indigenous communities, and have already made substantial headway thereto in recent years. Every stage of the development, implementation, and sustainability of such initiatives should occur in partnership with the communities in which they are aimed, and should be grounded in the principles of equitable access and respect.

REFERENCES

1. Maar, M, Seymour, A, Sanderson, B, Boesch, L. Reaching agreement for an Aboriginal eHealth research agenda: the Aboriginal Telehealth Knowledge Circle consensus method. Rural Remote Health. 2010;10:1299.
2. van Gemert-Pijnen J, Nijland N, van Limburg M, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res. 2011;13(4):e111
3. Chilisa, B. Indigenous research methodologies. University of Botswana: SAGE Publishing; (2012).
4. Ng M, Nathoo, N, Rudinsky, C, Tennant, M. Improving access to eye care: teleophthalmology in Alberta, Canada. J Diabetes Sci Technol. 2009;3(2):289–296.
5. Mutitt S, Vingeault R, Loewen L. Integrating telehealth into Aboriginal healthcare: the Canadian experience. Int J Circumpolar Health. 2004; 63(4):401–414.
6. Saini M, Quinn A. A systematic review of Randomized Controlled Trials of health related issues within an Aboriginal context. National Collaborating Centre for Aboriginal Health. Available from: http://www.nccah-ccnsa.ca/Publications/Lists/Publications/Attachments/94/RCT_EN_web.pdf.

Table 1. Towards a preliminary framework of eHealth adoption, implementation, and sustainability in an Indigenous community context.

Development	Implementation	Evaluation & Sustainability
• Community engagement, consultation and buy-in • Ongoing engagement with local community champions • Working in partnership to develop eHealth initiatives that address self-determined needs of community • Community-centred contextual inquiry • Recognize limitations of existing technology infrastructure and health human resources • Obtaining community, political and health sector leadership permission • The importance of respect, reciprocity and rapport in relationship-building • Shift from targeted interventions to co-researcher partnered relationships	• Maximize opportunity for all community members to access service • Recognize the diversity of communities and perspectives • Ensure access to ongoing support for front-line personnel • Ongoing engagement with culturally-safe practices	• Recognize "result demonstrability" is a fluid concept • Recognize difference in significance from a statistical and community-based service perspective • Appreciate that timelines are typically longer when working with Indigenous communities • Maximize contingency planning for funding • Recognize necessity of adapting to shifting community needs and priorities

Ketamine Infusions for Refractory Complex Regional Pain Syndrome: A Review

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ABSTRACT

Complex regional pain syndrome (CRPS) is a debilitating pain disorder that is often resistant to conventional treatment options. Although the precise pathophysiology of CRPS has not yet been fully elucidated, it is thought that central sensitization through the proliferation of N-methyl-D-aspartate (NMDA) receptors leads to the amplification of pain transmission within the central nervous system. Accordingly, the NMDA antagonist ketamine has been employed for its potential ability to reverse central sensitization and provide analgesia. Promising studies have shown that ketamine, when administered through prolonged intravenous infusions, may be effective for relieving pain in cases of refractory CRPS. Currently, ketamine infusions for CRPS are offered at select pain clinics in North America. However, it should be emphasized that evidence from high-quality trials is lacking and unresolved concerns over potenial neurotoxicity, urological toxicity, and hepatotoxicity of prolonged ketamine use remain. These concerns render the long-term use of ketamine questionable. Therefore, ketamine infusions should be used with caution, and may be a reasonable therapeutic option only for refractory cases of CRPS. Proper monitoring for signs of toxicity must be ensured. In addition, a physical intervention program should be used in conjunction with ketamine to fully restore function and quality of life for refractory CRPS patients.

RÉSUMÉ

Le syndrome douloureux régional complexe (SDRC) est un trouble de douleur débilitante qui est souvent résistant à des options de traitements conventionnels. Malgré le fait que la pathophysiologie précise du SDRC n'a pas encore été confirmée, certains chercheurs pensent qu'il y a une sensibilisation centrale par l'intermédiaire de la prolifération de récepteurs N-méthyl-D-aspartate (NMDA) qui conduisent à l'amplification de la transmission de la douleur dans le système nerveux central. En conséquence, l'antagoniste-NMDA, la kétamine, a été utilisé pour sa capacité de renverser la sensibilité centrale en créant un effet analgésique. Des études prometteuses ont démontré que la kétamine, lorsqu'administrée par des infusions intraveineuses prolongées, pourrait s'avérer efficace pour apaiser la douleur dans des cas de SDRC réfractaires. Des infusions de kétamine pour le SDRC sont offertes actuellement à des cliniques de douleur spécifiques en Amérique du Nord. Toutefois, il manque d'essais randomisés de qualité pour démontrer clairement l'efficacité de ce traitement. Des connaissances plus approfondies sur le potentiel neurotoxique, la toxicité urologique, et l'hépatotoxicité de l'utilisation prolongée de kétamine sont nécessaires. Ainsi, les infusions de kétamine doivent être utilisées avec précaution et ont un potentiel thérapeutique seulement pour les cas réfractaires de SDRC. Il est important d'assurer un suivi adéquat pour des signes de toxicité. De plus, un programme d'intervention physique devrait également être offert en plus des traitements de kétamine pour optimiser la fonction et la qualité de vie des patients avec un SDRC réfractaire.

INTRODUCTION

Complex regional pain syndrome (CRPS) is a severe pain disorder that is often characterized by chronicity and significant functional impairments [1]. First described over 160 years ago, the condition was assigned a variety of terms including: "neurovascular dystrophy", "algodystrophy", "causalgia", and "reflex sympathetic dystrophy" [2]. In 1994, the International Association for the Study of Pain (IASP) unified these terms by introducing "CRPS" as a new diagnostic label. The existence of such disparate terminology in the past reflects our evolving, yet incomplete, understanding of this disorder. To this day, CRPS is difficult to treat, and remains a significant barrier to rehabilitation.

The IASP currently defines CRPS as "an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion" [3]. CRPS most commonly occurs after traumatic events—in fact, up to 46% of cases can be attributed to bone fractures or

Keywords: Complex regional pain syndrome; Ketamine; Chronic pain

Table 1. Efficacy of current therapies for CRPS: abstracted from recent systematic reviews [10–12].

Treatment	Evidence for Efficacy in CRPS	Clinical Considerations
Drugs		
Bisphosphonates (IV)	Strong	Effective in patients with evidence of bone demineralization
Prednisolone (PO)	Limited	
TCAs	N/A	Studies show efficacy in neuropathic pain only
Anti-convulsants	N/A	
SSNRIs	N/A	
Opioids	N/A	
Physical Therapy (PT)		
Traditional PT	Limited	Benefits of standalone PT are unclear
Splinting	Limited	
Graded motor imagery	Strong	Promising, but research is currently limited
Mirror therapy	Moderate	
Invasive Procedures		
Spinal cord stimulation	Limited	Complications are common; effect declines over time
Guanethidine IVRSB	Weak	

Abbreviations: IV, intravenous; N/A, not available; PO, oral; TCA, tricyclic antidepressants; SSNRI, selective serotonin–norepinephrine reuptake inhibitor; IVRSB, intravenous regional sympathetic block.

crush injuries [4]. In addition, it may develop secondary to spinal cord injury, peripheral neuropathies, prolonged immobilization, brain injury, and even vascular events such as stroke and myocardial infarction [5,6]. The incidence and prevalence of CRPS in Canada is currently unknown. However, current estimates suggest that the overall incidence in the U.S. is at least 50,000 cases per year [2]. It has also been suggested that the true incidence may be even higher due to the under-recognition of this diagnostically challenging condition [7].

Clinically, CRPS usually presents in the extremities with a wide spectrum of signs and symptoms. Common characteristics can include allodynia, hyperalgesia, motor dysfunction, autonomic abnormalities (e.g., swelling, sweating, skin blood flow changes), or trophic changes such as muscle wasting and bone demineralization [5]. Further investigations may or may not reveal an identifiable nerve lesion. The exact pathophysiological mechanisms underlying these changes in CRPS are unknown but research in the last few decades suggests a multifactorial process [8,9]. Briefly, the development of CRPS may involve sympathetic nervous system dysfunction, neurogenic inflammation, autoimmune factors, psychological factors, and peripheral and central sensitization [8,9]. Unfortunately, due to the difficulty in identifying the underlying mechanisms, this condition is difficult to treat. Current therapeutic options that target these underlying mechanisms are limited and often fail to provide pain relief. In addition, evidence for conventionally used CRPS treatments, such as sympathetic nerve blockade, anticonvulsants, antidepressants, and opioids, has been largely insubstantial (Table 1) [10–12]. This means that a significant portion of CRPS patients can remain refractory to conventional treatments and may suffer long-term pain and disability.

There is a clear need for developing and evaluating novel treatment options for CRPS. Indeed, recent work has focused on therapy targeted against the role of central sensitization in CRPS. Although the pathophysiology is not fully understood, there is strong evidence that central sensitization is a key mechanism involved in both the induction and maintenance of pain in CRPS [13]. Central sensitization is a process which leads to enhanced transmission of excitatory signals in afferent pain pathways and therefore amplification of painful stimuli [14]. This process is thought to be mediated by the overactivation of N-methyl-D-aspartate (NMDA) receptors following prolonged tissue insult. Accordingly, the NMDA receptor antagonist ketamine has been employed for its potential ability to block these receptors, thus reversing central sensitization and ultimately providing pain relief [14].

A growing body of evidence suggests that ketamine, when administered via an intravenous (IV) infusion, may be effective in treating refractory CRPS [15–18]. However, current guidelines do

not recommend the use of ketamine in the routine management of CRPS due to a lack of high-quality evidence and concerns over long-term safety [19]. Despite these concerns, the use of IV ketamine is becoming increasingly accepted among pain specialists and is often employed off-label in select North American clinics, especially the U.S. It is therefore essential that physicians and patients are aware of the current evidence on the safety and efficacy of ketamine infusions for CRPS.

METHODS

A narrative review was conducted by searching English-language articles in PubMed until January 2015. The main search terms were: complex regional pain syndrome, ketamine, infusion, chronic pain, refractory, central sensitization, and safety. To examine the efficacy of ketamine infusions, only randomized controlled trials were selected for further discussion. However, one prospective trial was also included for illustrative purposes. To examine the long-term safety of ketamine, all article types including case series and cohort studies were selected.

KETAMINE

Ketamine is an anesthetic agent that was first introduced to clinical practice in the 1960s for its effective analgesic and sedative effects [20]. Since then, it has also been associated with short-term psychotomimetic side effects including: hallucinations, psychosis, euphoria, anxiety, and agitation. In fact, it was once administered to experimentally model schizophrenia [20]. Unfortunately, the side effects of ketamine have also made it a popular drug of abuse, mainly for its hallucinogenic and euphoric properties. A recent report ranked ketamine as the fourth most widely used club drug in the United Kingdom, after cannabis, ecstasy, and cocaine [21].

Pharmacologically, ketamine is complex as it interacts with a variety of receptors including opioidergic, muscarinic, and monaminergic receptors [14]. However, the analgesic efficacy of ketamine is presumably due to its non-competitive antagonism of NMDA receptors in the central nervous system [14]. In response to tissue or nerve damage, repeated nociceptive input may lead to the release of neuromodulators such as substance P, bradykinin, prostaglandins, and glutamate. This prolonged excitatory input results in the withdrawal of normal tonic inhibition of NMDA receptors, facilitating long-term potentiation of the neural circuitry responsible for pain and contributing to the allodynia and hyperalgesia typically observed in CRPS [14]. Ketamine is the most potent NMDA receptor antagonist available and it is purported to counter central sensitization by inhibiting the latter mechanism [14].

In the setting of chronic pain management, various forms of ketamine administration have been investigated. Oral bioavailability is poor and topical formulations are relatively understudied [22,23]. Prolonged IV infusions, typically spanning multiple days, have shown the most promising efficacy. In the management of acute pain, it has been observed that the analgesic effects of ketamine can often persist beyond what is expected for the half-life of the drug [24]. Therefore, it is speculated that prolonged IV infusions may effectively promote long-term desensitization of NMDA receptors, leading to analgesic effects that may outlast the duration of the infusions [14].

EVIDENCE FOR KETAMINE EFFICACY

Numerous studies have investigated the use of ketamine infusions in CRPS [15–17]. Most of these studies vary in their dosing regimens and infusion protocols. Some of the earlier trials utilized prolonged anesthetic dosages to induce a "ketamine coma" [15]. In an open label, prospective study by Kiefer et al. (2008), refractory CRPS patients were anesthetized with ketamine in the intensive care unit for 5 straight days [15]. At 1 month post-infusion, all subjects showed a significant reduction in self-reported pain. At 6 months post-infusion, 16 of 20 subjects had complete remission from CRPS while the 4 patients who relapsed at 6 months still reported significant pain relief. The authors concluded that anesthetic doses of ketamine can provide prolonged pain relief in refractory CRPS patients and that a randomized controlled trial is warranted to confirm its efficacy [15].

However, the intensive nature of the intervention employed by this study raised concerns over adverse events and safety. Seventeen of 20 patients required intubation and mechanical ventilation over the duration of their infusions. Post-infusion, all subjects experienced psychotomimetic side effects of ketamine including anxiety, dysphoria, nightmares, and insomnia. Most side effects resolved after 1 week post-treatment, however they persisted for over 1 month in 5 patients. In addition, 14 of the 20 patients experienced infectious complications (respiratory and urinary) during their intensive care unit stay. Some patients also experienced significant weight loss, as well as temporary muscle weakness and ataxia following treatment [14,15].

Due to concerns over morbidity and mortality in intensive care medicine as well as the high cost, the intervention used by Kiefer et al. (2008) has been largely regarded as infeasible [25]. Very few centres or clinicians around the world would offer the "ketamine coma" as a reasonable approach to managing CRPS [26].

Subsequent trials have shifted their focus to potentially safer protocols for ketamine infusions by utilizing prolonged, but subanesthetic dosages that do not require intensive monitoring. To date, two double-blind, randomized controlled trials have examined the efficacy of IV subanesthetic ketamine in CRPS [16,17]. Sigter-

mans et al. (2009) used a continuous, 4.2-day inpatient protocol on 60 CRPS patients [16]. Thirty patients received subanesthetic ketamine, which was titrated to analgesia and kept to a maximum of 0.43 mg/kg/h, while the placebo group was given normal saline. Results indicated a significant decrease in self-reported pain in the ketamine group compared to placebo, for up to 11 weeks post-infusion. Functional outcomes were assessed using the Radboud Skills Questionnaire (a quantitative measure of ability to perform activities of daily living with the affected limb) and the Walking Ability Questionnaire (evaluation of the impact of pain on walking performance). Interestingly, patients receiving ketamine did not report a significant increase in any of these functional outcomes compared to placebo, even in the weeks following treatment. The authors suggested that in addition to the pain relief achieved with ketamine, adjunctive physical rehabilitation may be necessary to regain functional ability [16].

Despite promising results, this study was not without criticism. Not surprisingly, there was a high incidence of side effects in the treatment group. For instance, 93% of patients receiving ketamine experienced some form of psychotomimetic effect, 63% experienced nausea, and 47% experienced vomiting [16]. The authors state that most patients found the intensity of the side effects acceptable. However, it is important to note that there were also 2 subjects who withdrew from the study because of intolerable psychotomimetic effects [16].

Another point of criticism was the use of a weak placebo (normal saline), which may have compromised blinding in terms of treatment allocation. Both the participants and investigators became aware of the treatment assignments based on the presence or absence of psychotomimetic side effects. In fact 74% of patients and 88% of investigators correctly guessed the administered treatment when surveyed after the trial [16]. Despite these weak points, this infusion protocol represents a more feasible alternative to the ketamine coma technique described earlier [16].

