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UTMJ

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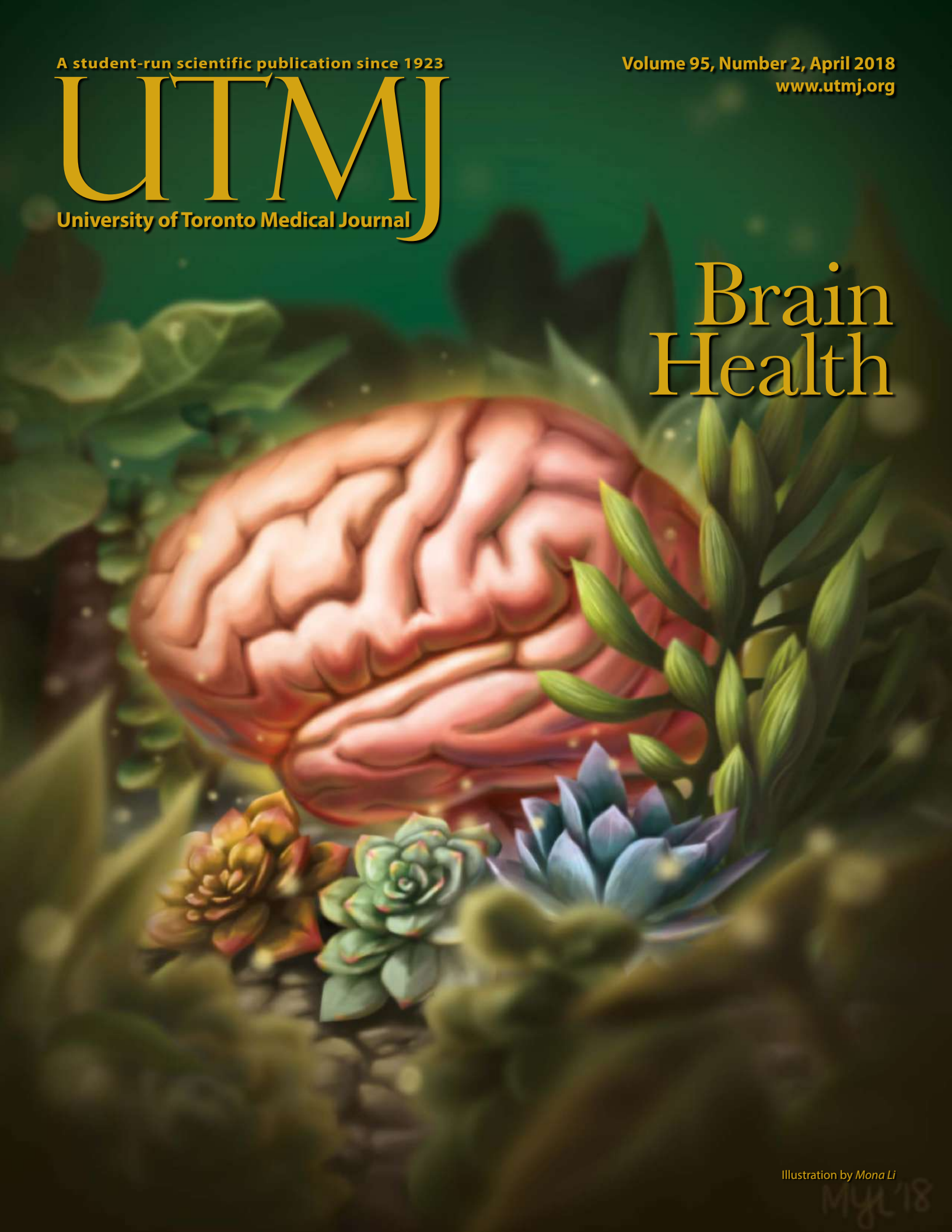
Brain Health



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Preface from the Editors

Dear Reader,

It is our utmost pleasure to share with you the second issue of the 95th volume of the *UTMJ*. For this issue, we set our sights on a rapidly-expanding field of research that has found a special place within medical and commercial realms. Among the myriad of human disease and illness, brain health stands out as an engrossing topic. While the subtle intricacies of the brain have long evaded yet intrigued us, groundbreaking advances in neuroscience research have been pivotal in furthering our understanding of this three-pound universe.

We are delighted to present research on a variety of specialties pertaining to brain health including neurology, psychiatry, and neurosurgery. This issue features interviews with clinician-educators and clinician-scientists conducting research at the forefront of their fields including the world-renowned Dr. Andres Lozano, who shares his experience with the surgical treatment of movement and psychiatric disorders. In addition, we shed light on controversial issues such as the medical marijuana debate and our healthcare system's historically-siloed treatment of comorbid mental illness and substance use disorder. Our commentaries from distinguished faculty researchers are equally diverse in scope and tone, ranging from a word of caution regarding the impending Alzheimer's Disease pandemic to a hopeful outlook on the future of antidepressant pharmacotherapy.

Brain health research is on the rise and is poised to uncover mysteries of the brain that were once thought to be unsolvable. It is in this spirit of advancement that the 2017-2018 *UTMJ* team has endeavoured to compile this issue. We would like to express our gratitude for the dedication and hard work of our diverse team of managing editors, associate editors, section reviewers, copy editors, the interview team, cover artist, and web developers. As always, we appreciate the generous sponsorships from our esteemed patrons. Last but not least, we would like to thank you, the reader – we hope you enjoy reading this issue as much as we enjoyed preparing it!

Sincerely yours,

Alexander Adibfar
Brij Karmur

Editors-in-Chief, UTMJ

The Impending Alzheimer's Disease Pandemic

Donald F. Weaver, MD, PhD, FRCPC[1]

[1] Director and Senior Scientist, Krembil Research Institute, University Health Network, University of Toronto

An epidemic occurs when a disease propagates uncontrollably within a population over some defined period of time. If the spread becomes worldwide, then the epidemic becomes a pandemic. Traditionally, epidemics have arisen from the rapid spread of an infectious disease, such as smallpox, plague, cholera, typhus, or malaria. For centuries, these pathogens wrought havoc on ill-equipped and ill-prepared populations. This year bears a potent reminder of the danger, as it marks the 100th anniversary of the 1918 Spanish Flu influenza epidemic, one of the most lethal diseases in human history which killed 50 million people.[1]

However, as society changes, so will the causes of our future epidemics and pandemics. One looming threat, and one for which we are woefully underprepared, is Alzheimer's disease (AD): an age-related disorder that causes progressive, and ultimately fatal, degenerative dementia. As lifespans increase around the world, and the massive baby-boomer generation approaches old-age, AD has begun to spread rapidly. At present, there are 7.7 million new cases per year worldwide – that's a new case of AD every four seconds.[2] The number of people with AD is projected to rise by 55% by 2030, and by 2050 more than 135.5 million people will be struggling with, and ultimately dying from, AD.[3] The spectre and spectrum of AD, combined with its health and socioeconomic impact, has the capacity to affect every population in the world.

In Canada, some 750,000 Canadians suffer from this mind-robbing condition that impairs memory, thinking, and behaviour, and one new person joins them every five minutes.[3,4] It is estimated that by 2030, this number will have nearly doubled to 1.4 million.[4] Considering that AD is already the seventh leading cause of death worldwide, the impending toll, as the pandemic fully manifests, may become catastrophic.[5]

There are no disease-modifying or curative agents for AD.[6] The design, development, and optimization of a pioneering disease-modifying drug is a neuropharmacological priority. However, halting the full impact of the impending AD pandemic is undoubtedly going to take more than a drug. Alzheimer's is a disease that devastates not only individuals but also families, societies, and nations. Accordingly, addressing this epidemic requires a multi-pronged attack targeting all aspects of the disease – from molecules to cells, from individual lives to their families and societies. To achieve this goal, we need to better understand all the varied aspects of AD.

Our molecular level understanding of AD is still evolving. In 2018, there are two dominant hypotheses concerning the cause of AD: the proteopathy hypothesis and the immunopathy hypothesis. The proteopathy hypothesis proposes that proteins such as beta-amyloid or tau misfold and become oligomerized or clumped. These species become toxic to the brain, destroying neurons and eventually causing AD to progress.[7] The immunopathy hypothesis proposes that immune cells in the brain called microglia become overactive in AD. These activated microglia then elicit the expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), influencing the surrounding brain tissue and damaging neurons, thus causing AD to progress.[8,9] Over the past 20 years, most research has focussed on proteopathy, whereas the immunopathy hypothesis has only recently garnered attention. However, it must be remembered that 40-50 years ago, researchers felt that aluminum exposure might be the cause of AD – a hypothesis that did not stand the test of time.[10] The eventual success or failure of the proteopathy and immunopathy hypotheses must therefore await experimental validation.

At the cellular and tissue level, AD is characterized by the death of neurons and the activation of glial cells. A normal adult human brain weighs 1300-1400 g; a person who has succumbed to AD will have a brain weighing less than 900 g.[11] The thick grey cortical mantle of cells that envelop and embrace the brain will be especially devastated.[12] Neuronal support cells are also involved, as immunotoxic microglial activation contributes to disease progression.[9] Ultimately, plaques (aggregates of beta-amyloid) and tangles (aggregates of tau) will become the tombstones of dead neurons as the brain irreversibly degenerates.

At the level of the individual, AD is truly devastating. Alzheimer's slowly destroys memory, thinking, and eventually all ability to function. The disease erases personality and makes even routine tasks like dressing and bathing impossible. The afflicted individual is unable to recognize their spouse of fifty years and is incapable of identifying their own children. More than cancer, more than heart disease or lung disease – for seniors, dementia is the single greatest cause of disability and debilitation. Its cruel course robs people of what they treasure most: memories, skills, relationships, independence – and then the body starts to wither and waste.

AD can also be overwhelming for the families of affected people and for their caregivers. Parents with dementia are often moved into family homes, causing domestic stress. Children often give up their jobs to care for their dementing parents, causing additional strains within a family unit. Moreover, it is being increasingly recognized that AD and domestic abuse are not independent processes. Up to 60% of people with dementia abuse their caregivers in some way and 12-55% of people with dementia are physically abused by their caregivers – a worrisome observation given the increased suscep-

tibility of the frail and elderly to bodily harm.[13,14] This dementia-domestic abuse correlation is not a simple cause-and-effect relationship but rather a complex, underappreciated (or perhaps simply ignored) medical-societal synergy.

Alzheimer's is not only a profound human tragedy but imposes an overwhelming economic cost as well. Dementia has significant socioeconomic implications in terms of direct medical, social, and informal care costs. Due to the length of time people live with and need care for the illness, it's among the most expensive medical conditions in the world and may soon become the most costly disease in human history.[15] Dealing with dementia already costs Canadians $15 billion a year, a figure that, by some estimates, will rise to over $150 billion annually by 2038.[3] In 2015, the total global cost of dementia was estimated to be $818 billion, equivalent to 1.1% of global gross domestic product (GDP). The total cost as a proportion of GDP varied from 0.2% in low- and middle-income countries to 1.4% in high-income countries.[16] Future costs for Alzheimer's threaten to bankrupt individual families and even national healthcare systems. It is estimated that if the number of patients increases as projected in the years ahead, the costs to care for them will exceed $1.2 trillion annually in North America alone.[16] This may pose an insurmountable fiscal challenge – one we cannot afford to ignore any further.

Despite being humankind's most prevalent dementia, the cause and cure of AD remain unknown. Yet the physical, emotional, and economic pressures continue to exert a devastating toll. AD is an immense and multifaceted disease that mandates urgent research, ranging from biomedical studies at the molecular level to health policy studies at the level of families and society. Challenging though it may be, if we are to reduce harm to patients with dementia and their caregivers, we must have the compassion and courage to address this problem from an academic, health, social, financial, and legal perspective. In short, now is the time to sound the alarm about the impending Alzheimer's disease pandemic.

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Medical Marijuana: Weeding Out The Truth

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Abstract

The advent of medical marijuana as a therapeutic tool remains a work in progress. The Canadian courts enacted the Marihuana for Medical Purposes Regulations (MMPR) on April 1, 2014, but the government of Canada has not endorsed the use of dried cannabis as a medicine. Despite the popular conception that dried marijuana is not addictive, there is clinical evidence of a cannabis use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders V and the World Health Organization. Indeed, the status of dried cannabis as a therapeutic agent is complicated and controversial. Cannabinoids, the primary psychoactive compound in cannabis, appear to possess a variety of beneficial medicinal effects, particularly as adjuvant analgesics, but also demonstrate an adverse side effect profile, including potential psychopathologies and toxicities. The merit of dried cannabis as a pharmacologic agent has been further compromised by questions of route of administration, dosing and efficacy. These observations highlight a double bind: the discrepancy between the law that sanctions the use of dried cannabis as a medicine, and the responsibility of physicians to adhere to evidence-based practice. The advent of regulated legal access to marijuana expected by July of 2018 mandates a robust understanding of this dilemma.

