UOJM JMUO

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Volume 5 Issue 2

UNIVERSITY OF OTTAWA JOURNAL OF MEDICINE
JOURNAL MÉDICAL DE L'UNIVERSITÉ D'OTTAWA

Neuroscience and Mental Health

CASE REPORT
Hidden in Plain Sight: Recognizing Catatonia Amidst its Medical Complications

INTERVIEW
Acute Stroke Research: Being Part of a Game-changer with Dr. Dar Dowlatshahi, Scientific Director of the Ottawa Stroke Program

REVIEW
A Review of Transgender Health

COMMENTARY
Exploring the Interdisciplinary Roles of Dermatologists and Psychiatrists in the Management of Excoriation (Skin-picking) Disorder

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Rotenone Neurotoxicity Causes Dopamine Neuron Loss in Zebrafish

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Objecting the Objective – How Passing the Person Fails Our Growth

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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

7 **Preface / Préface**
Ariana Noel, Nischal Ranganath, Paula Adler, Devon Johnstone

INTERVIEW

8 **Acute Stroke Research: Being Part of a Game-Changer with Dr. Dar Dowlatshahi, Scientific Director of the Ottawa Stroke Program**
Faizan Khan, Marc-Olivier Deguise

12 **Integrating Administration, the Clinic, and Research: An Interview with Dr. Jacques Bradwejn**
Ariana Noel, Nischal Ranganath

RESEARCH

16 **Rotenone Neurotoxicity Causes Dopamine Neuron Loss in Zebrafish**
Simon Martel, Jonathan Y. Keow, Marc Ekker

CASE/ELECTIVE REPORT

22 **Hidden in Plain Sight: Recognizing Catatonia Amidst Its Medical Complications**
Marion Malone, Timothy Lau

26 **Lithium Toxicity at Therapeutic Blood Levels: A Case Report**
Alexandra Quimby, Rajeev Sachdeva

REVIEWS

29 **The Importance of Longitudinal Neurocognitive Assessments in Heart Failure Patients Receiving a Left Ventricular Assist Device**
Sneha Raju, Vanessa Rojas-Luengas

35 **A Recent Clinical Update on Epilepsy in Pregnancy**
Isabel Arroyo

40 **A Review of Transgender Health in Canada**
Travis William Davidson

UOJM
UNIVERSITY OF OTTAWA JOURNAL OF MEDICINE

JMUO
JOURNAL MÉDICAL DE L'UNIVERSITÉ D'OTTAWA

46 **Through the Looking Glass: A Literature Review of a Rare Pediatric Neuropsychiatric Condition: Alice in Wonderland (Todd's) Syndrome**
Brittany Harrison, Adrienne Harrison

COMMENTARY

50 **Exploring the Interdisciplinary Roles of Dermatologists and Psychiatrists in the Management of Excoriation (Skin-Picking) Disorder**
Danielle Mintsoulis

55 **The Treatment of Sleep Disturbances in the PTSD Patient**
Kimberly Reiter

59 **L'entrainement, c'est ma vie!**
Eve Laplante

63 **Prévenir le VIH et l'hépatite C dans les prisons fédérales canadiennes : l'apport de la recherche et du militantisme dans l'instauration des programmes d'échanges de seringues en prison**
David Buetti, Novella Martinello

67 **A Time to Talk About Technology – Discussion About Medical Technology with the ATIME Group at The Ottawa Hospital**
Stephen Y.Y. Leung, Cindy C.Y. Law, Sonam Maghera, Daniel Goubran

HUMANITIES

70 **Objecting the Objective – How Passing the Person Fails Our Growth**
Kayla Ashley Simms

71 **Tears & Puzzle Pieces**
Julie El-Haddad

72 **Aortic Bloom**
Agata Dzwonek

Despair
Tetyana Maniuk

UOJM: Preface

In its fifth cycle, the University of Ottawa Journal of Medicine (UOJM) has made significant progress. Since the previous cycle, we have increased the number and scope of submissions with each issue. We have published a diverse range of works including clinical case reports, biomedical research articles, interviews, reviews, commentaries, and humanities pieces. Notably, UOJM is a bilingual publication that strives to integrate and promote the dissemination of knowledge in both English and French. The abstracts of each article are published in both languages and the current issue features two articles written in French. In keeping with this value, we encourage our readers to submit in French for future issues of UOJM!

In parallel, we are continuing to expand the reach of UOJM and develop our international collaboration with Shanghai Jiao Tong University with plans to train students in our peer-review process and the use of our online journal system adopted in 2014. UOJM had a very successful year, holding training seminars in peer review (Dr. David Moher), social media in research and medicine (Dr. Ali Jalali), and research in medicine (Drs. Phil Wells, Ian Stiell, and Viren Naik), as well as a CMAJ editing workshop (Dr. Diane Kelsall), case report workshop (Dr. Sean Bennett), and evidence-based medicine seminar (Dr. David Grynspan).

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. The UOJM executive and editorial team contribute not only as authors, editors, and reviewers, but also strive to promote and accrue sponsorship, contributing significantly to the success of this issue. Additionally, we would like to acknowledge our faculty advisors Drs. Phil Wells, Melissa Forgie, and David Moher for their guidance and direction of the journal, the editorial team training process, and the implementation of our online journal system. Finally, we would like to sincerely thank our sponsors without whom publication of UOJM would not be possible: Faculty of Medicine (University of Ottawa), Office of the Vice-President Research (University of Ottawa), Department of Cellular and Molecular Medicine (University of Ottawa), The Ottawa Hospital, the Children's Hospital of Eastern Ontario, and The Royal Ottawa Mental Health Centre.

As we look to the year ahead, we are excited to announce that the theme of our next issue, UOJM 6.1, will be "Preventative and Personalized Medicine." We have assembled a hard-working team from a pool of over 70 applicants. A goal for this year is to further increase our outreach and encourage submissions from outside the University of Ottawa. We look forward to another successful year and are already accepting submissions at http://uojm.ca/submissions/.

Volume 5, Issue 2 highlights cutting-edge research and updates in the fields of neuroscience and mental health. The current issue represents our largest publication to date, featuring 15 articles from graduate students, medical students, resident physicians, researchers, and clinician-scientists at the University of Ottawa. Neurological and mental health disorders are highly prevalent within our society and impose a significant burden on the healthcare system, as well as on the quality of life of affected individuals, and continue to carry significant social stigma. Despite the tremendous advancements in our understanding of disease pathogenesis and therapeutics, it is imperative to further characterize the clinical and psychosocial implications of mental health disorders, as well as develop practice-changing strategies to better manage these conditions and provide support for individuals living with these challenges. In this issue, we feature articles on the topics of acute stroke research, rotenone and lithium toxicities, prevention of HIV and hepatitis C in Canada's federal prisons, transgender health, and bigorexia, as well as a clinical update on epilepsy and an interview with Dr. Jacques Bradwejn, dean of the University of Ottawa's Faculty of Medicine. We hope you enjoy the Neuroscience and Mental Health issue!

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JMUO: Préface

Dans son cinquième cycle, le Journal médical de l'Université d'Ottawa (JMUO) a connu des progrès significatifs. Depuis le cycle précédent, nous avons augmenté notre nombre et portée de communications avec chaque édition. Nous avons publié une gamme variée d'articles, y compris des rapports de cas cliniques, de la recherche biomédicale, des entrevues, des critiques, des commentaires et des sujets en sciences humaines. Notamment, le JMUO est une publication bilingue, qui vise à intégrer et à promouvoir la diffusion des connaissances à la fois en anglais et en français. Les résumés de chaque article sont publiés dans les deux langues et le numéro actuel comporte deux articles en français. En accord avec cette valeur, nous encourageons nos lecteurs à soumettre en français pour les prochains éditions du JMUO!

En parallèle, nous continuons à étendre la portée du JMUO et à développer notre collaboration internationale avec l'Université de Shanghai Jiao Tong. Nous planifions de former des étudiants dans notre processus de revue par les pairs et dans l'utilisation de notre système de journal en ligne adopté en 2014. Le JMUO favorise l'éducation et la formation par le biais de séminaires organisés tout au long de l'année. Nous avons connu une année très réussie en tenant des séminaires au sujet de la formation en revue par les pairs (Dr David Moher), les médias sociaux dans la recherche et la médecine (Dr Ali Jalali), et la recherche en médecine (Drs Phil Wells, Ian Stiell, et Viren Naik), ainsi qu'un atelier de mise en page du JAMC (Dre Diane Kelsall), un atelier de rapport de cas (Dr Sean Bennett), et un séminaire au sujet de la médecine factuelle (Dr David Grynspan).

La publication du JMUO en ligne et la version papier ne serait pas possible sans le dévouement extraordinaire des étudiants de médecine et des étudiants aux études supérieures de l'Université d'Ottawa. L'équipe exécutive et l'équipe de révision du JMUO contribuent non seulement comme auteurs, éditeurs et réviseurs, mais font aussi la promotion du journal et assure la communication avec des commanditaires. Ces efforts ont contribué de façon significative au succès de cette édition du journal. De plus, nous aimerions remercier nos conseillers pédagogiques Dr Phil Wells, Dre Melissa Forgie, et Dr David Moher pour leur orientation et leur aide à diriger le journal. Nous sommes reconnaissants aussi pour l'aide de la part de l'équipe éditoriale en formation et ceux qui ont contribué à la mise en œuvre de notre système de journal en ligne. Finalement, nous aimerions sincèrement remercier nos commanditaires sans qui la publication du JMUO n'aurait pas été possible : Faculté de Médecine (Université d'Ottawa), vice-rectrice à la recherche (Université d'Ottawa), Département de médecine cellulaire et moléculaire (Université d'Ottawa), l'Hôpital d'Ottawa, le Centre hospitalier pour enfants de l'est de l'Ontario (CHEO), et le Centre de santé mentale Royal Ottawa.

Alors que nous nous tournons vers l'année à venir, nous sommes heureux d'annoncer que le thème de notre prochain numéro, JMUO 6.1, sera « la médecine préventive et personnalisée. » Nous avons réuni une équipe exceptionnelle à partir d'un répertoire de plus de 70 candidats. Un objectif pour cette année est d'accroître notre portée et à encourager les soumissions provenant de l'extérieur de l'Université d'Ottawa. Nous acceptons les soumissions pour JMUO 6.1 dès maintenant à http://uojm.ca/submissions/.

Le volume 5, édition 2 met l'emphase sur la recherche récente dans le domaine des neurosciences et de la santé mentale. L'édition courante représente notre plus grande publication à ce jour. Elle inclut 15 articles rédigés par des étudiants aux études supérieures, des étudiants en médecine et résidents, des chercheurs, et des cliniciens-scientistes de l'Université d'Ottawa. Les désordres neurologiques et les désordres qui affectent la santé mentale sont très prévalents dans notre société et imposent un fardeau significatif au système de santé, à la qualité de vie des individus affectés, et continue de répandre un stigma social. Malgré les avancements de nos connaissances au niveau de la pathogenèse et de la thérapie de ces maladies, il est impératif de continuer à caractériser les implications cliniques et psychosociales de maladies associées à la santé mentale. De plus, il serait primordial de développer des stratégies afin de mieux gérer ces conditions et fournir le support nécessaire pour les individus qui vivent avec ces défis. Dans JMUO 5.2, nous allons mettre en valeur des articles au sujet de la recherche sur l'accident vasculaire cérébral aigu, les toxicités de la roténone et du lithium, la prévention du VIH et de l'hépatite C dans les prisons fédérales du Canada, la santé transgenre, la bigorexie, ainsi qu'une mise à jour clinique sur l'épilepsie et une entrevue avec le doyen de la Faculté de médecine de l'Université d'Ottawa Dr Jacques Bradwejn. Nous espérons que vous profiterez de cette édition du journal sur les neurosciences et la santé mentale.

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Acute Stroke Research: Being Part of a Game-Changer with Dr. Dar Dowlatshahi, Scientific Director of the Ottawa Stroke Program

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ABSTRACT

Dr. Dar Dowlatshahi, MD/PhD, is a stroke neurologist, an assistant professor at the University of Ottawa, and a neuroscientist at the Ottawa Hospital Research Institute (OHRI). As the Scientific Director of the Ottawa Stroke Program, he is conducting cutting-edge research in the area of acute stroke, with a special interest in intracerebral hemorrhage (ICH). He was part of the recent ESCAPE trial, a national groundbreaking study that has redefined the scope of stroke therapy around the world. We had the incredible opportunity of speaking with Dr. Dowlatshahi about his exciting career as a clinician-scientist, as he educated us about the unique features of stroke, informed us of the recent advancements in his research, and provided advice for interested students and trainees who want to pursue a career in academic medicine.

RÉSUMÉ

Dr. Dar Dowlatshahi, MD/PhD, est un neurologue spécialisé en AVC, professeur adjoint à l'Université d'Ottawa, et un neuroscientifique à l'Institut de recherche en santé d'Ottawa (IRSO). Comme directeur scientifique du Programme d'AVC à Ottawa, il mène des recherches de pointe dans le domaine de l'AVC aigu, avec un intérêt particulier dans l'hémorragie intracérébrale (HIC). Il a fait partie de l'essai récent « ESCAPE », une étude révolutionnaire nationale qui a redéfini le cadre de la thérapie de l'AVC autour du monde. Nous avons eu l'incroyable opportunité de parler avec le Dr. Dowlatshahi à propos de sa carrière passionnante comme clinicien-chercheur. Il nous informa ainsi sur les caractéristiques uniques de l'AVC, des récents progrès dans ses recherches, et nous a fourni des conseils pour les étudiants et stagiaires voulant poursuivre une carrière en médecine académique.

TELL US A BIT ABOUT YOURSELF AND HOW YOU GOT TO WHERE YOU ARE RIGHT NOW.

I am a stroke neurologist at The Ottawa Hospital, and an Assistant Professor in the Departments of Medicine and Epidemiology & Community Medicine at the University of Ottawa. I am also the Scientific Director of the Ottawa Stroke Program, which means I run most of the clinical research concerning stroke. I was always interested in asking questions, particularly in grey areas of medicine and science in general, and that very naturally lead to a path of a clinician-scientist training; to ultimately try to ask questions that arise during my practice and generate the very data that, in later instances, I will use to treat my patients.

TELL US ABOUT YOUR EDUCATIONAL/CAREER PATH. HOW DID YOUR RESEARCH/CLINICAL INTERESTS DEVELOP TO WHERE THEY ARE NOW?

I started as a grade C level student in university. I got interested in psychiatric diseases and wondered why people acquire these diseases and what causes them. I met a very prominent researcher in that area who offered me to join on and do some advanced studies/research with him. At that point, I decided to pursue a Master's degree in that area. I absolutely loved the research I was doing and decided that I wanted to be a medical researcher. Thus, I started a PhD degree in neuroscience. During my PhD, I was captivated by clinical medicine because it provided better context for the disease I was studying. I got particularly inter-

Keywords: Acute stroke; Intracerebral hemorrhage; Clinician-scientist

ested in the areas of high acuity care, emergency care, and intensive care settings. Simultaneously, when you find something you like, your grades go up. Grades reflect interest. I suddenly became a high enough academic candidate for medical school. I was not trying to be a doctor; that was not my intention. My supervisor was a clinician-scientist who was a great role model. I just thought that I could conduct research more effectively if I had a clinical training and understood the disease from outside the lab. Thus, I applied to medicine, got lucky and got in. I decided not to quit my research because the desire to ask questions, particularly about disease causing phenomenon and its reversal, was always something I pursued and it was the primary reason I applied to medicine. Accordingly, I decided to combine the two degrees (MD/PhD).

During the medical program, I was exposed to neurology. I continued having a strong interest in neuroscience, and stroke involved fast and important decision-making; the high acuity area of neurology I was looking for. During my residency, I had an excellent mentor, Dr. Antoine Hakim, a very famous stroke researcher, who offered to support my first research project. My first year was a tremendous success with a couple of publications. Towards the end of residency, I met my other mentor, Dr. Andrew Demchuk, a brilliant stroke neurologist who asked me to join his research team in Calgary. At that time, I started ICH research since it had been mainly overlooked. It was a strong clinical/research year for me and job offers started coming in. I chose to come back to Ottawa as it was the perfect fit. They wanted to start a program and they wanted to give me all the opportunities to build it. I accepted the challenge. It ultimately grew into the Ottawa Stroke Program.

WHAT IS UNIQUE ABOUT STROKE AND ITS MANAGEMENT?

Stroke is the only neurological condition that gets better with time; thus, the natural history of stroke is towards improvement. On the other hand, stroke is a sudden onset [condition] that can cause lifetime disability for many patients that may never get back to their own initial functional state. Most people don't realize that death is [the] number two fear of your average Canadian. Disability is number one. Stroke is the primary cause of disability and becomes the primary fear of most people. I prefer to practise in the area of acute stroke and the unique thing about doing acute stroke research/therapy is that you literally have seconds to minutes to act. Every minute is 1.9 million brain cells lost. You have to act efficiently and precisely when you see a patient. A person's likelihood of being disabled for life, their number one fear, is on the line and only your choices and actions can actually allow avoiding this eventuality.

TELL US ABOUT YOUR PAST AND CURRENT STROKE RESEARCH PROJECTS.

There are three main areas of research in stroke: prevention, acute treatment, and recovery. Currently, we have over twenty projects at the Ottawa Stroke Program. In the prevention field, we are looking for new possible and modifiable risk factors for stroke, such as smoking cessation as well as targeting pre-diabetes. We are also investigating effects of stroke in the susceptible population that could lead to dementia and depression as well as the overlaps with other conditions.

As mentioned earlier, my personal work is often in the area of acute medicine. I spend some of my [time devoted to] research developing new diagnostic neuroimaging standards for identification of acute thrombus in the neck vessels that we often miss. More specifically, we are modifying our computerized tomography (CT) angiogram technology to be able to identify the thrombus more easily. Additionally, I have a strong research interest in intracerebral hemorrhage (ICH), [a condition in which] about a third of the patients that present are still bleeding in the brain, yet you can't see it. It is crucial for us to identify the bleeding in these patients because they require a different type of therapy. We developed a CT angiogram technique to image the ongoing bleeding in the brain. Consequently, we can target the therapies towards those patients that are affected by ongoing bleeding and not the ones who have already stopped bleeding.

We just made a major breakthrough in January as a large international collaboration to introduce a therapy called mechanical thrombectomy; removing blood clots from the brain. This study, called the ESCAPE trial [1, 2], has changed the way we treat stroke all across the world. This procedure has significantly reduced the death and disability rate from major strokes.

We have also started in stroke recovery research for the first time this year. We are using iPads to treat stroke patients who are in the hospital. We hypothesize that you can speed up recovery by providing the patient the tools to rehabilitate early (i.e., within two days) after stroke. Generally, about fifty percent of Canadians don't get into rehabilitation within two weeks. This project, called iRecover, allows patients to improve in various areas including speech, cognition, and occupation, using an iPad in their own time.

IN WHAT WAYS HAS THE MANAGEMENT OF STROKE CHANGED SINCE THE START OF YOUR CLINICAL/RESEARCH PRACTICE?

During medical school, back in 2001, I encountered a patient who had a stroke halfway through an interventional procedure, as a result of a complication. Unfortunately, the doctors had nothing to offer. At that time, there were no stroke doctors at this major

institution. The patient was completely disabled, ended up in a nursing home and almost certainly passed away from it. Later, I started pulling out all the data to realize that tissue plasminogen activator (tPA), a new clot-busting medication, not only worked, it very well could have saved that lady's life. But neurologists at the time did not believe in its effectiveness. Additionally, we now know that [a] mechanical thrombectomy procedure could have been used. In fact, we could have completely reversed her deficit, on that table, within minutes. However, we had no idea that it was feasible because those studies hadn't been done yet. Today, a patient with an intra-procedural stroke stays on that table and neurointerventionalists are quickly able to reverse the stroke with the same tools that were previously being used. These patients now walk off that table like nothing ever happened. It is a completely different world.

WHAT RESEARCH DO YOU THINK IS NEEDED IN ACUTE STROKE?

The biggest challenge is treating ICH. This forms one fifth of strokes and it accounts for most of the stroke-disabled patients. Moreover, forty percent of ICH survivors will die within the first two days. Thus, it is a very lethal and disabling type of stroke and there is no real effective therapy. In our recent studies, we have shown that blood pressure reduction could help. We are also working towards other therapies such as hemostatic approaches and neuroimaging techniques. Although we still work on all other areas in stroke research, including recovery, my major goal would be to treat patients with ICH; a type of stroke we cannot efficaciously treat yet.

WHAT IS A TYPICAL WEEK FOR YOU? TELL US ABOUT YOUR MULTIPLE ROLES IN THE ACADEMIC SETTING.

As a clinician-scientist, every day is different. I have my pure clinical days, where one day I'll run a stroke prevention clinic: I'll see patient after patient, review their risk factors, establish if they [have] had a transient ischemic attack (TIA) or an actual stroke, and work on preventing the next one. On another day, I'll be in the neurovascular unit treating the medical complications associated with acute strokes and trying to figure out why they had a stroke. This is a few of all the things I do during my clinical days. Then, there are my pure research days, where I'll run the Ottawa Stroke Program. I essentially set the directions of the research. I also have to secure funding for the program; therefore, I apply for grants, pitch in ideas, and raise awareness in order to move the science forward. I also have my own personal research days where I write my manuscripts and publish them. I have my education days where I give lectures to undergraduate medical students, residents as well as family physicians and neurologists. Lastly, I have a role for advocacy and knowledge translation, which means working on practice guidelines. With a team, I review and update all the guidelines routinely.

It forms kind of a cycle [Figure 1]. The interesting thing with being a clinician-scientist and an academic neurologist is that you get to see the entire loop. The loop starts with the research. The research then gets published and goes to guidelines committee. When it gets used for the guidelines, you then sit on the guideline committee where you incorporate others' research as part of the guidelines. This is knowledge translation. From there, you naturally take on the educational role and inform people on these guidelines and on the research leading to them. Next, you use the recommended treatment on your patient. While seeing the patient in the emergency room, you hit a grey area where you feel puzzled about the next step to take. This is your next research project and you go back to the beginning of the cycle. In a given week, I literally do all of that.

HAVING YOURSELF COMPLETED THE COMBINED MD/PHD PROGRAM, WHAT WOULD BE YOUR BEST ADVICE TO CURRENT AND INCOMING MD/PHD STUDENTS AND THOSE INTERESTED IN PURSUING A SIMILAR EDUCATIONAL PATH?

I think that there is no formal program that will make you what you want to be. The most important drivers are yourself, how flexible you are, and how you react to the external environment. It is crucial to understand that, sometimes, things will go badly and, other times, you will come across unexpected opportunities. Ultimately, you want to look at the horizon, and say that's where I want to be. You don't want to speculate on how long it is going to take for you to get there and start counting the years. In contemplating whether you should pursue [an education in] an MD/PhD program, an MD program, or a PhD program, look at the horizon, see where you want to be, and then look at what opportunity presents to you. Pick what seems to be the best fit for you at the moment. It might not be the program you wanted in the first place but this will gradually get you to where you want to be. Then, once this opportunity is over, think about what could bring

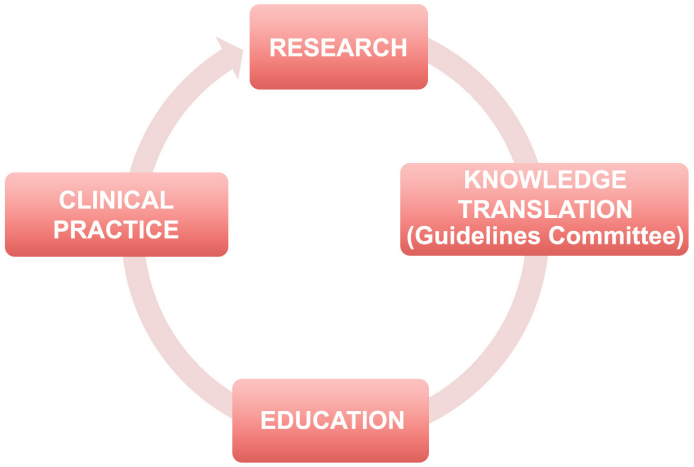

Figure 1. Progression of the various roles of a clinician-scientist.

you one step closer to your ultimate goal. The last thing you want to do is give up. Persistence and an overall sense of direction are critical, but flexibility and looking for unexpected opportunities are equally as essential.

ACKNOWLEDGEMENTS

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Integrating Administration, the Clinic, and Research: An Interview with Dr. Jacques Bradwejn

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ABSTRACT

Dr. Jacques Bradwejn is a Professor of Psychiatry, the Dean of the Faculty of Medicine, and a past Chair of the Department of Psychiatry at the University of Ottawa. He trained in Medicine at the University of Sherbrooke and in Psychiatry at McGill University. He completed a Research Fellowship in basic research in neuropsychopharmacology at Université de Montréal. He began his career as a clinician/researcher in the McGill University network and continued at University of Toronto, before coming to the University of Ottawa. He has also served as the Psychiatrist-in-chief at the Royal Ottawa Hospital and the head of Psychiatry at The Ottawa Hospital. In addition to his teaching and administrative engagement, Dr. Bradwejn has been extensively involved in translational neuropsychopharmacology research investigating the underlying biological etiology of anxiety disorders such as panic disorder and social phobia, as well as integrating clinical and psychological approaches towards the management of anxiety disorders. We were able to discuss with Dr. Bradwejn his dedication and extensive commitment to clinical care and advocacy, biomedical research, and administrative leadership, as well as his advice for medical students with regards to juggling a multitude of responsibilities and pursuing leadership roles within their careers.

RÉSUMÉ

Dr. Jacques Bradwejn est professeur de psychiatrie, doyen de la Faculté de médecine, et un ancien président du Département de psychiatrie de l'Université d'Ottawa. Il a été formé en médecine à l'Université de Sherbrooke et en psychiatrie à l'Université McGill. Il a complété une bourse en recherche fondamentale en neuropsychopharmacologie à l'Université de Montréal. Il a commencé sa carrière en tant que clinicien-chercheur dans le réseau de l'Université McGill et a continué à l'Université de Toronto avant de venir à l'Université d'Ottawa. Il a également servi en tant que chef de psychiatrie à l'Hôpital Royal Ottawa et à l'Hôpital d'Ottawa. En plus de ses tâches d'enseignement et d'engagement administratif, le Dr. Bradwejn a été largement impliqué en recherche en neuropsychopharmacologie traductionnelle, enquêtant l'étiologie biologique sous-jacente des troubles anxieux tels que le trouble panique et la phobie sociale, ainsi que l'intégration des approches cliniques et psychologiques envers la gestion des troubles anxieux. Nous avons pu discuter avec le Dr. Bradwejn de son dévouement et de son engagement extensif aux soins cliniques et à son plaidoyer, à la recherche biomédicale, et au leadership administratif, ainsi que ses conseils aux étudiants en médecine en ce qui concerne jongler une multitude de responsabilités et poursuivre des rôles de leadership au sein de leur carrière.

CAN YOU PLEASE TELL US ABOUT YOURSELF AND YOUR ROLE AS A PSYCHIATRIST, A RESEARCHER, AND THE DEAN OF UOTTAWA FACULTY OF MEDICINE?

In terms of my personal origins, I was born in Montreal and grew up in France. My mother was French from Brittany and most of my ancestors didn't speak French, they spoke Breton. My paternal background was from a Jewish family in Poland. My father basically lost all his family in the Holocaust, and then eventually he was given French citizenship after the war. He met my mother in France and eventually came to Montreal. I was born in Montreal, but grew up in Britanny until adolescence, So I'm basically the product of destruction on the father's side, but also on the mother's side because my hometown was on the Atlantic and the Germans had built U-boat bases by the sea, so they were bombed [to hell] by the allies.

DO YOU HAVE AN AREA OF SUBSPECIALTY? WHAT INTERESTED YOU IN THE MANAGEMENT OF ANXIETY AND PANIC DISORDERS?

When I was a medical student, there were a number of special-

Keywords: Psychiatry; Administration; Anxiety disorders; Jiao Tong University

ties that I particularly liked. One of them was psychiatry, but I liked internal medicine, neurology, cardiology. When I was a student at McGill, I rented a room in a house that was owned by the chair of psychiatry at the time in Montréal. He was from France and worked at Liège and sometimes I would help him translate some of his work. So, I got interested in the field. What interested me the most in psychiatry is that you dealt with medicine, you dealt with the brain, but it is also a field where you need to know a lot about people. Plus, there were a lot of possibilities for research. After I did one year of internal medicine, to have a better grounding in medicine, I went into psychiatry.

During my training as a resident I did some research in a specialty unit that was interested in mood and anxiety disorders, so I applied for a fellowship in mood disorder research. I had planned to do this fellowship at Yale University, and I received a FRSQ fellowship support to join the basic science laboratory of Dr. Claude De Montigny. Claude De Montigny was well known for his research on the role of serotonin and mood disorders [and] that's what I [had] applied for. By the time I had integrated into his lab, he had moved from Yale to Université de Montréal and had decided to expand his research to look at what was up and coming at the time, which happened to be brain peptides. It was to look at the role of cholecystokinin (CCK), which was a known gut peptide. It had been found by various research groups that there were high concentrations of fragments of CCK in the brain and at the time they were known to be co-localized with dopamine. Dopamine was [linked to] schizophrenia and therefore, the question that was of interest was what might be the role of CCK on dopamine neurotransmission and could there be a role for CCK in the treatment of schizophrenia. I was using an approach called microelectropheresis, which was the main tool of investigation used in De Montigy's laboratory. What you do is take a live rat, drill a burr hole and use a micropipette that records neuronal activity and enables you to inject pharmacological products and see how it modifies the firing rate. So for the first 6 months we used to say, "another day, another rat." We would inject some CCK and record the dopamine activity. One experiment would increase the firing rate, the other would do the opposite or have no effect. Six months were spent without consistent results.