In another double-blind, placebo-controlled trial by Schwartzman et al. (2009), the infusion protocol was made suitable for outpatient therapy [17]. Nineteen CRPS patients who failed conventional therapies were recruited and infused intravenously with either ketamine or normal saline (placebo) 4 hours daily for 10 days (5 straight days, followed by a 2 day weekend break, and 5 straight days again). Ketamine was titrated up to a maximum of 0.35 mg/kg/h. In addition, all patients, including those in the placebo group, received midazolam, a short-acting benzodiazepine, and clonidine, a centrally-acting sympatholytic agent. These agents were included for 2 reasons: 1) midazolam and clonidine may help control psychotomimetic side effects; and 2) given that the study patients were ketamine naïve, these agents may serve as an active placebo by producing noticeable side effects and thus resulting in a more robust blinding process [27].

Pain was assessed before and after the infusion protocol using a numeric rating scale (0–10) that assessed various pain parameters including: 1) *pain in response to deep pressure*, 2) *joint pain*, 3) *degree to which pain interferes with general activity,* 4) *pain in the most affected area*, 5) *burning pain*, 6) *pain in response to light touch*, and 7) *overall pain*. In the ketamine group, a significant score improvement was found in the latter four parameters. The greatest improvement was noted during the first month post-treatment. On average, pain scores decreased by 27% 1–4 weeks post-treatment, whereas the placebo group showed no significant improvement in any of the pain parameters. Similar results were demonstrated using the short-form McGill pain questionnaire. The average decrease in McGill pain score was 35%, which lasted 12 weeks post-treatment [17].

A closer look at the parameters of the pain questionnaire shows that no significant improvement was found for the "*degree to which pain interferes with general activity*". General activity levels of patients, which were recorded pre- and post-treatment by accelerometer-equipped wristwatches, showed no significant differences. Subjects also reported no change in quality of life, as measured by the American Chronic Pain Association quality of life questionnaire. Overall, this suggests that there was no improvement in function or return to activity following the infusions. Therefore, similar to the study by Sigtermans et al. (2009), decreased pain levels were not accompanied by improvements in functional outcomes [16,17].

Although the use of midazolam and clonidine as an active placebo presumably strengthened the blinding process of this study, no post-treatment data was reported on how well subjects were able to guess their assignment. The use of midazolam and clonidine did, however, help address the issue of psychotomimetic side effects. No participant from the ketamine group reported psychotomimetic side effects. The authors concluded that the concomitant use of midazolam and clonidine may effectively minimize the undesirable side effects of ketamine [17].

Compared to Sigtermans et al. (2009), this study by Schwartzman et al. (2009) appears to adopt a safer infusion protocol and a stronger experimental method [16,17]. However, there is one major criticism of this research trial that warrants discussion. Power analysis originally indicated 20 subjects per treatment arm; however the trial was terminated early, leaving a small sample size of only 19 subjects (9 ketamine, 10 placebo). The authors claimed that over the 2-year course of the trial, their continued experience with outpatient ketamine treatments indicated that higher doses (up to twice the maximum limit set by the trial) could be used to achieve much greater and longer lasting pain relief without added complications [17]. Therefore, the "principle of beneficence in clinical research" was cited to justify the early termination of the trial [27]. Although many of the pain

parameters showed statistically significant improvements in the study by Schwartzman et al. (2009), it is well known that small sample sizes are susceptible to overestimating treatment effects [17,28,29]. Therefore, a larger trial with sufficient power may be necessary to confirm the true efficacy of this infusion protocol.

In summary, the studies discussed above illustrate the different approaches to ketamine infusions to treat CRPS. The analgesic effects of ketamine are dose-dependent and the ketamine coma may offer the longest duration of pain relief. However, infusion with subanesthetic doses of ketamine is more feasible, and the outpatient protocol by Schwartzman et al. (2009) may be the most practical and cost-effective to implement [17]. Treatment with this protocol appears to provide pain relief that may last up to 12 weeks post-infusion. It is unknown whether long-term remission is possible, but repeated infusions would likely be necessary to maintain analgesia. The two randomized controlled trials discussed represent the best available evidence thus far [16,17]. However, both studies contain their own respective weaknesses. Despite promising results, the evidence across all studies is not strong and there is a need for larger, long-term studies to confirm the efficacy, as well as the long-term safety of ketamine infusions.

LONG-TERM SAFETY

There is a growing number of case reports related to the potential toxicity of ketamine [30–33]. Unfortunately, long-term safety data on the use of ketamine in chronic pain does not exist. Much of our current understanding on long-term ketamine toxicity comes from retrospective studies of chronic ketamine abusers [21,34]. Given that patients with refractory CRPS may be subject to multiple ketamine infusions over time, the toxicity associated with chronic ketamine abuse may provide pertinent information [34].

Neurotoxicity

Experimental models involving rodents and rhesus monkeys have demonstrated neurodegenerative effects after 24 hours of continuous ketamine administration [35,36]. It is unknown whether these effects are reversible. Although observations from animal studies have not been confirmed in humans, concerns remain on whether ketamine-associated neurotoxicity may cause potential deficits in neurocognitive processes.

Several studies have shown that long-term ketamine abuse is associated with deficits in cognitive function, especially in the form of impaired memory and attention [37,38]. One longitudinal study involving long-term ketamine abusers showed that psychotomimetic symptoms could persist even after complete cessation of the drug for 3 years [39]. Taken together, these suggest that permanent damage to the brain may be possible. An MRI study by Liao et al. (2011) observed significant decreases in gray matter volume of the bilateral frontal cortex in chronic ketamine abusers compared to healthy volunteers [40]. This suggests a structural basis for the observed deficits in cognitive function. However, these findings must be interpreted cautiously, since the study was retrospective and therefore unable to establish causation between ketamine and the observed structural changes.

Urological toxicity

Another harm which has been documented in chronic ketamine abusers is urological dysfunction, including ulcerative cystitis [41]. One case series described severe genitourinary symptoms including urgency, frequency, hematuria, and post-mictural pain in daily ketamine abusers [42]. Subsequent case reports in the literature have described similar incidences of urological toxicity in patients receiving ketamine in the clinical setting. For instance, Gregoire et al. (2008) reported a 16-year-old CRPS patient who presented with cystitis following the use of oral ketamine (8 mg/kg/day) as an analgesic adjunct after just 9 days of treatment [30]. Storr et al. (2009) described 3 cases of palliative pain patients who developed significant urological symptoms following administration of oral ketamine for 5–12 months [31].

The exact mechanism by which ketamine-induced cystitis occurs is unknown. It was once thought that all urological symptoms would resolve upon discontinuation of chronic ketamine use. However, a recent longitudinal study involving 44 ketamine abusers found that in 90% of subjects, urological symptoms persisted for 8 months following ketamine cessation [43].

Hepatotoxicity

There are also reports of potential liver toxicity associated with prolonged ketamine use. In a trial by Noppers et al. (2011), 3 out of 6 CRPS patients who were scheduled to receive 2 continuous 100-hour infusions (16 days apart) of subanesthetic ketamine developed signs of liver injury [32]. During the second infusion, all 3 patients had liver enzyme levels that were 3 times the upper limit of normal. The infusions were discontinued and the patients' enzyme levels slowly returned to normal within 3 months. However, concerns over hepatotoxicity were significant enough to warrant early termination of this trial.

Other studies using either anesthetic or subanesthetic doses of ketamine have reported mixed observations. For example, Kiefer et al. (2008) reported similar elevations in liver enzymes in 16 out of 20 subjects after the 5-day "ketamine coma" protocol, whereas Sigtermans et al. (2009) reported no elevations in liver enzymes in any of the 30 subjects who received a continuous, 4.2-day subanesthetic ketamine infusion [15,16]. Schwartzman et al. (2009) either did not measure liver enzymes or neglected

to report them in their study [17].

The mechanism of liver injury is unclear, but the risk may be higher with repeated infusions [34]. Currently, there are no long-term follow-up studies documenting hepatotoxicity from multiple ketamine infusions. However, a recent report described a case of liver cirrhosis that was potentially attributed to an 8-year history of oral ketamine use for managing chronic facial pain [33]. Unfortunately, the validity of this claim remains unclear and further research is needed.

CONCLUSIONS

CRPS is a potentially debilitating condition with limited therapeutic options. Therefore, any treatment with the promise of pain relief warrants serious consideration. Ketamine infusions may be an effective option for providing analgesia in patients with refractory CRPS. Unfortunately, the current evidence for this is not strong, and there is no consensus on the most effective infusion protocol. However, the outpatient subanesthetic regimen used by Schwartzman et al. (2009) likely demonstrates the best balance of efficacy and practicality based on the available data [17].

Importantly, both physicians and patients must be aware that there are potential long-term safety risks associated with ketamine infusions and further research is needed to ascertain the implications of prolonged ketamine treatment. In the meantime, ketamine infusions should be reserved for refractory cases of CRPS and only after careful consideration of both the risks and benefits.

For patients who do undergo ketamine treatment, proper monitoring must be ensured. Given the psychotomimetic properties of ketamine, a psychological evaluation prior to therapy may be prudent. Careful monitoring for urological symptoms and signs of hepatotoxicity is also advisable, especially for patients exposed to multiple treatments.

Finally, studies have consistently shown no measureable increases in functional outcomes following treatment with ketamine, despite reductions in pain scores [16,17]. This suggests that pain relief may be just one component in the overall complex management of CRPS. In addition to adequate pain control, a functional rehabilitation program may be necessary to help restore quality of life in patients with refractory CRPS.

REFERENCES

1. Schasfoort FC, Bussmann JB, Stam HJ. Impairments and activity limitations in subjects with chronic upper-limb complex regional pain syndrome type I. Arch Phys Med Rehabil. 2004;85(4):557–566.
2. Freedman M, Greis AC, Marino L, Sinha AN, Henstenburg J. Complex regional pain syndrome: diagnosis and treatment. Phys Med Rehabil Clin N Am. 2014;25(2):291–303.
3. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med. 2007;8(4):326–331.
4. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain. 2003;103(1-2):199–207.
5. Wasner G, Schattschneider J, Binder A, Baron R. Complex regional pain syndrome--diagnostic, mechanisms, CNS involvement and therapy. Spinal Cord. 2003;41(2):61–75.
6. Schwartzman RJ, Erwin KL, Alexander GM. The natural history of complex regional pain syndrome. Clin J Pain. 2009;25(4):273–280.
7. De Mos M, de Bruijn AG, Huygen FJPM, Dieleman JP, Stricker BHC, Sturkenboom MCJM. The incidence of complex regional pain syndrome: a population-based study. Pain. 2007;129(1-2):12–20.
8. Naleschinski D, Baron R. Complex regional pain syndrome type I: neuropathic or not? Curr Pain Headache Rep. 2010;14(3):196–202.
9. Bruehl S. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology. 2010;113(3):713–725.
10. Tran DQH, Duong S, Bertini P, Finlayson RJ. Treatment of complex regional pain syndrome: a review of the evidence. Can J Anaesth. 2010;57(2):149–166.
11. Cossins L, Okell RW, Cameron H, Simpson B, Poole HM, Goebel A. Treatment of complex regional pain syndrome in adults: a systematic review of randomized controlled trials published from June 2000 to February 2012. Eur J Pain. 2013;17(2):158–173.
12. Forouzanfar T, Köke AJ, van Kleef M, Weber WEJ. Treatment of complex regional pain syndrome type I. Eur J Pain. 2002;6(2):105–122.
13. Fisher K, Coderre TJ, Hagen NA. Targeting the N-methyl-D-aspartate receptor for chronic pain management. Preclinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage. 2000;20(5):358–373.
14. Schwartzman RJ, Alexander GM, Grothusen JR. The use of ketamine in complex regional pain syndrome: possible mechanisms. Expert Rev Neurother. 2011;11(5):719–734.
15. Kiefer R-T, Rohr P, Ploppa A, et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. Pain Med. 2008;9(8):1173–1201.
16. Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009;145(3):304–311.
17. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. 2009;147(1-3):107–115.
18. Shirani P, Salamone AR, Schulz PE, Edmondson E. Ketamine treatment for intractable pain in a patient with severe refractory complex regional pain syndrome: a case report. Pain Physician. 2008;11(3):339–342.
19. Goebel A, Turner-Strokes L. Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. London: Royal College of Physicians; 2012. 60 p.
20. Domino EF. Taming the ketamine tiger. 1965. Anesthesiology. 2010;113(3):678–684.
21. Morgan CJ, Curran HV. Ketamine use: a review. Addiction. 2012;107(1):27–38.
22. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth. 1981;53(8):805–810.
23. Persson J. Wherefore ketamine? Curr Opin Anaesthesiol. 2010;23(4):455–460.
24. McCartney CJL, Sinha A, Katz J. A qualitative systematic review of the role of N-methyl-D-aspartate receptor antagonists in preventive analgesia. Anesth Analg. 2004;98(5):1385–1400.
25. Koffler SP, Hampstead BM, Irani F, et al. The neurocognitive effects of 5 day anesthetic ketamine for the treatment of refractory complex regional pain syndrome. Arch Clin Neuropsychol. 2007;22(6):719–729.
26. Pickering AE, McCabe CS. Prolonged ketamine infusion as a therapy for complex regional pain syndrome: synergism with antagonism? Br J Clin Pharmacol. 2014;77(2):233–238.
27. Schwartzman RJ. Response to Drs. Bell and Moore commentary regarding the use of intravenous ketamine for CRPS. Pain. 2010;151(2):554–555; author reply 556–557.
28. Bell RF, Moore R. Intravenous ketamine for CRPS: Making too much of too little? Pain. 2010;150(1):10–11.
29. Button KS, Ioannidis JPA, Mokrysz C, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci. 2013;14(5):365–376.
30. Gregoire M. A pediatric case of ketamine-associated cystitis (Letter-to-the-

Editor RE: Shahani R, Streutker C, Dickson B, et al: Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 69: 810-812, 2007). Urology. 2008;71(6):1232–1233.
31. Storr TM, Quibell R. Can ketamine prescribed for pain cause damage to the urinary tract? Palliat Med. 2009;23(7):670–672.
32. Noppers IM, Niesters M, Aarts LPHJ, et al. Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. Pain. 2011;152(9):2173–2178.
33. Bevan R, Burke D. Ketamine as a possible cause of cirrhosis in a patient with chronic pain. Frontline Gastroenterol. 2013;5:208–210.
34. Bell RF. Ketamine for chronic noncancer pain: concerns regarding toxicity. Curr Opin Support Palliat Care. 2012;6(2):183–187.
35. Jevtovic-Todorovic V, Carter LB. The anesthetics nitrous oxide and ketamine are more neurotoxic to old than to young rat brain. Neurobiol Aging. 2005;26(6):947–956.
36. Slikker W, Zou X, Hotchkiss CE, et al. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci. 2007;98(1):145–158. .
37. Morgan CJ, Curran HV. Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology (Berl). 2006;188(4):408–424.
38. Morgan CJ, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction. 2010;105(1):121–133.
39. Morgan CJ, Monaghan L, Curran HV. Beyond the K-hole: a 3-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who have substantially reduced their use of the drug. Addiction. 2004;99(11):1450–1461.
40. Liao Y, Tang J, Corlett PR, et al. Reduced dorsal prefrontal gray matter after chronic ketamine use. Biol Psychiatry. 2011;69(1):42–48.
41. Chiew YW, Yang CS. Disabling frequent urination in a young adult. Ketamine-associated ulcerative cystitis. Kidney Int. 2009;76(1):123–124.
42. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. Urology. 2007;69(5):810–812.
43. Cheung RYK, Chan SSC, Lee JHS, Pang WL, Choy KW, Chung TKH. Urinary symptoms and impaired quality of life in female ketamine users: persistence after cessation of use. Hong Kong Med J. 2011;17(4):267–273.

Three-Dimensional Printing and Medical Education: A Narrative Review of the Literature

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ABSTRACT

Objectives: Three-dimensional (3D) printing has emerged in the past decade as a promising tool for the world of medicine. The focus of this article is to review how 3D printed models have been used in medical education.
Methods: PubMed was the article database used, and the search criteria included the terms *3D printing* and *education*. The exclusion criteria filtered out articles that were older than ten years, were not in English, and did not target a human population. There were 90 discovered articles, and 38 appropriate articles were determined after reviewing titles and abstracts.
Results: Three main themes emerged from this review: general medical education, surgical education, and patient education. The more specific findings can be further divided into: using 3D printed models for teaching anatomy and simulation training; and preoperative planning, intraoperative guidance, and postoperative evaluation.
Conclusions: The general consensus was that 3D haptic modelling was a useful tool for educating trainees, staff physicians, and patients. The models helped in increasing participants' understanding of anatomy and pathologies, and improving trainee skill set and confidence. There is much support to continue research in this area and to further develop ways in which 3D printing can help improve medical education.