Cannabis sativa, acquired from hemp plants, has been used recreationally and therapeutically since 2800 BC, but the regulatory status of this substance currently remains in limbo.[1,2] The Canadian courts enacted the Marihuana for Medical Purposes Regulations (MMPR) on April 1, 2014 in order to expedite the dispensation of dried marijuana for specified medical purposes.[3] However, the Government of Canada neither endorses nor approves dried cannabis as a medicine.[4]

Although dried cannabis is generally perceived by the public as a non-addictive substance, there is clinical evidence of a distinct cannabis use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) V and the World Health Organization.[5-7] This cannabis use disorder can be complicated by potential psychopathologies, including the precipitation of psychosis, as well as toxicities impacting upon major organ systems.[1]

On the other hand, there is no question that cannabinoids appear to possess a range of beneficial therapeutic effects, particularly as adjuvant analgesics, allowing for a reduced dosage of pain medication. It has been demonstrated that cannabinoids produce their pain relieving qualities by interfacing with the opioid system and by preventing the development of tolerance to narcotics.[1,8,9] Concurrently, animal experimentation has shown that the endogenous cannabinoid system, called the endocannabinoid system, can also act independently in the suppression of chronic pain and may be superior to the opioid system in terms of pain relief.[1,10]

A complex homeostatic balance including cannabinoid receptors type one (CB1) and two (CB2), physiologic receptor activators or agonists, known as endocannabinoids, exogenous agonists, including Δ9-tetrahydrocannabinol (THC), and antagonists or receptor blockers have been defined.[1] From a functional perspective, endocannabinoids are released post-synaptically as a "retrograde messenger" to inhibit presynaptic calcium channels leading to decreased neurotransmitter release.[1] The net effect of the endocannabinoid system is to function as a "rheostatic" mechanism modulating neuronal excitability.[1,11]

Smoking dried marijuana can flood the endocannabinoid system with THC, mimicking the brain's own natural cannabinoids and thus relieving pain.[1,12] It also directly stimulates the brain's final common pathway for addiction in the mesolimbic reward system. Since all drugs that lead to addiction raise hedonic tone and increase dopamine in this brain area, the end result of these neuroadaptations is a more rapid high than can be produced by the body's natural processes.[12] These brain changes are more likely to affect those individuals who are either genetically or environmentally vulnerable to addiction, with the latter category including persons afflicted with mental illness.[1]

The administration of cannabis by the inhalation route further complicates the issue of addictive liability because smoking is not a safe vehicle for pharmaceutical adminis-

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tration.[1,13,14] Marijuana smoke not only contains hundreds of chemicals that are potentially toxic to the respiratory system and other organs, but it is also a medium allowing for a rapid rate of diffusion of THC through the lungs into the nervous system, causing intoxication. As a consequence, an increased risk of motor vehicle crashes, poor school or work performance, and cognitive impairments have been more prevalent in active users.[14] Indeed, a long-term retrospective cohort study has reported that smoking cannabis is associated with an increased risk of lung cancer (hazard ratio: 2.12; 95% CI (1.08-4.14)).[15] Acute coronary events in young adults have also been linked to smoking marijuana (hazard ratio: 1.9; 95% CI (0.6-6.3)).[16] Furthermore, dried cannabis has also been contraindicated in individuals under the age of 25, those who have a history of psychosis, addictive disease, cardiovascular disease, respiratory disease, or those who are pregnant, planning to become pregnant or breastfeeding.[14]

The duration of analgesic action of smoked cannabis has been estimated at about three to four hours.[17,18] One controlled trial found that 25 milligrams, or one inhalation of 9 percent THC, relieved neuropathic pain with minimal intoxication. It has been suggested that four times daily dosing at this level be implemented to treat chronic neuropathic pain.[17,18] Indeed, a single inhalation of cannabis has been reported to produce a serum level of 45 micrograms per liter of THC, whereas levels associated with euphoria are in the range of 50-100 micrograms per liter.[14] Health Canada has endorsed prescriptions of up to 5 grams, or 5000 milligrams, per day, and licensed producers have been marketing potent strains containing 30 percent THC, thus raising issues of safety.[14,17]

Even a fixed dose of THC in a cannabis cigarette contains more than 480 compounds, including at least 66 cannabinoids, of indeterminate utility and harm.[19] The method and depth of inhalation, the length of time the breath is held, individual vital capacity, escaped smoke, and other factors further complicates precise dosing.[14]

There have been only five randomized controlled trials of smoked cannabis.[18,20-23] They range in duration from one to fifteen days, with a combined total of 182 participants comparing smoked cannabis with placebo rather than an alternative treatment.[17,18,20-23] Given this caution, researchers have suggested that cannabis proved more efficacious than placebo in managing neuropathic pain secondary to HIV infection and trauma, and in managing the spasticity associated with multiple sclerosis. It has been postulated that cannabis be considered for palliative care or reserved for patients whose pain is refractory to other pharmaceutical therapies.[17] However, it has also been emphasized that there is limited evidence of benefit from smoked cannabis in common conditions such as fibromyalgia or back pain, particularly when these maladies are associated with mental illness or substance use disorders.[17,24]

The College of Family Physicians of Canada, The Canadian Medical Association and The Federation of Medical Regulatory Authorities of Canada have universally opposed the use of smoked cannabis as a medicine.[17] However, these objections do not extend to the medical benefit of cannabis products in general. The pharmaceutical cannabinoid nabilone (Cesamet), a synthetic structural analogue of THC, has been used therapeutically as an appetite stimulant, adjunct analgesic for neuropathic pain, and anti-emetic.[1] Nabiximols (Sativex), a 1:1 mixture of THC and cannabidiol, has been approved by Health Canada as an antispasmodic for the treatment of multiple sclerosis.[1] Additionally, synthetic THC (dronabinol, Marinol) has been marketed as a Schedule III preparation, defined as drugs with a moderate to low potential for physical and psychological dependence, for similar indications in the United States.[1] These organizations have also continued to support additional research by Health Canada with a view to developing preparations with limited addictive liability, analgesic and anxiolytic efficacy, and other possible indications.[25] Non-psychoactive cannabinoids such as cannabidiol remain the subject of intense investigative interest, as does the function of the endocannabinoid system in the tonic regulation of food intake, cardiovascular tone, learning, as well as analgesia.[1] These inquiries recognize the phylogenetic persistence of the cannabinoid system and argue against abandoning cannabis as a useful medical substrate.

Moving forward, the regulated legal access to marijuana expected by July of 2018 does not relieve medical practitioners of their role as "gatekeepers" of the health-care system.[25] It has been suggested that timely access to dried cannabis for medical purposes can be achieved through a single, non-medical system and that patient requests for information might be satisfied by those involved in such retail distribution. However, there has been equal concern that the lack of physician supervision might blur the line between therapy and recreation, and open the door to misuse and possible dependency.[25] These considerations, combined with the stigma associated with having to purchase cannabis for medical purposes from a non-medical retail dispensary create a conundrum that has yet to be resolved. Whether distributed by a sales person or medical professional, the removal of prohibitions on dried marijuana involves risks to health, both known and unknown.[1,25] The evidence for the use of dried cannabis for therapeutic purposes has not yet met the standard set by the Food and Drug Regulations for pharmaceuticals in the Canadian marketplace, and there is a great incentive for further research that examines the drug as a bonafide pharmaceutical.

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Interview with Dr. David Chan

UTMJ Interview Team (Austin Pereira and Aidan McParland)

Dr. David Chan

David Chan is a staff neurologist at St. Michael's Hospital, specializing in electromyography and neuromuscular diseases. He is the Course Director of Concepts, Patients & Communities 2, a 16-week course in the Foundations Curriculum. He is also the Deputy Director of the Adult Neurology Residency Program at the University of Toronto.

UTMJ: How did you first become interested in the field of neurology?

DC: I started medical school at the University of Toronto in 1994. Back then, it was a much more didactic curriculum than Foundations, but problem-based learning was introduced a year or two before, and we also had weekly clinical skills sessions known as ASCM [Art and Science of Clinical Medicine], the predecessor of ICE: CS [Integrated Clinical Experience: Clinical Skills]. We had the "Structure and Function" course in Year 1, which focused on anatomy including cadaveric dissection. We then had "Brain and Behaviour" at the end of Year 1, where the neuroanatomy and clinical neurology were covered. There was a lot more basic science in the course – one of the recommended textbooks for the course was Kandel & Schwartz's Principles of Neural Science! It was during Brain and Behaviour that I realized my budding interest in neurology. I really find the analytical approach appealing – taking a neurological history and performing the physical exam to localize the lesion. At the same time, I did find the material to be complex but very rewarding once you were able to master it. I was at the Fitzgerald Academy, which at that time consisted of Wellesley Hospital and St. Michael's Hospital (SMH), with the Wellesley merging with St. Mike's in 1998. My ASCM tutor was Dr. Joseph Bruni, who is an epileptologist and a great bedside teacher – and remarkably is still practicing at St. Mike's! I decided to pursue some shadowing experience with Dr. Bruni in the summer after Year 1, so I could get more practice on my neurological exam skills and explore the specialty a bit more. Since he is an epileptologist, his patients always have very interesting histories regarding their seizures. Needless to say, I learned a lot. He always gave me something to read about after each case, and later on he even let me go to the inpatient ward and do a neurological examination on patients that neurology was consulted on. At that time, we had a large inpatient HIV ward at Wellesley, as AZT is the only anti-retroviral drug approved to treat this condition. Neurological complications are very common in HIV infection, so I got the chance to see many interesting neurological signs in these patients. I found that when something really grabs your interest, you naturally want to read up more on it, you don't get tired of it, and over time you will start to tell your peers about how exciting it is. To me, the neurology cases gave me this "rush" of excitement. In Year 2, the curriculum allowed us to get exposure to different medical and surgical specialties, but neurology always interested me the most. I think it is my love about the underlying neuroscience and the complexity of the nervous system that drives this interest. By the end of Year 2, I was fairly certain that I wanted to do neurology but tried to keep an open mind when I entered clerkship.

In the summer of Year 2, I decided to gain some research experience and, quite frankly, tried to get my CV ready for CaRMS [Canadian Resident Matching Service]. I worked at SickKids on a research project related to epilepsy. In Year 3, I did my surgery selective in neurosurgery just to get a taste of it but realized that the pace, the type of patients, and the lifestyle of neurology were better suited for me. That being said, I actually felt more excited about many aspects of the neurosurgical cases than the internal medicine ones! I think this was mainly because of my love of clinical neuroscience in general but also because I worked with two great neurosurgery senior residents, Drs. Michael Taylor and Farhad Pirouzmand, who are now staff at SickKids and Sunnybrook respectively, as well as my staff supervisor at that time, Dr. Rajiv Midha, who is now in Calgary. By the middle of Year 3, I was certain that I wanted to apply to neurology.

What I really like about neurology is its analytical aspect and clinical approach. You have to spend

your time listening, understanding the patients' symptoms, and in many ways scrutinizing every detail of the history provided and eliciting the most important and relevant parts in order to make a diagnosis. Patients often use very loose terms to describe their symptoms: "numbness" could be used to label anything from true loss of sensation to weakness or even stiffness. Also, the complexity of the neurological examination and the process of lesion localization are both very intellectually stimulating and rewarding. Some students prefer to be on the go and get attracted to the surgical specialties, but I prefer to sit down, dissect, and analyze clinical problems. Finally, even back in the 1990's, it was apparent that the field was going to advance rapidly in the future, both in terms of diagnostics and therapeutics, and I realized that these future advances would make it a very exciting specialty.

I also thought about pediatric neurology, which is a very different specialty, but I realized that I wasn't the right person to work with that age group and the neurological conditions that the patients have. I went through this whole process, got lucky enough to get matched to Toronto for adult neurology residency, and ended up doing all my training in Toronto.

UTMJ: You mentioned an initial interest in epilepsy, while your primary practice now appears to have a neuromuscular focus. How did you decide what field of neurology you should go into?

DC: That came much later in residency, and I have considered several subspecialties before settling on neuromuscular diseases. When I was a junior resident, I worked with Dr. Anthony Lang and the late Dr. James Sharpe, and I got interested in movement disorders and neuro-ophthalmology, respectively. If you know them, you can understand it will be hard not to be attracted to their subspecialties, as they are so passionate about their area of expertise and they are both great teachers. However, two significant experiences led to the choice of my current subspecialty. First, in PGY2, I found out somewhat serendipitously about a new advanced training program from the Department of Medicine: the Clinician-Educator Training Program. I saw an advertisement about this on a bulletin board while sitting outside an office at the Toronto General Hospital waiting to review the evaluation for my internal medicine rotation. Essentially, the program will support you to become an academic medical educator, including funding to pursue a Master's degree in Education. Dr. Catherine Zahn, who was a neurologist at Toronto Western Hospital and now the President and CEO of CAMH [Centre for Addiction and Mental Health], was the director of this program. I always love teaching, so an opportunity to become formally trained as a clinician-educator was really attractive to me. When I was in PGY3, I took the opportunity to talk to Dr. Zahn and she was very supportive of me applying to this program, as no one in neurology had done it before. Needless to say, I applied to the program, got accepted, and spent two years doing my Master in Education degree at OISE [Ontario Institute for Studies in Education], during which I worked with various faculty in the Department of Medicine as well as the Wilson Centre.

The second experience was the 6-month EMG rotation with Dr. Gyl Midroni at SMH, which is considered the best place to do an EMG [electromyography] rotation and where I am working now. I never thought I would be interested in neuromuscular diseases, because most residents are interested in the central nervous system first. Dr. Midroni is a great teacher (and now a great colleague) and I learned so much during that rotation. I really enjoyed how one can understanding the normal physiology and pathophysiology through the use of electrophysiological testing. I also like the large variety of conditions in the field, ranging from very common and relative straightforward cases such as focal neuropathies and radiculopathies to more complex ones such as myasthenia gravis, CIDP [chronic inflammatory demyelinating polyradiculoneuropathy], and ALS [amyotrophic lateral sclerosis]. As I aspired to become an educator, I figured that a subspecialty that had more relevance to generalists and non-neurologists would provide more opportunities for me to teach different learners, as opposed to something more niche like neuro-ophthalmology. To sum it up, it all came together for me in PGY4. I finished by PGY5 training after completing my Master's, passed my Royal College specialty exam, and started as a full-time staff at SMH in 2005.

I think at your stage of training, you don't have to worry about which neurology subspecialty you want to do – a lot can change during residency training. Instead, you want to have a broad view of neurology as a whole in order to decide if the overall specialty is for you. That's why I encourage students to spend some time on the neurology inpatient service and in ambulatory general neurology clinics, where you will encounter a wide variety of cases. If you like neurology – its clinical and diagnostic approach, the various common and less common diagnoses, the patients – you will always find a subspecialty that suits your personality and academic interests. For example,

some residents choose to do MS [multiple sclerosis] because they like to work with younger patients and enjoy the imaging and therapeutics that are rapidly evolving in that field. Or, if they really like to deal with acute presentations, they choose to do stroke, as the hyperacute management including endovascular therapy is one of the most exciting prospects in the field currently.

UTMJ: As you said, you were one of the first clinicians to go through the Department of Medicine Clinician-Educator Training Program. Many students, residents, and staff are trying to figure out what "extra degree" they should pursue to put them on the track of being a medical educator. What are your thoughts on this?