One day, by pure serendipity, because there was a fellow at the Douglas Hospital who had been giving high doses of benzodiazepines for acute psychosis and it would work without much sedation, I asked the question, what might be the role of benzodiazepine on dopamine activation. Because the micropipettes had 6 barrels in one I would put dopamine, in the other CCK and in another a benzodiazepine and look at the effect of interaction on each of these on each other and on neuronal firing. CCK, on its own, was known to activate neurons, as had been described in other laboratories. When I injected benzodiazepines with CCK, there was a full antagonism of CCK activation. I went to my boss, De Montigny, and asked if I could change projects and look at the role of benzodiazepine on CCK and the role of CCK in anxiety and he says, "Okay, I'll give you a few weeks on it and we'll see." That was fruitful. We found out a benzodiazepine receptor agonist could completely antagonize the excitatory effect of CCK in the hippocampus. Very low doses, such as 4–5 mg of Valium, acted very specifically and selectively on CCK; so that was a finding. My first paper on that was in Nature [1]. I thought to myself after a paper in Nature, from there it's only to be downhill with the next papers! After three years, I went back to a hospital career and did clinical research. I intended to have a career like [Dr. Michael] Schlossmacher, to do basic laboratory and do clinical work, but I became very allergic to rats, which is not unusual. I ended up finding a position in a McGill-affiliated hospital and setting up a clinical research unit. So, that's what got me into research and that worked well. We had lots of results, good grants, and publications. I eventually moved to Toronto to investigate the action of CCK in humans, using PET/MRI equipment that was readily available at the then Clarke Institute, which is now the Center for Addiction and Mental Health.

My area of subspecialty was dictated by research during the fellowship. We showed the benzos inhibited CCK-induced–neuronal activation, so the question was what the role of CCK may be in anxiety? That was the question from the original animal research. As I started my career at McGill, I chose St. Mary's Hospital, which was a smaller hospital. There were not many resources, but it was a good environment to set up a team and so I set up a clinical research team. The first question we tested was if CCK is anxiogenic. If its action is antagonized by benzodiazepines, could this peptide provoke anxiety in humans? So the first test was to inject it into patients. We were the first to report that a short fragment of CCK [acted as a] panicogenic. It very reliably induces a panic attack [within] 20 seconds, at doses as low as 25 mcg. That led to looking at where might it act, how might it act, it's interactions, which led to a lot of papers. Will we ever get a medication that comes out of that? That's yet to be done because it's very hard to produce peptide analogs. There were a few attempts, but there is much less being developed for neuroscience in terms of drug development right now. Aside from potential drug development, we also were able to show mutations at the CCK receptor gene that occur in a higher frequency in panic disorder patients than healthy controls. This finding has opened new research avenues in anxiety disorders.

WHAT GAPS EXIST IN THE UNDERSTANDING OF ANXIETY DISORDER? IN YOUR OWN RESEARCH OR IN THE RECENT LITERATURE, WHAT FINDINGS HAVE THE GREATEST POTENTIAL TO HAVE A BENEFICIAL IMPACT ON PATIENT CARE?

When I was in Quebec, I set up an association on anxiety disorders that all the faculties of medicine were a part of. It's called ATAQ (Association Trouble Anxieux Québec). The purpose of the organization was to not only [disseminate] educational material

to physicians, but also for patients, because in the 80's and 90's not too many family physicians knew about anxiety disorders. Patients could go on and suffer with panic disorder for an average of 10 years without getting a diagnosis and then being not well treated. We did a blitz of information in the media. We would publish small booklets that were sent to the Collège des médecins du Québec and to all of the family physicians to enhance general knowledge and to patients and it did work in enhancing awareness and knowledge of the anxiety disorders.

The challenge [today] is mainly access to treatment. [Although] more and more of the family physicians know about it, we have to keep promoting education because they are often overloaded with technical knowledge about all specialties. The challenges are access to treatment, [including] access to psychiatrists and psychologists, as well as competent treatment. The paradox in psychiatry for pathologies like panic disorder [is that] the treatments, [regardless] of whether they are pharmacological or psychological, do work. The success rate when they are given by experts is high, very high, much higher than [most] other pathologies in medicine, but the problem is access to them. The health care system is not well organized. The psychologists are not free. The challenge is not the pathology itself or the tools, but it's the access. That's the biggest problem.

There [is] potential to improve health organization. For example, when I was the chair of psychiatry, we implemented a program to organize mobile crisis units. It's a hotline that if necessary sends a team to go to your home and assesses whether there's a need for an appointment, facilitation of a quick referral, or bringing them to an emergency department. The team has a mental health worker and a police officer, so you can act on the spot and have a court order if necessary and it works well. [They stay] at The Ottawa Hospital for acute care, or The Royal or CHEO (Children's Hospital of Eastern Ontario) [for longer care]. This is an example of healthcare system integration that increases access to and efficiency of care that optimizes the use of existing diagnostic or therapeutic knowledge.

WHAT ADVICE WOULD YOU GIVE TO MEDICAL STUDENTS TO PREPARE THEM FOR THEIR FIRST CLINICAL EXPERIENCES IN PSYCHIATRY?

[As medical students], your bias, [whether] positive or negative, will determine your experience. Some students are more into the technical aspect of medicine and not comfortable with too much interpersonal interaction. In psychiatry, you have to interact with people. If there is some discomfort, the experience can be very, very hard. It stretches the level of comfort for some students. Others who perhaps may be interested in the field or family medicine or a field with more personal interaction could like it. As much as possible, [students] should have an open mind and have a bit of perspective.

The field of psychiatry [has] a very good future. However, as with the rest of medicine, it needs more humanism. It's one of the reasons we set up the Medicine and Humanities program. We noticed [that] after 4 years [of medical school] empathy goes down, [while] knowledge goes up. The risk is having technicians at the end—good technicians who come out with very poor people skills. In psychiatry, the core of the profession is the relationship. You have to have yourself together because people put not only their limb or their body part, but also their soul in your hands; so that's the core of the relationship. Then, there's more and more knowledge about pharmacotherapy and psychological techniques that do work and can be used from that core, specifically for a patient. Psychiatry was always about "personalized medicine" and will continue to be more so and that requires a strong relationship between the expert and her/his patients.

WORK-LIFE BALANCE IS A CRITICAL ASPECT OF WELLNESS AND MENTAL HEALTH. HOW DO YOU BALANCE YOUR CAREER RESPONSIBILITIES WITH PERSONAL TIME?

Balance is not a good concept for us. You know why? Because balance means I do more of one and less of the other. What happens if you like your profession and it involves a lot of your time and your passion and [leaves less time] for your marriage or your familial life or your friendships? That notion in the business world with executives was [discarded] 10–15 years ago. What's much more appropriate and practical is [the concept of] work-life integration. So what does that mean? It means that if you [shift your focus] from your interests to your core values, these values are going to drive whatever you do in whatever role you have. It's no longer who I am and how much time I can give my kids and my hobbies. It's more like who am I and how do I express who I am in what I do? At certain times, you might do more at work, and at certain times you might do more of something else. If you know what your core values are, you express it more in whatever you do. It's time management, but it's easier to see yourself like that because one role doesn't remove from another role when your core values are expressed through all of your roles.

That notion of integration, we have to articulate it for student life. You can put on hold some activities for a little while that you regain as hobbies. I used to do karate and I was very much into music. When you're in residency and you're on call, you give up a bit of that, but you can pick it up later. For every generation there's more and more drift towards values that are more material than are psychological and spiritual. The aspect that they are of the more superficial self keeps increasing. Therefore, more dependency on external factors such as money and looks, results in adding an external locus of control to wellness. It's why students have been more anxious in the last few years. Some of the specialties are chosen for more superficial reasons, which moves away from the internal locus of control and intrinsic values to more extrinsic attachment.

CAN YOU TELL US MORE ABOUT THE FACULTY'S PARTNERSHIP WITH JIAO TONG UNIVERSITY (SHANGHAI)?

We had been on a specific path to internationalization since 2007, using a preferred partner, joint investment tactic. We began with Université Paris-Descartes. By 2011, we questioned ourselves whether we should look for partners in the BRIC countries (Brazil, Russia, India, China). In 2011, Professor Daniel Figeys (a Tier-I Canadian Research Chair) suggested that we look into China. "I've been going there since 2006 and they are investing heavily into research." [Dr. Figeys] was at a meeting and they liked what he did and they [built him] a laboratory. They knew him well and [invited] him to come and explore more possibilities in China. So, in October 2011, a small delegation, including myself, the Chair of BMI [Biochemistry, Microbiology, and Immunology] at the time, Daniel Figeys, and the Vice-President of Research for the university, Mona Nemer, went to Shanghai. They knew Daniel, so they hosted the dean. At the end of the evening the vice-dean international, Zhang Yong (of the Shanghai Jiao Tong U Scholl of Medicine, SJTUSM) sat right beside me and he says, "bonsoir, monsieur doyen." in very good French. He said, "I didn't know you spoke French in Ottawa." So I said, "I didn't know you spoke French in Shanghai!" It so happens they have a French medical stream in Shanghai. This was another point of affinity we had in addition to medical research between uOttawa and SJTUSM.

[At that time], we were looking for a preferred partner, with whom to invest jointly, not to profit from. The fit was really good. It so happened that they were also looking for a preferred partner and we didn't know. They were discussing with some Ivy League school in the USA and with some Australian ones. But the relationship between us and SJTUSM evolved really well and the whole thing gelled. We also had strong interest from both of our countries to see a strong partnership created. Thus, we put $1 million on the table and asked if they would match it for a $2 million joint research program, in basic science and medical education and that was the first MOA (memorandum of agreement). We signed it with the Governor General when he was doing his tour in China, the mayor [of Ottawa, Jim Watson] was doing his tour, and the NAC (National Arts Centre) orchestra [was there]. In that MOA, right before going to Shanghai to sign it, literally the few hours before I'm embarking on the plane, [I noticed that] they added one last bullet: We want to open a medical school with you. So, I asked my contact, "are they serious?" and they said, "they put it in there. They're serious." The anecdote is that soon after we signed the MOA, on the Saturday afternoon, they told me: "you are very busy and you're going back home on Wednesday afternoon, but in the morning you have an hour and a half. Let's plan a medical school. An hour and a half is plenty of time!" So, Dr. [Melissa] Forgie and I show up there on the Wednesday morning. They said, "we want to build a medical school with you." And I said, "Well, what exactly do you want?" And they said, "we want it in English." I said, "Why don't you use our 4 year curriculum? Why don't you put it accreditation ready from the start? Why don't you send a few teachers here to see what we do and do shadowing?" They liked it and in an hour and a half we had the whole thing planned. Then in January, two professors show up at my door here [in Ottawa], "we're here to shadow!" They were here for 6 months and [that's how] the whole thing got going. Several months later the joint school called the Ottawa-Shanghai Joint School of Medicine was approved by the Shanghai and the Central China governments and it was officially opened in October 2014, in less than a year.

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Rotenone Neurotoxicity Causes Dopamine Neuron Loss in Zebrafish

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ABSTRACT

Objectives: We sought to determine whether rotenone, a commonly used pesticide, exhibits neurotoxicity in zebrafish by causing dopamine neuron loss through rotenone-induced oxidative damage. **Methods**: We exposed transgenic zebrafish embryos expressing green fluorescent protein under the control of the *cis*-regulatory elements of *dopamine transporter* (*dat*) to rotenone to determine the neurotoxic effects of rotenone on dopamine neuron abundance and pattern distribution, as well as the presence of apoptotic markers. The oxidative stress potential of rotenone on embryos was assessed using a live MitoSOX Red assay, and behavioural testing on adult zebrafish was assessed using video recordings of midline crossing events. **Results**: Zebrafish embryos treated with rotenone displayed a 50% reduction in dopamine neurons in the ventral diencephalon when exposed to 30µM rotenone (n=6, $p<0.001$), and rotenone-exposed zebrafish raised to adulthood demonstrate an anxiety-like behaviour (n=5, $p<0.01$). Furthermore embryos exposed to rotenone also demonstrated a logarithmic increase in markers of oxidative damage (n=3, $p<0.001$) and apoptotic activity in their diencephalic neurons. **Conclusions**: These results show that rotenone can induce dopamine neuron loss in zebrafish, providing a useful model for studying the environmental causes of Parkinson's disease.

RÉSUMÉ

Objectif: Nous cherchons à déterminer si la roténone, un élément commun dans les pesticides, démontre de la neurotoxicité dans les poissons-zèbres en causant une perte de dopamine dans leurs neurones à travers le dommage oxydatif induit par la roténone. **Méthode:** Nous avons exposé des embryons de poissons-zèbres transgéniques qui expriment la protéine fluorescente verte sous le contrôle d'éléments *cis*-régulateurs des *transporteurs sélectifs de dopamine* (*dat*) à la roténone pour déterminer les effets neurotoxiques de ce dernier sur les niveaux dopaminergiques dans leurs neurones. De plus, nous avons évalué la présence de marqueurs apoptotiques. Le stress oxydatif potentiel de la roténone sur les embryons a été analysé par le « live MitoSOX Red assay » et les tests comportementaux sur les poissons-zèbres adultes furent analysés en utilisant des enregistrements vidéo. **Résultats:** Les embryons de poissons-zèbres qui ont été traités avec la roténone ont démontré une réduction de dopamine de 50% dans les neurones localisés dans le diencéphale ventral, quand exposés à 30µM de roténone (n=6, $p<0.001$). Ils ont également illustré une augmentation logarithmique dans les marqueurs de dommage oxydatif (n=3, $p<0.001$) et une activité apoptotique dans les neurones du diencéphale. Les poissons-zèbres exposés à de la roténone qui ont atteint l'âge adulte ont démontré des comportements d'anxiété (n=5, $p<0.01$). **Conclusion:** Les résultats démontrent que la roténone peut induire une perte dopaminergique dans les neurones des poissons-zèbres. Ces résultats s'avèrent utiles pour étudier davantage les causes environnementales reliées à la maladie de Parkinson.

INTRODUCTION

Parkinson's disease is a neurodegenerative disease that presents as a chronic progressive movement disorder. In the majority of cases, Parkinson's disease (PD) is idiopathic, and more than 85% of patients have no known genetic association or other primary causes [1]. Parkinson's disease is now the second most common neurodegenerative disorder after Alzheimer's disease [2] and the incidence of idiopathic Parkinson's disease greatly increases with age. It is estimated that the disease affects over 1% of the population above the age of 65 [3]. This disease is caused by the progressive death of dopamine neurons in the substantia nigra, a deep midbrain region of the brain responsible for the modulation of motor signals via the basal ganglia. While many neurotoxic chemicals such as paraquat and oxidopamine (6-OHDA) [4] are suspected to contribute to the development of Parkinson's disease, very few have shown to cause dopamine neuron degeneration in live animal models. Longitudinal studies of exposure to chronic pesticide-use have been associated with the development of Parkinson's disease later in life [5], and further investigation of this phenomenon predicates itself on the development of a biologically representative animal model of PD.

In recent years, the zebrafish has become a prominent live animal model in many fields of medical and neurological research [6]. With a short generation time, high fecundity and transparent tis-

Keywords: Rotenone; Zebrafish; Dopamine Neurons; Parkinson's Disease

sue during embryonic development, zebrafish present a unique and novel platform for studying PD. Developing zebrafish larvae can be exposed to environmental neurotoxins simply by administering the neurotoxin to the fish water [7, 8]. Furthermore, the neurologic effects of these neurotoxins are readily apparent on the developing zebrafish, leading to behavioral abnormalities in the larvae and a series of morphological changes in the larval brain. Lastly, there are a number of genetic models of neurodegeneration in zebrafish due to the apparent ease with which we can genetically manipulate the well-annotated zebrafish genome [9]. The catecholaminergic system in zebrafish is very similar to that of other vertebrates, containing regions within the brain corresponding to homologous structures in more complex vertebrates. The posterior tuberculum neurons of the ventral diencephalon send ascending neural projections to the ventral telencephalon and appear functionally equivalent to the meso-striatal and meso-limbic systems in mammals [10]. Serotonergic neural clusters, such as the caudal hypothalamic neural cluster of the embryonic zebrafish, exhibit a strong susceptibility to the toxic effects of certain catecholaminergic neurotoxins (oxidopamine and MPTP). This leads to a decrease in serotonin within the fish brain, consistent with the supposed cause of behavioural and psychiatric deficits observed in patients with Parkinson's disease [10, 11]. Olfactory loss is very strongly linked to the development of PD and its rapid progression [12, 13], and changes within the olfactory bulb in zebrafish can be easily visualized.

Rotenone is one of the pesticides that have been associated with the development of PD [5], and displays a strong cytotoxic oxidative effect through mitochondrial complex I inhibition [14]. The only vertebrate model of rotenone-induced PD was until recently limited to the Lewis rat [15] with milder phenotypes seen in mouse models [16, 17, 18]. Although small scale neurotoxin screens (including rotenone) using behavioural analysis have been performed on zebrafish to identify potential PD-inducing agents, MPTP was the only toxin to yield conclusive results [19]. Here we show that rotenone affects the dopaminergic system of the zebrafish through a dose-dependent ablation of dopaminergic neurons in the diencephalon by oxidative stress–induced apoptotic activity.

METHODS

FISH CARE AND HUSBANDRY

Zebrafish embryos were obtained by natural spawning of adults maintained on a 14-hour light/10-hour dark cycle and fed a diet of fish pellets and *Artemia*. After cleaning and sorting, embryos were raised at 28.5°C from birth to 15 days post-fertilization (dpf) in embryo media (13mM NaCl, 0.5mM KCl, 0.02mM Na_2HPO_4, 0.04mM KH_2PO_4, 1.3mM $CaCl_2$, 1.0mM $MgSO_4$, and 4.2mM $NaHCO_3$). To prevent formation of pigmentation, phenylthiourea (Sigma-Aldrich) was added to the embryo media at 24 hours post-fertilization (hpf) to a final concentration of 0.2mM. A transgenic zebrafish line, Tg(*dat:EGFP*), in which the green fluorescent protein (GFP) is expressed under the control of *cis*-regulatory elements of the *dopamine transporter* (*dat*) gene, was used in this experiment [20]. The University of Ottawa Animal Care Committee approved all animal care procedures, and all animals used were governed by protocols in strict accordance with the recommendations of the Canadian Council for Animal Care.

ROTENONE PREPARATION AND ADMINISTRATION

Rotenone powder (Sigma-Aldrich) was freshly dissolved in DMSO (Fisher Scientific) at a concentration of 1mM, then serially diluted up to 1,000,000-fold in double distilled water to half-log working concentrations between 1nM and 1000nM of rotenone. Rotenone solutions older than 4 h were never used. Embryonic zebrafish were collected and raised in 6-well, 12-well or 24-well plates (Corning) with no more than 20 embryos per well. Embryos were exposed to a single dose of rotenone at 24 hpf without water changes until 7 dpf to ensure that embryos were exposed to the maximum bioavailable dose of rotenone. Controls were embryonic zebrafish exposed to a solution of 0.1% DMSO in embryo media, corresponding to the DMSO concentration used in the maximum concentration of rotenone exposure. A petri dish containing a bed of 2% agarose gel was prepared with 1 mm-deep troughs cut into the agarose using a standard glass microscopy slide. Embryos were then anesthetized with a 0.168 mg/ml solution of MS-222 (Sigma-Aldrich), gently placed into a trough in the agarose bed in a dorsal-ventral orientation, then imaged on a Leica MZ6 epifluorescence stereomicroscope to examine for changes in green fluorescence patterning in a single-blind fashion. Images were then assembled into panels using Adobe Photoshop CS5. Rotenone from a different source (Fisher Scientific) was also assessed, and demonstrated reproducible changes in neuronal patterning (data not shown). After exposure, all rotenone-containing solutions were bleached and subsequently disposed as hazardous wastes.

IMMUNOHISTOCHEMISTRY ON ZEBRAFISH EMBRYO CRYOSECTIONS

Embryos were fixed in 4% paraformaldehyde dissolved in phosphate buffered saline (PBS, 137mM NaCl, 2.7mM KCl, 4.3mM Na_2HPO_4, 1.47mM KH_2PO_4, PBS) overnight at 4°C, rinsed thrice in PBS and equilibrated in a 30% sucrose/PBS solution overnight at 4°C. Embryos were then flash frozen in Tissue-Tek ® O.C.T™ media (VWR Canada) and sectioned with a Leica CM 1850 cryostat (Leica Microsystems, Weltzar, Germany) at a thickness of 14µm on to Superfrost glass slides and stored at -20°C until use. After a short rehydration period for 10 minutes in PBS containing 0.1% Tween 20 (PBT), sections were blocked in 10% goat serum in PBT

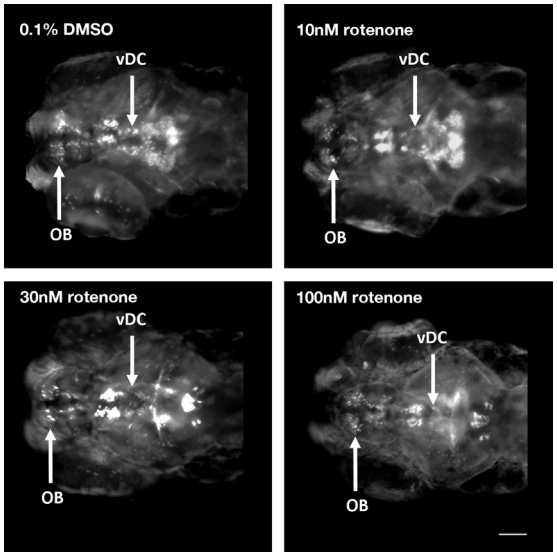

Figure 1. Morphology and distribution of dopaminergic neuron clusters in 7 dpf zebrafish embryos exposed to rotenone. Zebrafish embryos were exposed at 24 hours post-fertilization to either a 0.1% DMSO solution, or 10nM, 30nM, or 100nM rotenone solutions then imaged at 7 dpf. GFP expression was examined in the olfactory bulb (Ob), and ventral diencephalon (vDC). All animals are shown in a dorsal view, anterior to the left. Scale bar = 50µm.

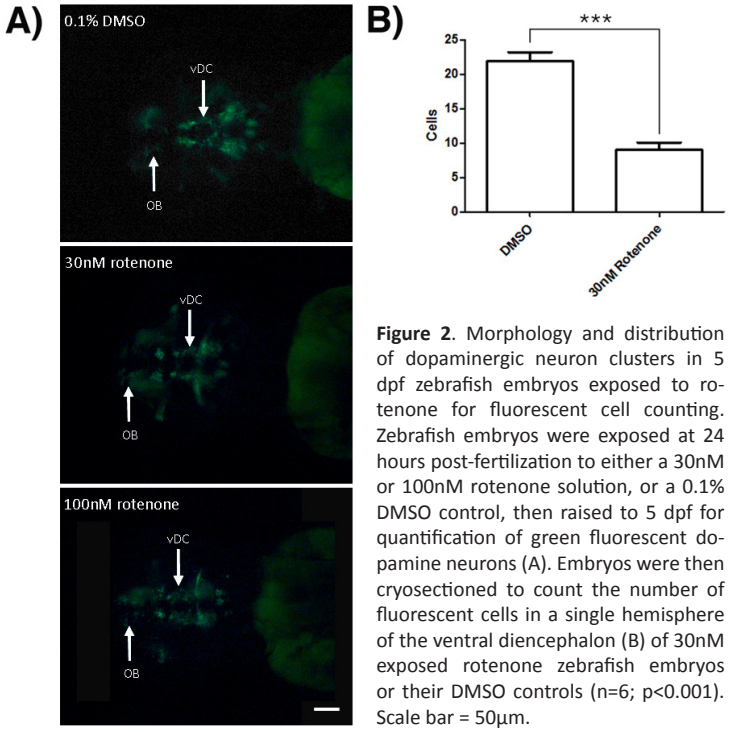

Figure 2. Morphology and distribution of dopaminergic neuron clusters in 5 dpf zebrafish embryos exposed to rotenone for fluorescent cell counting. Zebrafish embryos were exposed at 24 hours post-fertilization to either a 30nM or 100nM rotenone solution, or a 0.1% DMSO control, then raised to 5 dpf for quantification of green fluorescent dopamine neurons (A). Embryos were then cryosectioned to count the number of fluorescent cells in a single hemisphere of the ventral diencephalon (B) of 30nM exposed rotenone zebrafish embryos or their DMSO controls (n=6; p<0.001). Scale bar = 50µm.

at room temperature for 3 hours. Sections were then incubated overnight at 4°C with a 1:1000 dilution of monoclonal mouse anti-GFP antibody (AS-55887, Anaspec) and 1:1000 dilution of polyclonal rabbit anti-caspase 3 (AS-55372, Anaspec). After three washes in PBT, sections were incubated for three hours at room temperature with a 1:1000 dilution of goat anti-mouse antibody Alexa 488 conjugate (A-11001, ThermoFisher Scientific) and a 1:1000 dilution of goat anti-rabbit antibody Alexa 594 conjugate (A-11012, ThermoFisher Scientific), then washed three times in PBT. Sections were then incubated in NucBlue® Fixed Cell ReadyProbes® Reagent (R37606, ThermoFisher Scientific) for 10 minutes before being rinsed thrice and mounted in Aqua-Poly/Mount (18606, Polysciences Inc.) and viewed on a Zeiss Axiophot upright epifluorescence microscope. Images were assembled using ImagePro, FIJI and Adobe Photoshop CS5.

MITOSOX RED OXIDATIVE STRESS ASSAY

To assess for oxidative stress, we used a whole animal reactive oxygen species detection method as outlined in [21]. Embryos exposed to rotenone were grown to 3 dpf, anesthetized with a 0.168 mg/ml solution of MS-222, collected and rinsed thrice in Hank's Balanced Salt Solution (HBSS, Sigma-Aldrich). Embryos were then incubated in the dark for 15 minutes at 28ºC in a 5µM solution of MitoSOX Red (ThermoFisher Scientific) dissolved in HBSS. Following exposure to MitoSOX Red, embryos were then washed twice in HBSS then gently placed into a trough in an agarose bedded plate in a dorsal-ventral orientation, and imaged as described previously.

ADULT BEHAVIOUR ASSESSMENT

Zebrafish embryos that were exposed to either 0.1% DMSO alone, or 10nM or 100nM rotenone were raised for 12 months to adulthood in accordance with animal care protocols. These adult zebrafish were then placed into individual tanks in an isolated environment and allowed to acclimatize to their new environment for 30 minutes before being recorded for 5 minutes using a Nikon Coolpix A camera. Each tank had the midline depth demarcated with a rubber band, and manual analysis of the video recordings allowed us to count the number of times each fish crossed the midline depth of the tank. All behaviour experiments were performed in biological quintuplicates.

RESULTS

Rotenone induces a dose-dependent chemical ablation of the dopaminergic neurons in the ventral diencephalon (vDC) and olfactory bulb (OB) of zebrafish embryos

Transgenic zebrafish embryos expressing eGFP under the regulation of dopamine transporter *cis*-regulatory elements [11] were exposed to various concentrations (10nM, 30nM and 100nM) of rotenone and to a 0.1% DMSO vector at 24 hours post-fertilization. The embryos were imaged at 7 dpf (Figure 1) to examine changes in fluorescence patterning. Labelling in the ventral diencephalon is markedly reduced at 10nM in comparison to the 0.1% DMSO control, and reductions become more severe with a 30nM exposure. Neurons were judged to be either severely mispatterened or almost absent at a 100nM exposure, following

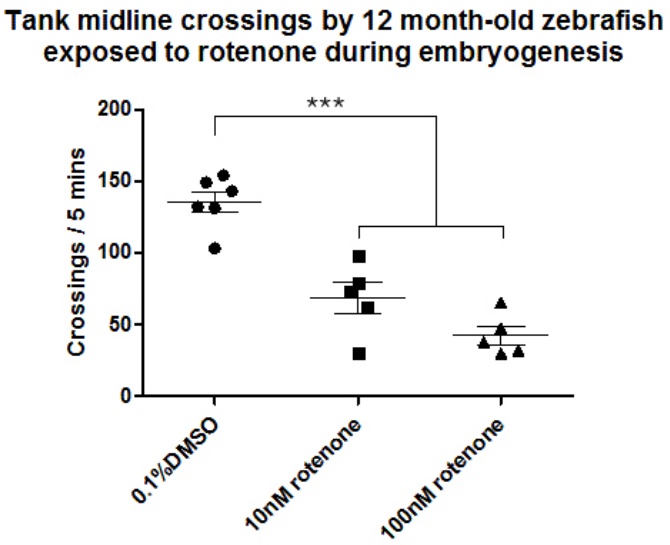

Figure 3. Tank midline crossings by 12 month-old zebrafish exposed to rotenone during embryogenesis. Adult zebrafish exposed to either 10nM rotenone, 100nM rotenone or 0.1% DMSO as embryos were placed in a standalone tank and monitored for five minutes for the number of times they crossed the midline depth of the tank (n=5, p<0.01).

the same criteria as [22]. A less severe dose-dependent reduction in fluorescence in the olfactory bulb became apparent, with the amount of labelled neurons decreasing with increasing concentrations of rotenone. Embryos exposed to a concentration of 300nM did not survive past the second day of treatment. The numbers of eGFP labelled neurons were also manually quantified in single hemispheres of 5 dpf embryos exposed to 30nM rotenone or DMSO alone (Figures 2A and 2B), and confirmed with immunohistochemistry (IHC) on frozen sections. At 5 dpf, the number of labelled neurons in the ventral diencephalon were reduced by more than 50–60% following exposure to a 30nM concentration of rotenone.