RÉSUMÉ

Objectifs : L'impression tridimensionnelle (3D) s'annonce comme un outil prometteur pour le monde de la médecine. Le présent article révisera comment les méthodes d'impression 3D ont été utilisées dans l'éducation médicale.
Méthodes : La base de données utilisée pour les articles fut PubMed et les critères de recherche ont inclus les termes *impression 3D* et *éducation*. Les critères d'exclusion ont omis des articles qui dataient de plus de dix ans, qui n'étaient pas en anglais, et qui n'avaient pas comme cible la population humaine. Il y a 90 articles qui furent trouvés en tout et 38 de ces articles ont été jugés adéquats pour la révision.
Résultats : Trois grands thèmes ont été ressortis lors de cette révision : éducation médicale générale, éducation chirurgicale, et éducation des patients. De façon plus précise, les thèmes spécifiques suivants furent dégagés : l'utilisation d'impression de modèles 3D pour l'enseignement de l'anatomie et la formation par simulation, la préparation préopératoire, le guide intraopératoire, et l'évaluation postopératoire.
Conclusion : Les modèles haptiques 3D étaient reconnus comme un outil efficace pour éduquer les stagiaires, les médecins, et les patients. Ces modèles ont aidé à augmenter la compréhension de l'anatomie et de la pathologie des participants et ont augmenté la confiance et les habiletés des stagiaires. Ces preuves démontrent l'importance de continuer la recherche dans ce domaine afin de développer davantage de façons d'optimiser l'éducation médicale à l'aide de l'impression tridimensionnelle.

INTRODUCTION

The advancements of three-dimensional (3D) printing or rapid prototyping has been realized in several industries, such as manufacturing, engineering, and aerospace [1]. There has been an evolution in the 3D printing field in recent times due to the opening up of patents, and more affordable 3D printing [1]. In medicine, the applications of 3D printing have been noted in a variety of areas, such as bio printing, customized prostheses, and as an educational tool [1].

3D printing is the means of creating a physical model by continually printing in two dimensions while moving up the vertical axis. This process is commonly referred to as additive manufacturing [1]. 3D model designs can either be newly synthesized by a user or created through utilizing common imaging modalities such as magnetic resonance imaging or computerized tomography data [1]. The design of each model involves an image that has a variety of two-dimensional slices. The 3D printer is able to build a model based on all of the data points derived from the two-dimensional slices [2]. Many printers are able to automatically build proper

Keywords: 3D printing; Rapid prototyping; Medicine; Surgery; Education; Simulation

support scaffolding for the models in order to ensure the model can be printed according to the design. There are a variety of different types of 3D printers, with some being industrial-built for research, and others built for the hobbyist, such as desktop printers. Along with these different printers, there are different methods of additive manufacturing as well. The more common methods are fused deposition modelling, selective laser sintering, and stereolithography [1]. In fused deposition modelling, heated synthetic elements are extruded through a nozzle according to the design, while moving up a vertical axis one layer at a time. This process can be likened to a hot glue gun that is progressively pushing glue out one layer at a time on top of the already hardened glue. With selective laser sintering, a laser or electron beam melts a shape out of a powder bed. More powder is added after the previous layer has hardened and the process repeats itself to build a model. Stereolithography involves a laser beam building up the model by focusing on certain parts of the liquid polymer in a vat. Consequent layers can be created through lowering the base of the vat as each resin layer is cured.

The focus of this review is to explore how 3D printing can be used as an educational tool; it is therefore important to define education. Education in this regard involves using 3D printed haptic models to teach a certain topic or to aid in the understanding of a certain principle or case. This type of review is quite novel in exploring how 3D printing may be used in general medical education, surgical education, and patient education. Other articles, which are described below, have focused on one of these specific topics, but have not explored all of these areas in one concise review. This type of literature review is important as the knowledge in this area is rapidly expanding. In July 2015, a similar review process lead to the discovery of 56 articles, with 29 directly appropriate for use in this review. At the current time—six months later—there are 90 articles, with 38 of them appropriate for use in this review.

Three main themes were determined in this review: general medical education, surgical education, and patient education. More specifically, these sections entail using 3D models for teaching students, simulating procedures, as a learning aid in specific surgical cases, and to educate patients.

METHODS

The PubMed database was searched in January 2016, with MeSH search terms including the keywords *3D printing* and *education*. The screening was carried out by the author. There was filtering for articles written in English, being published within the past ten years, and using humans. Filtering within the past ten years was intended to highlight the most current use of 3D printing in medical education. The initial search generated 90 articles, and was reduced to 38 appropriate articles after screening the titles and abstracts. Additional articles were added after reviewing the reference section of these initial studies. Article titles and abstracts were screened to ensure that the studies included models being used for educational purposes in either patients, students, resident trainees, or physician samples. Articles related to 3D modelling, surgical planning, and simulation were also included. Excluded were articles not related to medicine, or those that used 3D printing to explore transplantation, lab medicine, prostheses, or the creation of novel instruments. The present review includes 10 review articles, 9 pilot studies, 9 randomized controlled trials, 6 case studies, 3 prospective cohort studies, and 2 editorials.

RESULTS

General Medical Education

The premise of this section explores how 3D printed haptic models of human anatomy can be used effectively as a teaching tool and learning aid. These articles evaluated teaching and learning from a variety of perspectives. This section, however, will specifically discuss two major areas that have been highlighted: learning anatomy, including associated pathology and structure function; and using the models as a part of simulation training. The trainees under discussion in this section include medical students and residents. The education that trainees receive can be from general anatomical models or patient-specific models, allowing for both broad and targeted learning experiences.

Anatomy

The articles that specifically explored 3D printed models as a means of teaching medical anatomy all showed positive and promising results [2–4]. Human anatomy has traditionally been taught through cadaver dissection and, more recently, even through plastinated specimens. When analyzing these articles, there was clear discussion surrounding how 3D models were superior for anatomy teaching over the use of a cadaver or a plastinated specimen. This discussion included that 3D models are easy to store, reproducible, relatively cheap, scalable, capable of showing rare cases, dissectible, and do not entail the same ethical/legal issues as the previous methods of teaching anatomy [3]. Anatomy teaching has been further improved with recent advancements in 3D printing, such as being able to print in multicolour and using polymaterials in the models. In a pilot study by Lim et al. (2015), it was noted that for teaching anatomy, 3D models could also have value as an adjunct to a cadaveric-based curriculum [5].

In a randomized controlled trial by Li et al. (2015) there was examination of 120 medical students' understanding of complex spinal anatomy [2]. This examination occurred through a teaching module across groups utilizing a CT image, 3D image, or 3D

printed model [2]. The results showed the 3D printing model group to have a significantly superior, confident, and more rapid response (75% compared to 62.5% in the 3D imaging group). It was also noted that "pleasure, assistance, effect, and confidence were more predominant in students in the 3Dp [printing] group than in those in the 3D and CT groups" [2]. Another study by Huang and Zhang (2014) went on to further explain that 3D printed models were superior to book or digital learning. There were additional studies that solely examined the use of 3D printed models for learning anatomy [2–4,7,8], while other articles discussed anatomy learning as an aside to their main study objective [9–14].

Through the use of 3D modelling there was an increase in the understanding of organ functions, various pathologies, and how disease processes may occur [15]. Using models to help facilitate learning or aid trainees to gain a more comprehensive understanding of a topic is supported by several of the articles reviewed [4,6,9,11–13,15–20].

Simulation training

A major benefit to using 3D haptic models is in simulation training for trainees. The simulation training literature corresponding to 3D modelling was discovered in a variety of medical fields, such as Otolaryngology [21,22], Orthopedics [23], Cardiology [11,12], Plastic and Reconstructive Surgery [15,16,24], Ophthalmology [6,25], Neurosurgery [9,17,18,26–32], Urology [14,20,33], Cardiovascular Surgery [34,35], General Surgery [19], and Anaesthesia [10]. The simulation training on these models allowed trainees to explore specific anatomy and improve their understanding of spatial pathology [23]. These simulated dissections and mock procedures were performed on patient-specific or general models. There were positive outcomes in all of the simulation studies, where they found models being received with high likeness to human anatomy. Participants found the models helpful in increasing their knowledge base and surgical skill set [13]. It was additionally noted that this type of simulation training provided a safe and comfortable environment for trainees to learn from their mistakes [6,22,29,32]. In another study by Abla and Lawton (2015), there was mention that these simulations might present more like a video game in which trainees and surgeons could work on specific skills in a stimulating environment. When practising with the 3D models, individuals felt free to play around in training and push their limits, as the models could be easily replaced [19]. Certain increased skills reported were dexterity [25], communication skills, exposure to real life experiences including complications and a changing environment [25,32], surgical instruments such as manual twist drills and catheters [18], laparoscopic techniques and minimally invasive surgical procedures [33], and various other operative techniques [4,19]. In one study by Mashiko et al. (2013), students were taught how to clip an aneurysm through use of a 3D haptic model, and were shown the procedure in an actual operation video. Once the students had learned about the "clipping direction, selection of clip, and the shape of the aneurysm in the actual operation" [29] they were better able to understand the procedure prior to the actual surgery. Of the total number of surgeons in this study, 75% rated their level of understanding of the aneurysm structure as excellent, while 25% rated it as good [29]. The assessment from the trainees reported excellent (83%) and good (16%) in regards to how the 3D printed elastic model increased their knowledge of the patients' aneurysm. In addition to trainees, staff physicians reported benefits from using 3D haptic models. Through using 3D models, staff physicians ensured that they received adequate maintenance of their skill set, increased competency training, and practised rarely seen surgical techniques [32].

In addition to positive feedback, there were also limitations noted for the 3D simulation models. One limitation lay in the lack of differing materials to replicate certain soft tissues. It was mentioned that "due to the imaging processing techniques, the model does not have the ability to demonstrate the presence or extent of an intra-arterial thrombus and the aneurysm wall thickness" [27]. An additional limitation was in the lack of the model's ability to mimic the consistency of various aneurysms or branch arteries. This included the lack of complications that one would find if an intraoperative aneurysm was to tear [9]. A similar idea was mentioned in that the models did not show intra-aneursymsal hemodynamic information or true aneurysm thickness [32]. However, in one neurosurgery simulation the scientists created a 3D model with an inbuilt pathology of differing consistency and density. In this way Waran et al. (2014) were able to create a more realistic model including densities reflecting differing tissues types, such as skin, bone, dura, and tumour [31].

In a few of the articles it was mentioned that using 3D models may be a good form of trainee evaluation. This could allow for standardized testing of trainees' surgical skills, where they could receive rapid feedback in a safe and realistic setting [22,32].

Surgical Education

This section explores the use of educational 3D models for surgical cases. Specifically, this surgical education is categorized into preoperative planning, intraoperative guidance, and postoperative evaluation.

Preoperative planning

Simulation can be a vital part of a training curriculum, however surgical training differs in that it is targeted as practice for an upcoming surgery [32]. This way residents and staff can appreciate patient-specific anatomy, practise the procedure prior to the

actual operation (making note of potential difficulties), and map out the best surgical routes while determining the most appropriate tools needed [6,15,26–28,36]. In speaking towards surgical planning, Gerstle et al. (2014) suggested that by being able to handle the models, staff were able not only to appreciate complex underlying conditions and possible complications, but also to cut down on operating room time and increase efficiencies as well. Similar findings were echoed in other literature, noting that increased accuracy was attained during operations [13]. In exploring two recent cases, both Kiraly et al. (2015) and Pietrabissa et al. (2016) found the use of 3D models to be beneficial to their preoperative plan. Kiraly et al. (2015) used a printed model to explore a congenital heart disease in a 5-month-old infant with a complex obstruction. Pietrabissa et al. (2016) used a variety of models to increase residents' understanding of laparoscopic splenectomy prior to their operating. In exploring the residents' opinions on the benefits of the 3D models, 60% reported them as "very much useful", and 40% as "very useful."

Intraoperative guidance

In some articles there was mention of 3D models being used as a reference during a procedure in the operating room [1,13,27, 37]. The models were colour-coded to highlight certain areas; this indicated an area of pathology that a surgeon may want to excise or avoid [1]. This use of 3D modelling may also be helpful for the surgeons to orient themselves while operating, especially when there is complicated anatomy [37].

Postoperative evaluation

The final area of surgical education in this review is regarding the use of 3D models as a means of postoperative evaluation. The 3D models helped staff in reflecting on how procedures went, and in further learning from their operations [4]. In this study by Torres et al. (2011), the physicians were able to use the patient model to assess the accuracy of an orthognathic surgery they performed.

Patient Education

The last area of medical education explored was patient education. Patients had an increased understanding of procedures and outcomes through use of pre- and post-surgical models. This included an appreciation of possible complications and unintended results [15,38]. When the physician used the patients' 3D model for explaining procedures, patients were better informed and had an increased understanding of the procedure to which they were consenting [32]. In one study [38], patients and their families thoroughly enjoyed the anatomical models, and ten of these participants rated the models to be of "very high value" and the remaining two participants rated the models to be of "high value." In a separate case study by Liew et al. (2015), the patient responded a maximum positive value (5/5) in that the model provided her with much beneficial information preoperatively regarding her upcoming procedure. It was reported that the models used "during explanation gave her (the patient) a much better idea of what was to happen during surgery, which reassured her, and consequently she reported feeling more involved with decisions regarding her care" [17]. This section of the review did not contain a large amount of literature, which opens up an exciting avenue for future research.

Interpretation

In discussing the literature explored there was a variation in sample size and power. For example, the study by Li et al. (2015) included the use of 120 subjects that were divided into three different groupings, with one being a control group. The findings of this study can be interpreted with significance as there was an adequate number of participants to provide statistical power, as was the case in other studies [3,5,11]. Conversely, in the study by Mashiko et al. (2013) that explored using 3D models for teaching there were only six junior surgeons' responses collected. This means we cannot accept these particular responses with the same level of credibility as the Li et al. (2015) findings. This low number of participants used was a common theme in a select number of the various randomized control trials, pilot studies, and prospective cohort studies reviewed [10,12,17,18,21,23]. One reason that numbers may be lower than expected is due to the novelty of these studies. Many of these studies are exploring simulation or teaching using 3D models in a way that has not been documented before. The focus of these studies is concentrated on their proof of concept rather than in the number of participants utilized. As design and printing become refined, more studies will adhere to a high level of credibility and evidence in order to support their proposed findings.

It should be noted that this review has been limited in the use of only a single database for its search. Another limitation of this article is that most of the studies were related to surgery, and thus not many articles focused on other clinical areas of medicine.

CONCLUSION

This review article is consistent with other similar reviews, in that 3D models have a major benefit towards medical, and more specifically surgical, education [1,6,13,15,16,20,24,39]. This supports the current work being carried out in 3D haptic modelling, and in future work regarding 3D printing as a medical education tool.

The future of medical education and 3D modelling seems to point toward printing models with varying materials, and thereby featuring an even more realistic model. These models could have

a variety of colours, densities, textures, materials, and may even consist of working vasculature. Through the process of this review it is clear that 3D printing can be of help for medical schools, physicians, and surgeons in a variety of manners. Medical training programs could avail 3D modelling to help teach anatomy, and allow students to have a more hands-on approach. By creating a 3D printer friendly environment, students may suggest, and even print, models that will further advance their own independent learning and research pursuits. Physicians are able to implement the use of models to help them explain to patients how a certain pathology may be occurring, and empower patients to ask specific questions about their own health. Surgical staff can use a patient-specific model to simulate a procedure with a resident. They might also use these models to help determine how best to plan an upcoming surgery, and even take the model into the operating room as a guidance tool. There are no limitations as to how 3D printing can be applied to the field of medicine and, as mentioned earlier, there has been a significant increase in the number of articles published on this topic over the past year. In considering these previous notions, it is evident that the current research is timely and a promising area to continue exploring.