DC: This is a good question. It depends on your career aspirations. It doesn't mean that you need a Master's degree in education to get a faculty position, even though some type of advanced training in education is strongly encouraged. For example, the Department of Medicine has a Master Teacher Program, which is essentially a requirement for all junior faculty hired as clinician-teachers. It focuses on the practical skills in teaching and evaluating different learners in various settings. The Centre for Faculty Development at SMH also offers the Education Scholars Program. If you aspire to take on major educational leadership or administrative positions, such as a course director or a residency program director, I would definitely suggest pursuing a formal degree in education. The bar is only going to rise and it is never a bad idea to equip yourself with more specialized skills and to improve your competitiveness. The field of medical education is also advancing rapidly, so I think it will only help if one understands the science better. There are definitely more options nowadays than when I went through it in the early 2000's, and many of them are tailored specifically to health professional education. There are local programs, like the one offered by our Dalla Lana School of Public Health, as well as programs at John Hopkins University, University of Illinois, University of Dundee, Scotland, and University of Maastricht, Netherlands. Some of these programs can be done via correspondence or online for the majority of the curriculum. Some of our own junior faculty are pursuing these.

UTMJ: Neurology has many areas of fascinating research. We were wondering if you could discuss any research that you are involved with or any notable research happening in Toronto that comes to mind?

DC: For me, research is not my current focus. That being said, I have done several educational projects during my Master's and also in my early years as a junior faculty. I have looked at the reliability of a rating scale used for structured interviews in resident selection. I also worked with Dr. Wendy Levinson on the disclosure of medical errors and also on the reliability of evaluating communication skills over videoconferencing. Several years ago, I worked with a cardiology fellow to look at the reliability of residency interviews done over videoconferencing. So, I have been involved in several interesting projects like these ones, rather than having an established program of research. I enjoyed collaborating on these projects, and it's too bad that my current academic and family commitments don't really allow me to seriously pursue more scholarly work in education.

You are absolutely right that our division has many leading researchers. Our movement disorders program, led by Dr. Lang, is probably the most well known internationally, attracting many clinical fellows from all over the world. They have a comprehensive research program, including basic science, neurophysiology, and clinical research. Our MS program, under the leadership of our new Departmental Division Director, Dr. Xavier Montalban, a world-renowned researcher recruited from Barcelona, and with young faculty like Dr. Jiwon Oh, who is a clinician-scientist interested in MR imaging in MS, is poised to become even more prominent internationally. There are also several clinician-scientists and clinician-investigators in our stroke program: Drs. David Gladstone and Rick Swartz at Sunnybrook, Dr. Gustavo Saposnik at SMH, and Drs. Frank Silver, Leanne Casaubon, and Aleksandra Pikula at UHN. Their research interests include clinical epidemiology, outcomes and decision neuroscience, and neuroimaging in stroke. Dr. Sandra Black at Sunnybrook has a combined research interest in cognition, stroke, and neuroimaging. Some of our basic science researchers, exemplified by Dr. Peter St George-Hyslop, have been advancing our understanding of neurodegenerative diseases such as Alzheimer's disease, FTD [frontotemporal dementia], and ALS. It is hard to name everyone without omitting somebody, so I apologize in advance if I left someone out!

UTMJ: How do you feel about lifestyle in neurology and when choosing a specialty in general?

DC: Lifestyle seems to factor in more and more in the current generation of medical trainees and residents when they choose their specialties and subspecialties.

I think it is a very personal decision. Essentially, it is a balance between your academic pursuits and personal life. From what I've seen, the current generation of trainees places more weight on family time than perhaps my senior colleagues. I remember stories about senior neurologists spending most of their time at the hospitals doing their clinical and academic work and rounding on their patients, even on weekends. Family time was not necessarily emphasized as much, relatively speaking. I think this work-life balance has been more emphasized during medical training, and personally I think this balance is critical for one's well-being. Nothing can substitute time and effort if you want to get to where you want to go in the academic world, and there is only a finite amount of time. You have to think about how to distribute your time, because I think everyone who chooses to go into academics want to derive some gratification from being successful in it, right? How big this piece should be relative to your personal and family life will differ from one person to another. It's never too early to start thinking about this, and keep in mind that your personal circumstances will change, of course, such as getting married and having kids. All of these things will gradually shape the way you think about that question over time.

So, I think it's really important to consider lifestyle in choosing your specialty because work and academic success are not the only purposes in life, and while you can be very successful academically because of your utmost devotion, you may become less successful in other areas such as personal wellness and relationships. Taking care of yourself is as important as academic success, in my opinion.

UTMJ: In comparison to other specialties, how would you say the lifestyle compares in Neurology?

DC: Overall, I think lifestyle in neurology is generally considered to be very good. If you ask my colleagues, I think most of them would say the same thing. Of course, it varies somewhat depending on your subspecialty, but you can always choose the one that suits your clinical and academic interests as well as your preferred lifestyle the most. Obviously, if stroke is a major part of your clinical practice, things will be busier because of all the stroke emergencies that are amendable to time-sensitive treatments. At SMH, all of us participate in stroke call, as there are currently only two stroke neurologists, and call can get quite busy. All of us in academic centres typically take turn in doing inpatient service, but when we are not, we basically have an outpatient practice with very predictable hours.

UTMJ: What is the most gratifying part of neurology for you? What are things that make you smile when you go home at night?

DC: I would say the patients whom I helped and the learners whom I taught. In terms of helping patients, it can be as dramatic as treating their stroke with tPA [tissue plasminogen activator] and/or EVT [endovascular therapy] and seeing their deficits improve significantly in front of your eyes. There are very few things in medicine that can give you this kind of gratification. However, most of the time it is less dramatic but no less important. I treat and follow patients' chronic neurological conditions, listen to their concerns, and support them and their family in any way I can. Just a small thank you from my patients means a lot to me. For some patients, you eventually get to know them very well and develop a strong therapeutic relationship with them. Treating a patient's migraine and allowing them to get back on track with their life, and seeing a patient with myasthenia gravis who requires respiratory support in the ICU but then eventually recovers to become normal with appropriate immunosuppressive treatment, are a couple of examples. There will always be somewhat depressing moments when you really wished you could help that patient more but couldn't; however, this applies to all of medicine.

As teaching is one of my passions and the main reason that I chose this career path, I derive a lot of gratification from teaching medical students and residents – and seeing them become successful practitioners.

UTMJ: We have one last question for you. We have heard you are something of a wine connoisseur. Could you talk about some things you enjoy doing in your free time?

DC: That started a while ago [laughs]. During my Master's, one of my supervisors was Dr. Arthur Rothman, a PhD in Education. I'm not sure how this topic came up, but he told me about a wine club that he was part of. I just started to become very interested in wine at that time and I jumped on the opportunity to attend their tastings as a guest whenever there was an opening. The club was founded by David Goldberg, Professor Emeritus in the Department of Laboratory Medicine and Pathobiology, who was also a member of the Wine Writers' Circle of Canada. A significant part of his research is devoted to the chemistry of wine, such as resveratrol and other polyphenols and their potential health benefits. The club meetings started in the Banting Institute – that's before my

time – but now the tastings are held at the Faculty Club. I attended several of these tastings as a guest and thoroughly enjoyed them. We usually taste 8 to 10 wines under a specific theme, and there is always a "mystery" wine that everyone tries to identify what it is. We will take turn describing the wines and expressing our opinions about them. Over time, I became part of the wine club as a regular member, and I'm now the secretary of the club. We meet about 8 times a year and we take turns hosting tastings on different themes.

Apart from the social aspect of these tastings, going through them is also very intellectually stimulating. It fits with neurology very well. First, you really put your mind into something outside of medicine, which I think is a very effective way to reduce stress. It doesn't have to be wine tasting – it can be anything. I also love that I always get to learn from other people. I was the relatively junior member of that group initially, and there was a lot to learn from the more experienced tasters. Most importantly, I really liked the aspect of analyzing things, which goes back to my desire to become a neurologist in the first place. I find blind tastings to be fun yet very humbling. When you try to analyze a wine, you try to pick out individual characteristics and elements in the colour, nose and palate, and at the end you try to put everything together and pick out the type of wine or grape. In a way, this is similar to learning how to make a diagnosis, like the hypothetical-deductive approach in clinical reasoning. You have a hypothesis, you try to test it, you look at the colour, and if the wine has a lighter, ruby red colour, it is probably not a Cabernet Sauvignon, unless you make it the wrong way [laughs], but would be more consistent with varietals such as Pinot Noir, Nebbiolo, etc. You then try narrow it down further based on other characteristics on the nose and palate, and see if they are consistent with what you expect for these varietals. Similar to making a diagnosis, this process is filled with traps and pitfalls. Sometimes you get stuck on one little element, something that you are confident that it is present when in fact it's not, and that can totally take you down the wrong path. And sometimes with diagnoses too, if you close your mind too soon, or you get stuck on some elements of the history without considering others, that can lead you down the wrong diagnostic path as well. So, I see a lot of parallels with blind tasting and making neurological diagnoses, probably because of my clearly-nerdish way of thinking [laughs]. Of course, it is much less consequential to make a wrong guess during blind tasting than to make an incorrect clinical diagnosis! At the end of the day, I found blind tasting a good way to de-stress and I do that with my friends regularly. You also get to learn and read about something outside of medicine. I own many books on wine that I want to read, but I often don't have the time. So, overall, I am not encouraging indulgence, but it is the academic and intellectual aspects of wine that really resonate with me. My wife and I used to go on different trips to explore different wine regions, but since my son was born almost 8 years ago, that type of trip has been put on hold.

Interview with Dr. Mark Hanson

UTMJ Interview Team (Priya Dhir and Nicholas Scrivens)

Dr. Mark Hanson

Mark Hanson is a child and adolescent psychiatrist at the Hospital for Sick Children and is a Professor of Psychiatry at the University of Toronto. Previously, he was the Associate Dean / Director of Admissions and Student Finances for the MD Program at the University of Toronto Faculty of Medicine. Dr. Hanson is currently an Associated Medical Services (AMS) Phoenix Fellow, where he is advancing patient engagement in health professions admissions processes. Medical education scholarship and administration has been the focus of much of Dr. Hanson's career. His research has focused on medical school admissions, admissions tools and social responsibility. Earlier, his scholarship concentrated on the evaluation and recruitment of medical students into Child and Adolescent Psychiatry.

UTMJ: What is your role at SickKids and the Faculty of Medicine?

MH: I am a practicing Child and Adolescent Psychiatrist at The Hospital for Sick Children (SickKids) and a Professor of Psychiatry at the University of Toronto. My clinical focus relates to the psychiatric care of children, adolescents and their families. I am also the Fellowship Coordinator for Psychiatry and the Medical Psychiatry Alliance (MPA) Fellowship Coordinator at SickKids. I am the past MD Program Admissions and Student Finances Associate Dean/Director at the University of Toronto, Faculty of Medicine.

UTMJ: What is the Medical Psychiatry Alliance and how and at what levels of their training could future healthcare providers receive this formal training?

MH: The Medical Psychiatry Alliance (MPA) is a partnership across The Centre for Addiction and Mental Health (CAMH), The Hospital for Sick Children (SickKids), Trillium Health Partners (THP) and the University of Toronto in conjunction with the Ministry of Health and Long-Term Care (MOHLTC). The SickKids MPA fellowship aims to educate current and future healthcare professionals such as paediatric trainees and nurse practitioners about how best to support, diagnose and treat child and adolescent patients with co-occurring mental and physical illnesses. The MPA fellowship at SickKids is a training area that I am quite excited about, with its focus upon integrative training across child and adolescent psychiatry and paediatrics. There is a shortage of child and adolescent psychiatrists alongside the obvious fact that many children, adolescents and their parents consult with general paediatricians regarding children's mental and physical health status. It is a rare advanced training opportunity to address the mental health and medical care needs of children, adolescents and their families via the SickKids MPA fellowship. As part of the MPA fellowship, we offer senior paediatric trainees an opportunity to enhance their confidence in consulting regarding children's mental health concerns like anxiety, depression and attention deficit hyperactivity disorder (ADHD). We provide training opportunities not only in consultation but also in specific treatment modalities such as Cognitive Behaviour Therapy (CBT). This fellowship provides trainees with substantial direct clinical experience for 6-12 months. It is a small fellowship initiative and I really hope to see it grow, as it serves a key need in the delivery of mental health and medical care to children, adolescents and their families.

UTMJ: Do you think this MPA model extends to adult psychiatry?

MH: Yes – there is a comparable adult MPA fellowship program with 3-4 fellows including nurse practitioners. There are also MPA educational interventions as part of the pre-clerkship foundations curriculum called the Integrated Clinical Experience – Medical Psychiatry (ICE – MP). It was developed in response to the growing healthcare needs and challenges in caring for patients with both physical and mental health conditions. The ICE – MP program teaches pre-clerkship students how to understand and engage patients using a patient-centered approach in a variety of settings. The content builds on Clinical Skills teaching and provides opportunities to practice therapeutic communications and to understand experiences of patients who are living with complex medical and social issues.

UTMJ: Could you tell us about your psychiatry practice at SickKids?

MH: I am at SickKids Hospital in a general outpatient clinic practice. We see a number of children and adolescents with wide-ranging child and adolescent psychiatric problems including anxiety, ADHD, depression, behavioural problems, encopresis and enuresis. I also participate in the divisional tele-psychiatry program because many of the children's mental health centres in the province do not have access to child and adolescent psychiatric consultants, so this outreach program provides this consultation service across the province.

UTMJ: What is the Associated Medical Services (AMS) Phoenix Fellowship, and what is your research associated with this fellowship?

MH: The Associated Medical Services (AMS) Phoenix Program is an initiative that focuses on making a positive and lasting difference in how health professionals nurture and sustain the learning and practice of compassionate care.

I am an AMS Phoenix Fellow researching and advocating for patient engagement in health professions admissions processes. I really think that medicine needs to look more deeply into patient engagement within medical school admissions processes. At the University of Toronto MD Program, my colleague Dr. David Latter [current Director, Admissions and Student Finances for the MD Program] is taking an innovative leadership step in establishing a patient engagement admissions sub-committee of the MD Program's admissions committee. This is a first for Canada! Patients could be involved in many aspects of current admission processes. They could be involved in admissions interviewing, reviewing application materials, designing interview questions or admissions committee participation. As you can see, there are many possibilities for increasing the contributions of patients to the selection of medical students and all health professionals. I envision a day when patient engagement is as important as the MCAT in medical school admission processes. My Phoenix fellowship supports and makes my work in this area possible.