Neurodegenerative effects of rotenone cause behavioural changes in treated embryos

Having observed that rotenone had an effect at the cellular level, we wanted to investigate whether the neurodegenerative effects of rotenone translated into observable behavioural changes in treated fish. The tank midline-crossing test allowed us to assess motor function and behaviour patterns of adult fish. Reduced tank midline crossing indicates either hypomotility or anxiety-like behaviour [23]. Zebrafish that were exposed to rotenone showed significantly less midline crossing than the unexposed fish (Figure 3). Fish exposed to 10nM rotenone crossed the midline of the tank nearly 50% less than the controls, and the fish exposed to 100nM rotenone crossing the midline nearly 70% less often. This observed behaviour seemed to suggest a pattern of anxiety-like behaviour rather than overall hypomotility since we observed similar velocities and distance traveled between rotenone-exposed fish and their unexposed controls (data not shown).

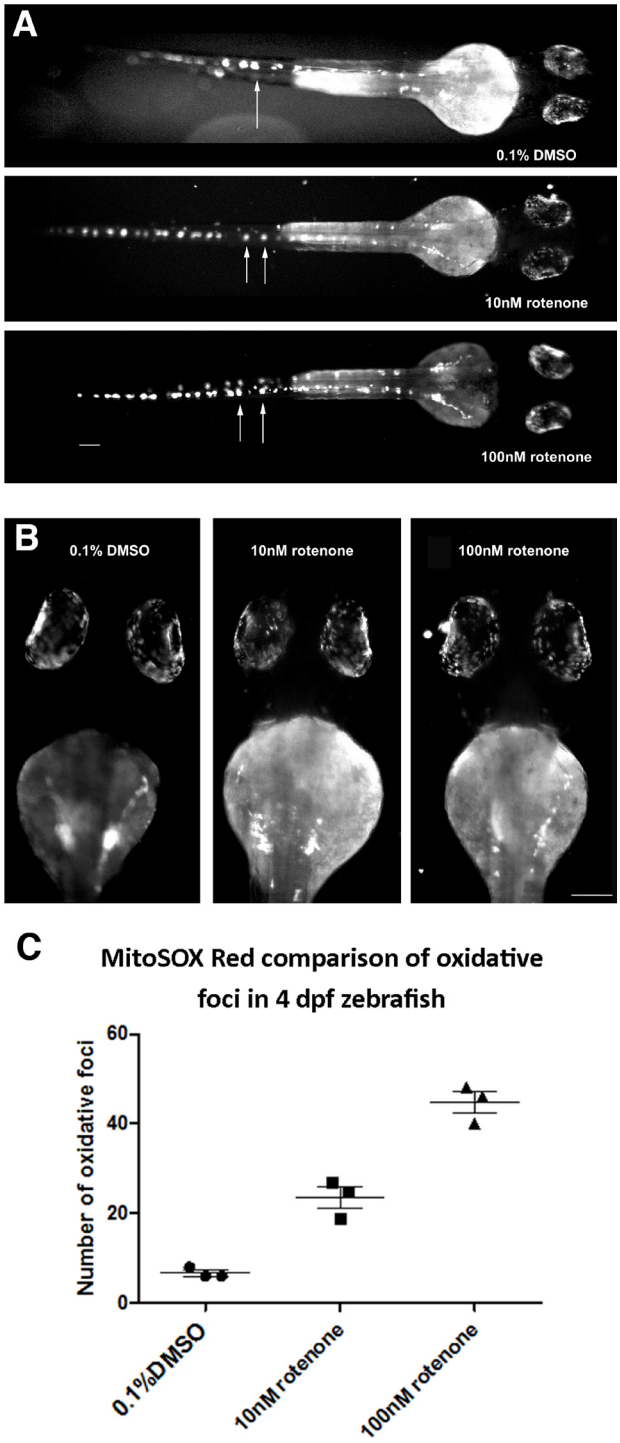

Figure 4. Assessment of reactive oxygen species–mediated damage in embryos exposed to rotenone by MitoSOX Red. Embryos exposed to either 10nM rotenone, 100nM rotenone or 0.1% DMSO raised to 4 dpf were assessed for foci of oxidative stress along the trunk (A, arrows) and head (B). The number of MitoSOX Red foci in the trunk of zebrafish embryos was manually quantified for each treatment group (C) as a marker of oxidative stress (n=3, p<0.001). All animals are shown in a dorsal view; embryos were oriented anterior to the right in panel A, and anterior to the top in panel B. Scale bars = 100µm.

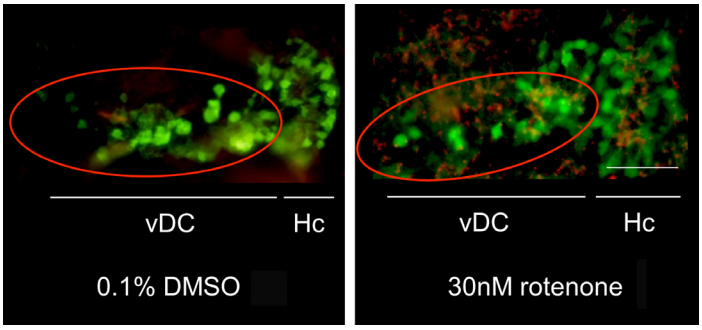

Figure 5. Immunohistochemistry for apoptosis markers in deep brain structures. Frozen sections (14µm thickness) of 5 dpf embryos exposed to 30nM rotenone (right) or 0.1% DMSO (left) were immunostained with anti-GFP (green) and anti-caspase 3 (red) in the ventral diencephalic cluster (vDC) and hypothalamic clusters (Hc) of a single hemisphere. The red ellipse marks comparable regions of neuronal mispatterning between the vDC of rotenone-exposed embryos to vehicle controls. Both panels are shown in a dorsal view, anterior to the left. Scale bar = 50µm.

Chronic rotenone exposure induces dose-dependent oxidative stress in zebrafish embryos

In order to explore the mechanism of action of rotenone on treated zebrafish, we used the mitochondrial superoxide indicator MitoSOX Red for live detection of reactive oxygen species damage. Since rotenone is believed to induce cell death by causing high levels of oxidative stress, this assay allows the determination of the levels of oxidative stress experienced by embryos treated at increasing concentrations of rotenone. Rotenone-exposed embryos raised to 4dpf were incubated with MitoSOX Red for 15 minutes, and subsequently imaged (Figures 4A and 4B). However, this incubation time was insufficient to yield reagent penetration and fluorescent foci formation in deep brain structures within the head of the embryos. Longer incubation times yielded embryonic toxicity and nonspecific superficial staining (data not shown). Although no fluorescent foci were observable in the cephalic regions of both the control and the exposed fish (Figure 4B), there appeared to be a correlation between the total number of red fluorescent foci along the trunk of the zebrafish embryo (Figure 4A, arrows) and concentration of exposed rotenone. Embryos exposed to higher concentrations of rotenone showed more red fluorescent foci than the control embryos (Figure 4C), demonstrating that rotenone is associated with dose-dependent oxidative stress.

Oxidative stress induces apoptosis in dopamine neurons

In order to improve cellular resolution and determine the cellular consequences of rotenone toxicity, immunohistochemistry was performed on frozen sections of 5dpf embryos. We sought to characterize the distribution of green fluorescent neurons, and investigate their co-localization with markers of apoptosis, a common cellular consequence of oxidative stress. We were able to resolve and co-localize green eGFP distribution (as a marker of dopamine neurons; green) with active caspase 3 (red) in double fluorescence images (Figure 5). Rotenone-exposed zebrafish showed a significant reduction in green fluorescent-labelled neurons in the ventral diencephalon (red circled area) when compared to unexposed embryo, showing an increase in apoptotic activity in zebrafish exposed to rotenone.

DISCUSSION

The zebrafish is a promising model for the study of environmentally induced Parkinson's disease. Our study aims to expand current knowledge in regards to the association between pesticides and an increased risk of developing PD. Additionally, since reliable live vertebrate models of Parkinson's disease are limited, this study may provide the foundations for a new model of environmentally induced neurodegeneration. While previous studies in the zebrafish focused on behavioural changes [19], our approach consists of studying changes at the cellular level to identify neurodegeneration-inducing compounds.

Embryos from the *dat*:eGFP transgenic zebrafish line express green fluorescent protein under the control of *dat* regulatory elements, a key protein in dopamine neurons [24]. This provides a powerful *in vivo* fluorescent marker for dopamine neuron health and distribution. In an example of leveraging the transparency of zebrafish embryos, we were able to visualize dopamine neurons *in vivo* of *dat*:eGFP embryos exposed to rotenone. Our results show that rotenone administered in a manner to mimic a single neurotoxic exposure during an embryonically plastic stage appears to cause pharmacological disruption of the diencephalic dopaminergic neurons in a dose-dependent manner. Treated embryos demonstrate a significantly reduced amount of dopaminergic neurons and severe mispatterning within the ventral diencephalon of the midbrain and the olfactory bulb in comparison to the untreated embryos. Dopaminergic neuron disruption in the ventral diencephalon of the treated zebrafish is particularly interesting since these posterior tuberculum neural populations are homologous to the human nigro-striatal pathways affected in PD [10, 25]. These data suggest that rotenone exposure may cause dopamine neuron death in a pathophysiologically similar pattern to human patients with PD. Unfortunately, only neurons expressing the dopamine receptor can be assessed using this protocol, and future work should aim to assess for rotenone's neurotoxic effects on other neuronal populations.

To corroborate our previous observations, we proceeded to verify if changes at the cellular level affected the behaviour and mobility of the zebrafish. Since zebrafish are active swimmers, reduced midline crossing has been associated with hypomotility and general anxiety during movement, two symptoms also observed in human PD patients [23]. Adult zebrafish exposed to rotenone during embryogenesis appeared more hesitant to explore the different tank regions (as evidenced by the impaired midline crossing), demonstrating that a loss of dopaminergic neurons may also affect the fish by inducing anxiety-like behav-

iour. Although this does not appear to correlate with a motor phenotype of PD, anxiety and other psychiatric symptoms manifest in the later stages of patients suffering from PD [26]. It is interesting to note that the 30nM concentration of rotenone used to treat the embryos for cellular counts and behavioural tests resulted in a 50–60% decrease in ventral diencephalic dopaminergic neuron populations, similar to a loss of at least 50%–70% of dopaminergic nigral neurons in human PD patients at symptom onset [27].

In order to investigate the mechanism of action by which rotenone induces neurodegeneration, we used MitoSOX red, an oxidative stress marker for detecting mitochondrial damage from superoxide formation in an attempt to quantify the levels of oxidative stress experienced by rotenone-exposed zebrafish embryos. While it is known that short exposures (under 15 minutes) to high concentrations of rotenone induce rapid and severe oxidative stress in zebrafish [22], few studies have examined the lasting neuronal effects and embryonic survival in response to much lower doses of the rotenone. The fish treated with sub-lethal concentrations of rotenone exhibited an increased number of red fluorescent foci on their bodies, indicating acute oxidative stress. In comparison to the DMSO control group, the number of oxidative foci nearly tripled in fish treated with 10nM of rotenone, and increased by seven-fold when the fish were exposed to 100nM of rotenone. This demonstrates that rotenone induces large amounts of mitochondrial oxidative stress. Oxidative stresses from rotenone toxicity may also disproportionately affect dopaminergic neurons due to the increased oxidative stress of synthesizing dopamine *de novo* within these neurons [28]. The inability to address the increased oxidative stress would typically lead to an accumulation of reactive oxygen species (ROS), which may overwhelm endogenous anti-oxidant capability. This can cause subsequent cellular damage, followed by programmed cell death by apoptosis. Our data demonstrated an increase in caspase signalling land other markers of cell death suggesting that apoptosis from ROS damage may be the mechanism of rotenone neurotoxicity. These results yield insight on the mechanism of action of rotenone, while linking oxidative stress to a decrease in dopaminergic neuron populations.

CONCLUSION

This study presents an interesting perspective on the established correlation between pesticide use and the increased risks of developing Parkinson's disease. In addition, these data provide a foundation for the study of environmentally induced Parkinson's disease using the zebrafish as a live animal model.

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Hidden in Plain Sight: Recognizing Catatonia Amidst its Medical Complications

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ABSTRACT

Although catatonia is a common syndrome, diagnosis is often delayed or missed altogether. The medical sequelae of catatonia can cloud the diagnostic picture, making it difficult to know what is the primary problem. In this case, a patient presented several times about 1 month apart with recurrent urinary retention, inability to walk, and delirium. This resulted in admissions to Internal Medicine and consultations to Urology with the underlying primary problem being missed until catatonia was later recognized and diagnosed. The elderly are more prone to complications from catatonia and, as a result, it is even more important that catatonia be recognized and treated in a timely manner in this population. In addition to exploring the case, this article reviews the diagnosis, etiology, prognosis, and treatment of catatonia, particularly as these pertain to the elderly.

RÉSUMÉ

La catatonie est un syndrome commun, mais son diagnostic est parfois difficile à faire. Les symptômes associés à ce syndrome peuvent rendre le problème médical primaire difficile à déceler. Par exemple, l'association récurrente de symptômes de rétention urinaire, des difficultés à marcher et des signes de syndrome confusionnel qui se présentent chaque mois sont souvent associés à d'autres maladies. Ces manifestations symptomatiques mènent à des admissions en médecine interne et des consultations en urologie. Les cliniciens peuvent perdre de vue le problème primaire, celui de la catatonie. Le diagnostic est alors manqué ou découvert plus tard. Les personnes âgées sont plus susceptibles à des complications liées à la catatonie. Ainsi, il s'avère important que ce désordre soit reconnu et traité dans un délai raisonnable chez cette population. Cet article évalue le diagnostic, l'étiologie, le pronostic et le traitement de la catatonie, particulièrement dans le cadre des personnes âgées.

CASE

A 72-year-old man was transferred from an acute care hospital to a geriatric psychiatry inpatient unit at a mental health care centre. He had been admitted to the acute care hospital for delirium. He had a history of schizoaffective disorder (bipolar type) and had been living in an assisted living home. At the time of admission, he was on risperidone and lithium.

He had had several previous admissions to Internal Medicine for exacerbations of schizoaffective disorder and possible episodes of delirium. These episodes had increased in frequency over the last year and a half and were occurring about every month. He would typically present with urinary retention and subsequently be diagnosed with a urinary tract infection (UTI) and have urinary incontinence. Urology was consulted for his urinary symptoms. In addition, he would develop paranoia, anxiety, acute dystonia of both arms, tremor, and worsened gait. It was thought that this might represent extra-pyramidal symptoms (EPS) due to increased sensitivity to his medications in the setting of his acute medical illness. He would improve rapidly when his medications were held. Once his medications were restarted, he would have no symptoms for several months until another seemingly spontaneous relapse occurred.

When he arrived on the geriatric ward, he was recovering from being unable to walk, talk, and eat. He displayed mild psychomotor agitation and an anxious affect. He had a resting tremor. No psychotic symptoms were evident. During admission, however, he had another one of these episodes that proved to be revealing. He became immobile, mute, and tremulous with a rise in creatine kinase (CK). He developed subsequent urinary retention and a UTI. The timing and causality appeared to be the reverse of what was originally assumed. Risperidone was stopped due to possible EPS. Lithium was stopped as he was unable to drink and thus was at increased risk of lithium toxicity.

Keywords: Catatonia; Elderly; Geriatrics; Psychiatry

1. Catatonia Associated with Another Mental Disorder (Catatonia Specifier) – The diagnosis of another mental disorder must also be made. This specifier can be used for the following diagnoses:
    a. Schizophrenia
    b. Brief Psychotic Disorder
    c. Schizophreniform Disorder
    d. Schizoaffective Disorder
    e. Bipolar Disorder
    f. Major Depressive Disorder
    g. Autism Spectrum Disorder
2. Cataonia Due to Another Medical Condition
3. Unspecified Catatonia

Figure 1. *DSM* Catatonia Types [5].

When able to observe the full-blown syndrome, the team recognized that he met criteria for catatonia and started him on regular lorazepam. His catatonia symptoms improved. He was started on clozapine and simultaneously weaned off lorazepam but his catatonia symptoms returned. As a result, clozapine was stopped and lorazepam restarted. He began to improve again and eventually returned to his baseline. He was discharged on lorazepam 1 mg PO TID. As a side note, electroconvulsive therapy (ECT) was also considered during the course of treatment but was not done as he had had complications during a past course of ECT.

WHAT IS CATATONIA?

Catatonia is a severe psychomotor syndrome associated with both psychiatric and medical conditions. It can present with seemingly opposing clinical features such as agitation and stupor. It can develop acutely and resolve quickly, lasting on the order of days, or in some cases can be chronic, lasting years [1,2,3].

EPIDEMIOLOGY

It is estimated that 10% of patients admitted to psychiatric units meet criteria for catatonia. Originally, catatonia was thought to be primarily associated with schizophrenia but it is now estimated that half of the cases are due to mood disorders and only 10–15% seem to be associated with schizophrenia. In hospitalized catatonic patients, 20–25% of cases are due to a general medical condition [3]. Elderly patients with major depressive disorder have the highest prevalence of catatonia [4]. Catatonia can also occur in the context of neurodevelopmental disorders such as autism spectrum disorder [3].

DIAGNOSIS

Catatonia was historically listed as a subtype of schizophrenia in the *Diagnostic and Statistical Manual of Mental Disorders*

Catatonia Associated with Another Mental Disorder:
The clinical picture is dominated by 3 or more of the following symptoms:

- Stupor (i.e., no psychomotor activity; not actively relating to the environment)
- Catalepsy (i.e., passive induction of a posture held against gravity)
- Waxy flexibility (i.e., slight, even resistance to positioning by examiner)
- Mutism (i.e., no, or very little, verbal response [exclude if known aphasia])
- Negativism (i.e., opposition or no response to instructions or external stimuli)
- Posturing (i.e., spontaneous and active maintenance of a posture against gravity)
- Mannerism (i.e., odd, circumstantial caricature of normal actions)
- Stereotypy (i.e., repetitive, abnormal frequent, non-goal-directed movements)
- Agitation, not influenced by external stimuli
- Grimacing
- Echolalia (i.e., mimicking another's speech)
- Echopraxia (i.e., mimicking another's movements)

Catatonia Due to Another Medical Condition:
Same symptoms as catatonia associated with another mental disorder. In addition:

- There is evidence from the history, physical examination or laboratory findings that the disturbance is direct pathophysiological consequence of another medical condition
- The disturbance is not better explained by another mental disorder
- The disturbance does not occur exclusively during the course of a delirium
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

Figure 2. *DSM-5* Criteria [5].

(*DSM*). In the *DSM-5*, catatonia is now listed as an independent syndrome, although it is still included under the section called 'schizophrenia spectrum and other psychotic disorders' [5]. There are three possible diagnoses (see Figure 1).

Most patients present with 5 or more of the symptoms that make up *DSM-5* criteria for catatonia (see Figure 2). The most frequent symptoms are mutism, negativism, and psychomotor arrest. Catatonia tends to be underdiagnosed. A Dutch study found that researchers identified catatonia in 18% of psychiatric inpatients but that only 2% were diagnosed clinically [3].

Multiple rating scales are available to aid in diagnosis including the Bush-Francis Catatonia Rating Scale, Northoff Catatonia Rating Scale, Braunig Catatonia Rating Scale, and Rogers Catatonia Rating Scale [2]. The diagnosis is also validated if a patient clearly and rapidly improves in response to treatment with lorazepam, also known as the lorazepam challenge test [3].

DIFFERENTIAL DIAGNOSIS

End-stage dementia, akinetic mutism due to specific brain lesions, and EPS should be considered as differential diagnoses [5,6]. Of note, catatonia cannot occur exclusively during the course of a delirium per *DSM-5* criteria (see Figure 2) and thus, a hypoactive delirium should also be included on the differential diagnosis. Neuroleptic malignant syndrome (NMS) shares several features of catatonia and some authors have argued that NMS should be considered a subtype of catatonia [7,8,23]. Although this remains up for debate, catatonia is at a minimum considered a risk factor for NMS [7,9].

ETIOLOGY

Catatonia can be caused by both psychiatric and medical disorders including psychotic, mood, neurologic, metabolic, autoimmune, and paraneoplastic disorders [1,5]. Catatonia is a descriptive syndrome for which the pathophysiology is still poorly understood. There is ongoing debate about whether it is better understood as a neurobiological or psychological disorder [10]. Like many of our psychiatric diagnoses, catatonia may in fact represent more than one disorder with differing etiologies. For instance, acute catatonia is generally thought to involve a hypodopaminergic state and may be worsened by the dopamine antagonism of antipsychotics but responds well to lorazepam. Conversely, chronic catatonia does not typically respond to lorazepam but instead antipsychotics are used to treat the underlying psychotic illness, suggesting a mechanism different from that underlying acute catatonia [11]. Catatonia is also associated with dysfunctional GABA and glutaminergic transmission [12,13], fitting well theoretically with the use of treatments such as benzodiazepines and NMDA receptor antagonists that act on these systems [16].

INVESTIGATIONS

No laboratory test is diagnostic of catatonia. Investigations should instead be targeted toward detecting potential causes and complications. The following investigations should be considered depending on the clinical context: complete blood count (CBC), electrolytes, blood urea nitrogen (BUN), creatinine, liver transaminases, CK, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), serum iron, urine toxicology, brain imaging, electroencephalogram (EEG), and lumbar puncture [2,6].

PROGNOSIS

Catatonia has an extremely variable prognosis, depending on severity and comorbidity [10]. Many patients recover fully if treated, while others may never recover and can develop chronic catatonia. If untreated, patients are at high risk for adverse outcomes from self-injurious behaviours, hyperpyrexia, malnutrition, and exhaustion. In rare cases of malignant catatonia, the syndrome can progress rapidly and lead to death. Patients typically require hospitalization due to decreased self-care. Prognosis is better for acute rather than chronic catatonia and for catatonia associated with mood disorders rather than schizophrenia [2,6,14].

TREATMENT

The cause of catatonia should be identified and corrected if possible. All patients should have their vital signs monitored and be provided with supportive care, such as intravenous fluids or a Foley catheter, as needed [6].

Treatment with lorazepam is well established in the literature and in clinical practice as the first-line treatment for catatonia, although no randomized clinical trials for acute catatonia have been completed [2,6,15,16]. A single dose of 1–3 mg lorazepam sublingually or intramuscularly is recommended to start [6]. If this has no effect, further doses can be repeated every 3 hours. Most patients "awaken" within 3 hours after receiving the first or second dose of lorazepam. The effective dosing regimen should be continued until treatment of primary disorder is well under way [6,10,14].

ECT should be considered if benzodiazepine treatment is not effective. It is the treatment of choice for malignant or lethal catatonia presenting with fever and autonomic instability. There have also been case reports of NMDA antagonists (amantadine and memantine) and antiepileptics (valproic acid and topiramate) being used effectively [13,17,18,19].

Antipsychotics should be started or reintroduced if necessary once the catatonic symptoms have resolved, given the increased risk of NMS during catatonia [6].

CATATONIA IN THE ELDERLY

Catatonia is often associated with general medical conditions in the elderly. Medical conditions are often overlooked in cases where the patient has a previous history of depression or schizophrenia [21]. Furthermore, catatonia in the elderly is often insufficiently investigated for differential diagnoses. Catatonia can imitate stroke, coma, and end-stage dementia [21,22]. Catatonia in association with NMS is also fairly common in the elderly. [21]. The diagnosis is often delayed longer in elderly patients, some-

times by several months. They are at increased risk of adverse outcomes due to delayed diagnosis. These adverse outcomes can include pulmonary embolus, pneumonia, and death [20]. Elderly patients may require more aggressive measures to prevent and treat complications. For example, elderly stuporous patients should be treated with deep vein thrombosis prophylaxis [21,22]. Catatonia is treated with lorazepam as in younger patients, although lower doses should be considered and fall risk should be monitored [6].

DISCUSSION

This case highlights the difficulty in recognizing catatonia amidst its medical complications and differentiating it from other clinical entities. A trial of lorazepam helped both to resolve the patient's symptoms and to confirm the diagnosis. His catatonia worsened with clozapine; as discussed, antipsychotics can worsen acute catatonia and should not be restarted until the catatonic symptoms have fully resolved. Similarly, this may explain why, during previous episodes, he would improve in hospital when his antipsychotic medications were stopped. Interestingly, he presented with many features of NMS, such as rigidity, elevated CK, and change in mental status, in line with speculation in the literature that NMS and catatonia may be part of the same diagnostic spectrum or at least frequently co-occur.

CONSENT

Consent was obtained from the patient's substitute decision maker.

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Lithium Toxicity at Therapeutic Blood Levels: A Case Report

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ABSTRACT

This report describes a case of lithium toxicity occurring at therapeutic blood levels in a 47-year-old man with bipolar disorder and a history of alcohol abuse. We discuss the clinical presentation of lithium toxicity, as well as factors that may contribute to a reduction in the blood levels required for the precipitation of toxic effects. In addition, we review the literature on cases of lithium toxicity occurring at therapeutic blood levels, including diagnosis and management thereof.

RÉSUMÉ

Ce rapport décrit un cas de toxicité au lithium se produisant à des niveaux sanguins thérapeutiques chez un homme de 47 ans avec un trouble bipolaire et une histoire d'abus d'alcool. Nous discutons la présentation clinique de toxicité au lithium, ainsi que les facteurs pouvant contribuer à une réduction des niveaux sanguins nécessaires à la précipitation des effets toxiques. En outre, nous passons en revue la littérature sur les cas de toxicité au lithium se produisant à des niveaux sanguins thérapeutiques, y compris son diagnostic et sa gestion.

INTRODUCTION

Lithium is a first-line drug in the treatment of bipolar disorder, of which subtypes include bipolar I and bipolar II. Bipolar I is defined as the presence of at least one manic episode, though patients almost always also experience major depressive episodes. Bipolar II is defined as having suffered at least one hypomanic and at least one major depressive episode, as well as the absence of any manic episodes [1]. Lithium is indicated for the treatment of acute mania as well as maintenance therapy in bipolar disorder; treatment of acute bipolar depression is also an off-label use [2]. Historically, lithium's exact mechanism of action has been poorly understood [3]. However, recent evidence has shown lithium to play a neuroprotective role, increasing gray matter volumes in several brain areas central to the pathophysiology of mood disorders, including the amygdala, hippocampus, and prefrontal cortex. At the cellular level, lithium exerts its effects by decreasing excitatory and increasing inhibitory neurotransmission [4]. While it is an effective drug for the treatment of bipolar disorder, lithium is associated with GI, cardiac, and central nervous system (CNS) toxicity when blood levels exceed its narrow therapeutic window (0.6–1.2 mmol/L) [5]. Lithium toxicity may be of an acute or chronic nature. Acute toxicity occurs in individuals not being treated with lithium, typically in the setting of accidental or intentional overdose. Early symptoms of acute toxicity include nausea, vomiting, diarrhea, and ECG changes. With increasing doses, neurologic findings such as sluggishness, ataxia, confusion and neuromuscular excitability may develop as the drug is allowed to penetrate the CNS. Chronic toxicity occurs in individuals being treated with lithium who develop renal dysfunction. In the setting of renal dysfunction, individuals experience decreased lithium clearance, and thus increased serum lithium concentrations. Chronic toxicity often manifests as gradual development of neurologic symptoms similar to those of the late phase of acute toxicity. Treatment of lithium toxicity includes hydration and supportive care, discontinuation of lithium, and in cases of severe toxicity, hemodialysis. Even after discontinuation of lithium, long-term sequelae can persist and may include cerebellar dysfunction, extrapyramidal symptoms, brainstem dysfunction and dementia. These sequelae are collectively referred to as SILENT (syndrome of irreversible lithium effectuated neurotoxicity) [6–11].

CASE REPORT

CASE PRESENTATION

A forty-seven year old male with a history of bipolar II disorder and alcohol abuse was referred to The Royal Ottawa Mental Health Centre (ROMHC) Inpatient Mood Unit for assessment. The patient had an approximately two-month history of increasing depression, poor concentration and memory, and, at times, dysarthria and gait ataxia. He had a history of alcohol abuse, and had sustained two DUI charges in the past several months. Several months prior, he had been admitted to hospital for the treatment of a major depressive episode. His medications at the time

Keywords: Bipolar; Lithium toxicity; Pharmacotherapy

included lithium and lamotrigine. He had been referred to ROMHC by his outpatient psychiatrist, who had performed a dementia workup to rule-out cognitive impairment, placed a neurology consultation, and ordered a CT and subsequent MRI head. Both of these imaging studies were reported as normal; neuropsychology testing was pending at the time of presentation. The working diagnosis at the time was psychomotor retardation as a feature of a major depressive episode. The patient was admitted to the Mood Unit for monitoring and further assessment.