REFERENCES

1. Malik HH, Darwood AR, Shaunak S, et al. Three-dimensional printing in surgery: a review of current surgical applications. J Surg Res. 2015;199(2):512–522.
2. Li Z, Li Z, Xu R, et al. Three-dimensional printing models improve understanding of spinal fracture—A randomized controlled study in China. Sci Rep. 2015;5(11570):1–9.
3. O'Reilly MK, Reese S, Herlihy T, et al. Fabrication and assessment of 3D printed anatomical models of the lower limb for anatomical teaching and femoral vessel access training in medicine. Anat Sci Educ. 2016;9(1):71–79.
4. Torres K, Staskiewicz G, Sniezynski M, Drop A, Maciejewski R. Application of rapid prototyping techniques for modelling of anatomical structures in medical training and education. Folia Morphol (Warsz). 2011;70(1):1–4.
5. Lim KH, Loo ZY, Goldie SJ, Adams JW, McMenamin PG. Use of 3D printed models in medical education: A randomized control trial comparing 3D prints versus cadaveric materials for learning external cardiac anatomy. Anat Sci Educ. 2016;9(3):213–221
6. Huang W, Zhang X. 3D Printing: Print the future of ophthalmology. Invest Ophthalmol Vis Sci. 2014;55(8):5380–5381.
7. McMenamin PG, Quayle MR, McHenry CR, Adams JW. The production of anatomical teaching resources using three-dimensional (3D) printing technology. Anat Sci Educ. 2014;7(6):479–486.
8. Vaccarezza M, Papa V. 3D printing: a valuable resource in human anatomy education. Anat Sci Int. 2015;90(1):64–65.
9. Abla AA, Lawton MT. Three-dimensional hollow intracranial aneurysm models and their potential role for teaching, simulation, and training. World Neurosurg. 2015;83(1):35–36.
10. Bustamante S, Bose S, Bishop P, Klatte R, Norris F. Novel application of rapid prototyping for simulation of bronchoscopic anatomy. J Cardiothorac Vasc Anesth. 2014;28(4):1134–1137.
11. Costello JP, Olivieri LJ, Krieger A, et al. Utilizing three-dimensional printing technology to assess the feasibility of high-fidelity synthetic ventricular septal defect models for simulation in medical education. World J Pediatr Congenit Heart Surg. 2014;5(3):421–426.
12. Costello JP, Olivieri LJ, Su L, et al. Incorporating three-dimensional printing into a simulation-based congenital heart disease and critical care training curriculum for resident physicians. Congenit Heart Dis. 2015;10(2):185–190.
13. Rengier F, Mehndiratta A, von Tengg-Kobligk H, et al. 3D printing based on imaging data: review of medical applications. Int J Comput Assist Radiol Surg. 2010;5(4):335–341.
14. Bernhard JC, Isotani S, Matsugasumi T, et al. Personalized 3D printed model of kidney and tumor anatomy: a useful tool for patient education. World J Urol. 2016;34(3):337–345.
15. Gerstle TL, Ibrahim AM, Kim PS, Lee BT, Lin SJ. A plastic surgery application in evolution: three-dimensional printing. Plast Reconstr Surg. 2014;133(2):446–451.
16. Chae MP, Rozen WM, McMenamin PG, Findlay MW, Spychal RT, Hunter-Smith DJ. Emerging applications of bedside 3D printing in plastic surgery. Front Surg. 2015;2(25):1–14.
17. Liew Y, Beveridge E, Demetriades AK, Hughes MA. 3D printing of patient-specific anatomy: A tool to improve patient consent and enhance imaging interpretation by trainees. Br J Neurosurg. 2015;29(5):712–714.
18. Ryan JR, Chen T, Nakaji P, Frakes DH, Gonzalez LF. Ventriculostomy simulation using patient-specific ventricular anatomy, 3D printing, and hydrogel casting. World Neurosurg. 2015;84(5):1333–1339.
19. Watson RA. A low-cost surgical application of additive fabrication. J Surg Educ. 2014;71(1):14–17.
20. Youssef RF, Spradling K, Yoon R, et al. Applications of three-dimensional printing technology in urological practice. BJU Int. 2015;116(5):697–702.
21. Hochman JB, Rhodes C, Wong D, Kraut J, Pisa J, Unger B. Comparison of cadaveric and isomorphic three-dimensional printed models in temporal bone education. Laryngoscope. 2015;125(10):2353–2357.
22. Rose AS, Kimbell JS, Webster CE, Harrysson OL, Formeister EJ, Buchman CA. Multi-material 3D models for temporal bone surgical simulation. Ann Otol Rhinol Laryngol. 2015;124(7):528–536.
23. Bizzotto N, Sandri A, Regis D, Romani D, Tami I, Magnan B. Three-dimensional printing of bone fractures: a new tangible realistic way for preoperative planning and education. Surg Innov. 2015;22(5):548–551.
24. Bauermeister AJ, Zuriarrain A, Newman MI. Three-dimensional printing in plastic and reconstructive surgery: a systematic review. Ann Plast Surg. 2015; Epub ahead of print.
25. Scawn RL, Foster A, Lee BW, Kikkawa DO, Korn BS. Customised 3D printing: an innovative training tool for the next generation of orbital surgeons. Orbit. 2015;34(4):216–219.
26. Fasel JH, Uldin T, Vaucher P, Beinemann J, Stimec B, Schaller K. Evaluating preoperative models: a methodologic contribution. World Neurosurg. 2015; Epub ahead of print.
27. Khan IS, Kelly PD, Singer RJ. Prototyping of cerebral vasculature physical models. Surg Neurol Int. 2014;5:11.
28. Klein GT, Lu Y, Wang MY. 3D printing and neurosurgery—ready for prime time?. World Neurosurg. 2013;80(3):233–235.
29. Mashiko T, Otani K, Kawano R, et al. Development of three-dimensional hollow elastic model for cerebral aneurysm clipping simulation enabling rapid and low cost prototyping. World neurosurg. 2015;83(3):351–361.
30. Tai BL, Rooney D, Stephenson F, et al. Development of a 3D-printed external ventricular drain placement simulator: technical note. J Neurosurg. 2015;123(4):1070–1076.
31. Waran V, Narayanan V, Karuppiah R, Owen SL, Aziz T. Utility of multimaterial 3D printers in creating models with pathological entities to enhance the training experience of neurosurgeons. J Neurosurg. 2014;120(2):489–492.
32. Wurm G, Lehner M, Tomancok B, Kleiser R, Nussbaumer K. Cerebrovascular biomodeling for aneurysm surgery: simulation-based training by means of rapid prototyping technologies. Surg Innov. 2011;18(3):294–306.
33. Cheung CL, Looi T, Lendvay TS, Drake JM, Farhat WA. Use of 3-dimensional printing technology and silicone modeling in surgical simulation: development and face validation in pediatric laparoscopic pyeloplasty. J Surg Educ. 2014;71(5):762–767.
34. Kiraly L, Tofeig M, Jha NK, Talo H. Three-dimensional printed prototypes refine the anatomy of post-modified Norwood-1 complex aortic arch obstruction and allow presurgical simulation of the repair. Interact Cardiovasc Thorac Surg. 2016;22(2):238–240.
35. Mahmood F, Owais K, Montealegre-Gallegos M, et al. Echocardiography derived three-dimensional printing of normal and abnormal mitral annuli. Ann Card Anaesth. 2014;17(4):279–283.
36. Liu YF, Xu LW, Zhu HY, Liu SS. Technical procedures for template-guided surgery for mandibular reconstruction based on digital design and manufacturing. Biomed Eng Online. 2014;13(63):1–15.
37. Spottiswoode BS, Van den Heever DJ, Chang Y, et al. Preoperative three-dimensional model creation of magnetic resonance brain images as a tool to assist neurosurgical planning. Stereotact Funct Neurosurg. 2013;91(3):162–

169.
38. Pietrabissa A, Marconi S, Peri A, et al. From CT scanning to 3-D printing technology for the preoperative planning in laparoscopic splenectomy. Surg Endosc. 2016;30(1):366–371.
39. Marro A, Bandukwala T, Mak W. Three-dimensional printing and medical imaging: a review of the methods and applications. Curr Probl Diagn Radiol. 2016;45(1):2–9.

Gene Therapy and Modification as a Therapeutic Strategy for Cancer

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ABSTRACT

Gene therapy is an exciting new field of personalized medicine, allowing for medical procedures that can target diseases such as cancer in novel ways. Technologies that involve gene transfer treatments allow for the insertion of foreign DNA into tumour cells, resulting in restored protein expression or altered function. Gene therapy can also be used as a form of immunotherapy, either by modifying cancer cells to make them better targeted by the immune system, or by modifying the body's immune cells to make them more aggressive towards tumours. Additionally, oncolytic virotherapy uses classes of genetically modified viruses that can specifically target and interfere with tumour cells. The ongoing development of the CRISPR/Cas9 gene editing tool may also have promise in future therapeutic applications, with the tool being capable of removing cancer-causing, latent viral infections, such as HPV, from afflicted cells. Nonetheless, there are still many questions of safety, efficacy, and commercial viability which remain to be resolved with many gene therapy procedures. There is also emerging controversy over the ethical, legal, and moral implications that modifying the genetic content of human beings will have on society. These concerns must be confronted and addressed if the benefits promised by gene therapy are to be properly realized.

RÉSUMÉ

La thérapie génétique est un nouveau domaine d'étude médicale personnalisée qui permet de cibler des maladies spécifiques comme le cancer de façon innovatrice. Cette thérapie utilise le transfert de gènes avec une insertion d'ADN étrangère dans les cellules cancéreuses dans le but de restaurer l'expression des protéines et de retrouver la fonction cellulaire. La thérapie génétique peut aussi être utilisée comme une forme d'immunothérapie, soit en modifiant les cellules cancéreuses pour qu'elles soient mieux ciblées par le système immunitaire ou en modifiant les cellules immunitaires du corps pour les rendre plus agressives envers les tumeurs. De plus, une virothérapie oncolytique utilise des virus génétiquement modifiés qui peuvent cibler spécifiquement et interférer avec des cellules cancéreuses. Le développement du système d'édition génétique CRISPR/Cas9 s'avère prometteur pour les applications thérapeutiques futures. Cet outil est capable d'enlever les infections virales latentes dans les cellules affectées qui peuvent causer le cancer, tel que l'HPV. Malgré ces découvertes, plusieurs questions importantes demeurent quant à la sécurité et à l'efficacité de leur application. Il s'agit d'un domaine controversé avec des implications éthiques, légales, et morales, car le tout implique une modification du contenu génétique humain. Ces inquiétudes doivent être adressées afin de pouvoir continuer à explorer les bienfaits de cette thérapie génétique. En poursuivant la recherche dans ce domaine, il serait possible de valider cette thérapie et optimiser ses bienfaits.

INTRODUCTION

Cancer is one of the most chronic and pressing health issues in the world today, causing over 8 million deaths per year, worldwide [1]. While existing surgical, radiation, and chemotherapeutical procedures have improved outcomes in some cancer types, many cancers still do not respond well to treatment [2]. Moreover, the overall prevalence and incidence rates of cancer are expected to continue to rise [2,3]. Consequently, there is a great impetus to explore novel approaches by which to treat different cancers in ways that current standard approaches cannot. In the past decade, gene therapy has emerged as a possible avenue to produce innovative anti-cancer treatment strategies [4].

Gene therapy employs the targeted delivery of genetic material, or methods of genetic modification, to produce a positive therapeutic outcome by altering specific cells or tissues [5]. This approach could broaden the range of available treatment options through a number of techniques, including the insertion of foreign DNA into target cells to affect or restore protein expression, targeting viruses to abnormal cells for lysis and death, and even repairing deleterious genetic mutations [5]. Consequently,

Keywords: Gene therapy; Cancer; CRISPR; Immunotherapy; Gene transfer; Review

gene therapy may prove to be an essential tool in personalized medicine, as it can design treatments that are specific to a patient's genetic composition. Although many of these techniques are largely experimental, the field has made significant progress in the past decade, with some gene therapy options becoming commercially available. In the context of cancer research, recent developments such as cancer vaccines, oncolytic virotherapy, and gene transfer treatments are emerging as promising technologies to treat certain cancers with a better efficacy and safety profile than current standard treatment approaches [5].

This review aims to describe the current state of gene therapy research into applications for cancer, highlight the relative advantages and disadvantages these approaches have over existing therapeutic options, and address the limitations currently being faced by the field and the future directions needed to overcome them.

GENE TRANSFER TREATMENTS

Currently, one of the most widespread and well-established methods of gene therapy is the insertion of foreign genes into target cells through a number of different transfer methods. Collectively, these methods are referred to as "gene transfer treatments." One common approach is through viral vectors, usually belonging to a group of viruses called adenoviruses, which carry and release a therapeutic gene into a target tissue [5]. Adenoviruses are powerful tools in gene therapy due to the ease with which foreign genes can be inserted into their genomes, the relatively mild host immune response they provoke, their low rate of imprecise host genome integration (which decreases the possibility of unwanted mutations), and their lack of replicative ability (which prevents continuation of the lytic cycle and spread to other cells) [6].

Indeed, many adenoviral vectors have been developed for use in the treatment of cancer, and have generated a remarkable deal of excitement over their therapeutic impact. The drug Gendicine, which became the first commercially approved gene therapy treatment in the world in 2003, is a recombinant adenovirus that contains the gene for the tumour suppressor p53 [7]. Delivery of Gendicine to tumour cells allows for the overexpression of p53, and restoration of p53 activity in cells with dysfunctional copies of this gene [7]. Gendicine was a landmark in the history of anti-cancer gene therapy, particularly squamous cell carcinoma, as it stimulated the apoptosis of tumour cells, increased the expression of other tumour suppressor genes, decreased the prevalence of multi-drug resistance factors, and reduced vascular growth towards the cancerous tissues, all with fewer side effects than conventional chemotherapy and radiotherapy [7]. Other viral classes, such as retroviruses or adeno-associated viruses, are also used for gene therapy, each with their respective strengths and efficiencies in different cell types. For example, the drug Rexin-G is a specially designed retrovirus that selectively integrates into the genome of pancreatic tumour cells [8]. It carries a modified gene encoding a construct that interferes with cyclin G1, thereby causing cell cycle arrest or death [8]. Rexin-G, which is currently in Phase III trials, has shown promise in the treatment of advanced pancreatic cancer as it increases mean survival time by almost 10 months compared to standard treatment [8,9].

Despite the promise that prospective gene transfer treatments may hold, several limitations and hurdles remain. In 2003, attempts to treat a rare disorder called X-linked severe combined immune-deficiency (SCID-X1) using a retrovirus-based agent unfortunately led to the development of T-cell leukemia in one patient due to integration of the virus within the patient's genome and subsequent genetic instability [10]. This highlighted the need to develop viral vectors that do not integrate into key regions of host DNA. Most current vector therapies are thus based on the safer adenoviruses or adeno-associated viruses, although these are often less effective at infecting a sufficient number of cells in target tissues to produce a clinically meaningful response. For example, these viruses often collect in the liver for unknown reasons, reducing their pharmacological efficiency and provoking a potentially harmful immune responses [5]. Furthermore, since the viruses do not replicate, additional viral loads must be injected periodically to sustain the expression of the therapeutic gene. Recurrent injections, however, trigger the development of an acquired immune response to the therapeutic viruses, which further reduces the efficacy of the treatment [11].

Currently, challenges relating to delivery methods are crucial deciding factors in the success of gene transfer treatments. To this end, viral vectors are becoming increasingly sophisticated, and non-viral means of transfer are emerging, such as the insertion of naked DNA directly into cells [12,13]. The ability to safely and precisely alter the function of tumour cells via gene transfer, in order to achieve the desired clinical outcome, will largely depend upon precise therapeutic delivery.

IMMUNOTHERAPY

Gene therapy can also be used to modify a patient's immune system in order to strengthen the response against cancer cells. Treatments that boost the immune system's ability to better target and destroy cancer cells are referred to as immunotherapy, and have been an aim of cancer treatment for more than a century [14]. However, the effectiveness of conventional immunotherapy is often limited by the ability of cancer cells to evade immune detection. As such, a number of different gene therapy techniques are being explored as methods to overcome this limitation [5].