[For more information on this topic visit: http://www.ams-inc.on.ca/people/mark-hanson/]

UTMJ: What advice would you give to medical trainees to ensure that they are looking after their own mental health?

MH: Well, this is very topical because today is Bell Let's Talk Day [January 31, 2018]. I think that it is important to realize that you are never alone on this journey. The Dean, Vice Deans, Associate Deans and members of the faculty deeply care about you and your well-being. If you have concerns, don't hesitate to find someone to talk to, whether it is a classmate, friends and family, faculty or others. It is important to not be quiet – there are always people there for you. I know as a psychiatrist that this can be one of the hardest things to do, to reach out to someone, but do remember that you are not alone. Another element is to find your passion in an area of medicine whatever you are doing because there will always be challenges in life and in a medical career so your passion can help you navigate through challenging times. It is also important to find ways to get away from medicine and find an outlet. My interest is in running, and finding outside interests and/or hobbies is extremely important. They give you an opportunity to think things through and step away from medicine.

UTMJ: What are your thoughts on the stigma surrounding mental health and how this is evolving?

MH: Stigma surrounding mental health and illness is part of the reason why people may not reach out to talk to people – let alone reach out to consult with a child and adolescent psychiatrist. But I think that society is moving in the right direction and lessening the stigma surrounding mental illness. Today, there is a great deal that can be done to help children, adolescents and their families. For instance, we consult regarding a number of very young children with anxiety problems and their families at the SickKids psychiatry clinic. Anxiety can be quite impactful for a very young child's development but today, there are treatments that can be quite beneficial. Years ago, it was thought that there was not much that could be done to assist these children and their families. The element of stigma may come from the idea that we don't want to label children as having a psychiatric problem. There is also a societal perception that children develop differently, which can prevent families from reaching out. We need to understand as a society that we can have developmental, psychiatric, and non-psychiatric problems, and there are ways that we can help. So, I think things are moving to break down this stigma – but there is still a long way to go.

Interview with Dr. Andres Lozano

UTMJ Interview Team (Priya Dhir and Nicholas Scrivens)

Dr. Andres Lozano

Andres Lozano, MD, PhD, FRCSC is the chairman of the Division of Neurosurgery at the University of Toronto, the Dan Family Chair in Neurosurgery, the RR Tasker Chair in Functional Neurosurgery at University Health Network and a Tier 1 Canada Research Chair in Neuroscience. Dr. Lozano received his medical degree from the University of Ottawa, his PhD in neurobiology, and his neurosurgical training from McGill University. He completed his postdoctoral training in movement disorders at Queen Square, London, UK and in cellular and molecular biology at the University of Toronto. In 1999, he became the youngest individual to become appointed as full professor in the Department of Surgery.

Dr. Lozano is best known for electrical recording and stimulation mapping of hitherto unexamined brain areas for the identification and testing of novel therapeutic targets for deep brain stimulation (DBS). He and his team have pioneered the "first in man" applications of DBS in Parkinson's disease, dystonia, Huntington's disease, depression, and anorexia. He is currently leading a large multicenter trial of DBS for Alzheimer's disease. He has the unique distinction of being named the most highly-cited neurosurgeon in the world and has published over 450 manuscripts and 90 chapters and edited 5 books.

UTMJ: Could you tell our readers a little bit about yourself?

AL: My name is Andres Lozano. I went to medical school at the University of Ottawa and then went to McGill for my residency. I did a PhD in neuroscience while I was at McGill. Following this, I did some fellowship training in London, UK and then came to Toronto in 1991 and stayed here ever since. So, I've been here for 26 years. I was always located at Toronto Western Hospital – I've only had 1 job in 26 years, and so far they tolerate me okay.

UTMJ: What triggered your interest in getting into neurosurgery in the first place?

AL: When I was about 15, I decided to be a neurosurgeon. I was inspired by watching Dr. (Wilder) Penfield on television. He was operating on patients with epilepsy and stimulating their brain, and these patients were recalling vivid memories of what they had experienced. I thought to myself, "This is the most interesting thing I can think of, so I'd like to do that too." That's why I went to medical school, and that's why I went to McGill for neurosurgery too, because that's where Dr. Penfield was – I thought that would be the best place to go. Since then, though, I think Toronto is the best place to go!

UTMJ: Being in the field for this many years then, what fascinates you about the brain?

AL: I think what fascinates me the most is that, despite all we have learnt, there is still a huge amount left to be discovered about the brain. I think that that's what really drives me: the curiosity and the interest to try to learn more and explore areas of the brain that are unknown. That's really what we do, in the kind of surgery that I do – I go to new areas of the brain and try to find out what they do and, more so, whether they can somehow be influenced to improve their function.

UTMJ: Speaking of the type of surgery you do, could you maybe provide a brief description for our readers that may not have heard of Deep Brain Stimulation?

AL: Yeah, absolutely. So, it turns out that if you have a psychiatric or neurological disorder, it can most of the time be related to malfunctioning of circuits in your brain. For example, if you have Parkinson's disease, it reflects malfunction within circuits that controls movement. If you have depression, that is malfunction within circuits that control your mood. If you have Alzheimer's disease, it represents malfunction within circuits that control cognition and memory.

Through deep brain stimulation (DBS), we're able to reach these circuits in the brain, intervene within them, and adjust their activity. This can be either turning them up, or down, using electricity. It's very much like having a dimmer switch. When there is excessive activity, for example, something like tremor or seizures, we might want to turn that area of the brain down. However, if the area being targeted is underperforming, as is the case in Alzheimer's disease,

we want to turn it up. So, we're able to basically go anywhere in the brain and adjust the activity of brain areas to see if we can improve function.

UTMJ: What was the timeline of seeing DBS go from being researched as a novel therapy to it being used in clinical practice?

AL: Well, some of this was done in the 1950s and 60s in animals. Then, the idea that this could be done in humans was first thought of in the context of Parkinson's Disease. So, we were involved in using DBS for Parkinson's, but also extracting from those trials – in that, if it could be used to treat a motor dysfunction, it can also be used to treat other parts of the brain for other disorders. It started with doing DBS for other kind of movement disorders, like dystonia. And then we started to experiment with psychiatric illnesses, like depression, obsessive compulsive disorder, Tourette's, and anorexia. The latest foray is into memory and cognitive disorders.

UTMJ: Is there a specific patient population that would get access to DBS? Or is it currently a treatment modality available to anyone with these disorders?

AL: For Parkinson's Disease, DBS is well-established and we operate on at least 3 patients a week. It's a done deal – very well characterized. Typically, when you're diagnosed with Parkinson's and you are put in medicine, you have a honeymoon period of approximately 2-5 years, where you take the drugs and you can be normal. However, with progression of the illness and ongoing exposure to drugs, you start developing complications. It is at this point that you can consider having a surgical intervention, because it can deliver more than what the drugs can do. Parkinson's is a progressive, neurodegenerative disorder. What we're trying to do is buy time and try to keep people functioning at a higher level for a greater period of time. However, it's not just the motor function that is in trouble; there are also impairments in cognitive function, depression and so on. So, we're merely addressing some of the aspects of the illness for a long time, but we recognize that these are symptomatic treatments and not a cure.

For the other disorders, DBS is still in evolution. They're still investigational and not approved. We're doing research, and typically our patient population for them represents those who have these disorders and have run out of options. They are still disabled, despite the best available medical therapy. In the case of Alzheimer's, it's easy, because the drugs don't do much. In the case of depression, there are at least 30 antidepressant drugs – and we only treat patients who, despite all the available therapy, are still disabled. If patients have tried everything, and still are not able to function in the way they desire, we become involved. I mean, it's a lot to ask for someone to be comfortable with a person drilling holes in their skull and putting electrodes in their brain. So, unless we've tried everything else, it's not going to be something we offer.

UTMJ: How did it feel for you, professionally and personally, to see DBS go from research to the clinic – and more importantly, to see the tremendous impact it had on patients?

AL: I think, for anyone, you want to go to work every day and do things that are exciting and meaningful. So, to take something where we've reached the frontier of knowledge and how much we need to know and say, "This is not acceptable. We want to do more," is making a bold statement. But that's how we move our knowledge forward, especially when it involves surgery of the brain. I think part of it is just saying that we have a bias for getting things done, and not accepting the status quo.

More than that, we rely on the tremendous courage of our patients, who are sometimes the first human beings in the world who are having these procedures. We always have to tell them that we're going to try this but have no idea if it's going to work. So, partnering with our patients is a critical aspect of what I do – and you have to admire their bravery in letting someone operate on their brain when the outcome is uncertain.

UTMJ: It definitely makes you think – if you were in their shoes, how much would you be willing to risk?

AL: Exactly. So, it depends on your outlook and how much you want to fight vs. accept.

UTMJ: Is there a particular patient encounter that has stuck with you over these years, something that may make you see medicine differently?

AL: Yeah, absolutely. Sometimes, we go to areas of the brain where no one has gone before, and when we stimulate those areas, all of a sudden, the brain is revealing itself. It's amazing to discover for the first time what that part of the brain is doing. It's a "eureka!" kind of moment. We've had several patients that that's happened with, because we've gone to areas where nobody has ever gone before. We've stimulated those

areas, and found out that it is where a particular function occurs. That's pretty exciting – there's no other real way of doing that, except via neurosurgery. This is really where neurosurgeons have a huge advantage, because we can actually go in the brain and can probe these areas, allowing it to reveal its secrets to us.

For instance, there was one case where we were treating someone for their obesity. We wanted to regulate their appetite in the hypothalamus. However, when we stimulated that area, we ended up probing very vivid memories. It's on the basis that we're now treating patients with Alzheimer's with DBS, since we have an area in the hypothalamus of the brain, that we can stimulate to drive and enhance memory. And this was totally by accident! However, when you see something novel and exciting, as such, you must grasp the importance of it and take advantage of it.

I think we are always justified by an unmet need in a patient. We see that there is a person who is disabled by an illness, and it's our job to try to help them. If the limits of medical knowledge have been exhausted, it's time to create new knowledge. We are lucky to work in a university and hospital where pushing the frontier of what is known, and what is possible, is encouraged. That, to me, is the excitement of neurosurgery. It really is about learning more, discovering more, and using that knowledge to help people. Ultimately, it's a choice patients and their families make. We don't know if we're going to win or not, and there's a risk because it is surgery. Our job, however, is to say, "This is where we are. This is an idea with pros and cons – are you in?" We hope that patients and families understand that and make an informed decision, and they're active participants. We are more dependent on how they help us, rather than the other way around.

UTMJ: How have you seen the field of neurosurgery change in the last 26 years?

AL: The trends are towards being minimally invasive. Big operations are going away, and we're trying to do smaller and faster surgeries. We are accessing the brain, not only by opening the skull but also by getting through the blood vessels of the brain. We are also using non-invasive methods. One of our new developments is focused ultrasound, which involves using ultrasound beams through the skull to treat people with tremors. So, we are now able to influence and intervene within the brain, without having to open the skull.

The other trend is that neurosurgeons are now taking on disorders that were in the province of neurology and psychiatry, such as Alzheimer's disease and depression. We're interested in an organ called the brain – and anything that has to do with the brain is of interest to us. We should not be pigeonholed into treating only some disorders. And most importantly, these are multidisciplinary efforts. We work with neurologists, psychiatrists, radiologists, and many other fields. It's exciting to work on projects where there's a team, and where you by yourself cannot do very much – but if you combine your efforts, you can do great things.

UTMJ: Do you think the fact that you are able to localize mental illnesses to certain parts of the brain, and treat them via neurosurgical techniques, helps with some of the stigma surrounding mental health?

AL: Yeah, absolutely. When you have these disorders, it's because there's something wrong in your brain. I don't think that depression is any different than diabetes. It's the same stuff: something is not quite working well, and the latter happens to be in a circuit within your brain. We're now learning where those symptoms are generated in the brain. We can reach those areas, intervene within them, and adjust the activity of those brain areas and hopefully that translates into improving our patients. It's absolutely transformative surgery, especially because we're dealing with a killer disease, such as depression. We deal with patients who have a very high suicide rate; it affects young people – and women twice as often as men. We've had several patients who committed suicide while in the process of deciding whether or not they should have surgery. These are very malignant disorders – and we're talking about patients who are very ill and have extinguished all their options. If you can take someone like that and transform their life, that's pretty remarkable.

UTMJ: Could you tell us more about the focused ultrasound techniques you've been working on recently?

AL: We have a new tool in focused ultrasound, and we're trying to figure out what it can be used for. Tremor disorders are kind of the beach head, but we think that it will also have applications across a number of other disorders. For example, we think that we may be able to ablate areas of the brain that are producing epilepsy without opening a head. We might be able to ablate brain tumours without opening a head. In addition, it turns out that we can open up the blood-brain barrier with ultrasound, and so we may be able to clear toxic proteins, such as those in Alzheimer's

disease. We've actually already been able to do this in animal models, and we are now testing if that could be the case in humans with our colleagues at Sunnybrook. It's a very exciting time, because the technology is there to do things that we couldn't do before. We can tackle problems that we previously ignored or gave up on. Now, with these new tools and understanding, we can do things that we've never been able to do before.

UTMJ: Would you have any advice for someone who may be interested in pursuing neurosurgery as a career?

AL: I think most people think that neurosurgery is quite an interesting area, just intrinsically, because it is technical and involves the brain. However, it is a tough training program – physically and mentally demanding. I think, unless you have enough drive and conviction, it's not a good area for people to go into. We tell people to see as much neurosurgery as they can, and rotate or do electives to see whether they feel comfortable with the acuity and illness of the patients, as well as the pace. If the answer to all of the above is yes, there is no field more rewarding or interesting.

UTMJ: What are your interests and hobbies outside of neurosurgery?

AL: Sleeping! If I'm not working, I'd really like to be sleeping! But all jokes aside, I just try my best to stay healthy, eat properly, exercise frequently, and read. I try to study other fields and how they may impact your own. Trying to learn as much as possible from anyone and everyone. I think these are all things that make my life more interesting.