DIAGNOSIS & TREATMENT

Once admitted to hospital, the patient was treated with three doses of intramuscular thiamine due to the possibility of Wernicke's encephalopathy. Blood work was drawn including a complete blood count, B12, ferritin, folate, TSH, liver enzymes, and lithium levels. All blood work was reported within normal limits; the patient's serum lithium level was at the lower end of the therapeutic range, at 0.62 mmol/L. Over the course of a week, the patient's mood gradually stabilized and returned to baseline. However, daily progress assessments revealed a lack of resolution of the patient's ataxia and dysarthria. The patient also began to report diplopia shortly after admission, which persisted thereafter. Tapering of lamotrigine was then attempted. Lamotrigine is an anticonvulsant drug shown to be efficacious as prophylaxis for bipolar depression. However, lamotrigine does not have a well-established therapeutic range for the treatment of bipolar disorder, and has the potential to cause adverse reactions similar to those experienced by the patient [12,13]. No change in the patient's symptoms occurred following tapering of lamotrigine. After several weeks of persistent symptoms, the patient himself broached the possibility of lithium toxicity occurring at therapeutic blood levels. The patient was reassured that this was extremely unlikely, but given his lack of symptom resolution, a decision was made to trial weaning from lithium. The patient's lithium dose was thus decreased in a step-wise fashion over a three-day period and finally stopped completely. On the fourth day, no symptom improvement had been noted, so the patient was transported to The Ottawa Hospital - Civic Campus for assessment by neurology. A repeat CT head with contrast was done, and the findings and assessment of the attending neurologist were threefold. Firstly, it was noted that there was a moderate degree of cerebellar vermal atrophy. Though impossible to ascertain a definitive cause for this finding, it was felt to likely be a result of chronic alcohol consumption. Secondly, the patient's symptoms of ataxia and speech incoordination were felt to be symptoms of lithium toxicity, the threshold for which had been lowered as a result of the underlying organic neurological impairment. Thirdly, the patient was found to have decreased visual acuity in the right eye, explaining his symptom of diplopia. The patient was sent back to ROMHC.

OUTCOME

Subsequently, on the morning of day five since beginning lithium tapering, the patient began to show improvement in both his speech and gait. By the evening of the same day, the patient's gait and speech had retuned to baseline. These findings were in keeping with the pharmacokinetic principle of complete drug clearance occurring after five half-lives: for lithium, the half-life is on average 24 hours. The decision was made for the patient to remain off of lithium, and to use lamotrigine instead as a mood stabilizer. Lamotrigine was subsequently titrated to therapeutic levels over the course of several weeks, to a final therapeutic dose of 200 mg/day in two divided doses. The patient's mood remained stable, and he was discharged from hospital.

DISCUSSION

Though rare, a few reports exist of patients who have exhibited findings of lithium toxicity at normal serum lithium levels [14–18]. In one such report by Bell et al. (1993), four cases are described, and it is outlined that risk factors for developing lithium toxicity at therapeutic levels include pre-existing EEG changes, undetected cerebral pathology, and pre-existing organic impairment, as well as rapid dose increases and genetic susceptibility. For our patient, it was proposed that the observed cerebellar vermal atrophy, which was likely secondary to the effects of long-term high alcohol consumption, had acted as a "primer" which allowed the cerebellar symptoms of lithium toxicity to develop at lower blood levels than what would normally be considered toxic. It was thus the interaction of lithium with pre-existing cerebellar pathology that precipitated the patient's toxic symptoms, despite lithium levels at the lower end of the therapeutic range. In keeping with our case, it has been noted in the literature that serum lithium levels may be misleading. Clinical symptoms of toxicity may correlate more accurately with red blood cell lithium levels, which better reflect intracellular drug accumulation [16]. Thus, our case has shown that clinical manifestations, rather than serum lithium levels, should be the primary basis for diagnosis and treatment of lithium toxicity.

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The Importance of Longitudinal Neurocognitive Assessments in Heart Failure Patients Receiving a Left Ventricular Assist Device

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ABSTRACT

Heart failure (HF) is a major global health concern that has continued to increase in incidence and prevalence, becoming a global epidemic. In Canada alone, there are 500,000 HF patients, with 50,000 new cases each year. Often, HF patients reach severe end stage HF (ESHF) and require a heart transplant or a left ventricular assist device (LVAD). Previous studies have shown that as the heart begins to fail, ESHF patients develop a global cognitive impairment (CI) that accompanies the reduction in blood pressure (BP) and cardiac output (CO). Several mechanisms have been attributed to the CI observed in ESHF patients. Cerebral hypoperfusion, due to a large decrease in CO, appears to be the most supported explanation. Although several studies to date have explored cognitive functioning after the treatment of HF, there is limited literature investigating the cognitive outcome in ESHF patients following LVAD implantation. Moreover, studies that examined the effect of LVAD implantation on cognition did not compare patient outcomes to pre-LVAD baseline levels. Taking into consideration the increasing number of EDHF patients in need of LVAD implantation each year, it is imperative to determine the effect of this intervention on CI in order to better inform LVAD patients and create effective rehabilitation programs for LVAD recipients.

RÉSUMÉ

L'insuffisance cardiaque (IC) est une préoccupation majeure de santé mondiale qui continue d'augmenter en incidence et en prévalence, devenant une épidémie mondiale. Au Canada seulement, 500 000 patients souffrent d'IC, avec 50 000 nouveaux cas chaque année. Souvent, les patients avec IC atteignent une phase terminale grave (ICT) et nécessitent une transplantation cardiaque ou un dispositif d'assistance ventriculaire gauche (DAVG). Des études antérieures ont démontré que lorsque le cœur est en insuffisance, les patients développent une déficience cognitive globale (DCG), accompagnant la réduction de la tension artérielle et du débit cardiaque. Plusieurs mécanismes ont été attribués à la DCG observée chez les patients en ICT. L'hypoperfusion cérébrale, en raison d'une diminution importante du débit cardiaque, semble être l'explication la plus soutenue. Bien que plusieurs études à ce jour ont exploré le fonctionnement cognitif suivant le traitement de l'IC, il existe une littérature limitée enquêtant le résultat cognitif chez les patients en ICT suivant l'implantation d'un DAVG. Par ailleurs, les études qui ont examiné l'effet de l'implantation de DAVG sur la cognition ne comparaient pas les résultats des patients avec leurs niveaux de base pré-DAVG. Prenant en considération le nombre croissant de patients en ICT en besoin d'implantation de DAVG chaque année, il est impératif de déterminer l'effet de cette intervention sur la DCG afin de mieux informer les patients avec DAVG et créer des programmes efficaces de réhabilitation pour les bénéficiaires de DAVG.

INTRODUCTION

Heart failure (HF) is a global epidemic carrying a lifetime risk of 20% [1, 2]. Heart failure is defined as a physiological state in which there is insufficient cardiac output (CO) to satisfy the body's needs. In the prospective cohort Rotterdam study, the prevalence of HF increased as patients got older from 0.9% in 55-year-olds to 17.4% in those over 85 years of age [2, 3]. While medical therapies have been able to reduce morbidity and mortality, the overall incidence and prevalence of HF continues to rise. Over 500,000 people suffer from HF in Canada, with 50,000 new cases per year [4]. 40–50% of these patients have a lifespan of less than five years [4-7]. Furthermore, the average annual mortality rate is 5-10% depending on age, co-morbidities, and severity of symptoms. In severe end stage HF patients, once medical therapy ceases to control symptoms, patients often require advanced mechanical therapies such as left ventricular assist devices (LVAD) or cardiac transplant [8, 9].

Although HF affects the circulatory system at first, it can eventually have detrimental effects on the nervous system. During the initial stages of HF, the carotid baroreceptors detect a fall in arterial blood pressure (BP), resulting in increased vasoconstriction. Although this may initially restore BP, it can increase peripheral resistance, augmenting heart workload. Over time, the heart will begin to fail, leading to a generalized reduction in BP and

Keywords: Cardiac; Surgery; End stage heart failure; LVAD; Transplant; Cognitive functioning; Chronic; ADL; Readmissions

CO [10,11]. Previous studies have shown that cerebral blood flow is substantially decreased, on average, by 31% in patients with ESHF. This hypoperfusion can be attributed to the generalized hypotension that accompanies HF, and can affect a vast number of cortical functions.

COGNITIVE FUNCTIONING IN END STAGE HEART FAILURE (ESHF)

Cognition is a collective term for higher cortical functions such as thinking, remembering, planning, knowing, and analyzing [12]. Cognitive functioning incorporates several cognitive domains including memory, attention executive functioning, psychomotor speed, language, and visuospatial ability [12-14]. Functional magnetic resonance imaging (MRI) and positron emission tomography (PET) studies have shown that individual cognitive domains involve diverse, overlapping regions of the brain [15-17]. Several methods are used to measure cognitive functioning, from the mini-mental state examination (MMSE), which measures global cognition and is used by physicians at the bedside, to more detailed neuropsychological assessments that examine individual domains.

Cognitive impairment (CI), or a decline in one or more cognitive domains, is common in ESHF [18-21]. A landmark paper in Lancet published in 1997 was one of the first studies to coin the term "cardiogenic dementia" and identify a link between CI and cardiac disease [22]. The prevalence of CI in HF patients varies from 25%-58% [23-26]. This wide range is due to varying study designs, severity of heart failure, diagnostic criteria, and battery of neuropsychological tests utilized. Due to their CI, HF patients have poor somatic awareness, reduced independence, and decreased ability to carry out activities of daily living. Since HF patients have decreased ability to care for themselves, they are at higher risk of mortality, morbidity, re-hospitalization, and worsening HF [27]. Most patients suffering from CI secondary to HF are diagnosed with mild impairment while around 25% have moderate to severe CI [27]. Treatments such as angiotensin converting enzyme (ACE) inhibitors and physical activity have resulted in cognitive rehabilitation [28]. In the past, cognitive rehabilitation has been defined as the improvement of cognitive functioning in either global cognitive functioning or specific domains. Such studies suggest that CI in HF can potentially be improved up to a certain degree.

DOMAIN SPECIFIC COGNITIVE IMPAIRMENTS IN HEART FAILURE

It is important to review existing literature on domain-specific CI in heart failure patients. Inconsistencies among studies in regards to the prevalence of CI and the domains involved may be due to the fact that most studies have used a wide variety of neuropsychological tests [19, 27].

MEMORY

Memory refers to the capacity to retain information and utilize it for adaptive purposes [29]. Registration, storage, and retrieval are the three main stages involved in memory [29]. Impaired memory isolates patients from meaningful contact with the world around them and renders them dependent on others. Even mildly to moderately impaired memory can be debilitating [29]. Memory testing is often carried out through an interview in which patients are asked about their personal lives and public events. Then, the California Verbal Learning Test (CVLT) and Rey Auditory Verbal Learning Test (AVLT) are used, in which patients learn a list of words that they are later asked to recall [27, 30]. Several studies have demonstrated HF patients' impaired cognitive performance on both initial learning and delayed recall tests [16, 31-38]. In contrast, other studies did not show a reduction in initial learning scores [27, 39-40].

LANGUAGE

There are many possible language deficits that HF patients may experience. These deficits may include difficulties in word finding and naming [29]. Patients may have impairment in word recognition when reading, use related words instead of the intended word (semantic aphasia), and have trouble following instructions and maintaining a conversation [31]. Neurocognitive assessments used to examine this domain in HF patients include naming, repetition, following commands, reading, writing, and verbal fluency tests. There are two main studies, both of which found impaired performance on language parameters in patients with HF [16, 32]. They used the Boston Naming Test (BNT), Benton Controlled Oral Word Association Test (COWAT), Token Test, and semantic fluency task. These have all been previously shown to be excellent indicators of changes in language functioning [41, 42].

EXECUTIVE FUNCTIONS

Executive functioning enables a person to engage successfully in independent, purposeful, self-directed, and self-serving behavior [29]. This domain involves verbal reasoning, problem solving, planning, multi-tasking, managing novelty and cognitive flexibility [33]. It is especially important because when impaired, even partially, one may not be able to self-care, work independently, or maintain social relationships, irrespective of how well preserved other cognitive domains are [33]. Thus, executive functioning is often defined as the cognitive abilities required to carry out activities of daily living. Executive function can be tested using a variety of methods, but the most popular one is the Trail Making B, in which the patient connects the dots between numbers and letters as fast as possible. There have been many studies looking at executive functioning in HF patients, and the majority have found significant impairments [34-40, 43]. There were two studies that did not find any differences in executive functioning [16,

44]. However, these studies used a different battery of neuropsychological assessments.

ATTENTION, WORKING MEMORY, AND PSYCHOMOTOR SPEED

Attention refers to processes that allow us to be receptive to stimuli and to how we process incoming stimuli [29, 45]. It allows us to concentrate and focus on stimuli of our choosing without being distracted by extraneous events. Working memory, which is what allows us to maintain and manipulate information for short periods of time, is a function of attention and relates to information processing [45]. The digit span and Trail Making Test A are commonly used to assess attention and working memory [12]. Psychomotor speed is the speed at which we process information and react to stimuli [29, 46]. Deficits in all three (attention, working memory and psychomotor speed) are commonly seen in patients with vascular, sub-cortical and multi-infarct dementia [47]. Most studies employed the Digit Symbol Substitution Test (DDST) to assess changes in psychomotor speed. Patients with severe HF were shown to have significant deficits in attention, working memory, and speed of processing in the majority of studies [20, 32, 34, 35, 38, 39, 44, 49-51]. However, there were a few studies that failed to show significant changes [35, 49, 52, 53]. The profile of deficits seen in HF patients shares a lot of commonalities with that of vascular dementia, but it is different from that of neurodegenerative dementia. This pattern seems to indicate that the former two clinical syndromes share similar pathophysiologic mechanisms.

VISUOSPATIAL FUNCTION

Visuospatial function describes visual perception of both the environment as a whole and the spatial relationships between objects [29]. It is used when we are getting dressed, grasping objects or trying to orient ourselves [29]. The most commonly used neuropsychological tests to ascertain changes in visuospatial function include the Benton Facial Recognition Test (FRT), Judgment of Line Orientation Test (JLO), and the Clock Drawing Test (CDT) [12]. While there have not been many studies looking at visuospatial function in HF patients, most found visuospatial deficits [36, 49]. There was a single study that suggested no differences in this domain for HF patients [32].

PATHOGENESIS OF CI IN HF

While there are several potential mechanisms explaining the CI that often accompanies HF, decreased cardiac output leading to cerebral hypoperfusion and in turn, neuronal degeneration is the most likely model [10, 54-57]. The Critically Attained Threshold of Cerebral Hypoperfusion (CATCH) hypothesis asserts that heart failure causes early vascular aging, leading to orthostatic hypotension, stroke, intracranial atherosclerosis, and small vessel disease [10]. Thus, the story appears to be more complex than a simple link between hypotension and CI.

While hypotension can impair cognitive functioning, hypertension has also been shown to play a role in cognitive decline. The surprising evidence that both extremes are implicated in cognitive decline may be explained by the concept of neurovascular coupling (NC) [11]. NC refers to interactions between endothelial cells, neurons, and other cells of the nervous system [58]. These interactions are responsible for ensuring that highly active areas of the cerebral cortex obtain adequate perfusion while perfusion of inactive areas decreases. The capacity of the NC system to respond to BP variations and increased metabolic demand is referred to as the brain vascular reserve (BVR). Patients with hypotension and/or hypertension have been shown to have decreased BVR and poor cerebral auto-regulation [11, 55].

Cerebral auto-regulation maintains stable perfusion over a 60 to 150 mmHg BP range [11, 59]. Thus, the auto-regulation curve plotting cerebral blood flow (CBF) against mean blood pressure assumes a sigmoid shape with the areas outside the auto regulatory ranges adopting an almost linear relationship. Conditions such as hypertension, hypotension, diabetes, stroke, and vascular disease can impair auto-regulation, leading to a near linear relationship [60-63]. With a linear relationship, cerebral perfusion becomes pressure-dependent. Importantly, many patients with end stage heart failure suffer from one or more of the aforementioned conditions [11].

Since patients in severe HF tend to be hypotensive at the time of LVAD implantation, it is pertinent to look at the following literature. There have been three major studies to date looking at the effects of hypotension on cognitive functioning: ARIC, MPP and the Helsinki Ageing study [64-66]. All three studies found that hypotension leads to poorer results on cognitive tests (neuropsychological tests and the MMSE). The mean follow up time of these studies was thirteen years. The cerebral perfusion in a hypotensive patient is fully dependent on the mechanisms of autoregulation [11]. Thus, hypoperfusion can result when BP is low (below the range where autoregulation is possible) or when there is impaired auto-regulation. In patients with chronically low BP (less than 120/70), having orthostatic hypotension increases the probability of developing cognitive impairment [67]. Conversely, it has been shown that the presence of orthostatic hypotension in hypertensive patients reduces the odds of developing CI [68].

There are a variety of factors mediating cerebral perfusion. A number of these factors have been implicated in cognitive changes in the context of hypotension. Low CO has been correlated with reductions in cognitive performance and increased incidence of dementia [27] while low systolic blood pressure has also been shown to be a predictor of cognitive impairment level in HF patients [69]. Lastly, cerebrovascular reactivity, which is the ability of cerebral vessels to change diameter to maintain CBF, is impaired in HF patients, correlating with the degree of HF [27].

These findings give further credence to perfusion abnormalities as the link between CI and HF.

Ample radiological evidence implicates systemic hemodynamics in the CI observed in HF patients. One study showed that CBF was reduced by 30% in patients with severe HF [15]. Another study showed that the degree of CI was related to regional reduction in CBF to certain brain regions, especially to the posterior cortical areas [16]. These results suggest that cognitive impairment in HF patients is closely related to cerebral perfusion measures. Additionally, there are multiple studies examining the effects of reduced cerebral perfusion, as measured using Doppler imaging, on cognitive decline [70-72]. Moreover, Zuccala et al. found a linear relationship between MMSE scores and left ventricular ejection fractions lower than 40% [73]. Finally, a different study revealed associations between CO and Trail B, Digit Symbol Substitution, and Stroop Test scores [74].

LVAD AND COGNITIVE REHABILITATION

Limited literature exists on neurocognitive assessments in advanced heart failure patients receiving LVADs (Figure 1). As this patient population continues to grow, it is important to document changes in cognitive performance, as this may predict patients' future health outcomes. Petrucci et al. looked at cognitive functioning post-LVAD at one, three and six months [42]. They assessed five neurocognitive domains using tests for (1) visual-spatial perception (Clock Drawing, Wechsler Adult Intelligence Scale III Block Design), (2) memory (Wechsler Memory Scale III-Logical Memory and Visual Reproduction), (3) executive functions (Trail Making B, WAIS III Digit Symbol), (4) language (Boston Naming Test), and (5) processing speed (Trail Making A) [42]. They found significant improvements in visual memory, executive functions, visual spatial perception, and processing speed over the six-month span. Results for the other assessments remained stable. While these are promising results, it is crucial to note that the study did not control for stress, depression, and pre-morbid estimates of IQ. All of these parameters have been shown previously to impact results of neurocognitive testing. In addition, while they showed improvement of cognitive functioning post-LVAD implantation, it is also necessary to examine differences in cognitive functioning pre- and post-surgery.

COGNITIVE FUNCTION AND BRAIN TISSUE OXYGEN SATURATION

Although CI in HF patients is believed to be largely due to hypoperfusion, monitoring of tissue oxygen saturation is not a priority during LVAD implantations. Although hemodynamic and respiratory monitors are employed during cardiac surgery to improve patient safety, little has been done to monitor cerebral function and perfusion during surgery. Increased adverse events pertaining to the central nervous system (including strokes and cognitive deficits) lead to increased mortality, length of hospitalization, and poor long-term outcomes [78]. The etiologies of these complications are known to be multifold. First, in surgeries using the cardio-pulmonary bypass machine (CPB) such as LVAD, coronary artery bypass, and heart transplantation, there are increased rates of embolization of gaseous and particulate emboli from the surgical site, as well as from placement and removal of the aortic cross clamp [79]. Second, there is transient hypoperfusion due to loss of cerebral autoregulation, which may lead to cortical damage [79, 80]. All of these mechanisms may result in tissue ischemia, leading to neuronal degeneration. There are a few options available to monitor cerebral oxygen saturation levels in order to detect ischemia. Most of these options are either invasive (jugular bulb saturations) or inaccurate (EEG, because the recordings are distorted by the isoelectricity caused by hypothermia/anesthetic agents). Cerebral oximetry, however, is a reasonable option as it is not invasive, and is not influenced by anesthetic agents [1, 82]

A few studies have examined the relationship between neurocognitive dysfunction and tissue oxygen saturation. Yao et al. found that perioperatively, patients with a cerebral oxygen saturation of less than 40% for over 10 minutes had increased incidence of neurocognitive dysfunction as measured by MMSE and the anti-saccadic eye movement test (ASEM) during cardiac surgery [83]. Murkin et al. investigated a prospective, randomized trial of 200 cardiac surgical patients and found that maintaining cerebral oxygen saturations over 75% of baseline decreased major organ morbidity and mortality [84]. Furthermore, studies in cardiac patients have shown that oxygen saturations in the perioperative stages are predictive of the incidence of postoperative cognitive dysfunction [85, 86]. Thus, perioperative factors can impair the

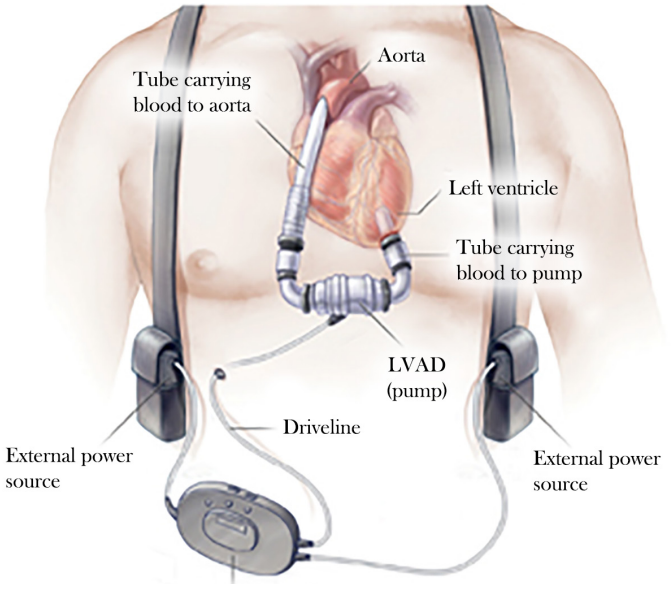

Figure 1. Left Ventricular Assist Device (LVAD) is one of the major interventions for severe end stage heart failure (ESHF). Further studies are needed to determine whether LVAD implantation leads to a decrease in cognitive impairment in ESHF patients. Image credit <http://www.mayoclinic.org/medical-professionals/clinical-updates/cardiovascular/mayo-pioneers-innovative-treatment-patients-end-stage-cardiac-disease>

potential for cognitive rehabilitation. However, the relationship between perioperative cerebral tissue oxygenation and cognitive rehabilitation has not been sufficiently explored in LVAD patients.

FINAL WORDS

In conclusion, the effect of LVAD implantation on patient cognition remains elusive. Although recent studies have begun to explore cognitive functioning in LVAD patients, they have been limited to postoperative cognitive assessments and have not compared these results to baseline preoperative cognitive assessments. In order to further understand the implications of LVADs on HF patient cognition, baseline measurements of cognitive function pre- and post-LVAD implantation are needed. In addition, several research groups have found that a lack of cerebral oxygen saturation perioperatively may increase the risk for neurocognitive dysfunction in patients undergoing surgery for LVAD implantation. Thus, it is imperative to investigate the role of cerebral oximetry during LVAD surgery. Importantly, recent research suggests that perioperative cerebral oxygenation may determine whether or not a patient achieves cognitive rehabilitation post-surgery. Considering that the prevalence of advanced HF patients in need of LVADs is skyrocketing, research in the field of LVAD-related neurocognitive effects is vital in order to optimize cognitive rehabilitation and establish predictive measures for long-term outcomes.

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A Recent Clinical Update on Epilepsy in Pregnancy

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ABSTRACT

Chronic diseases can have numerous effects across a person's lifespan. Epilepsy is a chronic disease that impacts all stages of life including pregnancy. Pregnancy is a sensitive time in one's life, especially for people living with a chronic disease. This review presents a recent update on the scientific findings surrounding epilepsy and pregnancy. Topics such as conception, seizure control during pregnancy, health risks to the mother and baby during pregnancy and side effects of anti-epileptic medications will be covered. Through the presentation of findings from 2013 to 2015, this review will update future clinicians on novel developments in the field of pregnancy and epilepsy that will aid with treatment of patients, while simultaneously identifying gaps in the literature and needs for future research. This review serves as a reminder that medicine needs to be tailored to the unique individual and that individuals living with chronic diseases may require altered treatment plans throughout their lives.

RÉSUMÉ

Les maladies chroniques peuvent avoir de nombreux effets au travers de la vie d'une personne. L'épilepsie est une maladie chronique qui touche tous les stades de la vie, y compris la grossesse. La grossesse est un moment délicat de la vie, en particulier pour les personnes vivant avec une maladie chronique. Cette revue présente une mise à jour récente sur les découvertes scientifiques au sujet de l'épilepsie et de la grossesse. Des sujets tels que la conception, le contrôle des crises pendant la grossesse, les risques pour la santé de la mère et du bébé pendant la grossesse et les effets secondaires des médicaments antiépileptiques seront couverts. Par le biais de la présentation des résultats de 2013 à 2015, cette revue servira de mise à jour des nouveaux développements dans le domaine de la grossesse et de l'épilepsie pour les futurs cliniciens et aidera avec le traitement des patients, tout en identifiant simultanément les lacunes dans la littérature et les besoins pour la recherche future. Cet examen sert comme un rappel que la médecine doit être adaptée à l'individu unique et que les personnes atteintes de maladies chroniques peuvent exiger des plans de traitement modifiés tout au long de leur vie.

INTRODUCTION

Chronic disease can affect different facets of one's life. For instance, women living with chronic diseases face particular medical risks and challenges during pregnancy. Epilepsy is defined as the occurrence of a seizure in an individual with a high likelihood of reoccurrence, two or more recurrent seizures, or a syndrome involving seizures [2, 3]. Epilepsy is the most common neurological disorder in pregnant women [1]. One and a half million women of childbearing age have epilepsy. Three to five births per 1000 are to mothers with epilepsy [2]. The challenge in the treatment of epilepsy during pregnancy is finding a balance between the detrimental effects of having uncontrolled seizures and the teratogenic side effects of seizure controlling medications on the fetus.

This review aims to present advances in the literature from 2013 to 2015 surrounding epilepsy and pregnancy, while identifying gaps in knowledge that require future research. Updates on important clinical topics involved in the treatment of women with epilepsy will be discussed. Subsequently, topics such as conception, seizure control during pregnancy, health risks to the mother and baby during pregnancy, and side effects of anticonvulsant medications will be covered. This review serves as a reminder that medicine needs to be altered for the individual in the context of comorbid disease.

CITATION SELECTION CRITERIA

A literature search using the University of Ottawa's library search engine was performed. An advanced search was employed using the keywords "epilepsy" and "pregnancy." The search was restricted to studies that were published from 2013 to 2015, written in English, and peer-reviewed. Cohort studies, case-control studies and clinical trials were all included. The subject tool was then applied, and the subject of "depression" was excluded

Keywords: Epilepsy; Pregnancy; Risks; Teratogen

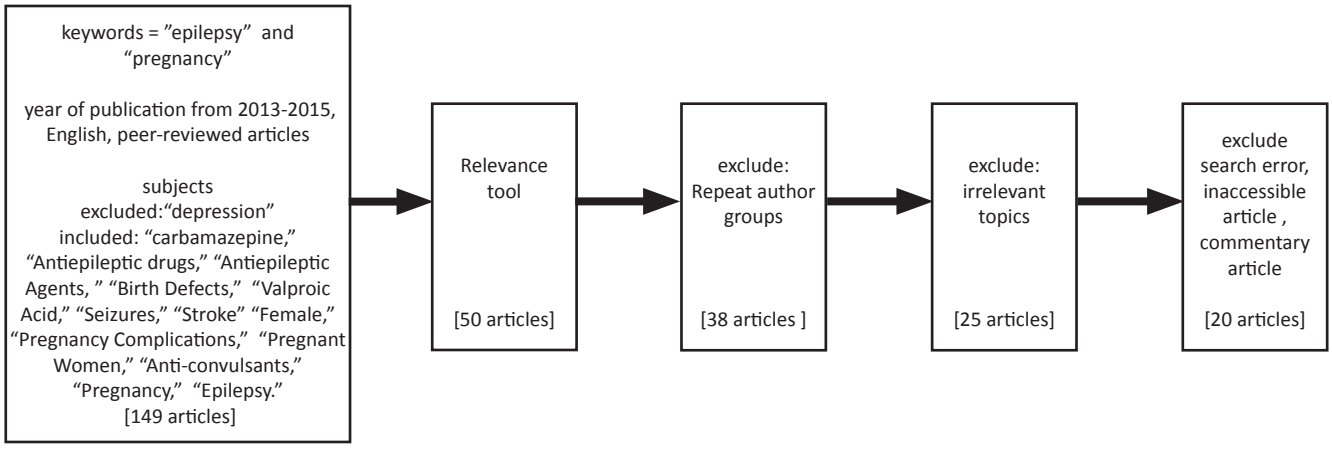

Figure 1. Methodology Inclusion and Exclusion Criteria
Note: Three articles were discarded because they did not fit the publication year or language criteria (search error)

because results including depression focused on the topic of postpartum depression. The following subjects were included: “Carbamazepine”, “Antiepileptic drugs”, “Antiepileptic Agents”, “Birth Defects”, “Valproic Acid”, “Seizures”, “Stroke”, “Female”, “Pregnancy Complications”, “Pregnant Women”, “Anticonvulsants”, “Pregnancy” and “Epilepsy.” This search strategy yielded 149 articles. The articles were sorted by relevance, and the 50 most relevant articles were included (the relevance of subsequent results declined greatly). In order to eliminate possible overrepresentation of one group of researchers, multiple articles written by the same author or group of authors were excluded. By eliminating repeated authors, the total number of articles was reduced to 38. 13 articles discussing the following subjects were deemed irrelevant by the author: specific nursing training initiatives, isolated animal studies, use of antiepileptic drugs in the setting of psychiatric illness, pregnancy risk factors for childhood epilepsy, neuroprotective effects of perinatal choline nutrition and pregnancy risk factors not associated with epilepsy. Two articles were excluded because they were erroneously included by the automatic search (one was not in English and the other was published in 2004). Additionally, the full text of one article could not be accessed online and was thus excluded. Lastly, one article was written in response to another article and was also excluded. The final number of articles included in the review was 20, as illustrated in the following flow chart (Figure 1).