One particularly interesting approach is that of cancer vaccines, which aim to cure or contain current cancerous growth by delivering material that trains the immune system to better recognize and attack cancer cells [4,15,16]. This is in contrast to prophylactic vaccines against bacteria or viruses, which are composed of molecules that mimic the infectious agent to help the body prevent future illness. The injected material of cancer vaccines is created by harvesting tumour cells from the patient's body and genetically modifying them through the addition of genes that produce antigenic and immunostimulatory proteins, such as those encoding for cytokines or other pro-inflammatory molecules [5]. This, in essence, serves to produce antigenic factors from the cellular debris, which are more potent than the endogenous tumour antigens. Upon injection, these modified tumour antigens increase the activity of antigen-presenting cells and cytotoxic T lymphocytes, thereby creating a stronger and more aggressive anti-tumour immune response [16]. Alternatively, a variation of this approach entails delivering the immunostimulatory and antigenic genes directly to the cancer cells in the body, which heightens immune recognition of these cells and leads to a more localized immune response [5].

A number of promising genetically modified cancer vaccines are currently being tested in clinical trials. A prominent example is GVAX, a vaccine which targets advanced pancreatic cancer and consists of tumour cells modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF) [17,18]. The presence of GM-CSF secreted by the injected cells stimulates the release of cytokines at the injection site, which activates antigen-presenting cells, as well as CD4+ and CD8+ T cells, to better recognize the circulating tumour-associated antigens and strengthen the targeted immune response [18]. The vaccine is currently in Phase II trials and recent reports indicate that for treatment of pancreatic adenocarcinoma, patients administered with GVAX had significantly higher survival rates compared to those administered with standard chemotherapy [5]. Most of the side effects observed have been limited to minor injection site reactions or flu-like symptoms [16,18]. Moreover, another advantage of the vaccine is that it can be designed specifically for the patient using their tumour cells (called an autologous vaccine), thereby increasing its specificity for the patient's unique immunological environment.

While the previously described concept focused on modifying the cancer cells to induce a more potent immune response, another strategy is to modify the body's immune cells directly, in order to render them more aggressive towards tumour cells [19]. This is done by extracting and culturing lymphocytes from a patient's peripheral blood, and then genetically engineering them to overexpress potent cytokines like interleukin-2 (IL-2), or to produce T cell receptors (TCRs) that are specific for antigens on certain tumours [5,19]. Presently, T cells engineered to express TCRs against the NY-ESO-1 antigen have been successfully employed in patients with metastatic melanoma and metastatic synovial cell sarcoma [20]. Trials have shown that 50–80% of patients demonstrate objectively better regression of the cancer compared to conventional chemotherapy, with no reported toxic side effects against other tissues [20]. One caveat of this technology, however, is that it is currently incredibly expensive. On average, genetic engineering of a patient's T cells is expected to cost between USD $40,000 and $75,000 [21].

In summary, immunotherapy is a promising therapeutic option that may be a source of future breakthroughs in personalized cancer treatment. The main hurdles, as it stands, are the immense cost and time needed to produce autologous vaccines and genetically engineered T cells. To this end, the replacement of autologous cells with allogenic cells (that is, derived from pre-existing cultured cell lines) is being investigated as a means to de-personalize and thereby streamline the process [5].

ONCOLYTIC VIROTHERAPY

A concept related to immunotherapy is oncolytic virotherapy, which employs genetically engineered viral particles to specifically target cancerous tumours [5,22]. These viruses do not replicate in healthy cells, and are therefore selective in their eradication of cancerous cells—an advantage over existing chemotherapy or radiation therapy [22,23]. While this is a relatively new and largely experimental area of research, several oncolytic viruses have performed very well in clinical trials, and some have been approved for market sale. Oncorine, an oncolytic virus used in nasopharyngeal cancer, is an adenovirus that has been engineered to lack the E1B protein, which is responsible for deactivating the p53 protein in the host cell [23]. The tumour suppressor p53 plays a crucial role in the host cell's ability to destroy the virus. Without viral E1B to deactivate the host's p53 defense, the host's normal cells will be able to clear the Oncorine infection. On the other hand, many cancerous cells have defective p53 genes (a main cause of neoplastic proliferation), and may therefore be infected by the Oncorine virus, resulting in toxicity/death [23]. Phase III trials of the drug have shown a response rate of 80% for head and neck tumours, which was double the rate in patients given standard chemotherapy [24]. Prior studies consistently demonstrated a good safety profile for Oncorine with only flu-like side effects [22,23].

A number of obstacles currently hinder the development of oncolytic virotherapies. First, the classes of viruses used to derive these therapies are fairly common in nature, meaning that many individuals will have been exposed at some point and therefore exhibit pre-existing immunity. Some possible solutions include the use of immunosuppressants to temporarily halt immune reactions, or carrier cells to deliver the viruses directly to the tumour [23]. Second, the rate of infection, replication, and death

Table 1. Summary outlining the mechanisms, advantages, and limitations of each of class of gene therapy, as they pertain to cancer treatment.

Class	Mechanism	Advantages	Limitations
Gene Transfer Treatments	Insertion of foreign genes into target cells, mainly through viral based vectors [5]. Other non-viral delivery methods are being developed as well [12,13].	Can alter tumour cell function, restore apoptotic or tumour suppression pathways, and enable targeted disruption of specific types of cancer cells [5–8].	There are difficulties with achieving efficient transfer methods, host immune responses to many viral vectors, and concerns about safety due to increased risks of mutations [10,11].
Immunotherapy	Modifies cancer cells to produce antigenic and immunostimulatory molecules, or modifies immune cells to express cytokines and T cell receptors against specific tumour antigens [14–16].	Creates a more aggressive and targeted immune response toward tumours, Can create 'cancer vaccines' that are personalized for the patient's tumour type and immunological environment [14–16].	Very time-intensive and expensive; some cost estimates can go up to USD $75,000 [14–17,21].
Oncolytic Virotherapy	Produces genetically modified viruses which target and attack tumour cells preferentially over normal cells [22].	Allows for treatment directed specifically against cancer cells with minimal side effects. Also enables targeting of certain cancers that do not respond to well to standard therapy [23,24].	Host can develop immune response against the viruses. Also not efficacious against fast-growing tumours due to growth rates that exceeds viral replication rate [21,22].
Direct Gene Editing	Tools like CRISPR/Cas9 can be used to edit or replace sections of the patient's genome in a highly accurate and practical manner [25,26].	Can remove latent cancer-causing viral infections such as HPV. Also, it is able to repair deleterious mutations, restore tumour suppression and apoptosis, and change alleles associated with cancer risk [25–30].	Current delivery methods of Cas9 constructs have difficulties with efficiency, and oncogenic viruses can develop resistance against the constructs [28]. There are also concerns over the ethics and effects of permanent genome modification [30–33].

of infected cancerous cells must be greater than the growth rate of the uninfected cancerous cells for the treatment to be able to effectively reduce tumour size. As such, this approach may not be suitable for very large or fast-growing tumours.

DIRECT GENE EDITING

The advent of CRISPR/Cas9 technology promises to revolutionize the field of gene therapy. This technique allows for precise modification of DNA sequences in an efficient and simple manner, which could serve many therapeutic purposes. CRISPR/Cas9 is one of the fastest-growing areas of gene therapy research, and has therefore generated a fair deal of excitement and controversy [25].

In the context of cancer research, the tool has shown remarkable success against viral infections linked to the development of cancer. For example, a CRISPR/Cas9 construct engineered to specifically target and cleave the E6 oncogene of human papilloma virus (HPV) in cervical cancer cells showed a substantial reduction in HPV viral load and restoration of normal apoptotic genes [26]. Administration of a similar construct in HPV-infected mice with cervical cancer found a significant reduction in tumour size [27]. This is not without limitation however, as viruses have been shown to evolve resistance to CRISPR/Cas9 constructs [28]. Moreover, as with gene transfer treatments, inefficient therapeutic delivery presents a large barrier to eventual clinical implementation of this treatment [25]. Additionally, CRISPR/Cas9 technology could be used to repair deleterious mutations or replace sections of DNA with any desired sequence [25,29,30]. Correcting accumulated mutations within cancerous cells or prophylactically fixing alleles associated with increased cancer risk have both been suggested as ways to control the development of disease [25,29,30].

As the CRISPR/Cas9 tool rapidly develops, ethical, moral, and

legal questions inevitably ensue from the ability to modify the genetic content of human beings [30–33]. Current issues include the extent to which traits and parts of the genome should be allowed to be modified, the ethics of manufacturing "biologically superior" individuals, inequalities that would result from socioeconomic access barriers, and the question of whether human embryos should be modified as a means to cure genetic diseases [30–33]. These approaches have also raised the concern of eugenics, provoking considerable controversy as well as opposition from several religious, philosophical, and legal bodies [32,33]. To this end, the developers of CRISPR/Cas9 have requested a ban on all attempts at human germline modification until society can have a discussion about its consequences [31].

CONCLUSION

Gene therapy is an exciting new technology that will generate novel medical procedures capable of targeting diseases like cancer in innovative ways. The development of gene transfer treatments, immunotherapy, oncolytic virotherapy, and direct gene editing are emerging as strong therapeutic applications (Table 1). They have demonstrated the ability to improve survival time and clinical benefit in many cancers that respond poorly to standard treatment options, while at the same time carrying fewer side effects than radiation and chemotherapy. However, many of these modalities are in experimental stages, and there are still some concerns over their safety, efficacy, and commercial viability. Moreover, the rapid development of gene editing technologies, such as CRISPR/Cas9, has led to controversy over the ethical, legal, and moral implications that human genome modification will have on society. These issues must therefore be addressed through prudent solutions and regulatory/legal frameworks before gene therapy and genome modification can become widely available for the treatment of human diseases [33].

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893–2917.
2. Varmus H. The new era in cancer research. Science. 2006;312(5777):1162–1165.
3. Siegel R, Desantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin. 2013;62(4):220–241.
4. Fioretti D, Iurescia S, Fazio VM, Rinaldi M. DNA vaccines: developing new strategies against cancer. J Biomed Biotechnol. 2010;2010:174378.
5. Cross D, Burmester JK. Gene therapy for cancer treatment: past, present and future. Clin Med Res. 2006;4(3):218–227.
6. Hermonat P, Muzyczka N. Use of adeno-associated virus as a mammalian DNA cloning vector: transduction of neomycin resistance into mammalian tissue culture cells. PNAS. 1984;81(20):6466–6470.
7. Li Y, Li B, Li C, Li L. Key points of basic theories and clinical practice in rAd-p53 (Gendicine) gene therapy for solid malignant tumors. Expert Opin Biol Ther. 2015;15(3):437–454.
8. Gordon E, Hall F. Rexin-G, a targeted genetic medicine for cancer. Expert Opin Biol Ther. 2010;10(5):819–832.
9. Chawla SP, Chua VS, Fernandez L, et al. Advanced phase I/II studies of targeted gene delivery in vivo: intravenous Rexin-G for gemcitabine-resistant metastatic pancreatic cancer. Mol Ther Nature Publishing Group. 2010;18(2):435–441.
10. Fischer A, Hacein-bey-abina S, Cavazzana-calvo M. Gene therapy for primary adaptive immune deficiencies. J Allergy Clin Immunol. 2011;127(6):1356–1359.
11. Ohlfest JR, Demorest ZL, Motooka Y, et al. Combinatorial antiangiogenic gene therapy by nonviral gene transfer using the Sleeping Beauty transposon causes tumor regression and improves survival in mice bearing intracranial human glioblastoma. Mol Ther. 2005;12(5):778–788.
12. Patil S, Rhodes D, Burgess D. DNA-based therapeutics and DNA delivery systems: a comprehensive review. AAPS J. 2005;7(1):E61–E77.
13. Zinn E, Pacouret S, Khaychuk V, et al. In silico reconstruction of the viral evolutionary lineage yields a potent gene therapy vector. Cell Rep. 2015;12(6):1056–1068.
14. Armstrong AC, Eaton D, Ewing JC. Cellular immunotherapy for cancer. BMJ. 2001;323(7324):1289–1293.
15. Nawrocki S, Wysocki P, Mackiewicz A. Genetically modified tumour vaccines: an obstacle race to break host tolerance to cancer. Expert Opin Biol Ther. 2001;1(2):193–204.
16. Hege K, Jooss K, Pardoll D. GM-CSF gene-modifed cancer cell immunotherapies: of mice and men. Int Rev Immunol. 2006;25(5-6):321–352.
17. Eager R, Nemunaitis J. GM-CSF gene-transduced tumor vaccines. Mol Ther. 2005;12(1):18–27.
18. Lipson E, Sharfman W, Chen S, McMiller T, Pritchard T, Salas J. Safety and immunologic correlates of Melanoma GVAX, a GM-CSF secreting allogeneic melanoma cell vaccine administered in the adjuvant setting. J Transl Med. 2015;13:214–238.
19. Rosenberg S. Raising the bar: the curative potential of human cancer immunotherapy. Sci Transl Med. 2012;4(127):127ps8.
20. Robbins PF, Morgan RA, Feldman SA, et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. J Clin Oncol. 2011;29(7):917–924.
21. Sharpe M, Mount, N. Genetically modified T cells in cancer therapy: opportunities and challenges. Dis Model Mech. 2015;8(4):337–350.
22. Russell S, Peng K, Bell J. Oncolytic virotherapy. Nat Biotechnol. 2012;30(7):658–670.
23. Guo Z, Thorne S, Bartlett D. Oncolytic virotherapy: molecular targets in tumor-selective replication and carrier cell-mediated delivery of oncolytic viruses. Biochim Biophys Acta. 2008;1785(2):217–231.
24. Garber K. China approves world's first oncolytic virus therapy for cancer treatment. J Natl Cancer Inst. 2006;98(5):298–300.
25. Barrangou R, May AP. Unraveling the potential of CRISPR/Cas9 for gene therapy. Expert Opin Biol Ther. 2014;15(3):1–4.
26. Yu L, Wang X, Zhu D, et al. Disruption of human papillomavirus 16 E6 gene by clustered regularly interspaced short palindromic repeat/Cas system in human cervical cancer cells. Onco Targets Ther. 2014;8:37–44.
27. Platt R, Chen S, Zhou Y. CRISPR/Cas9 knockin mice for genome editing and cancer modeling. Cell. 2014;159(2):440–455.
28. Wang Z, Pan Q, Gendron P, et al. CRISPR/Cas9-derived mutations both inhibit HIV-1 replication and accelerate viral escape. Cell Rep. 2016;15(3):1–9.
29. Doudna J, Charpentier E. The new frontier of genome engineering with CRISPR/Cas9. Science. 2014;346(6213):1258096.
30. Lokody I. Genetic therapies: correcting genetic defects with CRISPR-Cas9. Nat Rev Genet. 2014;15(2):63.
31. Baltimore D, Berg P, Botchan M, et al. A prudent path forward for genomic engineering and germline gene modification. Science. 2015;348(6230):36–38.
32. Lanphier E, Urnov F, Haecker S, Werner M, Smolenski J. Don't edit the human germ line. Nature. 2015;519(7544):410–411.
33. Ishii T. Potential impact of human mitochondrial replacement on global policy regarding germline gene modification. Reprod Biomed Online. 2014;29(2):150–155.

Preventative and Personalized Approach to the Treatment of Malignant Melanoma: A Case Report

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ABSTRACT

This case report is focused on malignant melanoma, a common potentially lethal skin cancer, and its unique management. In our patient's case, the primary cutaneous melanoma occurred 28 years prior to presenting with axillary lymphadenopathy, which was later determined to be a metastatic focus of melanoma; subsequent nodules were found in his spleen. After completion of his treatment and routine screening, additional nodules were discovered in his chest. Primary and secondary prevention were important in the management of this patient, as well as personalization of his treatment.

RÉSUMÉ

Cette étude de cas porte sur le mélanome malin, un cancer de la peau potentiellement mortel avec une gestion unique. Dans le cas de notre patient, le mélanome s'est présenté 28 ans avant la présentation d'une lymphadénopathie axillaire, ce qui a été démontré par la suite comme une zone étant métastatique du mélanome. Des nodules ont été découverts dans sa rate. Suite à la fin des traitements et des suivis de routine, des nodules additionnels ont été découverts dans sa poitrine. Des préventions primaires et secondaires sont importantes pour la gestion de ce patient ainsi qu'un traitement personnalisé.