UTMJ: Given how challenging the field of neurosurgery can be, what grounds you and keeps you going everyday?

AL: The sense of purpose. The sense that you're doing something that is interesting, challenging, and have a certain determination to be able to accomplish. And finally, I think it's the impact that we have. When you see what kind of impact you can have on someone and turn someone's tremor off, within a second, or stop someone from seizing, or take someone who was depressed and make them well – that's pretty satisfying.

Trichobezoar Causing Small Bowel Obstruction: Case Report

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Abstract

We describe a case of a previously healthy 6-year-old-girl presenting with a one-day history of bilious emesis, periumbilical pain, and feeding intolerance. Initial abdominal radiographs were unremarkable. Following continued episodes of bilious vomiting, an upper GI series was performed, which demonstrated coating of a non-occlusive intraluminal mass within the proximal jejunum. Serial abdominal radiographs document movement of the mass from the left upper quadrant to the right lower quadrant along with progressive dilatation of the proximal small bowel, suggesting small bowel obstruction. An abdominal CT confirmed a small bowel obstruction at the level of the barium coated intraluminal mass. At surgery, the obstruction was discovered to be due to a jejunal trichobezoar. Upon further retrieval of clinical history, it was determined that the patient had a history of eating her hair and couch cushions. A jejunal bezoar is a rare cause of small bowel obstruction. It can be a diagnostic challenge and can lead to significant complications if there is a delay in diagnosis. Throughout this case, we describe the clinical presentation of the patient and demonstrate the progression of radiographic findings of a small bowel trichobezoar.

Introduction

Bezoars are collections or concentrations of indigestible material in the gastrointestinal tract that can impair motility and cause intestinal obstruction.[1] There are several bezoar subtypes depending on the predominant components. These include pharmacobezoars, which are mostly undigested tablets or semi-liquid masses of drugs, phytobezoars, which are caused by non-digestible plant material, lactobezoars, which are exclusively found in infants and contain undigested mild curds, and trichobezoars, which are caused by ingestion of large amounts of hair.[2,3] Trichobezoars are the most common, comprising 55% of all bezoars.[4] In addition to dietary and psychiatric history, previous gastric surgery can predispose to bezoar formation.[5,6]

Trichobezoars usually occur in patients with a history of trichotillomania, a compulsive behavior disorder of pulling one's hair, combined with trichophagia, the compulsive ingestion of hair.[7-9] Trichobezoars typically occur in the stomach and rarely affect the small intestine.[8] Common clinical symptoms include abdominal pain, nausea, vomiting, and weight loss.[7] However, the majority of trichobezoars present late due

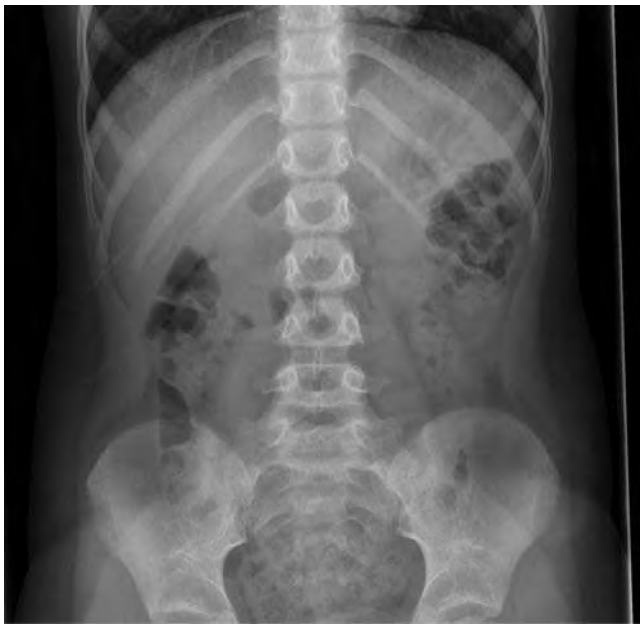

Figure 1. Normal abdominal radiograph on Day 1 of admission with no signs of bowel obstruction.

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to low clinical suspicion. Though intestinal obstruction due to trichobezoars is rare, as the bezoar progresses in size, obstructive symptoms along with hematemesis, perforation, or peritonitis may arise.[10]

Fluoroscopy, ultrasound, and computed tomography are all imaging modalities used to diagnose the presence of a trichobezoar. Although endoscopic management is available for proximal trichobezoars, surgical treatment is required for intestinal trichobezoars.

In this report, we describe a case of an atypical localization of a trichobezoar in a 6-year-old girl who presented with small bowel obstruction. The clinical presentation, radiographic findings, and clinical management are discussed.

Case Report

Our patient was a 6-year-old previously healthy, immunized, and developmentally normal female. She presented with a one-day history of 5-6 episodes of bilious emesis, periumbilical pain, and intolerance to fluids or solids. The emergency room physician was particularly struck by how foul the emesis smelled and how unusual it looked. She had two isolated incidents of nonbilious emesis in the past three weeks. The patient had no bowel movements for two days but was flatulent. The patient had a history of constipation. There was no family history of inflammatory bowel disease or celiac disease, but her mother did have a history of irritable bowel syndrome. On physical examination, the patient was afebrile and demonstrated periumbilical tenderness. Bowel sounds were present and her abdomen was nondistended. Laboratory investigations revealed a mild leukocytosis, with otherwise normal inflammatory markers. The patient was admitted into hospital, during which she had intermittent bilious vomiting. General pediatrics, gastroenterology, general surgery, and radiology services were involved in the care of this patient.

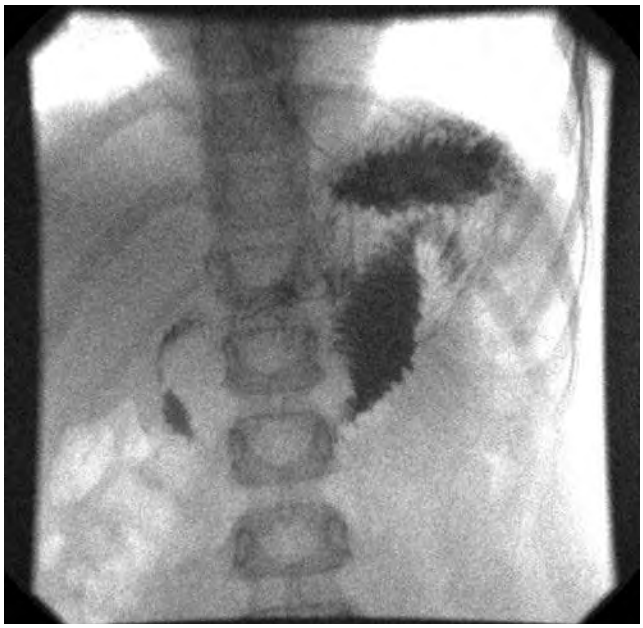

Figure 2. Upper GI series on Day 1 demonstrated slow transit with contrast in dilated proximal jejunum and mild mural thickening.

Imaging Findings

While admitted, numerous investigations (Abdominal x-ray, upper GI and small bowel series, abdominal ultrasound, upper GI endoscopy, and CT abdomen) were ordered to determine the etiology of her symptoms. On Day 1 of admission, an abdominal radiograph was normal, showing no signs of obstruction (Figure 1). An upper GI series follow-up demonstrated slow transit with contrast accumulating in a dilated jejunal loop with mild mural thickening (Figure 2). On Day 2, ultrasound examination demonstrated a mildly dilated, fluid-filled proximal bowel loop with mild wall thickening and no free fluid (Figure 3). The pediatric gastroenterology

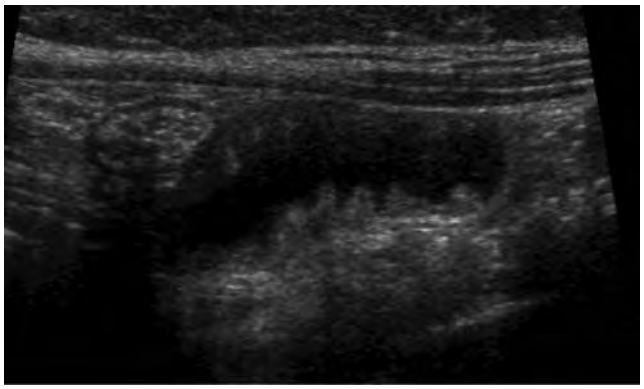

Figure 3. Sonographic image on Day 2 demonstrated mildly dilated, fluid-filled proximal bowel loop with mild wall thickening.

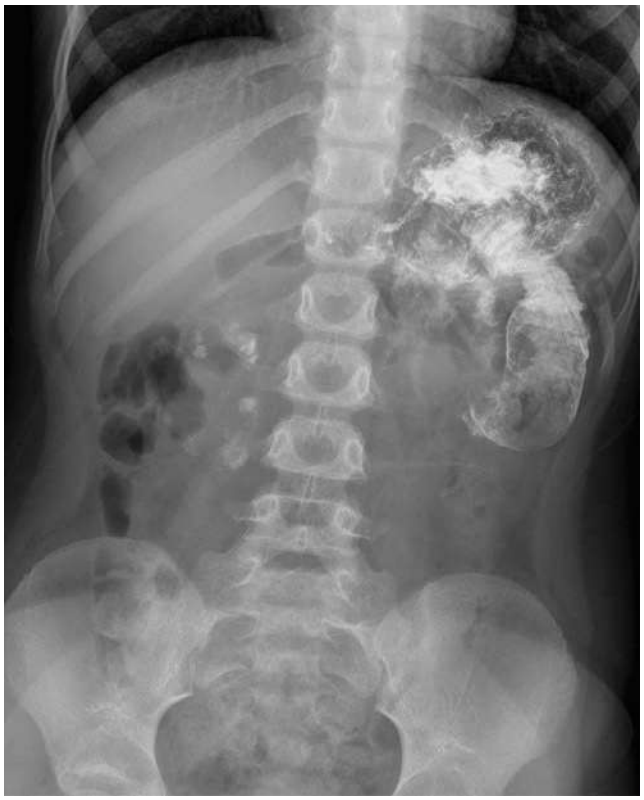

Figure 4. Abdominal radiograph on Day 3 demonstrated a barium-coated mass in the left upper quadrant and a few dilated proximal small bowel loops.

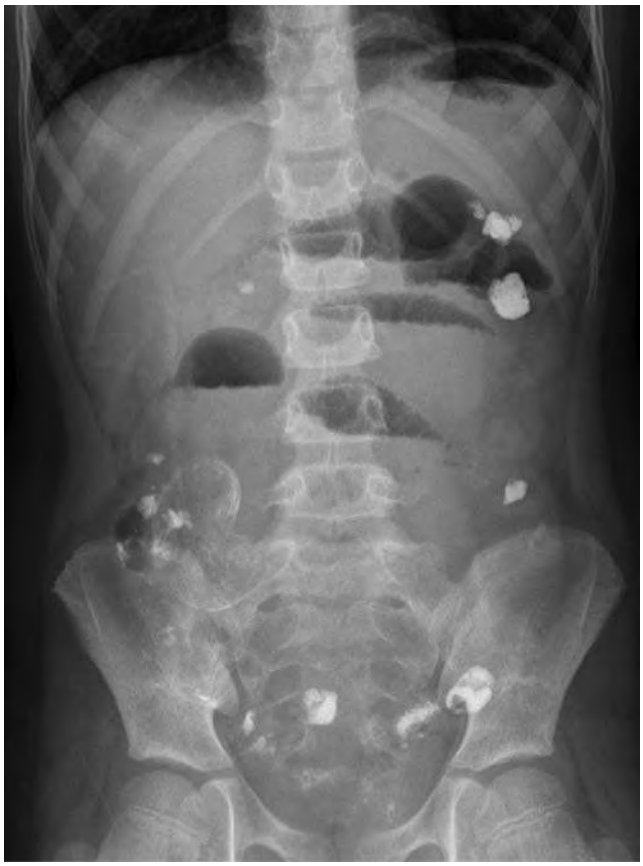

Figure 5. Abdominal radiograph on Day 5 noted multiple air fluid levels consistent with bowel obstruction and shift of intraluminal mass from LUQ to RLQ.

service was consulted at this point and an upper endoscopy was performed which was found to be normal. Radiograph performed on Day 3 following the upper endoscopy demonstrated a barium-coated mass in the left upper quadrant and a few dilated proximal small bowel loops (Figure 4). On the subsequent radiograph on Day 5, the barium coated intraluminal mass (from upper GI series) was noted to have moved from the left upper quadrant to the right lower quadrant and multiple central air fluid levels were present suggestive of bowel obstruction (Figure 5). No evidence of pneumatosis or pneumoperitoneum was seen on plain radiographs. On Day 6, a contrast-enhanced computed tomography (CE-CT) of the abdomen and pelvis was completed without oral contrast, as per normal protocols at our facility. This demonstrated a barium-coated mass (from upper GI study contrast) with a heterogeneous internal density in the distal jejunum/proximal ileum with no central contrast enhancement (Figure 6). There was a barium-coated "tail" extending distally from the mass (Figure 7). No gastric bezoar was noted.

General surgery was consulted, and the patient was taken to the operating room for a laparotomy. A periumbilical laparotomy was performed and a mass in the jejunum was discovered. Edema and dilatation of the proximal bowel was present, with collapse of the bowel distally (Figure 8). The mass could not be milked. A transverse enterotomy in the jejunum

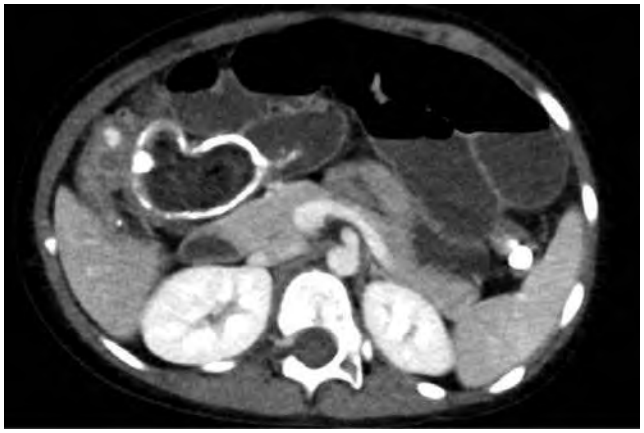

Figure 6. On Day 6, contrast enhanced CT was performed which showed a barium-coated mass with a heterogeneous internal density in the distal jejunum with no central enhancement.