CONCEPTION & FERTILITY

Many women with epilepsy have unique medical problems that may make conception difficult. A third of women with epilepsy are infertile, which is defined as lack of successful conception after a one-year period of unprotected sexual activity. Thomas et al. studied women who were either trying to conceive or in early pregnancy and followed them until their children were 12 years old [3]. It was found that the infertile women with epilepsy had higher levels of luteinizing hormone than dehydroepiandrostenedione, as well as lower levels of progesterone than women with epilepsy who were fertile [3]. The differences in hormone levels and association between epilepsy and infertility is hypothesized to be mediated by the fact that epilepsy is an endocrine disruptor, which can result in hypothalamic disruption and increased androgen levels in females. This effect on fertility is compounded by secondary outcomes of anti-epileptic drugs [3]. Therefore, patients with epilepsy should be supplied with additional counsel and treatment pertaining to infertility.

On the other hand, it is interesting that certain anti-epileptic medications have been hypothesized to interfere with the efficacy of birth control pills [1]. Medication interference with the oral contraceptive pill should be discussed with all female patients on antiepileptic medications. One study found that 26% of pregnancies in women with epilepsy result from contraception failure [1].

EFFECTS OF PREGNANCY ON SEIZURE CONTROL

Monitoring and controlling seizure frequency is important during pregnancy. Having one or more generalized tonic-clonic seizures during pregnancy is associated with a higher risk of preterm birth [4]. A recent study found that 19% of women experience an over 50% increase in seizure frequency during pregnancy, 8% experience a decrease in seizure frequency of 50% or more, and 72% have no change. The findings of this study are limited by a small sample size (36 cases and 72 controls); larger scale studies are required to corroborate these results [5].

Another important area of research is the efficacy of seizure control medications in pregnant individuals. Deterioration in seizure control during pregnancy is associated with physiological changes in the maternal body that result in increased drug clearance. For example, a study comparing monotherapy with carbamazepine, lamotrigine, phenobarbital and valproate used in pregnant women concluded that women using lamotrigine

had more generalized tonic-clonic seizures, were more likely to deteriorate in seizure control from their first trimester to their last trimester, and were more likely to require an increase in dose throughout their pregnancy [6]. However, this study is limited by the fact that randomized controls were not used and preliminary data on seizure control was not collected [6]. In general, studies on this topic are also limited by small sample sizes as well as regulations restricting the allowable volume of blood drawn from pregnant women [7].

RISK TO MOTHER

The risk of death during pregnancy for women with epilepsy is estimated to be ten times higher than in women without epilepsy [8]. A study analyzing data from the United Kingdom Confidential Enquiries into Maternal Deaths (UKCEMD), a report that collected data on all pregnancies in the United Kingdom from 2006 to 2008, found that 14 out of an estimated 13,978 pregnant women with epilepsy died from epilepsy-related complications during or shortly after pregnancy [8]. Of these 14 deaths, 11 were sudden and unexpected [8]. Sudden and unexpected death in epilepsy (SUDEP) is defined as death in a patient with epilepsy, excluding documented status epilepticus cases, where an autopsy has been performed to rule out trauma, drowning, and toxicological or anatomical causes of death [8]. Of the 14 deaths, 9 women were taking lamotrigine; the authors speculate that the high proportion of deaths in women taking lamotrigine reflects either an involvement of lamotrigine in SUDEP or physicians' preferences to prescribe lamotrigine in the United Kingdom [8]. One caveat of this study, which analyzed data from the UKCEMD report, is that the UKCEMD report did not record the number of women who had epilepsy [8]. Thus, the authors Edey et al. estimated the number of women who had epilepsy using a previously reported prevalence rate of epilepsy during pregnancy in the United Kingdom [8]. Evidently, more studies investigating the safety of lamotrigine use during pregnancy are needed.

RISK TO BABY

Authors Campbell, Devenney and Morrow observed that women with epilepsy who have had a previous child with congenital malformations have a 16.9% risk of having another child with congenital malformations [9]. In comparison, women with epilepsy who have not had a child with congenital malformations had a 9.8% risk of having a subsequent child with congenital malformations [9]. Although more studies are needed to confirm this phenomenon, these findings may suggest that genetics play a role in modulating the teratogenic effects of anti-epileptic medications [9]. On the other hand, a study analyzing pregnancy data from the Kerala Registry of Epilepsy and Pregnancy found that there is no increased risk of reoccurrence of congenital malformations in subsequent pregnancies: of those who had two pregnancies, 21 of 246 (8.5%) women had major congenital malformations in the first pregnancy and 22 of 246 (8.9%) had major congenital malformations in the second pregnancy. These numbers are comparable to the 7.2% rate of major congenital malformations in the children of women who had one recorded pregnancy [10].

It has also been observed that compared to the general population, women taking one anti-epileptic drug have twice as high a risk of giving birth to a baby that is small for gestational age, for their baby to have an Apgar score of less than seven (usually requires medical attention) at one minute after birth, or experience a spontaneous abortion [2]. Interestingly, another study showed that the increased risk of preterm delivery is only seen in mothers with epilepsy who are also smokers [2]. Contradictorily, a retrospective cohort study of 440 pregnant women with a self-reported seizure disorder found that women are not at an increased risk for intrauterine growth restriction, stillbirth, pre-eclampsia or premature delivery [11]. The perinatal risks of epilepsy seem to be unclear, and more data are required.

COMPARING TERATOGENIC EFFECTS OF MEDICATIONS

Up-to-date knowledge regarding the teratogenic effects of anti-epileptic medications is imperative in the treatment of women with epilepsy. Each year in the United States, 7 900 000 women aged 15 to 44 receive prescriptions for anti-epileptic drugs [12]. A study with a cohort of pregnant women with epilepsy taking anti-epileptic drugs, a cohort of epileptic pregnant women not taking any drugs, and a cohort of non-epileptic pregnant women showed that the rate of major congenital malformations was only increased significantly in the epileptic group taking medications [13]. The rate of major congenital malformation in the general population is anywhere between 2 and 4 percent [14]. In a prospective cohort study, Veiby et al. found that children who were exposed to anti-epileptic drugs in utero have an increased risk of abnormal gross motor skills and autistic traits at 18 months of age, with odds ratios of 2.0 and 2.7 respectively [15]. A study of 1290 pregnant women prescribed a regimen of valproic monotherapy found that valproic acid is associated with a 6.7% risk of major congenital malformations [16]. The use of valproic acid is associated with neural tube defects, reduced verbal abilities, oral-facial clefts, hypospadias, congenital heart defects and skeletal abnormalities [2, 17]. Furthermore, a population-based study in Denmark found that valproic acid use during pregnancy significantly increases the risk of autism spectrum disorders in offspring. The study included 508 children who were exposed to valproic acid in utero. This risk remained significant when the authors controlled for parental psychiatric conditions, epilepsy and comorbid major congenital malformations. When mothers who had previously been on valproic acid discontinued the medication for at least 30 days prior to conception, the risk of autism was found to be equivalent to that of the general population. The

implications of this study by Christensen et al. is limited because they did not control for folate supplementation or alcohol and illicit drug use during the course of the pregnancies [18].

Although the previous studies mentioned above found lamotrigine's control of seizures in pregnancy to be questionable, a study of 4000 pregnancies found that lamotrigine dosed at 300 mg or less results in the lowest risk of congenital malformations [19]. The most common malformation associated with lamotrigine is cleft lip. 2.3% of a sample of 2198 women on lamotrigine gave birth to babies with major congenital malformations. The same study found higher risk rates associated with carbamazepine and valproic acid (2.6 and 6.7 respectively) [16].

The incidence rate of major congenital malformations with carbamazepine monotherapy is 2.6%, which falls between those of valproic acid and lamotrigine [16]. In addition, the International Registry of Antiepileptic Drugs and Pregnancy Study found that low dose carbamazepine has a 3% risk of congenital malformations while the risk is 5% and 8.7% for medium and high doses respectively. [7].

Currently, newer drugs such as levetiracetam, oxcarbazepine and gabapentin are being used during pregnancy. Of 304 women who were exposed to monotherapy of levetiracetam, 2 women gave birth to children with major congenital malformations (0.70%; 95% confidence interval 0.19%-2.51%) [20]. Of 248 pregnant women taking a monotherapy of oxacarbazepine, 6 women gave birth to offspring with a major congenital malformation [14]. The rate of birth defects with gabapentin use is uncertain with reported values ranging from 0% to 6% [2]. A study of 223 pregnant women exposed to gabapentin and 223 pregnant controls demonstrated that the rate of major congenital malformation in the two groups was the same [21]. As mentioned before, it is important to stress that when compared to the risk of major congenital malformations in the general population (2-4%), the risks of major congenital malformation with lamotrigine, carbamazepine, levetiracetam, oxcarbazepine and gabapentin are not increased [14].

TREATMENT GUIDELINES

There are general treatment guidelines for epileptic control during pregnancy, but individually tailored treatment regimens may be necessary. First, women taking anticonvulsant medications should take folate to prevent neural tube defects. Although there is some controversy surrounding the recommended folate doses, the American College of Obstetricians and Gynecologists recommends that pregnant women taking anticonvulsants should take 4.0 mg of folic acid per day [2]. If a woman has been seizure-free for a year, one can consider removing all anticonvulsant medications during pregnancy [2]. If the patient has not been seizure-free for a year, the ideal treatment during pregnancy is monotherapy with a drug of relatively low teratogenicity at the lowest effective dose for that individual [2]. The medication dose may need to be increased during pregnancy to account for the increase in plasma volume, cardiac output, renal blood flow along with the decrease in albumin concentration, a drug-binding protein. Also, pregnant women have increased activity of cytochrome P450 enzymes; therefore, drug metabolism will increase. In particular, lamotrigine is thought to have increased clearance during pregnancy [7]. Medications should be continued throughout delivery and breastfeeding, but doses need to be readjusted after pregnancy to account for changes back to physiological baseline [2]. In terms of drug selection, the drugs of choice during pregnancy are levetiracetam, oxcarbazepine and gabapentin [22]. Valproic acid should be avoided in pregnancy as it has the highest rate of major congenital malformations [2]. A retrospective cohort study of 153 women that compared a group of women undergoing planned pregnancies versus a group of women undergoing unplanned pregnancies showed that the planned pregnancies group had more women on monotherapy (80% planned vs. 61% unplanned). Also, more women in the planned pregnancy group were not on valproic acid with 77% in the planned group not on valproic acid versus 56% of the unplanned pregnancy group [23]. Thus, planned pregnancies are safer than unexpected pregnancies in women with epilepsy as women often do not realize they are pregnant within the first trimester, a time when the fetus is most sensitive to teratogens [23].

CONCLUSION

Epilepsy during pregnancy is a complex medical issue to treat. The most recent research on epilepsy during pregnancy must guide treatment selection for these patients. Epilepsy can lead to problems from conception to the postpartum period. Clinicians must be vigilant about seizure control and choice of medication during pregnancy. Evidence supports the fact that valproic acid is associated with an increased risk of congenital malformations. This review presents studies published from 2013 to 2015 with the aim of updating clinicians on recent findings in this field. There are still many questions surrounding best evidence based practices. Overall, this review serves as a reminder that medicine needs to be tailored to the individual patient, unique as she is.

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A Review of Transgender Health in Canada

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ABSTRACT

Transgendered individuals are defined by having a gender identity different from their birth gender. These individuals form a prevalent distinct group within the Lesbian, Gay, Bisexual and Transsexual (LGBT) community that has specific health needs. The goal of the current work is to identify the health needs affecting transgendered individuals in order to guide potential health interventions to ameliorate their well-being. Transgendered individuals often experience elevated rates of social stigma, discrimination and prejudice, which can alienate them from other members of society including family members and health care professionals. This can have negative effects on their employment and socioeconomic status and may even render them targets of hate crimes. The combination of these factors can have significant ill effects on the physical and mental health of transgendered individuals. For example, high rates of depression and anxiety are observed within this population with a reported suicide attempt rate of over 30%. Transgendered individuals are also at high risk of being infected with HIV, with those having undergone the transition from male to female (MTF) being most affected. Although Canada is ahead of the curve in equal rights pertaining to the LGBT community compared to many countries worldwide that still have anti-homosexual legislation, there still exists a considerable amount of stigma around the transgendered community. There is a need to educate the population at large to combat social stigma in order to reduce discrimination, increase social support, improve access to health services and ultimately improve the physical and mental wellbeing of transgendered people.

RÉSUMÉ

Les personnes transgenres sont définies comme ayant une identité de genre différente de leur sexe de naissance. Ces personnes forment un groupe distinct au sein de la communauté des lesbiennes, gais, bisexuels et transsexuels (LGBT), ayant des besoins de santé spécifiques. Le but du travail actuel est d'identifier les besoins de santé touchant les personnes transgenres afin de guider les interventions de santé potentielles pour améliorer leur bien-être. Les personnes transgenres éprouvent souvent des taux élevés de stigmatisation sociale, de discrimination et de préjugés, ce qui peut les aliéner des autres membres de la société y compris les membres de leur famille et des professionnels de soins de santé. Cela peut avoir des effets négatifs sur leur emploi et leur statut socioéconomique et peut même les rendre cibles de crimes haineux. La combinaison de ces facteurs peut avoir des effets néfastes importants sur la santé physique et mentale des personnes transgenres. Par exemple, des taux élevés de dépression et d'anxiété sont observés dans cette population avec un taux de tentative de suicide déclaré de plus de 30%. Les personnes transgenres sont également à risque élevé d'être infectées par le VIH, celles ayant subi la transition d'homme à femme (MTF) étant les plus touchés. Bien que le Canada soit en avance dans l'égalité des droits se rapportant à la communauté LGBT par rapport à de nombreux pays à travers le monde, il existe encore une quantité considérable de stigmatisation qui entoure la communauté transgenre. Il est nécessaire d'éduquer la population dans son ensemble à lutter contre la stigmatisation sociale afin de réduire la discrimination, d'accroître le soutien social, d'améliorer l'accès aux services de santé et, finalement, d'améliorer le bien-être physique et mental des personnes transgenres.

INTRODUCTION

Society is currently advancing in an era where lesbian, gay, bisexual, and transgender individuals, collectively referred to as the LGBT community, are gaining social acceptance. While clinicians and researchers acknowledge differences within each group of individuals within the LGBT community, the LGBT populations are often combined into a single entity for research and advocacy purposes. Hence, clinicians face incomplete information about the health status and specific health needs of each distinct group [1].

The group of interest in the current work is the transgender community. Unlike the rest of the LGBT community, transgendered individuals are not defined by their sexual preferences. Instead, transgender individuals are described by their gender identity. Transgender is an umbrella term that refers to any individual whose gender identity differs from the social expectations of their physical sex. This includes many different gender statuses which are defined in Table 1, the best known being transsexuality.

Transsexualism is a more specific term where the transgendered individual identifies with the "opposite" gender assigned at birth.

Keywords: Health; Discrimination; HIV; Mental health

Table 1. Glossary of terms

Terms	Definitions
Bigender	Combined and coexisting male and female identities
Cisgender	Nontransgender; refers to those whose gender identity is aligned with their birth sex
Core gender	One's individual and core sense of being male or female, both or neither
Genderqueer	A gender identity outside the male-female binary
Gender fluid	A gender identity on a spectrum between male and female, perhaps changing over time
Gender identity	An individual's internal sense of their own gender. It is their sense of being a woman, a man, both, neither, or anywhere along the gender spectrum. A person's gender identity may be the same as or different from their birth-assigned sex
Gender spectrum	Refers to the fact that gender occurs on a spectrum, rather than as discrete categories; an individuals' sense of core gender may fall at varying points along that spectrum
Female to Male (FTM)	A transgender, transsexual, or transitioned person assigned female at birth who identifies as male or masculine
Male to female (MTF)	A transgender, transsexual, or transitioned person assigned male at birth who identifies as female or feminine
Medical transition status	The extent to which one has undergone a process of medically transitioning through use of hormones and/or surgeries to allow biological sex to more closely align with one's core gender
Social transition status	The extent to which one has changed the gender in which they live their day-to-day life to better align with their core gender; may involve changing a name, using a new pronoun, and/or changing gender-specific aspects of one's social presentation
Transgender	An umbrella term referring to those with a gender identity or expression that differs from societal norms for those of their birth sex
Transitioned people	Refers to those who identify simply as men or women with a medical history of transitioning sex, and no longer personally identify as transgender or transsexual
Transsexual	A more specific and clinical term referring to those with a gender identity "opposite to" the gender assigned at birth. Some transsexuals may simply identify as transgender or trans
Two-spirit	A term used by North American Native peoples to describe those who identify with both male and female gender roles and expressions

Within this group there exists both individuals transitioning from male to female (MTF) and those transitioning from female to male (FTM). A transgendered individual may have any sexual orientation. Therefore, there is some difficulty in measuring the sexual orientation of transgender people because some respondents may answer sexual orientation questions relative to birth sex (their own or their partner's). Some may respond according to their gender identity, and yet others may find it difficult to answer in terms of a male–female dichotomy [1-3].

The prevalence of transgendered individuals in Canada has yet to be accurately estimated. Studies conducted throughout Europe in the 1990s estimated FTM prevalence between 1:30400 and 1:104000 and MTF prevalence between 1:7400 and 1:42000 [4-6]; in other words, MTFs were 2.3 to 4 times more prevalent than FTMs. More recent estimates in the United States and countries of Latin descent have estimated a much higher prevalence of transgendered individuals ranging between 0.3% and 0.5% of the population [1, 7, 8]. If the more conservative estimate is extrapolated to 2011 Canadian census numbers, there would be approximately 100 000 transgendered individuals throughout Canada [9]. Transgendered individuals therefore represent a significant portion of the Canadian population and may require additional consideration since they have pronounced socioeconomic risks and health disparities [10, 11]. Certain notable institutions, such as the Institute of Medicine in the United States, have stated that the lack of attention to sexual and gender identity create health disparities in LGBT populations [1]. The goal of the current work is to expose the health needs of transgendered individuals in order to guide potential health interventions to ameliorate their well-being.

DETERMINANTS OF HEALTH AND HEALTH ACCESS

Transgendered individuals, whose LGBT identities often have physical manifestations, can experience elevated rates of stigmatization, discrimination and prejudice [12-15]. This stigmatization seems independent of socioeconomic status [14] and is known to lead to reduced social support, an important health determinant [16]. Many studies have found that transgender individuals have

limited social support from the general public compared to their cisgender peers [17-19] and they even have been noted to feel a lack of support from the LGB community [18, 20]. When social support was assessed in cisgender and transgender siblings, the transgender sibling perceived less social support from family than non-transgender family members [14]. Despite these adversities, studies have also found that some transgender individuals have created large and diverse social networks within the transgender community, most likely to compensate for the lack of a larger social support [21].

Additionally, studies have demonstrated that parental support is an important independent factor for well-being in a transgender individual. Higher parental support is associated with higher life satisfaction, lower perceived burden of being transgender, less at-risk sexual behavior and fewer depressive symptoms [22, 23]. Unfortunately, many transgendered individuals have had difficult upbringings with one study finding that more than half of transgender respondents had been forced to engage in sexual activities, and/or experienced violence in their homes, and/or had been physically abused [10].

Transgender individuals, who experience violence and abuse, are often victims of hate crimes [12] which often go unreported due to the fear that they will be mistreated by law enforcement officers [24]. A study of older transgender adults found that high degrees of internalized stigma and victimization are significantly associated with poorer physical health, higher chances of disability, more depressive symptoms and higher perceived stress [19].

Transgendered individuals also face the risk of discrimination, harassment, and victimization in the healthcare setting [12]. When compared to the general public, transgendered individuals have consistently reported greater difficulty obtaining medical care. A study in Philadelphia found that 26% of respondents reported being denied medical care because they were transgender [10]. A similar study conducted in Chicago reported that 14% of the respondents had difficulty obtaining emergency care because of their transgender status [25]. The Canadian TransPULSE project noted that 29% of the transgender people surveyed were unable to obtain emergency care when needed [26]. Additionally, 21% of the transgendered individuals surveyed reported avoiding emergency care on at least one occasion because of their transgender status [26]. This perception of potential mistreatment has led over 20% of transgendered individuals to not disclose their gender identity to their physician [18, 27]. Interestingly, the concealment of gender identity was also significantly associated with impaired mental wellness; specifically, higher degrees of depressive symptomatology and perceived stress [19]. This suggests that transgender individuals have unmet medical needs due to transgender-related stigmatization, which can be further impaired by a lower socioeconomic status.

Throughout the United States, a transgender person is twice as likely to be unemployed compared to their cisgender counterpart and rates of employment discrimination are further increased among MTF relative to FTM, especially a MTF from an ethnic minority [8, 12]. These results are further corroborated by a recent telephone health survey conducted in the state of Massachusetts which found that transgendered individuals had higher unemployment and poverty rates then their cisgender peers [28]. Considerable research has linked low socioeconomic status to poor health outcomes [29, 30]; however, the Massachusetts study found few health differences between the transgender and cisgender adults despite the significant financial differences between these groups. The authors attributed this similarity between the two populations to the Massachusetts' near universal access to health care and their sampling method, since the telephone survey can only include stably housed individuals, thus possibly representing the healthiest segment of the transgender population [28]. This second argument may have merit since it is estimated that transgendered individuals are approximately twice as likely to be homeless compared to the general public throughout the United States. Additionally, homelessness and unstable housing alone are associated with suboptimal physical and mental health independent of gender identity [31, 32].

Although a similar study evaluating the socioeconomic status of transgendered individuals has yet to be conducted in Canada, the TransPULSE project has established a link between limited financial resources in the transgendered community and at-risk behavior. Initial data analysis from the surveys conducted revealed that 49% of the transgendered respondents reported an income lower than $15,000 [33]. Additionally, the study found that a lack of financial resources, past negative experiences with health providers and lack of access to transition-related services were influencing factors for transgendered individuals to undergo non-prescribed hormone use and self-performed surgeries [34].

HEALTH REPERCUSSIONS

Overall, the current studies and statistics demonstrate that transgendered individuals often lack in many determinants of health impairing their physical and mental well-being. Resultant adverse health outcomes in transgender communities can include substance abuse [35-37], sexually transmitted infections (STI) including the human immunodeficiency virus (HIV) [33, 38] and mental health problems including suicidality [39, 40].

HIV

Systematic reviews have been conducted to observe the international burden of HIV on the transgender population; however, these reviews have focused mainly on MTF rather than FTM. A recent review found that transgender HIV data were only avail-

able for countries with male-predominant HIV epidemics; this included the USA, five Latin American countries, six Asia-Pacific countries and three European countries. The pooled HIV prevalence was 19.1% for the 11 066 MTF individuals recruited worldwide [41]. According to the calculated odds ratio, an MTF is 48.8 times more likely to be infected with HIV compared to all adults of reproductive age. Interestingly, the odds ratio did not differ between low and middle-income countries compared to high-income countries [41]. In addition, research comparing MTF sex workers with male and female sex workers in the same neighborhoods has consistently found higher HIV prevalence in transgender individuals. A meta-analysis conducted by Operario et al. (2008) found an HIV prevalence of 27.3% in MTF sex workers, 14.7% in MTF who aren't engaging in sex work, 15.1% in male sex workers and 4.5% in female sex workers [42]. There is still very little data on HIV prevalence in FTM individuals. Past studies suggest HIV prevalence between 0% and 3% [43]. In a more recent retrospective analysis of HIV status in attendees at sexually transmitted disease clinics in San Francisco from 2006 to 2009, HIV infection rates were similar for FTM (10%) and MTF (11%) [44]. Nevertheless, the vast majority of FTMs were found to engage in at least one high-risk sexual behavior in the prior 3 months (93.3%); however, the nature of the behaviors was not specified [45].

MTF transgendered individuals' high HIV prevalence may be due to their practice of having multiple casual sexual partners and engaging in unprotected receptive anal intercourse which has a high probability of HIV transmission [43, 46]. As shown with black male homosexuals in the USA, individual-level risks and sexual practices are insufficient to explain disease burdens in populations at high risk for HIV infection [47]. The crucial driver of sustained HIV incidences are network level risks, particularly the HIV prevalence in the subgroups of interest [47].

In Canada, the TransPULSE project found an HIV prevalence of 0.6% in FTM and 3% in MTF [33]. The authors noted that although these numbers are much lower than the international HIV prevalence, they are still higher than the national average. The lower HIV prevalence could be due to the high proportion of transgendered individuals who had not had a sexual partner within the last year (25% FTM and 51% MTF) and relatively low high-risk sexual experiences (7% FMT and 19% MTFs). However, conclusions on the actual HIV prevalence in transgendered Ontarians were not possible because of the wide confidence intervals associated with the data collected and the high proportion of trans people who had never been tested for HIV (46%) [33].

MENTAL HEALTH

The *Diagnostic and Statistical Manual of Mental Disorders* 5th edition (*DSM-5*), which was published in 2013, reclassified transgendered people from "gender identity disorder" to "gender dysphoria". This is a step towards social acceptance, as transgenderism is no longer identified as a pathological condition. However, the classification continues to stigmatize transgender people with a "mental disorder" classification that is dependent on "clinically significant distress or impairment" [48].

Two nationwide studies conducted in the United States found that rates of depression, anxiety, and overall psychological distress were disproportionately higher in transgendered individuals in comparison to cisgender women and men [19, 49]. The majority of transgendered individuals suffer from at least one mental illness, the most common being anxiety and/or perceived stress (52%), depression (43%), and adjustment disorder (26%) with regular alcohol use also being common (65%) [19, 38, 50]. Approximately one third of transgendered respondents (30.1% and 32%) in two separate studies had attempted suicide [10, 38].

In Canada, the TransPULSE Project has estimated that 36% of transgendered Ontarians had suicidal thoughts over the past year, and that 10% had attempted suicide in that time. Moreover, a young age and experiencing discrimination and lack of social support were found to be associated with a heightened risk of suicidal tendencies. Medical transition status also heavily influenced suicidality, with the most vulnerable being those who were planning their transition, but had not yet begun [51].

ADVOCACY

In summary, transgendered people are a distinct subgroup within the population that requires attention to address the stigmatization against these individuals in order for them to seek the proper help to ameliorate their mental health and other health issues, such as HIV. Therefore, changes are needed at the sociopolitical level to provide the optimal medical interventions.

At the international level, there is a large amount of variation: many countries have anti-homosexual legislation while others have decriminalized same-sex activity, which Canada did officially in 1969. In the United States, same-sex sexual activity was illegal with sodomy being a criminal offense in all 50 states prior to 1961 [52]. Nevertheless, Canada remains ahead of the curve when it comes to accepting the LGBT community by legalizing same-sex marriage, same-sex adoption and anti-discrimination legislation throughout the country. This acceptance is still lacking in many countries such as the United States where same-sex marriage is recognized at the federal level, but not in 13 of the 50 states. This lack of legislation in support of sexual and gender identity can lead to stigmatization of these individuals that differ from the norm. There have been attempts to provide further legislative support by protecting gender expression rights under the Canadian Human Rights Act. For example, a proposed Bill C-279

would include gender identity as a prohibited ground of discrimination under the Act and it would also amend the Criminal Code to include gender identity as a distinguishing characteristic protected under section 318 [53]. Although the House of Commons has passed this bill in October 2013, there is a history of opposition to giving transgendered individuals these rights. Bill C-389 (a bill nearly identical to C-279) was dismissed by an election call despite being passed in the House of Commons in February 2011 [54]. More recently, Senator Don Plett virtually abolished Bill C-279 in early 2015 by proposing an amendment that would prevent MTFs from entering female washrooms, branding these individuals as "sexual predators" [55].

This demonstrates that even the most forward-thinking countries require social changes to promote any possible political changes and ultimately advance the well-being of the transgender people. The TransPULSE project has produced a series of recommendations to improve the health of Canada's transgender population. These include policy advocacy, service provisions, access to transition care, and fostering accepting families and communities [51]. Education must be utilized in order to instruct policy makers, health practitioners, teachers and the general public to help reduce stigma towards transgendered people. For instance, the Amsterdam Gender Identity Clinic developed guidelines for the diagnosis and clinical management of children and youth with gender dysphoria [56, 57]. Pubertal suppression with gonadotropin-releasing hormone analog (GnRHa) therapy is suggested in pubertal children (i.e., Tanner stage 2 or 3) following the diagnosis of gender dysphoria. Suppressing puberty gives the transgendered individual more time to determine if they want to undergo a full transition to their perceived gender. If a full-transition is required, cross-sex hormones (androgens for FTM and estrogens for MTF individuals) are then gradually introduced to induce the physical changes of the desired gender. A study looking at the clinical management of gender dysphoria in Vancouver agreed with this approach, with the added condition that the medical treatment is to be given in collaboration with transgender-competent mental health professionals [58].