INTRODUCTION

Malignant melanoma is a common, potentially lethal skin cancer [1] with nearly 1,150 deaths and 6,800 new cases in Canada in 2015 [2]. Breslow depth is used as a prognostic measure where stage I cases ("thin melanomas") can expect long-term survival or cure, but thicker tumours (>2.0 mm) have poorer prognosis [3]. In fact, greater depth, presence of ulceration or mitoses, positive lymph nodes, including clinically unapparent lymph nodes, and visceral metastases are all associated with a worse prognosis [3]. The five-year survival over all stages of melanoma is 74.1% and 92.9% for blacks and whites, respectively; notably accurate staging was not well established in this study [3]. However, the five-year survival varies from >90% in stage Ia, to <30% in stage IV [4]. Distribution in acral areas is a common presentation in darkly-pigmented patients, and is often detected late, which may explain the worse prognosis for black patients [5].

The clinical presentation of melanoma varies largely on its type, of which there are four broad classifications: (1) superficial spreading melanoma; (2) nodular melanoma; (3) lentigo maligna; and (4) acral lentiginous. In general, a dermatology referral is indicated if a post-pubertal or longstanding nevus changes in shape, colour, or size; any nevi with three or more colours; a nevus that itches or bleeds; a new persistent skin lesion emerges, especially if pigmented or vascular in appearance; or a pigmented line in a nail or a lesion under a nail develops, especially if there is no history of trauma [6]. The ABCDEs of melanoma (asymmetry, border irregularities, multiple or dark colours, diameter ≥6mm, and evolution over time) are classically used to diagnose suspicious lesions, but the "ugly duckling sign" has recently become a surrogate for this method. The "ugly ducking sign" establishes suspicion by evaluating a patient's personal nevi pattern and identifying outliers [7].

We present the case report of a 63-year-old white man who presented to his family doctor with a history of axillary lymphadenopathy and a past medical history of melanoma. Lymph node biopsies demonstrated malignant melanoma.

CASE PRESENTATION

A 35-year-old white man was referred to a dermatologist with a 6-week history of a quickly evolving, bleeding nevus on the dorsal aspect of his right forearm. The nevus was asymptomatic, and he was otherwise healthy. Chronic exposure to sun with an-

Keywords: Melanoma; Chemotherapy; Immunotherapy; Management; Multidisciplinary

nual "burning then tanning" as a child was elicited on history. In fact, one of the patient's sunburns was "so bad he sat in chills for the entire night." Although he had blond hair, he noted a strong family history of lentigines and red hair. The nevus was excised with wide margins. Dermatopathology revealed a stage 2a superficial spreading melanoma with clear margins. The area was re-excised, as is the standard of care. At this time, the patient was considered cured and was educated regarding sun exposure and the prevention of melanoma.

Twenty-eight years later, the patient noticed a lump in his right axilla when applying deodorant and proceeded to visit his family doctor who ordered an ultrasound, followed by an ultrasound-guided biopsy. The patient was diagnosed with metastatic melanoma two weeks later. After being consulted about his treatment options, he decided to undergo a right axillary lymph node dissection. The lymph node dissection showed 7 nodes with cancerous cells, and a PET scan elucidated two previously unknown metastatic nodules in his spleen. A splenectomy was performed within two months, and he subsequently underwent adjuvant radiation followed by chemotherapy (dacarbazine). The radiation treatment was directed at the dissected axillary and contiguous supraclavicular nodal regions. 6MV photons 54Gy in 27 fractions / 5 fractions per week over 5.5 weeks were delivered. Bolus was used to ensure full dose to the axillary scar. Chemotherapy was discontinued shortly thereafter, as it was deemed ineffective, and ipilimumab was started. Ipilimumab is a first-in-class T-cell potentiator, which has shown significant benefit in progression-free survival and durable remission when compared to conventional treatment strategies for stage IV melanoma [8]. Our patient received four courses of ipilimumab; this treatment regime was completed within three months. He then underwent three PET scans, all of which showed no evidence of metastatic disease. Under the advice of his oncologist, he began serial chest CT scans after three months reprieve, the first of which showed evidence of metastatic disease.

Currently, other treatment options have been discussed, but not yet initiated. The options are: mono-immunotherapy anti-PD-1 treatment with nivolumab (Opdivo) or pembrolizumab (Keyturda); combination therapy with either nivolumab or pembrolizumab and ipilumumab; or, BRAF v600e mutation targeted treatment with vemurafenib or dabrafenib, given the BRAF v600e mutation present in his melanoma. An application to fund combination therapy for his unique circumstance is currently pending. Public funding for his proposed treatment exists only as a first line compassionate measure in patients who have not previously received ipilimumab; his previous immunotherapy disqualifies him for coverage under this provision.

Lifestyle modifications must also be mentioned. Given his previous illness, our patient increased his sun protection by using SPF 60 (UVA/UVB) sunscreen, sporting long sleeve t-shirts and pants, wearing a large hat, and avoiding peak ultraviolet radiation hours; it was life-changing in this case for the patient to know that sun exposure is cumulative and does not reset to zero. Prior to his chemotherapy, the patient began exercising (running, walking), eating healthily, adopting a positive outlook and a healthy sleep schedule. Alternative medicine providers (Naturopaths, Osteopath, Physiotherapist) have helped facilitate his lifestyle changes and psychological stress management, creating in him a sense of emotional well-being, which he hopes will increase the efficacy of his medical management.

DISCUSSION

Melanoma is a common and potentially lethal skin cancer; although it is most commonly found in sun-exposed regions, it may appear on any skin surface, especially in those with darker pigmentation, as well as in other places such as the eye and central nervous system. Over 90% of melanomas present in those 10 years of age or older [9] and rarely present in childhood or adolescence, with the incidence only increasing in those 20 years of age or older [10]. Morphologically superficial spreading melanoma, nodular melanoma, lentigo maligna, and acral melanoma are the most common; however, amelonotic melanoma and other sub categories do exist. As mentioned, melanomas typically present as quickly evolving, polychromatic, atypical nevi, which may ulcer or bleed when more advanced [7].

Our patient's case is a classic presentation with expected risk factors. A young, fair skinned male with a history of blistering sunburns as a child presented with a rapidly evolving atypical mole, which proved to be melanoma. On average, 16% of lymph node negative melanomas recur within 61 months, after which a patient is considered cured [11]. It is extremely uncommon for melanoma to relapse later than 5 years after the primary lesion, but it has been shown that men are at an increased risk for recurrence with long-term follow-up (≥15 years later) [12]. Our case demonstrates this with a 28-year delay in recurrence.

Primary and secondary prevention involves taking personal accountability for cumulative sun exposure, especially in demographically high-risk patients. Increasing safe sun practices (SPF 60 UVB/UVA, long sleeves/large hats, avoiding peak sun hours from 10:00 a.m. to 2:00 p.m.) is pivotal in the prophylactic management of melanoma. Any sun exposure or exposure to ultraviolet light may increase the possibility of primary melanoma in at-risk patients [13].

If prevention is not successful, a multidisciplinary approach must be employed in the management of melanoma, as well as an assessment of how each variable increases survivorship and/or quality of life. In our patient's case, the use of naturopathic

medicine, physiotherapy, exercise, optimal nutrition, and positive stress management have all played at least a subjective role in the quality of his life; it was important for him to establish a personalized treatment regime to alleviate stressors and improve his well-being. As anecdotal as one account remains, the psychological consequences of cancer treatment are well recognized, as is the utility of alternative medicines in alleviating this burden [14]. Synergistically, we recognize the efficacy of westernized, evidence-based medicine and alternative medicine in the holistic management of melanoma.

Surgical management used in our patient included excision of the primary melanoma with wide margins (and dermatopathology), lymph node dissection of axillary metastasis, and a splenectomy for splenic metastasis. Furthermore, local adjuvant radiation therapy, general chemotherapy, and targeted immunologics were implemented for curative measures. Adjuvant radiation therapy has been demonstrated in a Phase III trial to reduce regional nodal recurrence and improve disease-free survival when administered to patients judged to be at high risk for regional failure on the basis of resected nodal size, number of involved nodes, and presence of extracapsular spread. The clinical tradeoff is the acute radiation dermatitis that is generally shortlived but the more significant 15–25% risk of extremity lymphedema that results from the radiation fibrosis superimposed on surgical lymphatic extirpation [15]. Ipilimumab is a recombinant human IgG1 monoclonal antibody, which binds to cytotoxic T-lymphocyte associated antigen 4 (CTLA-1) blocking its pathway; this results in T-cell potentiation, which may augment the body's immunological attack against melanoma [16]. The eventual use of nivolumumab (or its equivalent pembrolizumab) will occur in our case. Nivolumumab is an IgG4 subclass program cell death 1 (PD-1) inhibiting antibody, which prevents the breakdown of PD-1 expressing T cells, B cells, and NK cells; thus potentiating the body's immune response to the melanoma. This therapy has prolonged survival in those with metastatic melanoma when used as a mono-therapy or in combination with ipilimumab [17,18]. In fact, beneficial outcomes were shown in melanomas irrespective of their PD-1 status (positive or negative) [18], but these treatments are not without risks. While the progression-free survival was greater in patients who received combination therapy, so were the risks of serious complications (54% for combination, and 24% for mono-therapy) [19]. Serious complications are classified as grade 3 or grade 4 (severe or life-threatening) and range in frequency with colitis, elevated alanine aminotransferase, and diarrhea being the most common [19]; it is noteworthy that 25–30% of the patients included in studies continued treatment, despite grade 3–4 complications. Lastly, genomic PCR for BRAF v600e, a common mutation in melanoma, and present in our case, makes accessible future avenues for treatment with targeted therapies. Vemurafenib, a BRAF kinase inhibitor and inhibitor of v600e, or Dabrafenib, a more selective inhibitor of mutated protein kinase BRAF (including v600e), have shown promise and remain possible recourses should our patient's current management be unsuccessful [20,21]. Patients treated with vemurafenib, despite the short duration of responses, have a high overall response rate and frequently experience dramatic tumor regression (>80% targeted inhibition is required for a clinical response) (22). Further work in the field to establish the utility of targeted therapy, in combination with other chemotherapies or immune modulators, has also shown promising results [23,24] and furthers our hope for an eventual cure.

CONCLUSIONS

Patients with metastatic melanoma may present in numerous morphologically distinct manners, which reduce in incidence when preventative measures are taken. Risk stratification is required to increase awareness of patients and their relatives. The management of melanoma, although surgical for early-stage cases, is multidisciplinary, patient-dependent, and potentially targeted depending on genetic factors. It is crucial to evaluate the impact of a patient's diagnosis on medical, physical, psychological, and spiritual well-being to increase survival rates and improve quality of life.

CONSENT

Written informed consent was obtained from the patient for the publication of this case report. The care and reporting conform fully to the Helsinki Declaration.

REFERENCES

1. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst. 2015;107(6):djv048.
2. Melanoma Statistics [Internet]. Canadian Cancer Statistics 2015. 2015 [cited 2016 Mar 13]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/skin-melanoma/statistics/?region=on.
3. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol. 2001;19(16):3622–3634.
4. Balch C, Gershenwald J, Soong S, et al. Final Version of 2009 AJCC Melanoma Staging and Classification [Internet]. American Society of Clinical Oncology. 2009. Available from: http://jco.ascopubs.org/content/27/36/6199.full.
5. Shoo BA, Kashani-Sabet M. Melanoma arising in African-, Asian-, Latino- and Native-American populations. Semin Cutan Med Surg. 2009;28(2):96–102.
6. Marsden JR, Newton-Bishop JA, Burrows L, et al. Revised U.K. guidelines for the management of cutaneous melanoma 2010. Br J Dermatol. 2010;163(2):238–256.
7. Gachon J, Beaulieu P, Sei JF, et al. First prospective study of the recognition process of melanoma in dermatological practice. Arch Dermatol. 2005;141(4):434–438.
8. Tarhini A, Lo E, Minor DR. Releasing the brake on the immune system: ipilimumab in melanoma and other tumors. Cancer Biother Radiopharm. 2010;25(6):601–613.
9. Lange JR, Palis BE, Chang DC, Soong S-J, Balch CM. Melanoma in children and teenagers: an analysis of patients from the National Cancer Data Base. J Clin Oncol. 2007;25(11):1363–1368.
10. Strouse JJ, Fears TR, Tucker MA, Wayne AS. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol. 2005;23(21):4735–4741.

11. Jones EL, Jones TS, Pearlman NW, et al. Long-term follow-up and survival of patients following a recurrence of melanoma after a negative sentinel lymph node biopsy result. JAMA Surg. 2013;148(5):456–461.
12. Tsao H, Cosimi AB, Sober AJ. Ultra-late recurrence (15 years or longer) of cutaneous melanoma. Cancer. 1997;79(12):2361–2370.
13. Newton-Bishop JA, Chang Y-M, Elliott F, et al. Relationship between sun exposure and melanoma risk for tumours in different body sites in a large case-control study in a temperate climate. Eur J Cancer. 2011;47(5):732–741.
14. Paul A, Cramer H, Lauche R, Altner N, Langhorst J, Dobos GJ. An oncology mind-body medicine day care clinic: concept and case presentation. Integr Cancer Ther. 2013;12(6):503–507.
15. Henderson MA, Burmeister B, Thompson JF, et al. Adjuvant radiotherapy and regional lymph node field control in melanoma patients after lymphadenectomy: Results of an intergroup randomized trial. J Clin Oncol. 2009;27(18s).
16. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010;11(2):155–164.
17. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014;32(10):1020–1030.
18. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23–34.
19. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372(21):2006–2017.
20. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–2516.
21. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367(2):107–114.
22. Holderfield M, Deuker MM, McCormick F, McMahon M. Targeting RAF kinases for cancer therapy: BRAF-mutated melanoma and beyond. Nat Rev Cancer. 2014;14(7):455–467.
23. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30–39.
24. Vennepureddy A, Thumallapally N, Motilal Nehru V, Atallah J-P, Terjanian T. Novel drugs and combination therapies for the treatment of metastatic melanoma. J Clin Med Res. 2016;8(2):63–75.

Going Blind in Nepal

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ABSTRACT

Following two months of backpacking in Southeast Asia, I arrived in Nepal in August 2014 for a much anticipated three-week global health elective in emergency medicine. Before I finished my first day, however, my trip took an unexpected turn; I began to experience a serious medical problem and was forced to seek immediate treatment. I was suddenly transformed from an enthusiastic student to a reluctant patient in a country whose medical system is very different from that of my own. This unfortunate circumstance did, however, allow me to learn about Nepalese medicine in ways that I never would have been able to as a medical student, and the lessons that I learned will undoubtedly help me in my future career.

RÉSUMÉ

Suite à deux mois de voyage en Asie du Sud-Est, je suis arrivé au Népal en août 2014 où j'ai fait un stage de trois semaines en médecine d'urgence. Suite à ma première journée de stage, j'ai dû me chercher un traitement médical pour un problème sérieux. J'ai été transformé d'étudiant enthousiaste en patient inquiet dans un pays où le système médical est très différent du mien. Mon expérience comme patient et étudiant en médecine au Népal m'a permis d'apprendre beaucoup au sujet de la médecine népalaise. Les leçons apprises dans ce pays étranger vont sans doute aider dans ma future carrière en tant que médecin.

Nepal is a mountainous South Asian country with 29 million people inhabiting a land mass similar to Canada's Maritime Provinces. Its medical system differs greatly from that of Canada. Sadly, only 61.8% of Nepalese households have access to health facilities within 30 minutes of their homes [1]. This general lack of accessibility may play a role in other discouraging statistics. For example, in 2007 only 36% of births were attended to by a skilled health professional [2], and a recent report suggests that inadequate access to surgical care accounts for 23% of deaths in Nepal [3]. Recently, however, some aspects of health care in Nepal have been steadily improving. From 1990 to 2012, Nepal's under-five mortality rate decreased from 142 to 40 deaths per 1,000 live births, and its maternal mortality rate has decreased from 790 to 190 deaths per 100,000 live births [2]. Nevertheless, there is still a lot of room for improvement, and one can imagine that the experience of a personal health emergency in Nepal is vastly different from one in Canada. I discovered this firsthand during the summer of 2014.