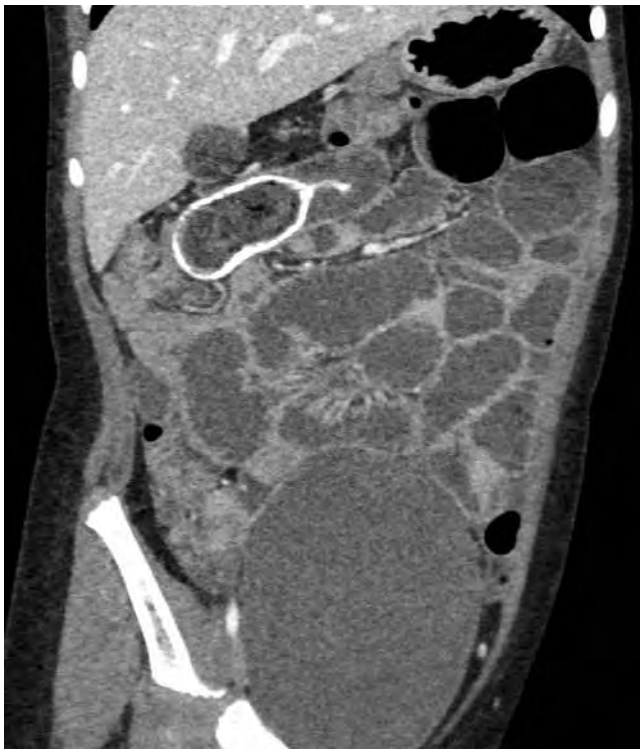

Figure 7. Coronal reformat demonstrated same barium-coated mass in distal jejunum in the RUQ with barium tail extending distally.

revealed a trichobezoar adhering to the mucosa (Figure 9). The trichobezoar was removed and bowel was closed. There were no other visceral abnormalities upon surgical investigation.

Post-operatively, upon further discussion with parents, clinicians were notified that their daughter had a history of eating her hair and the couch pillows one year ago. It was believed that she was no longer doing this. The patient had an uncomplicated post-operative course. She was seen a month later in the general surgery clinic for follow-up and was doing well. A psychiatric referral has been arranged.

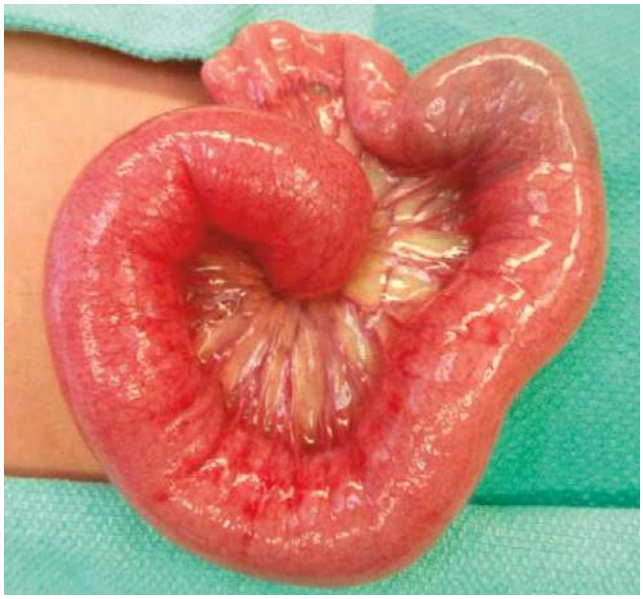

Figure 8. Intraoperative visualization of distal small bowel obstruction secondary to jejunal bezoar.

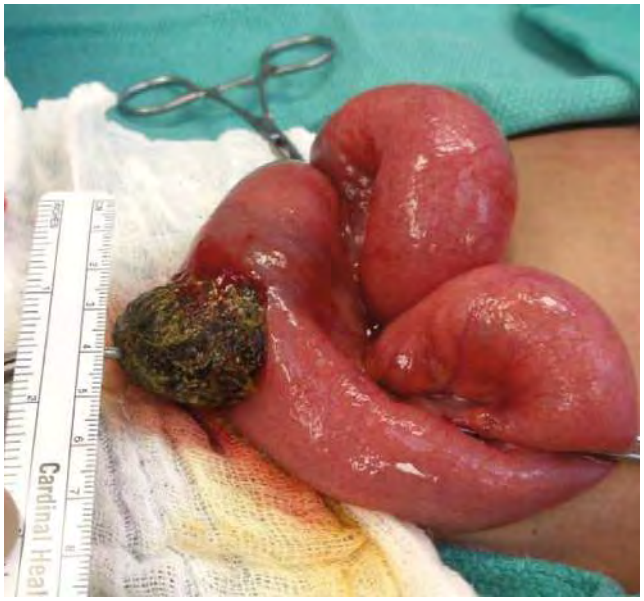

Figure 9. Transverse enterotomy for trichobezoar resection.

Discussion

Trichobezoars mostly originate at the level of the stomach, as the stomach is unable to move the hair out of the lumen because the friction surface is not sufficient for propulsion by peristalsis.[8] Detachment of a portion of a gastric bezoar, with subsequent distal movement in the GI system, results in the creation of a Small bowel bezoar.[9] Rarely are small bowel trichobezoars seen without associated gastric bezoars, as in our case.[9] The most common sites of obstruction for bezoars are the gastric outlet or duodenum, with obstruction at distal parts of the small bowel or large bowel being extremely rare.[9] Rapunzel syndrome is a reference to a specific distribution of a trichobezoar with a tail extending from the stomach to the jejunum, ileum, or the ileocecal junction.[4]

Common presenting symptoms of bezoars are abdominal pain, nausea, vomiting, weight loss, malnutrition, hematemesis, diarrhea, or constipation.[3] On physical examination, an epigastric mass may be palpated. In patients with suspected trichobezoar or history of trichotillomania, clinicians should examine patients for alopecia.[3]

Upon presentation, most patients will undergo a series of imaging studies to determine the etiology of their pain. On plain film, a mass of opaque soft tissue with a calcified rim in the region of the bezoar is often seen and if the bezoar causes bowel obstruction, air fluid levels with distended bowel loops may be noted.[7,9] Ultrasound and CT imaging are especially helpful in the diagnosis.[3] On ultrasound examination, a bright echogenic band and shadow over the region of the bezoar may exist.[3] CT scan is the most useful diagnostic modality because it reveals the localization of the obstruction and it demonstrates a heterogeneous, mottled intraluminal mass with low attenuation in the transition zone of the obstruction.[11] CT scan may also demonstrate a mottled gas pattern representing air bubbles within the bezoar.[12] As CT scans are high radiation dose modalities, they should be used judiciously given the rarity of this condition presenting either acutely or chronically. More recently, researchers have recommended magnetic resonance imaging (MRI) for the evaluation of small bowel-disease, which displays the bezoar as a luminal small bowel mass containing mottled and confluent low signal intensities on both T1 and T2 weighted images.[13]

Several management options exist for the treatment of bezoars. Endoscopy has been used in the diagnosis and management of proximal, small trichobezoars. However, it comes with a small risk of bowel perforation.[9] Although more invasive, both laparoscopy and laparotomy have been successfully utilized to treat bezoars.[14,15] Patients treated laparoscopically have been found to have fewer post-operative complications and reduced hospital stays. However, major drawbacks of laparoscopy have included abdominal spillage with concomitant contamination and longer operative times.[14,15] Regardless of the chosen surgical approach, it is mandatory to do a thorough investigation of the small intestine and the stomach looking for retained bezoars.[16] Conservative treatment is reserved for patients who have no signs of acute abdomen.[17] Although not often used, Huang et al. have described the successful use of laser ignited mini-explosive technique.[18]

Trichobezoars commonly occur in patients with psychiatric disturbances who chew and swallow their own hair, but only 50% have a history of trichophagia.[4] Although the diagnosis of trichobezoar is often discussed alongside trichotillomania and trichophagia, the exact relationship is often not statistically detailed. Frey et al. describe that only 30% of patients with trichotillomania will engage in trichophagia, and of these, only one percent will ingest their hair to the point of requiring surgical removal.[19] Nonetheless, psychiatric follow-up is recommended for patients presenting with a trichobezoar to prevent recurrences.

Conclusion

Trichobezoars are a rare clinical entity but should be on the differential for patients with abdominal complaints, particularly with a history of trichophagia or trichotillomania. The majority present in the stomach, with very few seen in the small bowel. Patients often present with nonspecific gastrointestinal symptoms and rarely present with an acute abdomen. Various imaging modalities can be used to localize and diagnose the bezoar. Surgical management is required for intestinal trichobezoars. Psychiatric referral is helpful in preventing recurrences.

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An Adolescent with Sore Throat and Odynophagia: A Case Report of Ludwig's Angina

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Abstract

We report a case of Ludwig's angina in an immunosuppressed adolescent presenting with sore throat and odynophagia. Ludwig's angina is a rare but potentially life-threatening infection of the submandibular space. We present an overview of the presentation, risk factors, microbiology, diagnosis, and management of this condition in addition to our case report. We present this case to highlight the importance of considering this condition, especially in an immunosuppressed pediatric patient.

Case Presentation

A 16-year-old female presented to a community pediatrics clinic with a three-to-four-day history of sore throat, low grade fever, and worsening odynophagia beginning after a water park trip where the patient came in contact with a friend with upper respiratory tract infection symptoms. Following the trip, she reported feeling unwell and having a sore throat, in addition to being mildly febrile. A throat swab at a walk-in clinic two days prior to presentation was negative for Group A *Streptococcus*.

The patient's history was significant for Crohn's disease, polyarticular juvenile idiopathic arthritis, and a distant tonsillectomy and adenoidectomy for recurrent Group A streptococcal infections. She had not had any recent dental manipulations or infections, and her last dental cleaning occurred approximately two months prior to presentation. Her medications included methotrexate; approximately one month prior to presentation, she had also started infliximab and discontinued sulfasalazine. Her immunizations were up to date.

Upon presentation to her pediatrician, the patient endorsed odynophagia and sore throat, which was impairing her ability to eat both solids and liquids. On examination, the patient appeared unwell: she was drooling with her tongue protruding and her voice was hoarse, though she was now afebrile. On auscultation, the chest was clear, including absence of stridor. She had submandibular tenderness but no palpable lymph nodes. The patient was sent to the local community hospital for assessment by the pediatrician on call.

Diagnosis and Management

At the hospital, the patient was further noted to have trismus, mild posterior oropharyngeal erythema, and submandibular tenderness with visible edema; there was no airway compromise. Neck x-ray and computed tomography (CT) were unremarkable except for mild swelling of the tonsils, and her white blood cell count (WBC) was 12.9×10^9/L. The patient was then seen by an experienced otolaryngologist, who diagnosed her clinically with Ludwig's angina based on presentation and a bedside flexible nasopharyngoscopy.

Pending microbiology results, the patient was treated with broad-spectrum antibiotics, with attention to her immunocompromised status and exposure to water and sick contacts. She was administered intravenous piperacillin-tazobactam, vancomycin, and azithromycin. Furthermore, her methotrexate was held, she was admitted to the intensive care unit for airway monitoring, and intravenous dexamethasone was administered.

Outcome

Following treatment overnight, the patient reported significant improvement, with greatly reduced edema of the floor of the mouth and only residual throat discomfort. She was transferred to the general pediatric floor. By the following day, her WBC had returned to 6.6×10^9/L, and she was stepped down to oral azithromycin and amoxicillin/clavulanic acid. She was determined to be well enough to be discharged and was asked to finish her course of antibiotics following discharge. Blood cultures and nasopharyngeal swabs were ultimately negative for all tested bacterial and viral agents. On follow-up in the hospital's pediatric outpatient clinic three days later, the patient had fully recovered. However, she returned to her pediatrician three weeks later, once again complaining of odynophagia and throat pain. This was assessed as a possible return of the Ludwig's angina, and she was successfully treated with a further course of azithromycin and amoxicillin/clavulanic acid.