CONCLUSION

In conclusion, transgendered people are a distinct Canadian subpopulation comprising of an estimated 100 000 individuals. Transgendered individuals differ from the social norms by having a gender identity different from their birth gender. Consequentially, they experience elevated rates of stigmatization, prejudice and discrimination leading to a lack of social and parental support. These factors lead to an increase in victimization, which is associated with poorer physical and mental health. Transgendered status is associated with a very high rate of HIV infection, with MTF being particularly affected, and mental illness with depression and anxiety being the most common. Furthermore, transgendered people experience barriers to health care access due to their lower socioeconomic status and social stigmatization. Although Canada has taken many steps at the sociopolitical level in order to accept and protect the rights of transgendered individuals, interventions are still required to educate the population and provide the optimum health services to this vulnerable population.

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Through the Looking Glass: A Literature Review of a Rare Pediatric Neuropsychiatric Condition: Alice in Wonderland (Todd's) Syndrome

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ABSTRACT

Alice in Wonderland Syndrome (AIWS), a.k.a Todd's Syndrome, is a neuropsychiatric disorder characterized by a collection of rare, visually distortive symptoms such as micropsia, telopsia, macropsia, metamorphosia, pelospia, impaired passage of time and zooming of the environment. This article aims to review and organize the relevant articles written on AIWS, including a summary of the original research on etiology, imaging, comorbidities and treatments of AIWS, as well as historical accounts of cases from the 1950s, when it was first described. The articles included in this review were collected via the databases PubMed, SCOPUS and MedLine; a total of 18 articles were reviewed. Articles that were not in English were omitted from this review. Articles were not restricted by date of publication, as the goal was to incorporate the historical references of AIWS. In summary, AIWS is mainly a pediatric phenomenon, though there have been cases of comorbidity with depression and Lyme disease in adults. The syndrome is seen to be associated with infection, trauma, and migraine headaches. Imaging studies have discovered areas of hypo-perfusion in certain areas of the brain during episodes of AIWS; these areas mainly include the occipital lobe, but there are reports of frontal and temporal hypo-perfusion as well. This is a rare and interesting neuropsychiatric syndrome that presents with unique visual hallucinations. In the pediatric population, it may be a sign of undiagnosed viral infection that warrants further testing.

RÉSUMÉ

Le Syndrome d'Alice au pays des merveilles (AIWS), aussi connu sous le nom de Syndrome de Todd, est un trouble neuropsychiatrique caractérisé par une multitude de symptômes rares, de distorsion visuelle tels que la micropsie, telopsie, macropsie, metamorphosie, pelospie, troubles de passage du temps et le zoom de l'environnement. Cet article vise à examiner et organiser les articles pertinents écrits sur AIWS, y compris un résumé de la recherche originale sur l'étiologie, l'imagerie, les comorbidités et les traitements d'AIWS, ainsi que les comptes historiques de cas à partir des années 1950, quand le syndrome a été décrit pour la première fois. Les articles inclus dans cette étude ont été assemblés via les bases de données PubMed, SCOPUS et MedLine ; un total de 18 articles a été examiné. Les articles non-rédigés en anglais ont été omis de cette revue. Les articles n'ont pas été limités par date de publication, car l'objectif était d'incorporer les références historiques d'AIWS. En résumé, AIWS est un phénomène essentiellement pédiatrique, bien qu'il y ait eu des cas de comorbidité avec la dépression et la maladie de Lyme chez les adultes. Le syndrome est associé à des infections, traumatismes, et migraines. Les études d'imagerie ont découvert des zones d'hypo-perfusion dans certaines parties du cerveau pendant les épisodes d'AIWS ; ces zones comprennent principalement le lobe occipital, mais il existe aussi des rapports d'hypo-perfusion frontale et temporale. Ceci est un syndrome neuropsychiatrique rare et intéressant qui présente avec des hallucinations visuelles uniques. Dans la population pédiatrique, il peut être un signe d'infection virale non diagnostiquée qui justifie des tests supplémentaires.

INTRODUCTION, HISTORY & SYMPTOMOLOGY

Alice in Wonderland Syndrome (AIWS), a.k.a Todd's Syndrome, is a neuropsychiatric disorder that manifests with debilitating visually distortive symptoms. In 1955, the British psychiatrist Dr. John Todd recognized a small group of his migraine patients describing objects' size as out of proportion to the environment. He later named the disease after Lewis Caroll's literary character, Alice in Wonderland, who suffered similar distortive hallucinations [15,16].

An episode of AIWS may include any number of the following symptoms: micropsia and macropsia, which is when objects are perceived as smaller or larger than they are in reality; telopsia and pelopsia, which is when a stationary object appears further or closer than it is in reality; metamorphosia, which is when straight lines on objects appear distorted; and impaired passage of time and zooming of the environment, which is somewhat similar to vertigo [1-5]. While micropsia and telopsia are the most common symptoms [5], AIWS may also include subjective feelings such as

Keywords: Todd's Syndrome; Alice in Wonderland Syndrome; Hallucinations

derealization, somatopsychic duality, altered sense of touch and illusory alterations of the passage of time [1]. The average age of onset is between 5-10 years of age, although there have been case reports of comorbidity with depression and adult onset episodes [2,6]. This unusual neuropsychiatric picture can often be confused with psychosis or drug intoxication [4].

BURDEN TO PATIENTS

There are a few online forums and support groups, like aiws.info, for sufferers of AIWS. Here, patients express feelings about how AIWS affects their daily lives. Patients who experience daily spells have a high disease burden and have noted a number of troublesome symptoms that severely affect their lives, such as: "seeing the world through a fish-eye lens is very difficult"; "I'm unable to judge distances accurately"; "I would often move clumsily or overcompensate". "Crossing the road feels dangerous, walking in a straight line is tricky, I run into door frames"; "sometimes it's impossible to tell if my window is just 1mm high, or a huge window miles away" [7]. Many patients have to alter their lives to work from home, and some have started to avoid socializing all together. When the frequency and duration of episodes starts to affect functioning, AIWS can be quite a debilitating disorder.

PROGNOSIS

In paediatrics, many of these cases resolve fully, but a number of patients can suffer with the syndrome for their entire lives [8]. In one retrospective chart review study of 48 patients, follow-up revealed that of all diagnosed patients with AIWS, 40% had no further AIWS events, 40% had continued to experience perceptual distortions, and 20% had more than one episode after diagnosis, but had been symptom-free for at least 6 months. The average interval between diagnosis and telephone contact by the research team was 6.5 years. In addition, 27% subsequently developed migraines, and one rare case had developed a seizure disorder [5]. This study also revealed that family history is present in 33% of patients [5].

ETIOLOGY

The average age of onset for AIWS was shown by one study (n=48) to be 8.1 years [9]. The etiology of AIWS is infection in 33% of cases, while head trauma and migraine each account for 6% of cases [9]. The remainder of cases did not have an identifiable cause [3, 9-10]. In various studies, Epstein Barr virus, and other febrile viral infections, such as varicella, coxsackievirus B1, and H1N1, have been implicated along with complex partial epilepsy [6,8,11]. The trigger of each case of AIWS is determined to be migraine when the patient's visual complaints occur in association with a headache, seizure if the visual complaints have an electroencephalogram (EEG) correlate on random or ambulatory monitoring, and infection if the visual complaint occurred within days of febrile illness [5]. Numerous studies have concluded that any young child presenting with AIWS should undergo examination for Epstein-Barr virus infection [9].

As well as the above listed etiologies, recent studies have demonstrated a link between AIWS and Lyme disease. A case report of a healthy 7-year-old boy showed 3 events of distorted perception, specifically a feeling of himself becoming smaller. He expressed that book print appeared further away. During a 36-hour EEG recording, none of these events displayed seizure activity, nor were these events accompanied by abnormal motor activity [11]. Lyme disease Western blot immunoglobulin M on day 10 of the illness tested positive in both serum and cerebrospinal fluid of this patient [11]. It has therefore been suggested that Lyme disease should be added to the clinical spectrum of people presenting with AIWS with an unknown cause [11].

In the adult world, depressive psychiatric illness is more commonly the cause of AIWS [6]. There have been cases of admitted psychiatric patients with diagnoses of major depressive episodes developing macropsia and metamorphosia; in these cases, both the depression and the AIWS were cured with 10 cycles of electroconvulsive therapy, with no signs of relapse [6].

PATHOPHYSIOLOGY

Though no precise pathophysiologic process has been determined, there have been a number of hypotheses; the majority believe that cerebral perfusion or edema is the mechanism that causes neuronal compromise. Studies of cerebral perfusion note that patients have decreased perfusion near the visual tract and visual cortex [9]. Another projection is that focal hypo-perfusion resulting in ischemia can alter central neurotransmitter efficacy [13]. Others believe that an acute inflammation in the brain parenchyma in conjunction with increases or decreases in perfusion can manifest with the clinical symptoms [14]. There is no clear consensus on the exact mechanism for this constellation of symptoms. It is likely different in each individual patient.

NEUROIMAGING

Since the initial publication in 1955, advances in medical technology have been made, allowing neuroimaging techniques to capture a number of episodes of AIWS. Imaging of the brain during episodes of AIWS has been predominantly in pediatric cases related to Epstein-Barr virus. Structural abnormalities can rarely be linked to AIWS when assessed by computed-tomography (CT) and magnetic resonance imaging (MRI) [1, 12], as the likely pathophysiology is due to a perfusion issue, which cannot be demonstrated by these two imaging modalities unless enhanced with contrast to more clearly demonstrate vascular changes. However, one study published in Japan has reported an abnormal MRI finding during an episode of AIWS. The MRI demonstrated "transient T2 prolongation and swelling of the cerebral cortex, especially at the bilateral temporal lobes, bilateral cin-

gulate gyrus, right upper frontal gyrus, bilateral caudate nucleus and bilateral putamen" [12]. Electroencephalography (EEG) and single-photon emission computed tomography (SPECT) scanning yield more useful results when trying to pinpoint the functional origin of these episodes because these scans can demonstrate dynamic changes. EEG can show only electrophysiologically abnormal lesions, while SPECT scan methods can portray perfusion and metabolism [7].

EEG

In a number of pediatric cases, aged 10–16, episodes of visual hallucinations (specifically micropsia) show changes at the parieto-occipital and occipital EEG electrodes [3,10]. These changes demonstrated "normal background alpha rhythms with a few generalized series of sharp, high voltage waves in the parieto-occipital region" [3,10]. Others showed "some overall slowing and irregularity of background activity in the occipital region" [13]. Overall, EEG has demonstrated non-specific signalling abnormalities when capturing an episode of AIWS. The occipital regions are often affected, but, to this date, an exact pathway has not been determined. Many of the EEG studies were followed up with MRI, CT or SPECT scanning studies.

SPECT SCANNING

Blood perfusion of brain tissue using SPECT scanning has reported hypo-perfusion in various areas of the brain. The right parietal and occipital cortices were affected in 9 of 13 cases in one study. In the same study, none of the 13 cases demonstrated left parietal hypo-perfusion [2]. Others have reported hypo-perfusion in the right frontal and right frontotemporal regions [14], and decreased cerebral perfusion near the visual tract and visual cortex in the studied patients [18].

It has been concluded that in most patients with AIWS, the EEG, CT and MRI are unable to determine any precise pathological areas [14]. However, neuroscientists are confident that structural lesions are not the cause of these hallucinations. It is a functional, hypo-perfused, lesion that contributes to the constellation of symptoms [3,18-19].

TREATMENT

Treatment of AIWS is largely dependent on the etiology. If a viral infection is manifesting itself within days of the hallucinations, symptomatic treatment is the only indicated therapy but may not resolve the symptoms [5]. When epilepsy is the cause, AIWS hallucinations resolve with treatment of the seizure [5]. In children who have primary AIWS, without an infectious trigger, repetitive transcranial magnetic stimulation (rTMS) at a frequency of 1Hz overlying Brodmann's area 40 was the prescribed treatment. In this case report, metamorphosia symptoms completely regressed for 8 months [20]. The authors of this article believe rTMS should be further investigated as a treatment option for AIWS.

DISCUSSION AND CONCLUSION

AIWS is a clinical entity that has been documented to be related to a number of etiologies. Migraine was the initial associated disorder, but with the development of new testing techniques and diagnoses, a number of infectious (varicella, Coxsackievirus, H1N1, and EBV), traumatic, and psychiatric (depression) causes have been found to be associated. AIWS is mainly a pediatric phenomenon, though there have been cases of comorbidity with depression in adults. Relatively new imaging studies have discovered areas of hypo-perfusion in various areas of the brain during episodes of AIWS; these affected areas are mainly occipital, but there are reports of frontal and temporal hypo-perfusion as well. Judging by the number of associated conditions, some neuroscientists believe that there may be a common neurotransmitter implicated in many of the cases, so further research may be needed to pinpoint its exact mechanism of action. As many as 40% of initial presentations will relapse throughout the lifetime of AIWS sufferers, so further investigations into pathophysiology may lead to treatment options for these patients. This article should help bring to light the lack of controlled research for this disorder, and the need for further research in the future.

This is a rare and interesting neuropsychiatric syndrome that presents with unique visual hallucinations. In the pediatric population, it may be a sign of undiagnosed viral infection that warrants further testing. Given that it affects mainly children, and that it is comorbid with diseases like Lyme disease, more awareness of AIWS and therefore earlier diagnosis could have an impact on the wellness of patients affected. Parents might take comments of distortion and discomfort from young children as part of an "active imagination", but it could indicate more serious neurological issues.

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Exploring the Interdisciplinary Roles of Dermatologists and Psychiatrists in the Management of Excoriation (Skin-picking) Disorder

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ABSTRACT

Excoriation disorder is a mental health disorder characterized by excessive picking of one's skin resulting in clinically significant functional impairment. Diagnosing this condition has been historically challenging due to the varied associated behaviours and lack of inclusion in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). As dermatologists and psychiatrists are the specialists most likely to encounter these individuals, this article discusses the new *DSM-5* criteria and outlines the approaches and treatment options for these specialists to optimally manage patients with excoriation disorder.

RÉSUMÉ

L'acné excoriée est un trouble de santé mentale caractérisé par le grattage et l'arrachage excessif de la peau qui mènent à une dysfonction clinique significative. Le diagnostic précis de cette condition demeure un défi lorsqu'on tient compte de la variété des comportements qui y sont associés et le manque d'inclusion des caractéristiques de ce problème de santé dans le *DSM* (*Manuel diagnostique et statistique des troubles mentaux*). Étant donné que les dermatologues et les psychiatres sont les spécialistes les plus susceptibles de traiter ces problèmes de santé mentale, cet article présente les nouveaux critères du *DSM-5* et décrit les grandes lignes cliniques, les approches nécessaires et les options de traitement afin que ces spécialistes puissent intervenir auprès des patients avec l'acné excoriée de façon optimale.

INTRODUCTION

Excoriation disorder (also called psychogenic excoriation, dermatillomania, pathologic or compulsive skin picking, neurotic excoriations, or acne excoriée) [1-2] is characterized by repetitive and compulsive picking of one's skin. This frequently causes tissue damage leading to infection, scarring, ulcers, and physical disfigurement [3]. Common locations include the face, arms and hands, but any area on the body can be targeted [4-5]. Typically, patients with this disorder start picking due to a dermatologic condition such as acne vulgaris, but eventually continue to pick even when the skin is normal [4,6]. While "mild" skin picking is fairly common in the general population, pathologic skin picking has been documented to have a prevalence of 2% in dermatology patients [7], 4% in college students [8] and 5.4% in the community [9]. The disorder is more common in females and has a bimodal age of onset, appearing more often in late childhood to early adolescence and between the ages of 30–45 years [10-11].

Excoriation disorder has recently received new diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorder* (*DSM*). Under the previous *DSM-IV-TR*, excoriation disorder was classified under 'impulse control disorders not elsewhere specified'. In accordance with an impulse control disorder, most patients report acting automatically and experiencing tension prior to picking and subsequent relief or pleasure afterwards [6]. However, under the new *DSM-5*, excoriation disorder is now classified under a new diagnostic group called 'obsessive compulsive and related disorders' to reflect the growing body of evidence that it is also ritualistic, ego-dystonic and highly co-morbid with obsessive compulsive disorder (OCD), body dysmorphic disorder (BDD), and trichotillomania (hair-pulling) [12]. To be diagnosed according to the *DSM-5* criteria, the individual must have made repeated attempts to decrease or stop the skin picking, which causes clinically significant distress or functional impairment, and the skin picking must not be better explained by symptoms of another mental disorder [12].

Although excoriation disorder is a psychiatric condition at its core, these patients are more frequently seen at dermatology clinics. Shame and embarrassment towards skin picking may prevent patients from seeing a psychiatrist. Thus, dermatologists should be aware of this condition in order to mediate a referral to psychiatry and potentially even provide initial treatment. This article will examine the roles of these two specialties in managing excoriation disorder and how interdisciplinary care in the form of combining different treatment approaches can improve the overall management of this distressing condition.

Keywords: Excoriation disorder; Psychogenic excoriation; Dermatillomania; Neurotic excoriations; Pathologic skin picking; Compulsive skin picking

Table 1. Fried and Fried's 10 diagnostic categories of pathologic skin pickers [14].

Category of Pickers	Clinical symptoms	Recommended treatment
Angry	Underlying anger often expressed through sarcasm and passive aggressiveness (i.e., skin picking)	Anger management techniques with concomitant use of SSRIs or anxiolytic medications
Anxious/depressed	Feelings of tension, fatigue, or sadness that are transiently decreased with skin picking	SSRIs or TCAs for depressive symptoms; benzodiazepines for acute anxiety
Body dysmorphic	Preoccupation with a minimal or imagined defect in appearance	SSRIs and adjunctive psychotherapy
Borderline	Significant emotional instability, chronic feelings of emptiness, boredom, unhappiness, poor judgement, limited impulse control	Long-term psychotherapy; anxiolytic and antipsychotic medications during acute episodes; very difficult to treat
Delusional	Rigidly held belief that is not based in reality (e.g., skin infestation or skin defect)	Pimozide, olanzapine, risperidone; standard antipsychotic medication and psychiatric hospitalization for more generalized symptoms
Guilty	Fearful, guilt-ridden individuals picks as a self-punitive measure to rid oneself of impurity or imperfection	Proper education about the nature of the condition; gentle reassurance and humour
Habit	Picks to reduce underlying anxiety without any associated obsessions or compulsive behaviours	Behaviour modification, hypnosis, standard dermatologic treatments
Narcissistic	Inability to accept imperfection, spend hours studying themselves in a mirror; pick as an attempt to rid themselves of "an intolerable stain on an otherwise perfect image"	Emotional support and reality-based objective assessments of the imperfections; very difficult to treat
Obsessive compulsive	Intrusive, obsessive thoughts accompanied by compulsive, ritualistic behaviours	SSRIs with concomitant CBT (exposure and ritual response prevention)
Organic	Picks in response to an itch or cutaneous dysesthesia	Treat underlying condition

SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; CBT: cognitive behavioural therapy

THE DERMATOLOGIST

It is challenging for dermatologists to manage those who pick their skin. Patients are often ashamed and embarrassed of their behaviours and attempt to downplay the severity of their condition when interviewed [13]. These patients are also more likely to have co-morbid psychiatric conditions, which lie outside the expertise of the dermatologist. Prior to the inclusion of excoriation disorder in the *DSM*, the lack of any organic cause for skin picking led patients to be inappropriately labelled as "crazy pickers and scratchers" [14]. This inevitably made it difficult for the dermatologist to determine the underlying problem or to formulate an adequate treatment plan. Now with the classification of excoriation disorder in the *DSM-5*, objective evidence of its legitimacy as a medical disorder exists. The goal for the dermatologist then is to develop an approach for these patients during the first encounter and to initiate the therapeutic process.

Fortunately, there are several articles in the literature that provide guidance for dermatologists managing patients with excoriation disorder. Fried described a "three-level approach" comprising of a lesional level, emotional level and cognitive level [15]. At the lesional level, traditional dermatologic treatments such as occlusion, topical or intralesional corticosteroids, mentholated compounds, tar preparations, emollients, and cryosurgery can be helpful in both treating any skin lesions or complications and deterring patients from engaging in their picking behaviours [14-15].

The emotional level utilizes a "listen, ask, tell" approach to understand the patient's mental status [15]. By *listening* to the patient, it will allow the dermatologist to get a better understanding of *why* the individual picks their skin. This information will then allow for determination of other possible co-morbid psychiatric conditions (e.g., anxiety, depression) that may explain their pathologic behaviour [15]. At this point a differential diagnosis can be created and the dermatologist may proceed to the *ask* phase. Here, a series of focused questions can determine the severity of the emotional symptoms and whether there is a negative impact on daily functioning [15]. This will determine if there

Table 2. *DSM-5* criteria for excoriation (skin-picking) disorder under the Obsessive-Compulsive and Related Disorders category [12].

- Recurrent skin picking resulting in skin lesions.
- Repeated attempts to decrease or stop skin picking.
- The skin picking causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The skin picking is not attributable to the physiological effects of a substance or another medical condition.
- The skin picking is not better explained by symptoms of another mental disorder.

is a clinically significant disorder that needs to be treated. Additionally, it is important to screen for risk of suicide. Lastly, it is important to *tell* the patient that their struggle with skin picking is very real and that treatment options are available and effective [15]. The aim of the "listen, ask, tell" approach is to create a strong therapeutic alliance, providing both emotional support and a sense of hope for the patient.

The cognitive level attempts to put patients back in control of their own body and mind [15]. These individuals commonly believe that their skin picking is entirely their fault, a pervasive belief often stemming from underlying guilt. An effective strategy to shift the blame away from the patient is to provide education about the condition with particular emphasis on the biologic component to their behaviours [15]. The patient will be more willing to accept this type of explanation compared to a psychogenic cause and should be more eager to seek pharmacological treatment. As well, this level explores the opportunity for the dermatologist to propose alternative behaviours to skin picking, such as squeezing their fists or practising deep breathing techniques when patients feel the urge to scratch [15]. This shows the patient that the physician is aware of their urges and can provide meaningful solutions instead of simply saying, "you should stop picking" [14-15].

This "three-level approach", based on the biopsychosocial model of disease, provides dermatologists with the appropriate tools to initially manage excoriation disorder. Addressing the lesional, emotional and cognitive aspects of this complex condition will hopefully create a comprehensive assessment and a strong therapeutic alliance with the patient. Fried's approach has been utilized in numerous articles since its original publication and continues to be one of the few non-pharmacologic approaches recommended for dermatologists in the literature [6,16].

In a more recent article, Fried and Fried expanded on the original approach to divide skin pickers into ten categories based on emotional states such as anxious/depressed or obsessive compulsive (Table 1) [14]. Conceptualizing patients into a particular subgroup provides a framework for non-psychiatrists to tailor specific treatments [14]. However, this strategy relies on the dermatologist to become comfortable prescribing psychiatric medications. Therefore, it is suggested that dermatologists become familiar with starting one or two agents such as a selective serotonin reuptake inhibitor (SSRI) or benzodiazepine at a low dose [14]. Of note, the American Academy of Dermatology Task Force on Psychocutaneous Medicine endorses these medications and supports their use whenever necessary [14].

Despite his or her best efforts, the patient with excoriation disorder may have to be referred for psychiatric evaluation and treatment. It is important that the dermatologist be aware of the psychiatric services involved in their community and, if available, psychiatrists specializing in psychocutaneous disorders. This knowledge, along with expressing empathy and a sense of hope, will encourage these individuals to seek appropriate treatment and feel validated in their journey towards managing their condition.

THE PSYCHIATRIST

It is important to first understand that patients with excoriation disorder rarely seek treatment. In a study of 31 patients with this condition, 45% actively sought treatment, and of that group only 19% sought dermatologic treatment despite obvious infections or visible craters [13]. While this may be due to shame or the perception that the condition is untreatable, it may also stem from the fact that until recently, it was not recognized as a psychiatric disorder with its own criteria for diagnosis. Excoriation disorder is now included separately in the *DSM-5* as an obsessive compulsive and related disorder, and psychiatrists should expect to see more patients with this disorder referred to their practice as awareness of this condition increases among family physicians and dermatologists. The role of the psychiatrist in the management of these patients will involve assessing for the condition and any other co-morbid disorders, and providing treatment in the form of pharmacotherapy and psychotherapy.

Table 2 shows the *DSM-5* diagnostic criteria for excoriation (skin-picking) disorder under the obsessive compulsive and related disorders category [12]. A key criterion is that symptoms must not be better explained by another mental disorder. Excoriation disorder is commonly misdiagnosed as OCD or BDD due to the overlap of features [17]. These conditions are now under the same category in the *DSM-5*; thus, psychiatrists should be aware of the key differences between the disorders in order to make the appropriate diagnosis. These differences include the presence of an obsession (intrusive thoughts that cause significant

anxiety) and/or compulsions (a repetitive behaviour that is performed in response to the obsession) as seen with OCD, or the presence of repetitive behaviours in response to preoccupations with an imagined defect in appearance as seen with BDD [12]. As well, there are many other co-morbid mental disorders that may require formal diagnosis. Certain personality disorders such as obsessive-compulsive personality disorder and borderline personality disorder are often associated in these patients, occurring in 71% of patients in one study [13]. Mood and anxiety disorders are also highly prevalent, ranging from 48–68% and 41–65% of these patients, respectively [13]. The proper diagnosis of excoriation disorder and other mental disorders will prove helpful for both the patient and the psychiatrist, with the latter being more equipped to formulate appropriate treatment plans.

Various studies have shown the effectiveness of common psychiatric medications for excoriation disorder. SSRIs have been studied the most due to their traditional use in OCD [3]. In particular, fluoxetine has been shown to be significantly more effective than placebo in reducing skin picking behaviours in two randomized controlled trials (RCTs) [18-19]. These results were seen within 2 to 4 weeks of treatment at a daily dose of 20mg or 40mg, reaching as high as 80mg in more clinically resistant patients [18-19]. Other SSRIs that have been examined in open label studies include fluvoxamine [20], sertraline [21] and escitalopram [22], which have all demonstrated some effectiveness in improving skin excoriations. The anti-epileptic drug lamotrigine has also been shown to be effective in an open-label trial [23]. Although further RCTs of other pharmacologic agents may be beneficial, numerous options are currently available with promising results. Treatment of other co-morbid disorders must also be considered to manage the patient beyond their skin excoriations.

Psychotherapy, in particular cognitive behavioural therapy (CBT), has been less studied in the treatment of excoriation disorder. In the literature, there is only one RCT that studied the habit reversal technique [24]. This individualized therapy involves numerous steps: 1) response description (patient describes and demonstrates the picking behaviour); 2) early warning (patient is taught to notice hand movements towards areas of excoriation); 3) situation awareness training (patient becomes aware of situations or stressors associated with the urge to pick); 4) habit inconvenience review (patient is educated about the negative consequences of their behaviour); 5) competing response practice (patient learns exercises that are incompatible with their picking such as clenching their fists); 6) generalization training (patient learns to perform these exercises without disrupting daily activities); and 7) symbolic rehearsal (patient practices these exercises in front of the clinician) [24]. Patients practicing the habit reversal technique experienced a decrease in the urge to pick and a reduction in the amount of skin picking behaviours by 77% after one month compared to those who did not receive this therapy (16%) [24]. These results were also sustained at a 3- to 4-month follow-up, maintaining a decrease of 77% versus 27% [24]. This technique shows promise and may provide an alternate treatment option with sustainable results, although further studies are required before it becomes more widely employed.

CONCLUSION

Excoriation (skin-picking) disorder is a legitimate and prevalent psychiatric disorder in society. With its inclusion in the *DSM-5*, diagnosing and treating this condition has become clearer and more objective for any health care professional involved. Both dermatologists and psychiatrists have unique roles and approaches in managing these patients, and when combined as effective interdisciplinary care, yield optimal therapeutic outcomes. As further treatment options are discovered and more non-psychiatrists become comfortable assessing those with skin excoriations, patients with this condition will be able to receive appropriate care and regain control of their mind and skin.

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The Treatment of Sleep Disturbances in the PTSD Patient

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ABSTRACT

Introduction: Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder that develops in 25-30% of individuals exposed to a traumatic event. Sleep disturbances (i.e. nightmares and restless sleep) are common symptoms of PTSD, affecting approximately 70-87% of patients. Studies have shown that improving sleep disturbances improves disease severity and therapeutic outcomes. Although selective serotonin reuptake inhibitors (SSRIs) are considered first-line therapies for PTSD, sleep disturbances often remain refractory and require additional therapies for their resolution. **Discussion**: Pharmacological and non-pharmacological modalities are available for the treatment of PTSD sleep disturbances. Although cognitive behavioural therapy (CBT) is well supported to alleviate sleep disturbances, studies have shown patient drop-out by the time of long-term follow-up, suggesting CBT may be viewed as challenging to complete. Under these circumstances, the use of pharmacological therapies can be considered independently or in adjunct. Conflicting evidence surrounds the benefit of SSRIs in the treatment of sleep disturbances. Moreover, there is limited research surrounding the use of trazodone in this patient population. Benzodiazepines are poorly supported and the side effect profile of atypical antipsychotics limits their routine use. Prazosin holds the most promise and is the most well supported pharmacological agent in the literature. Nabilone, although a controversial agent, also holds promise of benefit. **Conclusions**: Several pharmacological and behavioural therapies are available to treat PTSD sleep disturbances. However, the evidence supporting any of these modalities as being superior is limited. Larger, randomized controlled trials are needed to gain a greater understanding of efficacious therapies available to address this clinical problem.