The initial signs of trouble occurred when I was sitting in a circle, meeting the people that I would be living with in a large house in Pokhara, owned by the Work the World group. I started to feel an itch in my left eye as I was introducing myself to the team. While the itch initially did not concern me, another student pointed out that my eye looked quite red. I shrugged it off as a simple contact lens irritation. As the night progressed, however, the itchiness turned to pain, which increased to the point of interfering with my sleep. As I had never experienced conjunctivitis before, I assumed that it was the cause of my worsening symptoms. I decided that I would ignore the pain and wait for the irritation to resolve. In retrospect, the lack of attention that I paid to my symptoms was irresponsible; my excitement for this elective was all-consuming, and I did not want to face the disappointment of missing out on it should I have had a more serious medical condition. My subconscious was determined to steer my attention far away from my eye.

During the second day of orientation, my vision started to blur. My visual acuity was similar to what it would have been if I was wearing glasses that carried a power of -15 in the left eye instead of my usual -6. The pain was still there, constant and burning. Without stopping to consider the severity of my symptoms, I decided that the blurriness must be attributable to discharge pooling in my eye from conjunctivitis and clouding my vision.

The next morning, a conversation with my mother transformed me back into my normal, rational, sensible self. I ran to a private ophthalmologist's office in downtown Pokhara, cursing myself for being so oblivious. After paying a few American dollars at the reception, I saw him quickly. When he first looked at my eye after staining my cornea, his face was grim, lacking emotion. I immediately knew that something was wrong. He told me that I had

Keywords: Global health; Ophthalmology; Corneal ulcer; Medical student; Medical elective; Nepal; Infection

three corneal ulcers near my pupil, and was at risk of permanent vision loss in my left eye. In an impassioned tone, he said that I had to get to a hospital as quickly as possible, because time was running out.

Although I had been travelling alone for months and making daily decisions for myself, I suddenly could not think clearly. Panic took control of me, and even hailing a taxi to take me to the hospital was a challenge. Upon arrival, I experienced firsthand what it was like to be a patient in one of the poorest countries in the world. First, a patient must be triaged to see the physician that will look after them. The patient then receives a list of drugs that the physician will use for treatment and must wait in line at the hospital's pharmacy to buy them. Next, the patient must queue in another line to pay the hospital bill. The patient must then enter a third line to buy the tools that the physician will need, including such things as gloves, a scalpel, bandages and even a surgical cap. This process is mandatory regardless of the acuity of the visit; even patients with life-threatening illnesses require family members to follow these instructions. The whole process took me over 30 minutes to complete, during which time I continued to ponder the risks of further delays to treatment.

Once these tasks were completed, I returned to the ophthalmology department with the supplies that I had purchased. The team briefly explained to me that they needed to do a bacterial culture and sensitivity, and that I should lie down on the bed. The procedure that followed was traumatic, involving surgical linen being placed around my face, a hole cut into the linen around my eye, local anaesthetic dropped onto my cornea and a scalpel being used to scrape off the superficial layers of the ulcers. Next, an aggressive regimen of antibiotic and anti-inflammatory eye drop treatments was instituted. Although I later found out that this was almost identical to the treatment that I would have received in Canada, the fact that I was in a foreign environment, and at the time had no way of knowing if I was receiving the standard of care, made the experience much more distressing.

Within a couple of days, the pain settled down and my vision returned. Thankfully, I was still able to complete a week of shifts in the emergency room for my elective, but was then strongly advised to return to Canada quickly to start treatment with steroid eye drops, as my next placement was scheduled to be in a more remote setting.

Although shaken by the whole event and the potential consequences that could have ensued, I decided to view it as an important learning experience for my future career. Being a patient in a developing country was a priceless opportunity for learning and growth, and I decided to share the insights I gained with fellow students and colleagues at home.

Above all else, we as physicians and students need to take care of ourselves. It is easy to ignore our own health needs when we are focused on providing care or we are in an exciting learning environment. Although long working hours, stress and a dedication to patient-centered care frequently take priority over personal considerations, maintaining our own health is paramount to being able to care for those who depend on us. I have often witnessed medical personnel sacrifice their own health by staying late at the hospital, skipping meals, and not taking adequate breaks. Lack of self-care while abroad is also a problem for many learners. In 2014, Bhattari and colleagues looked specifically at 210 medical students on electives in Nepal, and found that 90 of them (42.8%) experienced at least one injury during their clinical rotation [5]. Furthermore, an estimated 60% of international medical schools lack adequate education on basic injury prevention [6]. Thankfully, this lack of preparation is not the case at the University of Ottawa, where the importance of self-care is taught both in our third year link block and in the school's mandatory pre-departure training.

The stress that I experienced in Nepal opened my eyes to the fear and anxiety that many patients I have met must have felt. Often the patients we see at home feel as foreign to their environment as I felt in Nepal. Having experienced a medical emergency as a patient, I hope I am able to relate to patients in a more understanding way than I could before.

Despite the many resources which are lacking in the Nepalese system, as a student in the hospital I was very impressed by what I saw and the physicians that I spoke to. Nepal is currently the 29th poorest country in the world according to the International Monetary Fund, with a GDP of $2,376 per capita [7], however, despite financial constraints, the medical system appeared to function well from my perspective as a patient. What I can take away from my time in the hospital is how I was *treated*, how it made me *feel*, and how I can use this experience to improve the *care* that I provide to my future patients. After all, these soft skills may not correlate directly with a country's GDP.

Upon reflection, what created the most anxiety for me was the lack of communication that I received, which was not attributable to a language barrier, as all the physicians were fluent in English. I was never fully informed of what was happening to me, and was not given any choice in terms of what treatment I would or would not be receiving. Additionally, I never consented to any procedures that were performed. This lack of adequate communication may be an isolated event, or the culture of Nepalese medicine may in fact be more paternalistic than its Canadian counterpart. Regardless, the lack of communication simply serves as a warning for me to treat my patients the way that I would want to be treated if I was in their position.

Finally, this experience made me incredibly grateful for a medical system that can provide excellent care regardless of a patient's ability to pay. Although by our standards, the care I received was extremely cheap, totalling about $25 USD, Nepal has no universal health coverage, and many Nepalese citizens may not be able to afford this care. What was a short and limited scare to me might have been a life sentence of blindness to an average Nepalese citizen.

My experience with the Nepalese medical system will always be in the back of my mind. I will always be reminded to maintain self-awareness when I travel in foreign environments, and no matter where I am, to always monitor and address my own health needs. I will never forget to treat patients the way that I, in that hospital as a patient, wished I had been treated. By writing this I want to encourage you, as a physician, future physician, or other health care professional, to always remember to do the same.

REFERENCES

1. Mishra SR, Khanal P, Karki DK, Kallestrup P, Enemark U. National health insurance policy in Nepal: Challenges for implementation. Glob Health Action. 2015;8:28763.
2. Nepal: WHO statistical profile [Internet]. World Health Organization; [updated 2015 Jan; cited 2015 Sep 4]. Available from: http://www.who.int/gho/countries/npl.pdf?ua=1.
3. Gupta S, Shrestha S, Ranjit A, et al. Conditions, preventable deaths, procedures and validation of a countrywide survey of surgical care in Nepal. Br J Surg. 2015;102(6):700–707.
4. Reid MJ, Biller N, Lyon SM, et al. Reducing risk and enhancing education: U.S. medical students on global health electives. Am J Infect Control. 2014;42(12):1319–1321.
5. Bhattarai S, KC S, Pradhan PM, Lama S, Rijal S. Hepatitis B vaccination status and needle-stick and sharps-related injuries among medical school students in Nepal: a cross-sectional study. BMC Res Notes. 2014;7:774.
6. Villaveces A, Kammeyer JA, Bencevicå H. Injury prevention education in medical schools: an international survey of medical students. Inj Prev. 2005;11(6):343–347.
7. World economic outlook database [Internet]. International monetary fund; [updated 2015 Apr; cited 2015 Sep 4]. Available from: http://www.imf.org/external/pubs/ft/weo/2015/01/weodata/index.aspx.

Medicine and the Art of Seeing

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ABSTRACT

This Humanities in Medicine article is an examination of the use of formal fine arts training in medical curricula to enhance diagnostic skills. A great amount can be discerned about pathology and pathophysiology using visual cues. Conventional medical education stresses the importance of physical diagnostic skills but often omits explicit teaching on how to methodically observe for information that could be useful for diagnosis. The current curriculum could be greatly complimented by the study of fine arts, which deals directly with the careful observation, description, and interpretation of the visual world.

RÉSUMÉ

Cet article sur la médecine et les humanités est un aperçu sur la pertinence d'incorporer une formation formelle des beaux-arts dans le curriculum médical afin d'optimiser l'habileté des cliniciens à poser un bon diagnostic. L'utilisation de repères visuels est d'une grande utilité pour discerner la pathologie et la physiopathologie de différentes maladies. L'éducation médicale conventionnelle souligne l'importance de l'examen physique lorsqu'on doit poser un diagnostic, mais néglige parfois l'enseignement d'une approche méthodique qui utilise activement l'observation afin de repérer des informations qui pourraient être très utiles dans le diagnostic d'un patient. Le curriculum actuel pourrait très bien incorporer l'étude des beaux-arts, car celle-ci implique une observation, une description et une interprétation du monde visuel qui nous entoure.

William Osler, one of the most celebrated doctors in Canadian history, once said that the "whole art of medicine is in observation" [1]. Indeed, a great deal of diagnostic power can be drawn from the visual world. Currently, medical educators train students by teaching them the cardinal features of disease and how to differentiate between normal and abnormal signs and symptoms. The skills underpinning this process are often taken for granted, however, and students may never be taught how to carefully and methodically observe their patients for all the relevant visual data points. The skill of deliberate looking falls into the realm of fine arts, where artists are trained in observing, describing and interpreting colours, textures, and shades; skills which are also essential to being an effective diagnostician. Formal training in fine arts for medical students has been shown to translate into better clinical skills and could have an increasing role in medical education.

One method of enhancing visual literacy that has been used with success in medical education is known as visual thinking strategies (VTS), which encourages students to answer open ended questions about the content and meaning of specific works of art and build upon the ideas of their classmates. A family medicine residency program in Los Angeles incorporated VTS into their curriculum using well-known medical works of art including "Mr. S is Told He Will Die" (Figure 1) and "The Doctor" (Figure 2) [2–4]. Facilitators found that, in addition to improving teamwork among the residents, VTS improved their ability to "decode" the images in the paintings and develop a unified idea of what each piece of art was communicating. After these learning modules, residents reported improved ability to discern the nuances in color, texture, perspective, and shading of the various art pieces they examined while also broadening their interpretation of the artwork by scaffolding on the ideas of their classmates. Facilitators suggested that this would help the students solve more complex problems in medicine that draw on the same skills, like reading X-rays or ECGs [2].

On a larger scale, a study at Harvard used fine arts in their medical education program by using a nine-week elective format and employing VTS in combination with didactic sessions exploring core artistic concepts [5]. Additionally, they gave participants a chance to directly apply what they had learned through art to a physical assessment of patients with a variety of conditions that could be elucidated with visual inspection. The study found that students who received this fine arts regimen were more likely to make accurate observations and diagnoses of these conditions than students who only received conventional physical diagnosis training.

Keywords: Medical education; Visual arts; Arts in medicine

Figure 1. "Mr. S is Told He Will Die" by Robert Pope [3].

Figure 2. "The Doctor" by Luke Fildes [4].

The study of fine arts has proven useful even when applied to works of art that do not specifically contain medical themes. When examining art that contained less familiar imagery and representations, such as surrealist and abstract pieces, medical students still experienced improvements in skills that would help them in clinical settings [6]. After undergoing a curriculum of three two-hour sessions that included abstract art, students reported that they were able to develop a systematic approach to the visual world and found that they were able to identify patterns more readily, a skill which would translate into improved ability to make connections between patient cases [6]. In addition to developing pattern recognition skills, studying non-representational art encourages creative, on-the-spot interpretation because of its dearth of familiar imagery. It is one thing to examine and analyze a work of art full of easily recognizable symbols, but it is another thing entirely to examine non-representational art and make rapid decisions about its meaning. This makes for excellent practice in decision-making and in gaining comfort with uncertainty. These skills would undoubtedly be useful when encountering new cases and navigating unfamiliar territory during medical training.

A great amount of information can be discerned about pathology and pathophysiology using visual cues. Conventional medical education stresses the importance of physical diagnostic skills but often omits explicit teaching on how to methodically observe for information that could be useful for diagnosis. The current curriculum could be greatly complimented by the study of fine arts, which deals directly with the careful observation, description, and interpretation of the visual world. By encouraging medical learners to spend time dissecting works of art in addition to the traditional cadaver, their observational acuity can develop and enhance their efficacy as diagnosticians.

REFERENCES

1. Osler W. The natural method of teaching the subject of medicine. JAMA. 1901;36(24):1673–1679.
2. Reilly JM, Ring J, Duke L. Visual thinking strategies: a new role for art in medical education. Fam Med. 2005;37(4):250–252.
3. Fildes L. The Doctor. Available from: http://www.tate.org.uk/art/artworks/fildes-the-doctor-n01522.
4. Pope R. Mr S is told he will die. The Robert Pope Foundation.
5. Naghshineh S, Hafler JP, Miller AR, et al. Formal art observation training improves medical students' visual diagnostic skills. J Gen Intern Med. 2008;23(7):991–997.
6. Shapiro J, Rucker L, Beck J. Training the clinical eye and mind: using the arts to develop medical students' observational and pattern recognition skills. Med Ed. 2006;40(3):263–268.

Doctor Jérôme Lejeune's Gaze at the University of Ottawa

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"Dad has, above all, a gaze. His blue eyes sparkle with intelligence and humor and they look at you with infinite tenderness. Still they are demanding because they love the truth. They are tirelessly seeking the 'why' and the 'how' of what they see."

CLARA LEJEUNE

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ABSTRACT

From January 29th to February 1st, 2015, a group of University of Ottawa undergraduate students and I hosted an exhibit about the life and research of French physician Dr. Jérôme Lejeune, who in 1959 discovered Trisomy 21, the genetic origin of Down syndrome (DS). Considered the father of modern genetics, Dr. Lejeune believed medicine should serve the patient and not the disease. The exhibit focused on Lejeune's profound humanity and compassion that accompanied his commitment to scientific truth. It also showed how this great scientist maintained an unshakeable adherence to his faith and conscience despite challenges and adversity.

RÉSUMÉ

Du 29 janvier au 1er février 2015, un groupe d'étudiants au premier cycle universitaire ont organisé une exposition portant sur la vie et les travaux de recherche du médecin français Dr Jérôme Lejeune, qui en 1959 a découvert la trisomie 21, l'origine génétique du syndrome de Down. Dr Lejeune est considéré comme le père de la génétique moderne. Il croyait que la médecine devait se concentrer sur le patient et non seulement sur sa maladie. L'exposition a mis en valeur l'humanité et la compassion du Dr Lejeune en illustrant comment ce grand scientifique a su maintenir sa foi et ses croyances malgré les défis à relever.

HOW IT STARTED

My first encounter with Dr. Jérôme Lejeune occurred in the late 1980s when I was a practising pediatrician in Italy. Although I had never heard of him, I attended a lecture he gave in Milan. His smile and gaze, and the way he deeply communicated with the 3,500 people in attendance that day, impressed me. He appeared to direct his loving attention to the children listening to him in the front rows. Though his topic was challenging, I was surprised to see how well they seemed to follow his words. Then suddenly, I realized that I was surrounded by many children affected by Trisomy 21, all of whom were listening in silence and in awe. Right next to me, a father, whose son was affected by Down syndrome (DS), turned to me with tears in his eyes and said, "I am coming from France to listen to the Professor, he helped my whole family and my son like nobody else ever did!"