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Discussion

Ludwig's angina is a severe manifestation of submandibular space infection involving both the sublingual and submylohyoid spaces that comprise the submandibular space. The two compartments communicate, allowing infection to spread between them.[1] The infection can further spread into the parapharyngeal space via the buccopharyngeal gap and, from there, to the retropharyngeal space and superior mediastinum, resulting in the rare complication of mediatinitis.[2]

Patients with Ludwig's angina usually present with fever, chills, mouth pain, neck stiffness, drooling, and dysphagia. They may have a muffled voice or be unable to speak.[2] There is also submandibular and submental neck swelling, induration of the floor of the mouth, and swelling of the tongue.[3,4] Prior case series show that children comprise 24-35% of cases of Ludwig's angina, and the condition has been diagnosed in a neonate as young as 12 days in one case report.[4,5]

Ludwig's angina is most often caused by spread from dental infections, most frequently of the second, and in adults, the third, mandibular molars.[6] Odontogenic causes are more common in adults (70-90%), but still make up 50% of the causes in children.[7] Other sources include peritonsillar abscesses, mandibular fractures, oral lacerations, piercings, and oral malignancies.[7] Patients can further be predisposed by recent dental procedures, systemic illness, malnutrition, and, as in the case of this patient, impaired immune function.[3,5,8] Notably, in children, 25% of Ludwig's angina can occur without any precipitating cause.[4] The most common causative organisms include viridans group streptococci and oral anaerobes, such as peptostreptococci and *Fusobacterium nucleatum*.[5,8] Gram-negative bacteria, including *Neisseria catarrhalis*, *Escherichia coli, Pseudomonas aeruginosa*, and *Haemophilus influenzae*, may also be present.[5]

Ludwig's angina is usually diagnosed based on history suggestive of submandibular infection and clinical presentation, including swelling and erythema of all tissues and compartments of the floor of the mouth, superoposterior displacement of the tongue, firm induration of the submandibular and anterior neck area, trismus, voice change, and dyspnea.[9] Imaging may support the diagnosis, in which case CT is usually the preferred modality[10] to search for presence of abscesses.[9] Blood culture may be indicated to check for bacteremia, though 65-83% of cultures may not show any growth.[4]

Ludwig's angina is particularly noted for the risk of airway obstruction and subsequent asphyxiation that may result from superoposterior displacement of the tongue and progressive swelling. Airway obstruction may be imminent particularly if the patient presents with stridor, cyanosis, or an inability to swallow.[4] Although mortality was once greater than 50%, modern antibiotic therapy and improved imaging have reduced this to 0-8% in the general population, and 10-17% in the pediatric population.[7,10]

Treatment includes airway management and empiric broad-spectrum antibiotics. Currently, no clinical trials have been performed on antibiotic regimens for Ludwig's angina, so antibiotic choice should be informed by the expected or known microbiology. For immunocompetent patients, antibiotics should cover beta-lactamase-producing aerobes and anaerobes. Recommended antibiotics for initial treatment of Ludwig's angina prior to culture results include penicillin G with metronidazole, or clindamycin, which is the drug of choice in those with penicillin allergies. If methicillin-resistant *Staphylococcus aureus* (MRSA) is a concern, the patient should also be treated with vancomycin. Antibiotic treatment should continue for two to three weeks until there is clinical improvement and resolution of fever and leukocytosis.[10] In patients found not to be at risk of imminent airway compromise, management may initially begin with close observation and antibiotics. In some cases, intravenous steroids have circumvented the need for invasive airway management.[7] With progression of swelling, however, control of the airway should be gained immediately. Fibre-optic nasotracheal intubation is the recommended approach, but tracheostomy and cricothyrotomy are also options if this is impossible or unsuccessful. It has been recommended that blind nasal intubation should be avoided due to low success rate and risk of trauma and laryngospasm with repeated attempts. It is also recommended to avoid the use of direct laryngoscopy; distorted airway anatomy and tissue immobility lead to difficult access,[11] and mucosal friability and proneness to edema can make further attempts to gain airway control more difficult.[12] Furthermore, the requirement for general anesthesia to perform direct laryngoscopy can precipitate complete airway closure, making mask ventilation and tracheal intubation impossible.[11]

In immunocompromised patients and particularly in children, gram-negative species may also be present. As such, empiric antibiotic treatment should also include coverage of gram-negative bacteria in addition to the coverage recommended for immunocompetent patients. A common regimen includes a cephalosporin with action against Pseudomonas, such as cefepime, combined with an agent targeting oral anaerobes, such as metronidazole. For more advanced infections, a carbapenem or piperacillin-tazobactam may be used. As with immunocompetent hosts, vancomycin should be included in the regimen if there is concern about MRSA.[9]

Conclusion

Ludwig's angina is a potentially life-threatening condition that can usually be resolved with early identification and treatment. Given that children make up a large portion of cases of Ludwig's angina, and that pediatric cases may present without any identifiable precipitating factor, it is especially important to keep Ludwig's angina on the differential diagnosis in clinical presentations such as these, especially in those who are immunosuppressed or immunocompromised.

Informed Consent

The authors verify that informed consent was obtained from the patient's caregiver, in addition to assent from the patient herself.

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Late Presentation of Hardware Related Osteomyelitis of the Radius

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Introduction

While internal fixation related osteomyelitis is common, it is usually diagnosed within the first few years after implant insertion.[1] We report our experience with a rare case of a late presentation of hardware related osteomyelitis of the radius 8 years after bony fixation, as well as successful treatment with irrigation, debridement, removal of hardware and antibiotics. This case represents the latest initial presentation of osteomyelitis after its hardware insertion that has been reported in the literature. Full and informed consent for publication of this case and associated images was obtained from the patient.

The Case

A 53-year-old male and otherwise healthy patient underwent open reduction and internal fixation of his left scaphoid and radius with no complications (see Figure 1). Eight years later, he developed open wound with intermittent drainage near his proximal incision site. He denied new trauma. Otherwise, he had no infectious symptoms including no fevers or chills nor elevation in white blood cell count or other inflammatory markers. Other than the inconvenience of intermittent drainage, he had no functional limitations and his range of motion in the affected wrist was unchanged.

T2 weighted contrast MRI demonstrated healed radius with no evidence of osteomyelitis, with no periosteal reactions and no sequestrum.

As clinical suspicion was high and symptoms were persistent, we proceeded with surgical exploration. He underwent a surgical excision of the draining sinus as well as removal of the deep buried hardware (see Figure 2). The draining sinus, upon exploration, demonstrated obvious penetration to the radius fixation plate. Intraoperative cultures demonstrated scant growth of *Staphylococcus aureus*. The Infectious Disease service arranged oral levofloxacin and rifampin for a total duration of 6 weeks. The patient healed uneventfully with no further complications.

Discussion

Subacute and chronic osteomyelitis results when an inflammatory reaction creates locally collected exudates, leading to blood vessel constriction. In turn, this leads to focal bone necrosis, creating a sequestrum of avascular bone fragments and often harbouring infection. This process usually takes 3 weeks to occur but can be subclinical for years.[2] Biofilms at retained hardware remain a significant risk factor.[3]

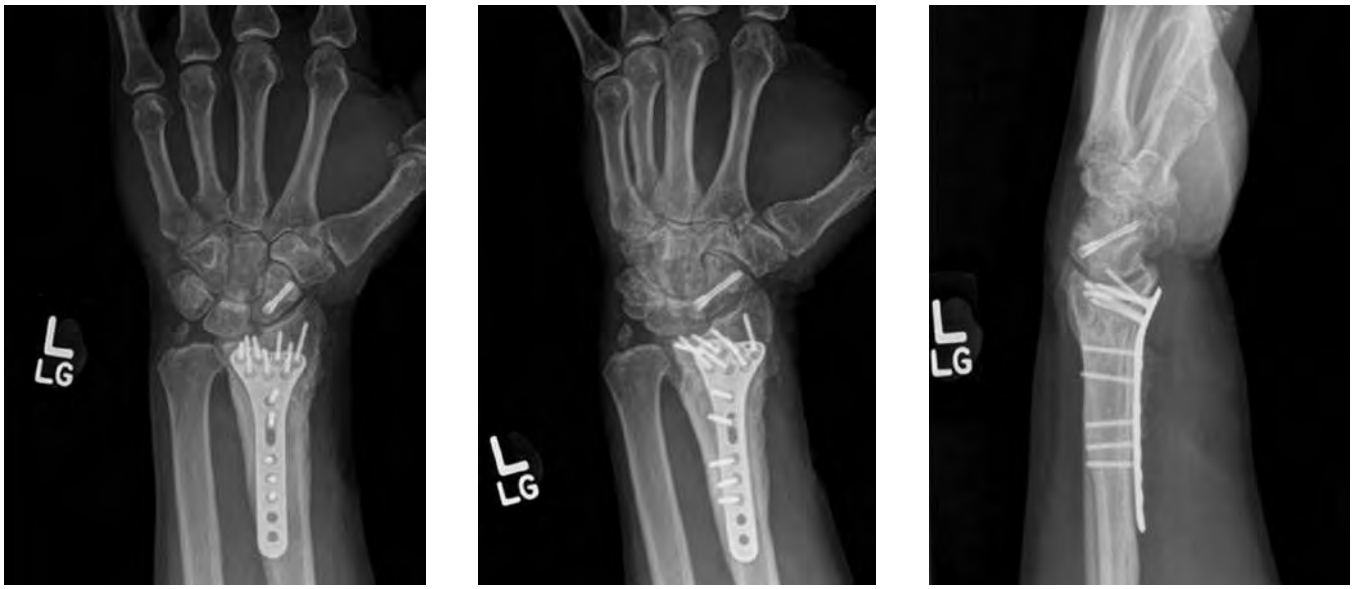

Figure 1. Original patient x rays upon presentation, demonstrating hardware location.

Risk factors for osteomyelitis include penetrating trauma and recent surgery, hematologic or untreated systemic infection, neurologic disorders such as paraplegia leading to pressure ulcers and adjacent soft tissue infections, immunocompromised state, uncontrolled diabetes, and vascular insufficiency (particularly in adults).[2,4,5] Specific relative risk ratios for these factors has not been studied. *Staphylococcus aureus* is the most common etiologic agent.[2,5]

For patients with postoperative osteomyelitis, the condition is often recognized early due to symptomatology. Implants are usually removed, with placement of an external fixation device for stability. Some surgeons may allow temporary implant retention to allow bone healing prior to infection treatment. Other early revision strategies, such as irrigation and debridement with temporary hardware maintenance, have also been described for the more common presentation of relatively early osteomyelitis treatment shortly after initial hardware placement.[3] Clinical outcomes tend to be better for acute rather than chronic osteomyelitis treatment.[6]

Chronic osteomyelitis can lead to pain and lesser ability to participate in activities of daily living, even after eradication of infection and fracture union. Other complications may include sepsis, relapses, and the risk of malignant transformation. While the optimal duration of antibiotic therapy is not well studied, most physicians treat patients with antibiotics for 6 weeks. Despite this, there is no consensus on the best agents, routes of delivery, and duration.[6]

This late first presentation of a hardware-related osteomyelitis highlights the importance of recognizing remote causative factors, even in otherwise healthy patients demonstrating seemingly minimal symptoms.

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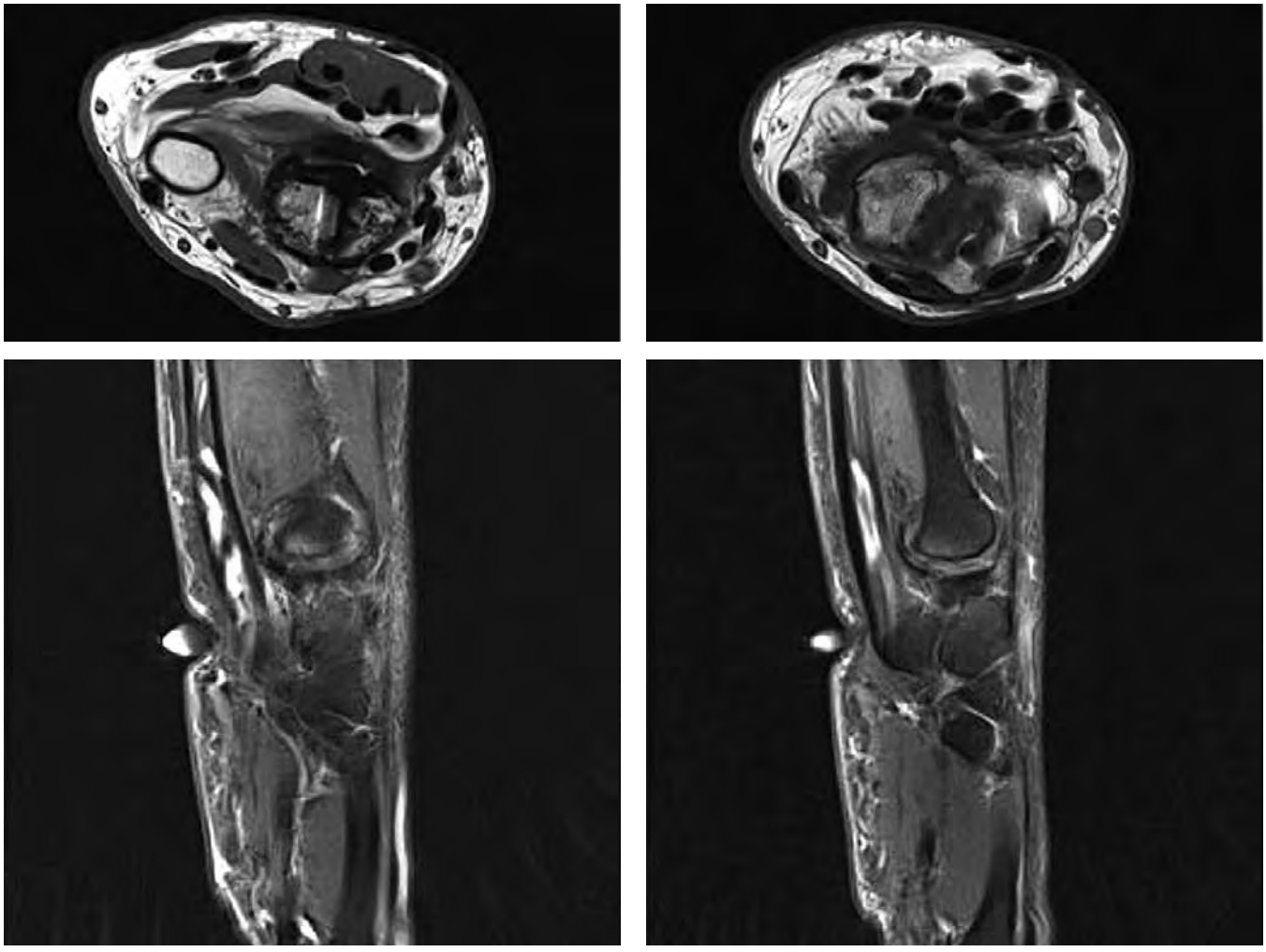

Figure 2. Postoperative MRI Images.

Impact of an Unknown HIV Serostatus on the Risk of Postoperative Cardiovascular Morbidity and Mortality

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Abstract

Background: The impact of an unknown human immunodeficiency virus (HIV) serostatus on postoperative outcomes, such as major adverse cardiovascular events (MACE), in surgical settings with a high prevalence of HIV infection has not yet been established. This was the impetus for the current study.

Methods: This was an unmatched case-control study of 460 patients who underwent vascular/general surgery at a tertiary South African hospital (patients with MACE/cases = 92 and patients without MACE/controls = 368). Data related to age, gender, and the presence of established cardiovascular risk factors in surgical settings were extracted from patient medical records. HIV serostatus for each patient was recorded as positive or negative (where preoperative documentation of such test results existed) or unknown (where no preoperative documentation of an HIV test result existed). Data were analyzed in accordance with recommendations for unmatched case-control study designs.