RÉSUMÉ

Introduction: Le trouble de stress post-traumatique (TSPT) s'avère un trouble d'anxiété qui se développe chez 25 à 30% des individus qui sont exposés à des évènements traumatiques. Les troubles du sommeil tels que les cauchemars et l'insomnie sont des symptômes typiques du TSPT qui affectent entre 70 et 87% des patients. Plusieurs études démontrent qu'une amélioration des troubles du sommeil peut diminuer la sévérité du TSPT et augmenter l'effet thérapeutique. Malgré le fait que les inhibiteurs sélectifs de la recapture de sérotonine (ISRS) demeurent la première ligne de traitement pour le TSPT, les troubles du sommeil demeurent un symptôme important et des thérapies additionnelles sont nécessaires pour leur résolution. **Discussion:** Les modalités pharmacologiques et non pharmacologiques sont disponibles pour le traitement des problèmes du sommeil associés au TSPT. Malgré le fait que la thérapie cognitivo comportementale (TCC) a démontré des effets positifs pour minimiser les symptômes de troubles du sommeil, les études démontrent que les patients ont de la difficulté à respecter les critères de l'étude lorsqu'ils sont évalués au suivi, suggérant que la thérapie TCC est difficile à compléter. L'utilisation de la pharmacothérapie peut se faire de façon indépendante ou combinée à la TCC. Il y a des preuves contradictoires au sujet des bénéfices associés aux ISRS dans le traitement des troubles du sommeil. De plus, il y a des preuves limitées au sujet de l'utilisation de trazodone dans cette population cible de patients. Les benzodiazépines ne sont pas très bien tolérées par les patients à cause de leurs effets secondaires, ce qui limite leur utilisation. La prazosine donne de bons résultats et demeure l'agent pharmacologique le plus recommandé dans la littérature scientifique. Le nabilone, toutefois, est un agent controversé qui semble démontrer beaucoup de bienfaits potentiels. **Conclusion:** Plusieurs thérapies pharmacologiques et comportementales sont accessibles pour aider aux problèmes du sommeil reliés au TSPT. Toutefois, les preuves des bienfaits de ces modalités de traitement sont limitées. Des résultats d'essais aléatoires contrôlés à plus grande échelle sont nécessaires afin de mieux comprendre l'efficacité des thérapies qui sont disponibles dans le but d'optimiser le soin des patients atteints de troubles du sommeil.

CASE EXAMPLE

Mr. X is a 51-year-old male with a history of post-traumatic stress disorder (PTSD) who is currently admitted to hospital following an overdose on Seroquel (atypical antipsychotic medication). Mr. X was previously hit by an OC Transpo bus, which required amputation of his left leg. Since the accident, Mr. X reports vivid and distressing night terrors ranging anywhere from three to seven times per week where he re-experiences the traumatic event. He also reports difficulty falling asleep and staying asleep as a result of this distress. Mr. X has taken a leave of absence from work and his wife has become increasingly concerned regarding his de-

Keywords: Post-traumatic stress disorder; Sleep disturbances

pressive mood. She finds him to be increasingly withdrawn, not engaging in interests he previously enjoyed as well as very anxious and 'on-edge'. This is not the first time Mr. X has overdosed on Seroquel. He previously developed neuroleptic malignant syndrome (a rare and life-threatening side effect of neuroleptic medications, such as Seroquel, characterized by fever, muscular rigidity, altered mental status and autonomic dysfunction) following another overdose leading to an ICU admission a few months prior. Given his history of Seroquel misuse and his history of distressing PTSD symptoms (sleep disturbances, cognitive and mood disturbances), it was obvious to the team that Mr. X needed to switch to a new medication to help better manage his symptoms and improve his quality of sleep. This raised the clinical question, "What other options are available to treat PTSD sleep disturbances, particularly nightmares"?

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a chronic and debilitating anxiety disorder that affects up to 6.8% of the United States population [3]. As defined by the *DSM-V* (Fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*), PTSD is an anxiety disorder that may develop after an individual is exposed to a traumatic event. Reports show that anywhere between 25-30% of individuals who have experienced a traumatic event go on to develop PTSD [8]. Although the exact etiology of PTSD is not fully understood, it is thought that patients with a personal or family history of major depressive disorder or anxiety disorders may be at risk for symptom development [8]. The *DSM-V* groups PTSD symptoms into four categories: intrusive/re-experiencing, avoidance, negative alterations in cognition and mood, and hyper-arousal [3]. Within these categories sleep disturbances can be grouped as hyper-arousal and/or intrusive symptoms.

Sleep disturbances are a fairly common and rather disturbing symptom of PTSD, affecting approximately 70-87% of the patient population [1]. Improving sleep quality and reducing the occurrence of nightmares has been shown to improve both disease severity and therapeutic outcomes of PTSD [2]. Sleep deprivation that occurs secondary to sleep disturbances (i.e. chronic nightmares) has been shown to negatively impact many areas of functioning including, but not limited to, memory, learning, mood, and attention [3]. Most importantly, sleep deprivation is associated with poor psychiatric outcomes such as worsening of depressive symptoms and thoughts of suicide [3]. Sleep disturbances in patients with PTSD can have variable manifestations including: nightmares, anxiety-provoking dreams, frequent awakenings, difficulty falling asleep (sleep latency), difficulty staying asleep (sleep fragmentation), decreased total sleep time, and restless sleep. Selective serotonin reuptake inhibitors (SSRIs) are well supported in the literature to improve many of the symptoms of PTSD and are considered first-line therapy for PTSD, regardless of the symptom that is most prominent [1,2,3]. However, although treatment for PTSD can lead to improved sleep in some patients, often these sleep disturbances are refractory and require additional treatment for their resolution [1,2,3].

NON-PHARMACOLOGICAL THERAPIES

COGNITIVE BEHAVIOURAL THERAPY (CBT)

The most effective form of non-pharmacological therapy shown in the literature to improve sleep disturbances in the PTSD patient is cognitive behavioural therapy (CBT). CBT is an evidence-based psychotherapy whereby a therapist helps the patient identify cognitive distortions and maladaptive beliefs. The therapist then uses behavioural therapy to facilitate symptom reduction via thought exercises and improved overall functioning. CBT incorporates education, coping skills training, stress management and relaxation exercises into its therapy. Its success hinges on applying the cognitive and behavioural skills acquired in therapy in the outside setting. More specifically, the subtype of CBT known as Image Rehearsal Therapy (IRT) is well supported as an effective non-pharmacological option for sleep disorders associated with PTSD. IRT involves having the patient recall the nightmare, write it down, and then change an aspect of the nightmare into something more positive. The patient then rehearses the positive change while awake so that they can displace the original nightmare when it reoccurs. IRT has been proven to reduce the number of nightmares per week, improve sleep quality and decrease mean PTSD severity scores (Clinical Administered PTSD Scale [CAPS]) [3].

Although the Veterans Association and Department of Defense consider CBT-based treatments as first-line therapies [3], these strategies are often difficult to implement. This is especially true in a hospitalized patient who is admitted for a short period of time, because the long-term use of CBT is a key contributor to its success. Moreover, several studies examining CBT use in PTSD patients have shown increasing drop out rates and loss to long-term follow-up (i.e. one study showed only 114 of 168 participants followed up at the three and six month mark). This data suggests that perhaps CBT may be viewed as challenging or difficult to complete by patients [3]. Pharmacological modalities are often beneficial under these circumstances and have been shown to be effective choices when used both independently and in combination with CBT [3].

PHARMACOLOGICAL THERAPIES

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

SSRIs are typically the mainstay treatment for PTSD and are considered first-line therapies, with sertraline, paroxetine, and fluox-

etine carrying FDA indication for treatment of PTSD. However, the evidence regarding efficacy of SSRIs in treating sleep disturbances is inconsistent. Some studies have shown that SSRIs can lead to significant improvements in nightmares [1], sleep onset latency, total sleep time, and wake after sleep onset. In contrast, other studies report that SSRIs decrease total sleep time and increase daytime sleepiness [3]. Placebo-controlled trials have shown paroxetine to be effective in managing sleep disturbances [7]. However, fluvoxamine was ineffective in one study but effective in another in alleviating sleep disturbances [7]. Moreover, in a large randomized control trial, sertraline did not improve sleep quality and insomnia was a frequent side effect noted in 35% of the treatment group [7]. Given the conflicting evidence, SSRIs may have no impact or only minimally improve sleep disturbances and thus this class of medications needs to be further explored in this context [1].

TRAZODONE

Although the evidence supporting the use of trazodone for PTSD-related sleep disturbances is also limited within literature, the results have been positive. One study found that more than 70% of PTSD patients who completed an author-designed questionnaire reported improvement in sleep onset, maintenance, and nightmares with the use of trazodone [1,9, 15]. Additionally, two open-label studies with trazodone noted that sleep complaints globally improved, particularly nightmares and insomnia [7, 15, 16]. Further insight and studies examining trazodone use for PTSD-related sleep disturbances would be beneficial when considering this medication as a treatment option as it is mainly prescribed off-label for PTSD patients experiencing sleep disturbances. As well, potential side effects need to be appropriately advised to patients as one study noted a higher than expected occurrence of priapism with trazodone use [16].

BENZODIAZEPINES

Benzodiazepines are typically avoided in the PTSD patient despite being the mainstay treatment for insomnia in the general population. Substance abuse is a common co-morbidity affecting this patient population [1]. As a result, benzodiazepines should be used with caution to reduce the risk of dependence. Additionally, benzodiazepines may worsen sleep apnea or impair cognition [1,10]. Studies have shown that benzodiazepines have limited effect on improving PTSD-related sleep disturbances. For example, a single-blind, placebo controlled, crossover trial showed that with 1-2 mg of clonazepam there were improvements in sleep initiation and maintenance, but no reduction in nightmare intensity in PTSD patients [3, 13,14]. As a result, the study concluded that clonazepam was an ineffective agent for the treatment of PTSD-related sleep disturbances. Other studies have shown similar inefficacy with use of benzodiazepines in the PTSD patient population [3, 13, 14], further supporting their limited role in the treatment of PTSD-related sleep disturbances.

ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics including Seroquel, olanzapine, and risperidone, like many of the aforementioned medications are not well-supported in the literature, but are prescribed off-label to treat sleep disturbances in the PTSD patient [1, 3]. Small studies and case series have shown improvements in sleep disturbances with low doses of these medications such as, decreased sleep disturbances, reduced occurrence of nightmares and flashbacks, and decreased hyper-arousal [1, 11, 12]. One case-based series showed olanzapine to be effective for treatment-resistant nightmares [12]. Although there may be potential benefits to the use of atypical antipsychotic medications for treatment of PTSD-related sleep disturbances, their side effect profile (i.e. tardive dyskinesia, weight gain) limits their routine use [1]. As a result, they should typically be reserved for patients who have co-morbid psychosis, agitation, and aggressive behavior.

PRAZOSIN

Prazosin is the pharmacological agent with the most evidence and support in the literature for the treatment of sleep disturbances, such as reducing nightmares and improving overall sleep quality in the PTSD patient. Prazosin indicated as an anti-hypertensive agent, is an alpha-1-adrenergic receptor antagonist that is highly lipophilic and readily crosses the blood-brain-barrier. Within the central nervous system, stimulation of alpha-1-adrenergic receptors is believed to contribute to the generation of PTSD-related nightmares [1]. Moreover, PTSD nightmares appear to arise from light sleep and/or disrupted REM sleep. Studies have shown that prazosin reduces light sleep and normalizes REM sleep [4], thereby reducing nightmares. Miller, LJ showed that patients in the prazosin group reported more than a 50% reduction in recurring distressing dreams in comparison to the placebo group who reported only a 15% reduction [1]. In addition to its efficacy, prazosin is also well tolerated and side effects such as orthostatic hypotension and dizziness have been reported as minimal [4]. Several studies have shown that with prazosin use significant improvements were achieved in a short duration (within weeks) such as, improvement in trauma nightmares and fewer distressed awakenings [1,5]. Moreover, one study compared prazosin to Seroquel, and it was found that participants were more likely to continue using prazosin over Seroquel due to fewer side effects and better long-term effectiveness [5]. Prazosin is generally started at an initial dose of 1 mg, so that hypotension can be monitored after the first dose. Sudden discontinuation of prazosin could lead to rebound hypertension and patients should be cautioned accordingly. The dose is then gradually titrated up and increased to maintenance levels of 2-10 mg [5]. It is unclear if higher doses

of prazosin would serve to be beneficial in treatment-resistant patients. The current literature positively supports this agent as a treatment modality for problematic, recurrent nightmares in patients with PTSD, with the additional benefit of rapid effectiveness and minimal adverse effects.

NABILONE

One final drug to review is nabilone. It is currently controversial if the use of this endocannabinoid receptor agonist would serve as an effective agent for the treatment of PTSD-related sleep disturbances. The endocannabinoid system appears to play a role in alleviating anxiety and symptoms related to PTSD, as attributed by anecdotal reports of symptom relief through self-medication with cannabis. One study showed that a group of patients with treatment-resistant nightmares (not alleviated with SSRIs or hypnotics), benefited from adjunct nabilone therapy [6]. These patients experienced either a cessation of nightmares or a significant reduction in nightmare intensity. More specifically, this study reported that 72% of participants experienced either a total cessation or a lessening of the severity of nightmares when taking an average dose of 0.5 mg of nabilone one hour before bedtime. It is suggested that a starting dose of 0.25 mg should be initiated and then titrated up as tolerated. Nabilione certainly holds promise of benefiting patients who are refractory to other pharmacotherapies, and although it is a controversial treatment option, further studies and randomized controlled trials will provide further insight into nabilone's efficacy for the treatment of PTSD-related sleep disturbances, particularly nightmares [6].

CONCLUSIONS

In conclusion, several pharmacological options and behavioral modalities are available for the treatment of sleep disturbances and nightmares in the PTSD patient. However, the evidence supporting any of these therapies as being superior to one another is limited and there is no unified agreement amongst the medical community as to which agent is the most efficacious and which agent(s) should be considered as first-line therapy. Larger, randomized controlled trials are needed to further examine this topic in order to gain a greater understanding of efficacious treatment options. Although prazosin currently holds promise of filling the void, other medications such as nabilone, trazodone, benzodiazepines, antitypical antipsychotics, and SSRIs need to be further studied and compared to one another.

Sleep disturbances and nightmares are significant and relevant problems affecting the vast majority of PTSD patients. As exemplified by the case of Mr. X, treatment of nightmares and sleep disturbances holds the potential to improve therapeutic outcomes, such as improving underlying depressive symptoms and reducing the risk of suicide. Further insight and research holds the promise of gaining a greater understanding of efficacious modalities that can be used to treat a clinical problem that does not currently have a clear-cut answer.

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L'entrainement, c'est ma vie!

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RÉSUMÉ

Nul ne peut ignorer que les centres d'entrainement physique sont plus que jamais fréquentés. Particulièrement populaire, l'entrainement prend désormais une grande place dans la vie de plusieurs. Habitude saine, certes, mais jusqu'à une certaine limite. Cette limite se trace par ailleurs au moment où l'un des résultats de l'entrainement musculaire, soit une apparence corporelle musclée, deviennent l'unique préoccupation. La dysmorphie musculaire, ou communément appelée la « bigorexie », est le nom que l'on donne à ce trouble psychologique. Il décrit l'obsession compulsive de l'entrainement et des muscles. Cette maladie étant complexe, de raisons variées et d'importantes conséquences et complications s'y rattachent.

ABSTRACT

No one can ignore that physical training centers are more popular than ever. With its increased popularity, training now takes an important place in the lives of many. Although certainly a healthy habit, there are limits. These limits become evident when one of the results of strength training, a muscular body appearance, becomes one's only concern. Muscle dysmorphia, or commonly called "bigorexia," is the name we give to this psychological disorder. Bigorexia is a compulsive obsession with training and a muscular build. This disease is complex, for varied reasons and related to important consequences and complications.

BEAUTÉ, PERCEPTIONS & EXIGENCES

J'essaie de rester en forme. Un peu comme la majorité de nous tous, je cherche un équilibre parfait entre travail, étude, famille et sport. J'ai bien précisé équilibre. Il est parfois difficile de trouver un juste milieu dans ce monde occidental où les demandes de performance s'accumulent dans tous les domaines et où nous vivons avec le stress au quotidien. Lorsque je suis au gym, il n'est pas rare que j'entends des femmes parler d'exercice pour avoir des fesses musclées ou encore voir de jeunes hommes contempler leurs biceps devant le miroir des poids libres. Ensuite, en ouvrant Internet, il y a un bombardement de photos d'hommes plus musclés que jamais et de femmes au derrière proéminent portant de petites culottes serrées. Suite à ces expériences personnelles, il me semble qu'aujourd'hui, pour être beau, on nous laisse sous-entendre qu'il faut être musclé, qu'il faut être « fit ». Comme quoi on ne peut plus se contenter d'avoir un poids santé et pratiquer des sports pour le plaisir; il semble maintenant impératif de suivre un programme d'entraînement intensif au gym, peu importe qu'on soit athlète ou non. Il n'y a pas si longtemps, l'accent était mis sur les femmes trop minces et l'on dénonçait les médias et la société de mener nos jeunes, femmes particulièrement, vers l'anorexie. Désormais, cette maigreur ultime se transforme vers une musculature exagérée, démesurée. Mes impressions me mènent à me demander si l'on ne va pas d'un extrême à l'autre ? Évidemment, une vie active par l'exercice et le sport fait partie des saines habitudes de vie pour rester en santé et je suis la première à le promouvoir. Je reviens cependant sur ma première précision : tout repose dans l'équilibre.

DYSMORPHIE MUSCULAIRE

Récemment comprise et expliquée, la dysmorphie musculaire, communément appelée la bigorexie, est une psychopathologie menant à une obsession compulsive de l'entrainement et de l'apparence physique qui en résulte. Elle est une sous-catégorie des troubles de dysmorphie corporelle, avec l'anorexie [1]. On la surnomme d'ailleurs l'anorexie inverse. Les personnes atteintes de ce trouble ont une perception brouillée de leur apparence physique. Ne se rendant pas compte de leur véritable masse musculaire, ils tentent toujours de se surpasser afin de l'augmenter constamment.

Plusieurs peuvent se sentir concernés et insultés par ce phénomène, mentionnant qu'il ne fait que critiquer négativement le dévouement à un sport. Il est donc important de comprendre les particularités de cette maladie mentale et ses effets néfastes sur la santé physique, psychologique, sociale et émotionnelle. D'abord, le terme « dysmorphie » est spécifiquement choisi afin de décrire une déformation des muscles. En analogie avec l'alcoolisme, un autre trouble de dépendance, les personnes atteintes de bigorexie n'arrêteront pas leur obsession malgré la

Keywords: Dysmorphie musculaire, Bigorexie, Exercice, Psychopathologie, Muscles, Activités physique, Culturisme, Gym, Dépendance

Body Dysmorphic Disorder*

1. Preoccupation with an imagined defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive.
2. The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
3. The preoccupation is not better accounted for by another mental disorder (eg, dissatisfaction with body shape and size in anorexia nervosa).

Muscle Dysmorphia

1. The individual is obsessed with the belief that his or her body should be more lean and muscular. Significant amounts of time devoted to weight lifting and fixation on one's diet are common.[6,7,18–20]
2. At least 2 of the following 4 criteria should be met[20]:
   a. The uncontrollable focus on pursuing the usual training regimen causes the person to miss out on career, social, and other activities.
   b. Circumstances involving body exposure are preferably avoided; if avoidance is not possible, significant unease and worry occur.[19]
   c. Performance in the work and social arenas is affected by the presumed body deficiencies.
   d. The potentially detrimental effects of the training regimen fail to discourage the individual from pursuing hazardous practices.[21]
3. Unlike anorexia nervosa, in which the person is concerned about being overweight, or other types of body dysmorphic disorder, in which the concern is with other physical aspects, the individual with muscle dysmorphia believes that his or her body is insufficiently small or muscular.[7,18,20]

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Figure 1. Critères de diagnostic de la dysmorphie musculaire selon de DSC, tiré de la référence [1].

présence éminente de danger pour leur corps et leur santé. Au même titre que l'alcoolique continuera à consommer malgré les avertissements de son médecin face à la mauvaise condition de son foie, le bigorexique continuera de fréquenter le gymnase pour augmenter sa masse musculaire même si son physiothérapeute l'informe d'une blessure musculaire nécessitant le repos ou un changement dans son entrainement.

CAUSES

Les causes de cette maladie sont multiples et mal définies. Plusieurs croient que c'est en effet la pression des médias et les critères de société qui poussent les personnes à modifier leurs corps se rendant jusqu'à la dysmorphie musculaire, alors que d'autres affirment que c'est plutôt des causes psychologiques et des facteurs prédisposant de chaque individu qui les ont menées vers ce trouble [1]. Plusieurs études ont également montré que les personnes atteintes de bigorexie avaient une piètre estime de leur image corporelle générale et se considèrent en moins bonne santé que ceux qui suivaient également un programme d'entrainement, mais sans présenter les symptômes de dysmorphie musculaire [2]. Les personnes atteintes de bigorexie sont moins satisfaits de leur image corporelle et présentent une beaucoup plus faible estime de soi [3]. Cependant, je reste sceptique à comprendre si une faible estime personnelle est à la base de la maladie ou si elle est une conséquence de la dysmorphie musculaire. D'ailleurs, un article publié en 2008 explique que ceux qui souffrent de dysmorphie musculaire sont en effet plus sensibles aux critiques et présentent une pauvre estime personnelle, et que ce serait, par conséquent, ces caractéristiques qui les rendent plus vulnérables aux pressions de la société moderne, et donc, plus à risque de développer la maladie [4]. Néanmoins, ce trouble d'étiologie qu'on pourrait jusqu'à présent qualifier d'inconnue est présent dans notre société actuelle. Une définition claire de la maladie reste nécessaire afin qu'on puisse bien diagnostiquer et prendre en charge ceux qui en souffrent. La figure 1, tirée de l'article « Recognition and Treatment of Muscle Dysmorphia and Related Body Image Disorders » de Gray, Leone et Sedory, explique comment le *DSM* (*Diagnostic and Statistical Manual of Mental Disorders*) établie les critères de diagnostics de la dysmorphie musculaire.

De façon générale, les critères de diagnostics supposent que les personnes atteintes de bigorexie ne se trouvent jamais assez musclées et ont une obsession sur leur apparence physique et une crainte mortelle de la prise de poids. Elles passent un temps considérable à l'entrainement, affectant celui prévu pour le travail, les amis et loisirs. Aussi, les autres activités sociales sont affectées par la déformation de leurs muscles, et les connaissances des dangers sur leur corps et leur santé ne les découragent pas à arrêter leurs exercices.

SEULEMENT LES HOMMES?

Les maladies peuvent en effet paraître sexistes. L'anorexie et la boulimie sont plus souvent associées aux femmes qui désirent un corps mince alors que la bigorexie pourrait s'apparenter à la masculinité des hommes et leur besoin d'être musclé. Quoique ce trouble touche majoritairement la gent masculine, la bigorexie ne leur est pas exclusive. Peu d'études présentent des résultats sur les femmes et la bigorexie. Néanmoins, des cas de cette maladie ont déjà été diagnostiqués sur des femmes et selon une étude publiée en 2013, les femmes culturistes sont autant à risque d'avoir une dépendance à l'exercice et de développer la dysmorphie musculaire que les hommes [5]. Bien à comprendre que nul n'est à l'abri de maladies psychologiques.

COMPLICATIONS

Outre les symptômes présentés ci-dessus, la dysmorphie mus-

culaire peut mener à d'autres complications. Notamment, on voit souvent des comorbidités se développer en même temps, autant sur le plan physiologique que psychologique. Principalement au niveau psychologique, on voit l'abus et la dépendance de drogue, dont le stéroïde qui est très populaire, survenir ainsi que l'entament de régimes nocifs [1,6]. Évidemment, nous savons les conséquences générales que les drogues peuvent avoir sur la dégénérescence du corps et comment les régimes et diètes mal formulés peuvent mener à des excès et déficiences de certains macro et micro nutriments ainsi que les effets négatifs qui peuvent en résulter. Une étude effectuée en 2005 a également montré que les personnes atteintes de dysmorphie musculaire avaient une qualité de vie généralement plus faible et qu'ils étaient beaucoup plus propices à faire des tentatives de suicide. [6] Bref, la dysmorphie musculaire ne s'arrête pas aux premiers symptômes de diagnostic, mais elle se projette bel et bien dans plusieurs sphères de la vie des personnes atteintes et les affecte négativement.

PERTINENCE DE FAIRE CONNAÎTRE LA BIGOREXIE

En Occident, l'obésité et ses complications, notamment diabète, maladies cardiovasculaires, hypertension, sont des maladies chroniques qui persistent au sein de la population. Non exhaustivement, mais très fréquemment, la population juge et dénigre ceux en surplus de poids. La maladie qui lui est opposée, l'anorexie, est aussi très présente et néfaste, et maintenant, un autre extrême est apparu avec la bigorexie. Définir et essayer de mieux comprendre la dysmorphie musculaire n'est pas une tentative de pointer du doigt les adeptes du sport, de l'entrainement et du bien-être physique, ni d'encourager le surplus de poids. Au contraire, il s'agit plutôt de promouvoir sainement l'activité physique, sans excès, selon les besoins et la morphologie particulière de chacun. À mon propre avis, les explications de l'émergence de cette maladie psychologique sont une combinaison de deux théories déjà établies (mentionné dans la section « causes »), soit que la société soit à la genèse de ce trouble, mais que certaines caractéristiques personnelles peuvent être des facteurs qui renforcent le risque d'en souffrir un jour. C'est d'ailleurs un raisonnement systématique qui est probablement l'opinion de l'ensemble des professionnels de la santé. De ce fait, des programmes de promotion en santé mentale sont primordiaux pour garder une collectivité saine, mais également des programmes d'estime de soi et d'acceptation de soi sont également nécessaires pour en éviter quelques-unes, dont les maladies qui font partie des troubles de la dysmorphie corporelle. En m'inspirant de la thérapie cognitvo-comportemental qui a pour objectif de modifier les pensées pessimistes que les personnes ont d'eux-mêmes ainsi qu'en modifiant leur comportement [6], je crois qu'être en mesure de bien comprendre les capacités du corps humain et ses véritables fonctions permettrait assurément d'aider certaines personnes à faire face aux défis importants que comprend la dysmorphie musculaire.

CONCLUSION

Finalement, la prévention en santé mentale est outil primordial de la psychologie. Personnellement, je crois qu'un conseil essentiel est d'enseigner dès le plus jeune âge de pratiquer des sports au lieu d'aller simplement au gymnase. Il faut motiver la population à faire de l'activité physique dans un but d'y retirer du plaisir et pour avoir une bonne santé physique plutôt que par exigence et par désir de répondre à des critères sociaux en modifiant son corps. La prévention permet d'ailleurs d'éviter certaines stigmatisations en n'associant pas les troubles psychologiques à l'individu directement. En modifiant l'environnement de la population et en leur enseignant l'importance de l'activité physique et de l'acception d'eux-mêmes, on s'attaque à la situation pathogène en considérant que c'est le contexte social qui provoque la maladie. [7] Au lieu de voir les personnes atteintes de dysmorphie musculaire comme une personne malade que l'on doit guérir, on devrait voir la bigorexie comme une réponse à la société critique.

Pour conclure, ce phénomène est encore récent parmi nous. Plusieurs articles scientifiques explorent les signes et symptômes de la dysmorphie musculaire ou encore les conséquences à court ou long terme. Cependant peu de recherche existe sur ce qui peut amener des personnes à souffrir de la bigorexie. C'est d'ailleurs pourquoi je crois que la prévention est primordiale et que mes conseils sont ainsi formulés en ce sens. Dans le futur, il serait pertinent d'approfondir nos connaissances sur cette psychopathologie afin de mieux comprendre les mécanismes cérébraux qui se développent autour de la dysmorphie musculaire et ainsi être en meilleure position pour aider les personnes qui en souffrent.

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Prévenir le VIH et l'hépatite C dans les prisons fédérales canadiennes : l'apport de la recherche et du militantisme dans l'instauration des programmes d'échanges de seringues en prison

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RÉSUMÉ

Les auteurs souhaitent faire le point sur la santé des détenus sous responsabilité fédérale, se centrant plus spécifiquement sur les épidémies de virus de l'immunodéficience humaine (VIH) et d'hépatite C qui s'y propagent. Ils exposeront d'abord le portrait sociodémographique des prisonniers, en focalisant sur les problèmes de toxicomanie qui y prévalent. S'appuyant ensuite sur des études canadiennes et internationales, ils argumenteront pour la mise en place de programmes d'échanges de seringues en prison, démontrant du même coup ses bienfaits pour la société dans son ensemble. Finalement, ils discuteront de l'engagement communautaire des scientifiques et des chercheurs comme une modalité pouvant engendrer leur implantation dans les milieux carcéraux.

ABSTRACT

The authors wish to review the health of federal inmates, focusing more specifically on the epidemics of human immunodeficiency virus (HIV) and hepatitis C. They first expose the sociodemographic portrait of prisoners, focusing on substance abuse issues. Then, based on Canadian and international studies, they argue for the introduction of prison needle exchange programs, at the same time demonstrating its benefits to society as a whole. Finally, they will discuss community involvement of scientists and researchers as a modality to lead to the implementation of such programs in prison settings.