I remembered Dr. Lejeune discussing the difficulty of doing research when faced with the complexity of the human organism and all the molecular processes involved (Figure 1). Using music as an analogy, he explained, "The orchestra of life has about 50,000 musicians… to have a tiny extra piece of chromosome is like having one additional musician in an orchestra who is playing faster or slower than everyone else. It would cause cacophony," he said, and then added with a smile, "I am trying to find the discordant musician!" At that very moment I realized that Dr. Lejeune was like a father to the children with DS, and that what was transpiring between him and his audience was unique. Throughout my academic career (in both Europe and Canada) I have yet to attend to such a riveting and inspirational lecture.

Fast-forwarding to about three years ago, I received a book entitled "Life is a Blessing" [1] as a Christmas gift. It was the biography of Dr. Lejeune as told by his daughter, Clara. On the first page, to my surprise, a dedication: "À Emanuela en souvenir de Jérôme Lejeune qui nous a encouragés à avancer sur le chemin de l'espérance. New York, 14/1/2011 Birthe Lejeune" [*To Emanuela in remembrance of Jérôme Lejeune who encour-*

Keywords: Genetic medicine; Advocacy

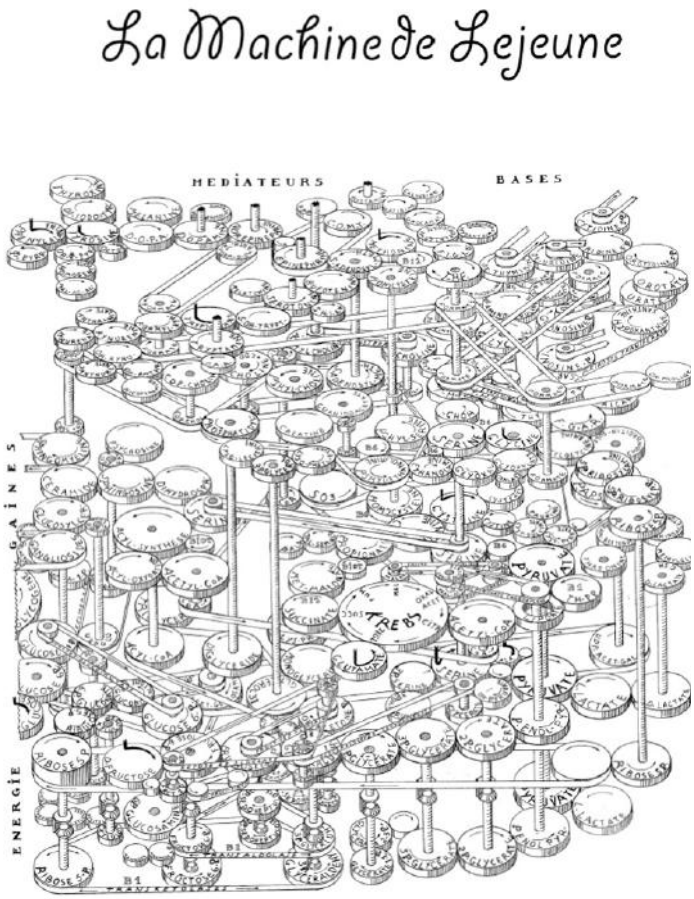

Figure 1. Lejeune's machine (reprinted with kind permission of the Jérôme Lejeune Foundation). According to a recent review by Strippoli et al. (2013) [9], Dr. Lejeune anticipated the field of systems biology decades before it became popularized. In this diagram he conceptualizes complex interrelated molecular pathways as analogous to a system of mechanical gears. He attempted to understand how a central defect—Trisomy 21—can have such diverse effects.

aged us to advance on the path of hope. New York, 14/1/2011. Birthe Lejeune]. This book became my companion until the day I entered the University of Ottawa's Faculty Development office and asked if I could organize an exhibit about Dr. Lejeune's life. When asked why I wanted to take on such a laborious project, I told them of how I had come to meet Dr. Lejeune, and how I wanted to share his unique perspective on patient care with my peers. I explained that this three-day exhibit, which I had seen in Italy, and later, at McGill University in Montreal, would ignite a rich discussion amongst undergraduate medical students as well as faculty in regard of what it meant to be human. I wanted my students and colleagues to learn how his passion for life—that he defended from the very beginning—had been the centre of an unprecedented scientific, ethical, societal, political, and religious debate. Furthermore, I wanted them to see a glimpse of Dr. Lejeune's gaze!

THE PREPARATION

What followed was almost a year of preparation, during which I joined with a group of seven undergraduate students, four colleagues, and two mothers of children affected by Trisomy 21, to learn how to guide the exhibit. We spent countless hours striving to learn the nature of Dr. Lejeune's work and of his monumental accomplishments, as well as how he had suffered in order to advocate for his patients. But who was he?

After completing his medical training in 1951, a young Jérôme Lejeune joined Professor Raymond Turpin's team at the Centre National de la Recherche Scientifique in Paris as a research assistant, where he was instructed to study the causes of DS. At the time, no one knew the cause of this condition. Some scientists suspected it was the result of a sexually transmitted disease like syphilis; others thought it represented a form of racial evolution. For these reasons, people affected by the syndrome faced terrible discrimination.

In the 1950s, when scientists had just determined that each human being had 46 chromosomes in 23 pairs, Dr. Lejeune began to look at the chromosomes of patients with DS and discovered an extra chromosome in the 21st pair, ergo the name Trisomy 21 [2]. By identifying the genetic cause, Dr. Lejeune helped restore dignity to those affected by DS; for the first time in the history of medicine distinct symptoms were connected to a specific alteration of the genetic material. In addition, this opened the door for further research into the genetic basis of disease, and led to the discovery of many other conditions such as Cri du Chat, Fragile X, Turner, and Klinefelter syndromes [3].

As a result of his work, Dr. Lejeune was the recipient of many prestigious awards. In 1962, he was awarded the Kennedy Prize by United States President, John F. Kennedy, for his discovery of Trisomy 21. He later went on to receive the William Allan Memorial Award in 1969, which was the highest accolade from the American Society of Human Genetics. During his acceptance speech, Dr. Lejeune summoned geneticists and left them speechless by asking, "What is man, and when does a human being begin?" [4].

The purpose of Lejeune's scientific work was to learn passionately about a disease in order to develop a cure. To him, however, providing his vulnerable patients with appropriate care and hope was of equal importance. In addition to his brilliant discoveries, Dr. Lejeune was a caring clinician who established a "legendary" relationship with his 5,000 patients in the DS clinic; knowing each one of them by name [8]. One couple described going to an appointment with their son. He sat their child on his lap, asked him questions and treated him with such love that the couple said afterwards, "He was not examining a sick individual, but our child.

Figure 2. The speakers. From left: Dr. Lise Poirier-Groulx (University of Ottawa), Dr. Emanuela Ferretti (University of Ottawa), and Dr. Mark Basik (McGill University).

He explained everything to us, the nature of the illness, what future our child could expect and we left with our child and with peace in our heart. He made us discover the love of parents." [1].

In the aftermath of his discovery, Dr. Lejeune was faced with the reality that its clinical impact was to enable antenatal detection and termination of affected individuals. A mechanistic cure for those affected, as he had initially hoped for, was proving elusive. Here was a single individual personally facing what has now become one of the most complex issues of modern society. Ultimately Lejeune, a man of faith, was guided by his faith and took a public stance against termination of fetuses with Trisomy 21. Lejeune paid a huge price for this. One of the most listened to scientists in the world, and the first in France to be appointed to the Chair of Fundamental Genetics, became ignored and ostracized by the medical, academic, and political elite of France. He lost research funding and faced harassment. Despite all this, Lejeune remained steadfast, stating that, "It cannot be denied that the price of these diseases is high—in suffering for the individual and in burden for society. Not to mention what parents suffer! But we can assign a value to that price: it is precisely what a society must pay to remain fully human" [5,6].

THE OPENING

Finally, on January 29th, the opening evening of the exhibit had arrived (Figure 2). At a panel discussion, Dr. Mark Basik from McGill University described how Dr. Lejeune's example guided his work researching the genetic causes of metastatic breast cancer. Dr. Basik said, "He inspires me in so many ways, especially the way his research was driven by the love for his patients; he was not afraid of being scooped—he just wanted to spread the news. His motivation was to find a cure, and do something to help his patients."

Then, family physician Dr. Lise Poirier-Groulx, a lecturer for the University of Ottawa Faculty of Medicine, shared her personal journey as a mother of a now 15-year-old boy with DS, describing the isolation and brokenness she and her family experienced. "This didn't happen to me; it usually happened to my patients…," she said. Yet her experience transformed her into an advocate for those with disabilities. "When I prepare the first year medical students on coping and adapting to disability, I tell them that it's not about who is disabled but it is much more about when we become disabled," said Dr. Poirier-Groulx. "Without being pessimistic and unless we exit this life suddenly, we all be incapacitated or become disabled at some point."

THE EXHIBIT – (Figures 3, 4)

During the guided tour of the exhibit, we all experienced how Dr. Lejeune still touches the hearts of different people. On the first day, I was explaining to a group of people of how Dr. Lejeune had testified in front of the judges of the Supreme Court of Canada in 1983 on the nature of the unborn child. On one of the panels we read Lejeune's message, "Our duty has always been not to inflict the sentence but to try to commute the penalty. In any foreseeable genetic trial, I do not know enough to judge, but I feel enough to advocate" [4]. A man in the crowd identified himself as Dr. Lejeune's driver throughout the duration of the trial, and told us of how charming and resolute Dr. Lejeune had been at the time, and how seeing Dr. Lejeune's words here had brought him back.

On the second day, while I was guiding one of my colleagues through the 36 panels of the exhibit, he reflected, "When I see the way Lejeune has lost fame, power, and money to fight for the vulnerable, I need to reflect on my own… the way I advocate pales in front of him; we do not understand what advocacy for our patients truly means!" Even when Lejeune was seriously ill, he worried for his patients, saying "I was the doctor who was supposed to cure them, as I leave; I feel I am abandoning them" [1].

By the third day into the exhibit, I noticed that my students seemed to have found inspiration in learning about Dr. Jérôme Lejeune's life. One of my student-guides, Stephan, while pointing at a poster displaying the gigantic smiling face of Dr. Lejeune said, "He is the doctor I want to be!" I too grew to love Dr. Lejeune's humanity and personality. His straightforward way to live his faith has undoubtedly impacted my personal and professional life.

THE NEXT STEP

The next stop for Dr. Lejeune's exhibit will be the Mayo Medical School Campus, after which it will travel to several other uni-

Figure 3. The protagonists. Five of the seven student guides of the Jérôme Lejeune exhibit. From left: Brian, Stephan, Caroline, Stephanie and Batoul (Alex and Nohémie are missing.)

Figure 4. Alex leading an interactive tour of the exhibit at the University of Ottawa (Roger Guindon Hall atrium).

versities within the United States. Meanwhile, a professor from the Department of Innovation in Medical Education who saw the exhibit emailed me a brilliant idea: "What a remarkable display… I wonder if some of this material could be worked into an on-line module as Case Based Learning for the first year medical students… since it contains the elements of history of Medicine, medical ethics, professionalism…".

In our time the prevailing view of illness has taken a stance of distance from the diseased. The ultra-specialization of medicine has fostered in medical students an emphasis on knowledge and technical skills, with a neglect of the Hippocratic aspect of the practice of medicine. Dr. Lejeune was a near-perfect clinician-researcher whose thinking was ahead of his time. His teaching could offer, to our medical students, a vision that uses science to serve the patient, not the disease. His outlook has taught me that, in a field that is constantly moving and changing, the only trend worth following is the search for truth. Clearly, truth for him was no more and no less than what he was seeing through his microscope. But to honestly love the truth means to make all of your practical professional endeavors revolve around it, without compromise. As the world-renowned ethicist Dr. Edmund Pellegrino once stated, a doctor "binds himself to competence as a moral obligation" and "places the well-being of those he presumes to help above his own personal gain. If these two considerations do not shape every medical act and every encounter with the patient, the profession becomes a lie: the physician is a fraud and his whole enterprise undiluted hypocrisy." [7].

My students prepared to become exhibit guides with great passion and enthusiasm, and I am sure that they have found in Dr. Lejeune a role model who put truth at the core of our medical profession and research. While we were dismantling the exhibit, we were talking about Lejeune's relentless attitude to follow what is real. Alex—one of the undergrad student-guides—said, "He had always a central question in his mind: What is man? (He meant in the ontogenetic and metaphysical sense.) And from that fundamental question he found all answers." Dr. Lejeune's words then resounded in my mind: "A physician that doesn't have hope will never find the solution." Lejeune's ultimate judgment of humanity, despite all he went through, was optimistic and he exhorts this optimism—to the physician—as a moral obligation.

I have slowly started to grasp what "to advance on the path of hope" means. As I pass through the atrium of the university, I recall how my students had truly been the heart and soul of the exhibit. I wish for them to be inspired and to consider different ways to be physicians, or researchers, if that is to be their path. I have confidence that they too will learn that their future happiness will lie not only in their capabilities, success, and accomplishments, but foremost in their deep affection combined with devotion to their patients (what Dr. Lejeune used to call "compassion"), and their awareness of their own limitations (Dr. Lejeune's definition of "humility").

Finally, I hope that the exhibit will come again to Ottawa and continue to inspire future generations of students and physicians in training.

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REFERENCES

1. Lejeune-Gaymard, C. Life is a Blessing: A Biography of Jérôme Lejeune. Jérôme Lejeune Foundation (Paris, France) and the National Catholic Bioethics Center (Philadelphia,PA), 2012. Originally published as La Vie est un Bonheur: Jérôme Lejeune, mon père. Editions Fleurus, Paris, France, 1997. ISBN 978-0-935372-59-5.
2. Lejeune J, Gauthier M, Turpin R. Les chromosomes humains en culture de tissus. CR Hebd Seances Acad Sci. 1959; 248(4):602–603.
3. Lejeune J, Lafourcade J, Berger R, et al. Trois cas de délétion partielle du bras court d'un chromosome 5. CR Hebd Seances Acad Sci. 1963;257:3098–3102.
4. Lejeune J. The William Allan Memorial Award lecture. On the nature of men. Am J Hum Genet. 1970;22(2):121–128.
5. Jerome Lejeune Foundation USA. Legendary Geneticist Jerome Lejeune [Internet]. Ottawa (ON): University of Ottawa, Department of Medicine; 2013 July 29. Available from: https://www.youtube.com/watch?v=0MA42QKsEWQ.
6. Lejeune J. 21 Thoughts [Internet]. Ottawa (ON): University of Ottawa, Department of Medicine; 2013. Available from: http://lejeuneusa.org/advocacy/21-thoughts-dr-jérôme-lejeune.
7. Caplan L. Edmund Pellegrino [Internet]. Ottawa (ON): University of Ottawa, Department of Medicine; 1986 April 27. Available from: https://www.washingtonpost.com/archive/lifestyle/magazine/1986/04/27/edmund-pellegrino/334406d8-cf5a-4349-8655-0cdbf656f6f3/.
8. Israël L, Arnaldez R. Notice sur la vie et les travaux de Jérôme Lejeune (1926-1994): séance du mardi 4 mars 1997. Académie des sciences morales et politiques (France), Paris, France, 1997.
9. Strippoli P, Pelleri MC, Caracausi M, et al. An integrated route to identifying new pathogenesis-based therapeutic approaches for trisomy 21 (Down Syndrome) following the thought of Jérôme Lejeune. Sci Postprint. 2013;1(1):e00010.

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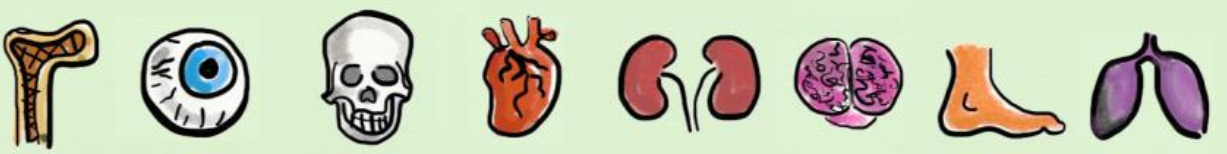

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