INTRODUCTION

Alors que les conservateurs se disent préoccupés par le bien-être des détenus sous responsabilité fédérale, plusieurs professionnels en santé publique dénoncent la sévérité des épidémies de virus de l'immunodéficience humaine (VIH) et d'hépatite C qui y sévissent, et ce, sans nécessairement y trouver les ressources pour y faire face [1]. Pour plusieurs détenus, vivre avec de telles infections met en péril leur réhabilitation, et contribuent à leur stigmatisation de la part d'autres détenus et même du personnel soignant [2]. De surcroit, puisque la majorité d'entre eux finiront par quitter les milieux carcéraux, ils peuvent ensuite propager les infections à l'extérieur des centres de détention [1, 2]. Dans ce contexte, il est proposé de se pencher sur ces épidémies, dévoilant la nécessité d'instaurer des programmes de seringues en prisons (ci-après PSP). Pour ce faire, le portrait sociodémographique des prisonniers sera d'abord rapporté, en insistant sur l'ampleur de la disponibilité des drogues qui subsistent dans les milieux carcéraux. Par la suite, des résultats de recherches canadiennes et internationales seront mis en lumière afin d'alimenter l'argumentaire visant la mise en place univoque des PSP en territoire canadien. Finalement, certaines pistes de réflexion seront abordées afin de contrer le statisme politique quant à l'implantation des PSP.

Keywords: Toxicomanie; Prison; Prévention

1. PORTRAIT DE LA CONSOMMATION DE DROGUES INJECTABLES DANS LE MILIEU CARCÉRAL CANADIEN

Le Service correctionnel du Canada se charge de l'incarcération d'environ 14 000 hommes et femmes, purgeant des peines de plus de deux ans [2]. Dans ces établissements, on note une surreprésentation importante de personnes à faible revenu, d'Autochtones et de minorités raciales [2, 3, 4]. Par exemple, alors qu'ils ne représentent que 3 % de la population canadienne en 2011, les Autochtones représentaient 20 % de la population carcérale fédérale [3]. Les individus de race noire composent, quant à eux, près de 10 % des détenus même s'ils ne constituent que 2,9 % de la population canadienne [5]. Bien que ces surreprésentations puissent sembler importantes, elles sont en constante progression depuis la dernière décennie [6].

De l'ensemble de la population carcérale, de 60 % à 90 % sont

aux prises avec de graves problèmes de dépendance, souvent en concomitance avec ceux de santé mentale [6, 2]. Pour plusieurs, la drogue agit comme une source d'apaisement permettant de surmonter les conséquences de la pauvreté, de l'exclusion sociale, des traumatismes vécus dans l'enfance ou du stress résultant des conditions de vie en prison [2]. La consommation ou la vente de drogue fut d'ailleurs, pour plus de la moitié d'entre eux, l'un des motifs qui les avaient préalablement incités à commettre leur infraction [2, 7]. En 2007, le Réseau juridique canadien VIH/sida avait constaté que les détenus d'établissements fédéraux étaient 30 fois plus susceptibles que les autres Canadiens à s'être injecté de la drogue au cours de leur vie [8]. Un rapport de 2010, produit par le Service correctionnel du Canada, confirme que près de 17 % des hommes et 14 % des femmes faisaient usage de drogue injectable en prison [9]. Même si ces chiffres sont élevés, ils sont fort probablement minimisés en raison des conséquences répressives liées à la divulgation d'un tel comportement. Indubitablement, ce portrait démontre que les drogues sont, d'une part, disponibles en prison et, d'autre part, consommées par les détenus malgré l'intensification des mesures visant leur éradication par le gouvernement conservateur [2, 9].

2. VIH ET HÉPATITE C EN PRISON : UNE ÉPIDÉMIE IGNORÉE DES POLITICIENS ET DE LA POPULATION

Le portrait élaboré ci-haut cache une réalité tout aussi inquiétante : celle d'une prévalence élevée du VIH et de l'hépatite C parmi les détenus [7, 9, 10]. Les estimations de la prévalence du VIH dans les prisons fédérales au Canada varient entre 2 % et 8 %, soit dix fois plus que la population canadienne [10, 12]. Celle de l'hépatite C n'est pas moins inquiétante. Le « Canada Communicable Disease Report » de 2004 estime cette prévalence à au moins 20 fois plus que dans la population générale [7].

Bien que plusieurs comportements augmentent le risque d'infection — tels que les relations sexuelles non protégées [11] et le tatouage avec des aiguilles non stérilisées [7] —, les recherches démontrent que son principal vecteur est le partage de matériels d'injections entre les détenus [2, 7, 12]. En effet, la rareté des seringues stériles mène plusieurs à utiliser des seringues usagées. Plus précisément, un rapport du Service correctionnel de 2010 expose que, parmi les utilisateurs de drogues injectables, 55 % des hommes et 41 % des femmes ont déjà utilisé la seringue d'un autre détenu [9]. De ce nombre, 34 % l'on fait avec une personne atteinte du VIH, de l'hépatite C ou dont le statut sérologique est inconnue [9]. Notons d'ailleurs que ces seringues peuvent se partager entre une vingtaine de personnes, augmentant le risque et la rapidité de la propagation des épidémies tant en milieu carcéral que dans la population générale. [2, 9]. En plus de ne pas être stériles, les seringues en circulation peuvent être conçues de façon artisanale (sous la forme d'un stylo, par exemple), engendrant abcès, hospitalisations et décès par surdose [2, 10].

3. LES PROGRAMMES DE SERINGUES EN PRISON : UNE NÉCESSITÉ POUR LA SANTÉ DES COLLECTIVITÉS.

Pour les auteurs, cette iniquité entre la santé des prisonniers et celle de la population générale est injuste et évitable; les drogues poursuivront leur entrée dans nos prisons, et ce, malgré les mesures répressives en place. Considérant également les impacts sanitaires s'associant au manque de mesures visant à réduire les méfaits liés au partage de matériel d'injection entre prisonniers, les décideurs publics se doivent d'agir rapidement.

Les professionnels de la santé publique et les militants luttent depuis maintes années pour la mise en place de PSP [2, 10]. Ces programmes n'ont pas pour objectif de remplacer ou de diminuer les services de traitements ou de prévention. Plutôt, les PSP fournissent du matériel sécuritaire pour l'injection de drogues par voie intraveineuse. Il s'agit donc d'une mesure pragmatique qui permet de réduire les risques entourant le partage de seringues usagées. Les seringues sont ainsi remises aux prisonniers qui en font la demande, par l'entremise de médecins, d'infirmières cliniciennes ou par le biais de machines distributrices [13].

Pour l'Organisation mondiale de la Santé, les données empiriques appuyant l'implantation de ces programmes pour la santé des populations ne sont plus à faire [14]. Jusqu'à présent, les PSP ont été mis sur pied dans plus de 60 prisons d'au moins 11 pays différents [13, 14]. Ils sont ancrés à l'intérieur de divers systèmes carcéraux, de tous les niveaux de sécurité et dont la capacité peut varier entre 50 détenus jusqu'à 1600 [13, 14]. À cet égard, Lines et ses collaborateurs ont rédigé un rapport d'envergure analysant de façon exhaustive les PSP [13]. En voici quelques conclusions :

Premièrement, les PSP n'augmentent pas la consommation de drogue dans les établissements carcéraux. En effet, les évaluations scientifiques provenant de onze différents programmes ont démontré de façon unanime que la disponibilité de seringues stériles en prison n'entraîne pas une hausse de la consommation de drogue chez les détenus [13]. Rappelons d'ailleurs que les prisonniers qui souhaitent s'injecter le font déjà, mais à l'aide de seringues artisanales ou souillées contribuant à l'exposition du VIH et de l'hépatite C dans la collectivité.

Ensuite, se basant sur des recherches internationales [13, 14], ces programmes ne menacent pas la sécurité des employés. Plutôt, le personnel est en mesure de connaître précisément le nombre de seringues en circulation, permettant par le fait même un contrôle accru. D'ailleurs, advenant un regrettable incident de violence envers le personnel, il serait d'autant plus préférable qu'il soit commis par une aiguille stérile qu'une aiguille souillée et utilisée par plusieurs détenus.

Encore, les PSP en prisons représentent un coût minime com-

parativement au traitement à vie que requièrent les personnes infectées par l'hépatite C et VIH [13,15]. À ce propos, un rapport australien a conclu que sur une période de dix ans, ces programmes avaient permis d'éviter près 25 000 nouveaux cas de VIH [15]. Par conséquent, les autorités australiennes ont évalué que les 150 millions de dollars investis dans ces programmes ont entraîné des économies estimées entre 2,3 et 7,37 milliards de dollars canadiens [15].

Finalement, les PSP ont des effets bénéfiques sur la santé des prisonniers et de la collectivité [2, 13, 14]. Parmi les études analysées par Lines et ses collègues, 80 % des prisons ont connu une forte réduction du partage de seringues [13]. En plus, la prévalence du VIH et de l'hépatite C a cessé d'augmenter dans 60 % des institutions carcérales et a même régressé dans 40 % d'autres [13, 14]. Les programmes ont également contribué à la réduction de surdoses mortelles de drogues chez les prisonniers et à l'augmentation de leur aiguillage vers des soins de traitement pour la toxicomanie [13].

4. VERS LA MISE EN PLACE DES PSP EN TERRITOIRE CANADIEN : L'APPORT DE LA RECHERCHE ET DU MILITANTISME.

Les données probantes se montrent très favorables aux PSP. Il s'agit de programmes efficaces en santé publique qui concèdent que l'on trouve des drogues en prison, que les détenus s'en injectent, et que l'intensification des réponses coercitives du gouvernement actuel a une portée limitée. Malgré cela, plusieurs réticences, majoritairement idéologiques, entravent la mise en place de ce projet dans les établissements de détention sous responsabilités fédérales. Or, que pouvons-nous faire afin de contrer ces résistances, favorisant ainsi l'implantation de ces programmes?

N'ayant pas la prétention d'apporter ici une réponse exhaustive, il paraît toutefois nécessaire de rappeler la contribution des sciences politiques et, plus globalement, des sciences sociales à cette question [17, 18]. Pour plusieurs, il y a assurément un lien étroit entre la recherche, le militantisme et les politiques sociales [16, 17, 18]. Les données produites par les recherches s'avèrent une puissante rhétorique quant aux décisions politiques basées sur des principes moraux plutôt qu'à une analyse logique de validation empirique. Elles peuvent soutenir les militants qui exercent des pressions sur les décideurs, leur conférant des sources valides d'informations afin d'appuyer leurs actions. Pourtant, comme le remarque Labonté [17], les chercheurs sont fréquemment critiqués de ne pas s'engager politiquement, préférant s'en tenir à des publications de recherche parfois difficilement accessibles pour la population. Considérant l'importance de la recherche pour le militantisme politique, les chercheurs doivent entamer une démarche de réflexion quant à leur production de connaissances [17]. Plusieurs questionnements, tant sur le plan du contenu de la recherche que la diffusion des résultats, permettront d'arrimer plus justement la science au militantisme. Quelles données peuvent soutenir les militants afin de contrer la résistance idéologique au détriment de la justice sociale et du droit à la santé ? Quels résultats peuvent guider de façon explicite les politiques sociales ? Quelles mesures peuvent faciliter l'accessibilité des résultats d'une recherche à la population ? Ce type de questionnement critique permettra non seulement de produire des résultats valides, mais également de stimuler le climat politique favorisant l'instauration des PSP [18].

Les chercheurs ont une position privilégiée afin de défendre les intérêts des populations vulnérables. Les droits de la personne sont applicables à tous et à toutes. Les détenus ont ainsi le droit de recevoir, y compris à titre préventif, des soins équivalant à ceux qui sont mis à la disposition de la communauté. Le choix de ne pas entreprendre de projet pilote d'échanges de seringues en prisons, alors les études démontrent que le VIH et l'hépatite C se propagent dans celles-ci, constitue une renonciation injuste du droit à la santé des détenus et, à terme, celle de la communauté. Dès lors, il est de notre devoir de s'engager dans un processus de revendication en étroite collaboration avec la communauté et les militants.

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A Time to Talk about Technology – Discussion about Medical Technology with the ATIME Group at The Ottawa Hospital

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ABSTRACT

In recent years, the use of technology in medicine has become increasingly common. Medical technology has the potential to introduce innovative solutions to clinical problems and supplement current methods of medical education. Advancements in Technology In Medical Education (ATIME) at The Ottawa Hospital is dedicated to discovering and sharing advances in technology with the medical community, as well as promoting the appreciation and use of technology in the next generation of physicians.

RÉSUMÉ

Au cours des dernières années, l'utilisation de la technologie en médecine est devenue de plus en plus commune. La technologie médicale a le potentiel d'introduire des solutions innovatrices à des problèmes cliniques et de compléter les méthodes actuelles en éducation médicale. Advancements in Technology In Medical Education (ATIME) à L'Hôpital d'Ottawa est dédié à la découverte et au partage des progrès en technologie avec la communauté médicale, ainsi que voué à la promotion de l'appréciation et de l'utilisation de la technologie dans la prochaine génération de médecins.

INTRODUCTION

Technology in medicine is a growing field that impacts almost every aspect of medical practice. While most medical students recognize its importance, many have only a superficial knowledge of current technologies and their medical applications. In hopes of shedding some light on the topic, the New Engineering and Technology in Medicine Interest Group (NEAT) at the University of Ottawa, Faculty of Medicine, discussed ideas with the Advancements in Technology In Medical Education (ATIME) group within The Ottawa Hospital (TOH), which is centered on promoting awareness and use of technology in medicine.

WHO AND WHAT IS ATIME?

ATIME was formed two years ago as a part of the Department of Innovation in Medical Education (DIME) at the University of Ottawa. ATIME is led by Dr. James Chan, an internal medicine physician at the Ottawa Hospital, and the group currently consists of 18 members (and growing) including physicians, residents, researchers, medical students, undergraduates, and non-healthcare individuals who are interested in the role of technology and its application to medicine. NEAT Medicine had the opportunity to speak with a select group of these members: Dr. James Chan, Dr. Robert Bell, Dr. Kyle Walker and Tim Wood.

ATIME's mandate is to connect the hospital and university by bringing together individuals who are passionate about advancements in technology and its application to the medical profession. ATIME is built on three major foundations: 1) sharing of ideas in the world about technology, 2) supporting each other in introducing new technologies in clinical practice or medical education, and 3) shaping the next generation of physicians who will be proficient in technology and its application to medicine.

WHY WAS ATIME FORMED?

Two and a half years ago, Dr. Chan recognized that a potential problem in implementing medical technologies was the overlap of ideas between several groups within the same hospital. He was thus inspired to create ATIME as a central hub for sharing ideas about medical technology amongst hospital staff. Over time, ATIME hopes to implement a system to help developers navigate the challenges of app development and technology implementation in healthcare, such as dealing with intellectual property, lawyers, and obtaining hospital support. One of ATIME's accomplish-

Keywords: Medical technology; Medical education; ATIME; Innovation

ments is the development of an electronic platform for health and wellness at TOH. It allows open dialogue between staff to promote wellness by sharing their experiences about maintaining a healthy work-life balance. ATIME was also involved in the implementation of eHandover at TOH, an app that improves continuity of care during handovers at the hospital.

TECHNOLOGY AND ITS ROLE IN MEDICINE

Is technology changing the way medicine is practiced clinically? Five years ago, all staff at The Ottawa Hospital received iPads to access OACIS – the hospital's management system of electronic health records (EHR). However, no formal training was provided on how to use the iPads effectively to access OACIS. Thanks to the app-based nature of tablets and smartphones, ATIME members have put the iPad to good use with handy tools such as Read (centralized database of medical literature), Calculate by QxMD (clinical criteria calculator), and eClinicalMobile (secure access to patient records). Other non-medical apps frequently used include ToDo, Dropbox, and Evernote. Combining these tools simplifies workflow, reduces errors, and allows for more effective retrieval of information. For example, Read by QxMD is a personalized system that allows for ongoing retrieval of articles of interest. It searches multiple journals for a specific area of interest (denoted by keywords) and provides the user with a list of the most recent articles published in the field. From there, the user can organize, and download full PDF's to their device for use on their own time.

We asked ATIME about the process of inventing a new technology and introducing it to clinical practice. ATIME notes that there are many examples of widely used technologies in the medical field. In ophthalmology, doctors are able to show patients an image of their retina using a device that exports the photo to a computer/iPad. Another example of the use of technology in medicine is portable bedside ultrasound machines. While technology may seem lucrative in this field, unfortunately, not all innovative ideas are successfully implemented into day-to-day clinical practice. To continue down the pipeline successfully, new technologies must be financially viable before they are supported by the hospital. From a hospital perspective, any time spent on developing a technology is time taken away from clinical duties. ATIME's advice for introducing new technology is to be prepared for setbacks but have a strong proposal that makes financial and logistical sense.

TECHNOLOGY AND ITS ROLE IN MEDICAL EDUCATION

Advances in medical technology can have many applications in medical education. Education is an area in which innovative tools can be implemented to enhance student learning and supplement current methods of teaching. For example, Stethee™ is an electronic wireless stethoscope that vibrates to the heartbeat and uses colors to indicate arrhythmias. Stethee™ is currently in development and born from KickStarter™, a crowd-sourced funding initiative. Innovative technologies like these have the potential to revolutionize the way medical students are trained by providing students with a medium to practice their skills before going into a clinical setting. When asked about technologies such as Stethee™, Dr. Chan explains that these technologies can be used during bedside teaching. Another example of the use of technology in medical education is Harvey® The Cardiopulmonary Patient Simulator used in the University of Ottawa Simulation Center. Harvey® provides medical students with the opportunity to learn to identify pathological cardiac conditions on physical exam; it mimics S3 and S4 heart sounds and murmurs in addition to presenting with associated physical findings such as thrills and heaves. Practice sessions with simulators like Harvey® enhance clerkship readiness and imbue students with confidence when examining patients during their rotations.

Technologies aimed solely at medical education mitigate many issues surrounding patient safety and confidentiality. In the wards, apps that keep track of patient data or bedside ultrasound machines must all go through certification to ensure it is secure and safe with respect to patient data. In medical education however, teaching tools such as 3D anatomy visualization, Harvey®, and Stethee™ can be used without having to certify the device for patient safety. In essence, it is easier to bring these technologies onto the market since patient care will not be compromised. Without the risk of breaching patient confidentiality or compromising safety, developing tools for medical education purposes is a simpler process than those being developed for clinical use.

WHAT DOES THIS MEAN FOR FUTURE TRAINEES?

Ideally, students should be introduced to technologies as early as possible in their training. This would allow time for students to learn how to integrate technology into everyday workflow. This generation of medical trainees will play a key role in pushing technology forward within the medical field. With the advent of multiple start-up companies focusing on health related products, it is imperative that medical students and trainees learn how to evaluate these technologies and their potential use in clinical practice. All change requires a time period of implementation before the benefits of the change can be seen. In hopes of seeing similar advancements, such as the iPad implementation at the TOH, medical students and trainees need to be receptive to novel and unconventional ideas.

CONCLUSION

It is important to encourage students to embrace medical technology, as they will shape the role of technology in the practice

and teaching of medicine and patient care in the future. Over time, with increasing exposure, knowledge, and use, students will feel comfortable using technology in a clinical setting and are more likely to incorporate technology in their day-to-day routine as physicians in the future. Technology already plays a large role in the way medicine is practiced at TOH. In the future, we expect technology to have an increasingly important role in patient care. Medical technology can introduce innovative solutions to clinical problems and supplement current methods of teaching. Groups such as ATIME are leading the way in the incorporation of more technology in medicine. *Expect to see more of ATIME and their work in the future!*

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Objecting the Objective – How Passing the Person Fails Our Growth

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In a program overloaded by information and essential skills, objectives assist medical students in the self-directed triage of imperative take-home points and applicable details of clinical practice. From weekly small group sessions during the Pre-clerkship years to the daily clinical encounters of Clerkship, objectives present an expansive framework for continuous self-assessment and formal examination of the medical trainee. In Canada, the most widely-accepted framework of categorizing medical education and competency is presented by the Royal College of Physicians and Surgeons of Canada (RCPSC) and known simply as CanMEDS [1].

Developed in response to a widely-cited need to provide medical trainees with a relevant frame-work to address evolving health concerns [2], CanMEDS is said to represent the "big picture" of medical education, assessment, and certification. In 1998, Educating Physicians for a Future Ontario (EPFO) conducted a five-year collaborative project in hopes of standardizing resident evaluation [3]. Eight physician competencies were identified and subsequently incorporated into five participating Ontario MD programs. Enduring several phases of development and refinement, the nearly 20-year old RCPSC CanMEDS framework enables Canadian medical institutions to emphasize framework-coherency as an objective standard of student assessment and physician competency [4]. Today's framework is comprised of seven standards of practice: Medical Expert, Communicator, Collaborator, Leader, Health Advocate, Scholar, and Professional [1]. Despite the explicit removal of one of the eight original roles from today's framework, the University of Ottawa, along with several other Ontario MD programs, has continued to house the abandoned eighth role: Person.

In a one-size-fits-all curriculum, comprised of standardized subsets of professional competencies, the Person role exists not within a framework of self-directed personal growth, but as part of a larger tool of idealized perfection. The issue becomes not of the role itself, but of the objectified curriculum which lacks the socially negotiated and contextual nature of the role's definition. Although objectives certainly help to formulate a simplistic means by which students may tangibly assess gaps in their knowledge, the biggest deterrent of meaningful education is built upon the objectives' association with a Pass/Fail grading system (or as medical students like to say, "P=MD"). A grade devoid of increasing value above a specific threshold empowers students to place collegiality above competition. This also means that within a Pass/Fail system, objectives ultimately define the perimeter of failure and not excellence.

The detriment to medical students develops within the context of the curriculum's perceived dichotomy of this role, where there is now an opportunity to not only "Pass" as a Person, but also to "Fail". Where objectives focus on minimally acceptable levels of competence, they can provide pertinent guidance to ensure the integrity and provisions of the medical professional are maintained. Ultimately, it is the fine line between a "P" and an "F" that forms the premise of students' engagement with curriculum objectives; whereby the fear of failure supersedes the drive to excel.

The idea of the Person role, as both a concept and a competency, is not inherently debilitating in the process of fostering a capable physician. When isolated from the medical school curriculum and the supposed measurable standards of competence, the Person role encourages the exam-driven medical student to take time for personal development and focus on those individualized activities that make for a well-balanced student. Within the confines of formal education, however, the Person role serves a counterintuitive outcome for the medical trainee.

When combined with competency-based education and objective standards of supposed failure, the Person role and the opportunity to explore individual growth becomes halted in the face of benchmark assessments. The competent medical trainee becomes defined by statutes of enablement, abided by those who successfully forgo the Person they once were (or could have been) in order to meet the measurable standard and receive a

Keywords: Person; Wellness; Humanities; Medical Education

passing grade. To fully succumb to the normalization of educational objectives is to rob future patients of the intangible character traits that could enable medical students to develop into outstanding physicians.

Our best weapon to combatting the well-documented loss of self and cynicism medical trainees experience as they progress through the curriculum is to create a culturally safe environment by which students can explore personal growth without the fear of constant assessment and failure [4]. Encouraging medical students to nurture their individual identities through self-reflective practice is important, but requires a medium abdicated of concrete expectations or gold standards. Reducing the role of the Person to accompany those components of training, which are comprised of reproducible measurements and checklists, does not aid in the development of individuality, but of empty competency dichotomized between a "P" and an "F". If to "Pass" as a Person requires meeting prescribed conventions marked by the constant pressure to perform based on reductive standards, then perhaps failing this competency highlights the true objective of personal success.

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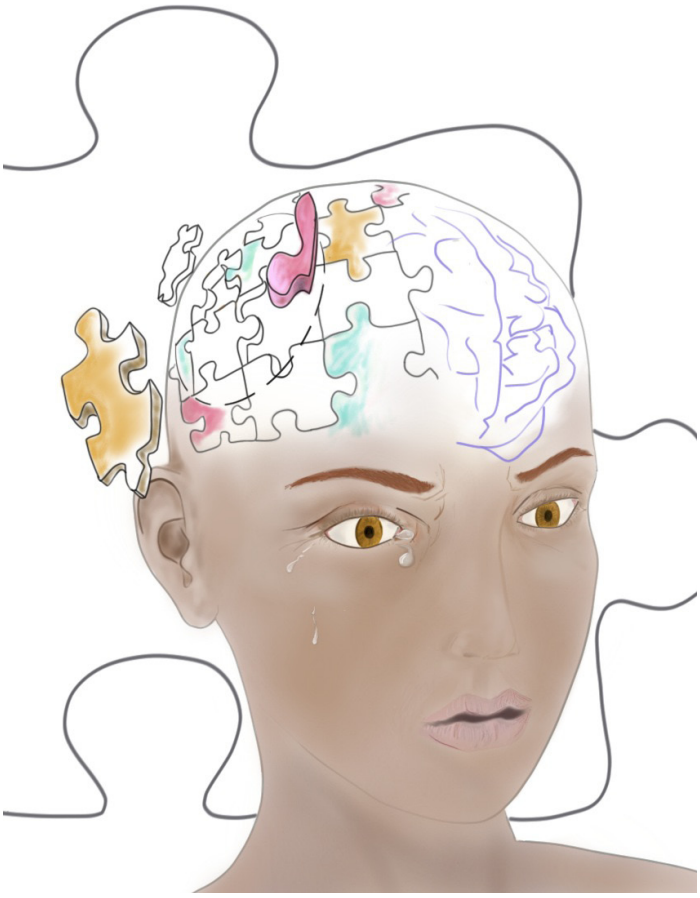
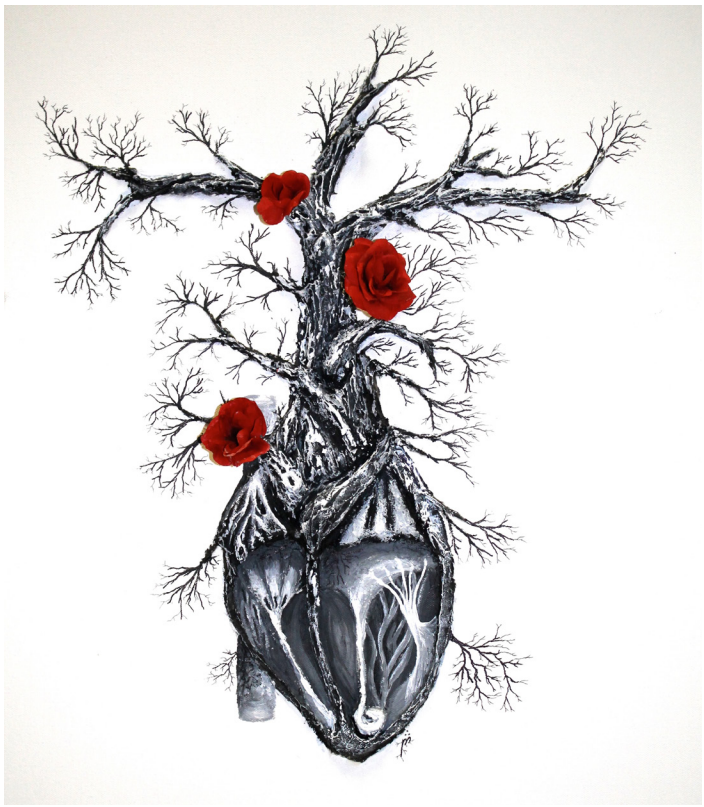


Tears & Puzzle Pieces
Digital art
Julie El-Haddad

With the changes in attitudes towards mental health in Western society, we have seen an increase in awareness of the biochemical basis of certain psychological disturbances. However, we shouldn't forget that the human component of mental health remains the primary focus.

Avec tous les changements dans les attitudes par rapport à la santé mentale dans la société occidentale, nous avons remarqué une augmentation de nos connaissances sur les bases biochimiques de certains désordres psychologiques. Toutefois, nous ne devons pas perdre de vue l'aspect humain de la santé mentale.



Aortic Bloom
Agata Dzwonek
Acrylic and moulding paste on canvas

This piece portrays the crossroads where my passions for art and medicine creatively collide. It was inspired by Helen Keller's quote, "*The most beautiful things in the world cannot be seen or even touched, they must be felt with the heart.*"

Cet œuvre d'art représente un carrefour où entre mes passions pour l'art et la médecine se rencontrent de façon créative. Cette création a été inspirée par la citation de Helen Keller: « *Les plus belles choses du monde ne peuvent être vues ou même touchées. Elles sont ressenties avec le cœur.* »

Despair
Tetyana Maniuk
Acrylic

This piece represents what an individual may feel when under the influence of a mental illness. They can feel weak, hopeless and like they're alone in an abyss. I tried to capture this feeling by using unnatural, or sickly, colours for the skin and making the man look almost incapacitated. The darkness around him represents the 'unknown'. There is smoke and fog surrounding him, which shows the mysterious nature of mental illness and how it can cloud our judgement. Finally, there are 'hands' that are trying grab the man coming from the fog to represent that even though mental illness is not 'physical' it can still take a powerful hold of the those who have it.

Cette œuvre d'art représente ce que peut ressentir un individu lorsqu'il est sous l'influence d'une maladie mentale. Ils peuvent se sentir faibles, désespérés et comme s'ils sont seuls. J'ai essayé de capturer ce sentiment en utilisant des couleurs plus foncées et des tons non naturels pour la peau qui illustrent un homme qui paraît affaibli et dépourvu de pouvoir. La noirceur qui l'entoure représente « l'inconnu ». Il y a de la fumée et de la brume qui l'encercle démontrant la nature mystérieuse de la maladie mentale et comment celle-ci peut venir interférer avec nos pensées et embrouiller notre jugement. Finalement, il y a « des mains » qui sortent de la brume et elles essaient de capturer l'homme dans le but d'illustrer que la maladie mentale n'est pas nécessairement un concept « physique », mais elle peut quand même avoir une influence puissante sur ceux qui en sont atteints.

Winner of the Michelangelo (University & College Students) category at the 2014 Brain & Mental Health Art Show (run by The Society of Neuroscience)

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