Results: Adjusted analysis revealed that there was no difference in the risk of postoperative MACE between HIV-negative (reference group), HIV-positive (odds ratio: 1.16, 95% confidence interval: 0.42-3.21) and HIV-unknown serostatus (odds ratio: 0.85, 95% confidence interval: 0.47-1.54) groups.

Conclusion: Our study findings suggest that an unknown HIV serostatus is not a risk factor for postoperative MACE. HIV serostatus should not be included in cardiovascular risk stratification methods in surgical settings with a high prevalence of HIV.

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Introduction

Globally, over 30 million people are infected with human immunodeficiency virus (HIV).[1] In South Africa, 11-20% of the population is thought to be infected with HIV.[2] However, there appears to be suboptimal uptake of HIV counseling and testing in the South African adult population, with almost half of adult patients not knowing their HIV serostatus.[2] The large proportion of the South African adult population with an unknown HIV status is alarming. Findings from a recent study of medically-treated (non-surgical) patients attending a South African hospital located in a region of the country with a high prevalence of HIV infection suggest that an unknown HIV serostatus might potentially be associated with undesirable patient outcomes.[3] Determining HIV serostatus is important in high prevalence settings as this facilitates identification of patients with previously undiagnosed HIV infection, thereby allowing for the initiation of antiretroviral therapy and effective disease management in these patients.[4] An increasing burden of infectious, non-communicable disease with high levels of injury and trauma has resulted in a growing South African population requiring surgical intervention and treatment requiring surgical intervention for the treatment of these conditions at some point during their lifetime.[5] Many of these patients are at risk of developing complications following their surgery, with major adverse cardiovascular events being amongst the most important complications during the postoperative period.[6] A study by Redman et al. found the incidence of postoperative cardiovascular morbidity and mortality to be similar in South African vascular surgery patients with or without HIV infection.[7] Many patients in that study did not consent to HIV counseling and testing, so the unknown HIV serostatus group was not included in the final data analysis.[7] Surgical patients who are known to be HIV-positive prior to their surgery are initiated on antiretroviral therapy. Patients with unknown HIV serostatus, particularly in HIV-endemic settings, are potential undiagnosed HIV-positives. However, as antiretroviral therapy is only provided to those patients who are diagnosed HIV-positive, undiagnosed HIV-positives go untreated. HIV-positive surgical patients who receive antiretroviral therapy are at a lower risk of perioperative mortality when compared with HIV-positive surgical patients who do not receive antiretroviral therapy.[8] As there is cardiovascular involvement in a large proportion of deaths following non-cardiac surgery,

it is possible that antiretroviral therapy reduces the risk of perioperative cardiovascular complications in HIV-positive surgical patients. This possibility is somewhat supported by Redman et al., who reported a lower incidence of perioperative cardiovascular morbidity and mortality in HIV-positive vascular surgery patients who received antiretroviral therapy versus an antiretroviral therapy naïve vascular surgery patient group (9% versus 18%).[7] It would appear that universal testing of surgical patients for HIV in high-prevalence settings, and initiating those who test positive on antiretroviral therapy, could potentially reduce perioperative cardiovascular morbidity and mortality in this patient population. However, the rollout of universal HIV testing for all surgical patients in resource-constrained settings can only be considered once a direct link between an unknown HIV serostatus and postoperative cardiovascular morbidity and mortality is established. Therefore, this study sought to determine the impact of an unknown HIV serostatus on postoperative major adverse cardiovascular events (MACE) in a setting with a high prevalence of HIV infection.

Methods

Study design, setting, and study population: This was an unmatched case-control study of adult (aged 18 years old or older) South African patients who underwent vascular or general surgery procedures between January 2012 and July 2016 at the Inkosi Albert Luthuli Central Hospital in Durban, South Africa. The hospital provides medical and surgical services at a tertiary level to the residents of the KwaZulu-Natal Province, South Africa. Vascular surgery and general surgery patients were selected for this study. as these surgical specialties have been previously associated with a high incidence of poor postoperative patient outcomes at the hospital.[9] In addition to the high incidence of poor postoperative outcomes in both vascular and general surgery populations, it was decided to use both surgical groups to ensure that there was adequate representation of patients who were undergoing major surgery. The unmatched case-control study was conducted using the methodologies suggested by Breslow and colleagues.[10]

Case and Control Definitions

Cases were defined as surgical patients who suffered postoperative MACE while in hospital. Postoperative MACE was determined from hospital discharge summaries and was defined as a diagnosis of myocardial infarction (based on elevated cardiac biomarkers and one of the following: ischemic symptoms, evidence of myocardial ischemia on electrocardiogram, or echocardiographic evidence), stroke (a new onset neurological deficit of vascular etiology of duration ≥24 hours, or resulting in death within 24 hours), or all-cause mortality following surgery, which occurred while patients were still hospitalized. Troponin-I was used as the cardiac biomarker, with a measurement of ≥0.1 ng/ml within the first three postoperative days considered a positive test result. The ECG criteria for MACE included the following: new pathologic Q waves; ST-segment elevation ≥2mm in leads V1, V2, V3, or ≥1mm in other leads; ST-segment depression of ≥1mm; or T-wave inversion of ≥2mm in two contiguous leads. Any new or presumed new cardiac wall motion abnormality was considered a positive echocardiogram result. The choice of this composite outcome is similar to that used in other studies reporting cardiovascular morbidity and mortality following surgery.[11] There is evidence to suggest that there is some cardiovascular involvement in postoperative death of non-cardiovascular etiology,[12] which further supports our decision to use this composite patient outcome. Controls were defined as patients who did not suffer postoperative MACE while in hospital.

Sample Size Calculation

The sample size required for this study was 460 patients (92 cases and 368 controls). This was based on the following parameters: anticipated odds ratio (OR) 2.0 (we considered this to be the smallest clinically significant OR to be detected), estimated exposure of controls 25% (we anticipated that this would be lower than the 50% reported for the general South African adult population, as it was likely that patient HIV serostatus might have been determined at lower level healthcare facilities prior to their admission at the tertiary level facility), alpha risk 5%, power 80%, and a case-control ratio of 1:4. We determined the case pool during the study period to be 100 patients and the control pool to be 2,620 patients. The required number of cases and controls were then selected from each pool using a random number generator to reduce selection bias.

Patient demographics and cardiovascular risk factors

A chart review of case and control patient medical records was conducted. Data related to age, gender, and clinical characteristics comprising Lee's Revised Cardiac Risk Index (RCRI, established risk factors associated with postoperative cardiovascular morbidity and mortality, including history of ischemic heart disease, congestive heart failure, stroke, diabetes, renal impairment, and major surgery).[13] The definitions for the RCRI components were adopted from the original study conducted by Lee and colleagues.[13] The total number of established risk factors present was used to compute the RCRI score for each patient, with each risk factor being allocated a single point. Higher RCRI scores are associated with a higher risk of postoperative cardiovascular morbidity and mortality.[13] HIV serostatus was also determined from the patient medical record. A patient was considered HIV-positive or HIV-negative if they had preoperative documentation of these test results in their medical records. Patients without documented preoperative HIV test results in their medical records were classified as patients with an unknown HIV serostatus in this study. Data extracted from the medical records of each patient were entered onto a password protected database in preparation for statistical analysis.

Statistical Analysis

Data were analyzed in accordance with recommendations for unmatched case-control studies.[10] Univariate (crude) statistical analysis of the study data was conducted using χ^2, Fisher's Exact, or Mann-Whitney tests as appropriate. Results for the univariate analysis are presented as frequencies with

percentages or medians with interquartile ranges (IQR). For the multivariate (adjusted) analysis, an unconditional logistic regression model was used to account for potential confounding in the unmatched case-control study design. All clinical characteristics were entered as independent variables into the logistic regression model, with postoperative MACE being the dependent variable. Results for the multivariate analysis are presented as OR with 95% confidence intervals (95% CI). A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 (IBM Corp., USA).

Study Ethical Approval

Use of patient hospital data for research purposes was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, South Africa.

Results

The characteristics of the study population (combined cases and controls) are shown in Table 1. The median age for the entire study population suggests that many of the patients were middle aged, with a slightly higher proportion of the study population being female. Diabetes, major surgery, and ischemic heart disease were common in the study population (prevalence of 21.3%, 20.2%, and 12.2%, respectively). Fifteen percent of the entire study population was determined to be high risk for postoperative cardiovascular morbidity and mortality (RCRI ≥2 points). HIV serostatus was not known in half of the study population. The proportion of vascular to general surgery patients was 41.3% : 58.7%. The majority of patients in the vascular surgery population had undergone infrainguinal procedures, including lower limb amputation and peripheral arterial bypass grafting. The majority of patients in the general surgery group had undergone open gastrointestinal procedures including cholecystectomy, colorectal resection, and surgery for breast cancer. The incidence of MACE in the vascular surgery group was 21.3%. The incidence of MACE in the general surgery group was 19.3%.

The proportions of several characteristics investigated in this study were statistically higher in cases when compared with controls (p<0.05 at the univariate level of statistical testing, Table 1). These included: older age (p<0.001), male gender (p=0.003), ischemic heart disease (p<0.001), renal impairment (p=0.002), major surgery (p<0.001), and RCRI score ≥2 points (<0.001). There were no differences (at the univariate level of statistical testing) in the proportions of the following characteristics between cases and controls: congestive heart failure (p=0.262), stroke (p=0.569), diabetes (p=0.068), or HIV serostatus (p=0.294).

The results of the multivariate analysis are shown in Table 2. Statistically significant associations at the multivariate level of testing were observed between the following characteristics and postoperative MACE: older age (p<0.001), ischemic heart disease (p=0.004), renal impairment (p=0.013), and major surgery (p<0.001). No statistically significant associations at the multivariate level of statistical testing were observed between any of the remaining characteristics (including HIV serostatus) and postoperative MACE.

Table 1. Respondent Demographics

Characteristic	Sub-Category	Entire Population (n=460)	Cases (n=92)	Controls (n=368)	p-value
Median age in years (IQR)	N/A	51.0 (36.3-64.0)	62.5 (52.3-70.8)	48 (35.0-61.0)	<0.001
Gender					0.003
	Female	239 (52.0)	35 (38.0)	204 (55.4)	
	Male	221 (48.0)	57 (62.0)	164 (44.6)	
Ischemic heart disease					<0.001
	No	404 (87.8)	66 (71.7)	338 (91.8)	
	Yes	56 (12.2)	26 (28.3)	30 (8.2)	
Congestive heart failure					0.262
	No	455 (98.9)	90 (97.8)	365 (99.2)	
	Yes	5 (1.1)	2 (2.2)	3 (0.8)	
Stroke					0.569
	No	440 (95.7)	87 (94.6)	353 (95.9)	
	Yes	20 (4.3)	5 (5.4)	15 (4.1)	
Diabetes					0.068
	No	362 (78.7)	66 (71.7)	296 (80.4)	
	Yes	98 (21.3)	26 (28.3)	72 (19.6)	
Renal impairment					0.002
	No	449 (97.6)	85 (92.4)	364 (98.9)	
	Yes	11 (2.4)	7 (7.6)	4 (1.1)	
Major surgery					<0.001
	No	367 (79.8)	44 (47.8)	323 (87.8)	
	Yes	93 (20.2)	48 (52.2)	45 (12.2)	
RCRI score ≥2 points					<0.001
	No	391 (85.0)	59 (64.1)	332 (90.2)	
	Yes	69 (15.0)	33 (35.9)	36 (9.8)	
HIV serostatus					0.294
	Negative	172 (34.7)	38 (41.3)	134 (36.4)	
	Positive	56 (12.2)	7 (7.6)	49 (13.3)	
	Unknown	232 (50.4)	47 (51.1)	185 (50.3)	

IQR: Interquartile range, N/A: Not applicable, RCRI: Revised Cardiac Risk Index.

Table 2. Characteristics independently/not independently associated with postoperative MACE

Characteristic	Sub-Category	OR (95% CI)	p-value
Age (per year increase)	N/A	1.04 (1.02-1.06)	<0.001
Gender			
	Female	Reference	
	Male	1.72 (0.98-3.01)	0.057
Ischemic heart disease			
	No	Reference	
	Yes	3.48 (1.50-8.07)	0.004
Congestive heart failure			
	No	Reference	
	Yes	3.48 (0.45-26.84)	0.231
Stroke			
	No	Reference	
	Yes	1.50 (0.44-5.06)	0.516
Diabetes			
	No	Reference	
	Yes	1.29 (0.60-2.78)	0.523
Renal impairment			
	No	Reference	
	Yes	5.70 (1.44-22.61)	0.013
Major surgery			
	No	Reference	
	Yes	11.31 (5.68-22.55)	<0.001
RCRI score ≥2 points			
	No	Reference	
	Yes	0.76 (0.30-1.97)	0.578
HIV serostatus			
	Negative	Reference	
	Positive	1.16 (0.42-3.21)	0.780
	Unknown	0.85 (0.47-1.54)	0.599

IQR: Interquartile range, N/A: Not applicable, RCRI: Revised Cardiac Risk Index.

Discussion

Our study findings suggest that an unknown HIV serostatus has no impact on postoperative MACE. There is a possibility that HIV serostatus, irrespective of what it might be, does not have any impact on postoperative cardiovascular outcomes. This possibility was also considered by Redman et al., who found no difference in cardiovascular risk between HIV-positive and HIV-negative vascular surgery patients.[8] Cardiovascular risk in patients with an unknown HIV serostatus was not reported in that study. While our findings confirm those of Redman et al., regarding cardiovascular morbidity and mortality in HIV-negative and HIV-positive patients, our findings appear to add to the findings of their study in that the potential impact of an unknown HIV serostatus on postoperative MACE has now been reported.[8] Therefore, it appears that HIV serostatus does not need to be included in preoperative cardiovascular risk stratification methods in surgical settings with high HIV prevalence. While HIV serostatus might not have been associated with poor outcomes in this study, determination of HIV serostatus in patients for whom it is unknown remains important, as it allows for the identification of HIV-positive patients who might subsequently require antiretroviral therapy.

Increasing age was found to be associated with a higher risk of postoperative MACE in this study. Increasing age is usually associated with the acquisition and increase in severity of comorbidities, including some of those comorbidities associated with cardiovascular complications.[14] Acknowledgement that age might be an important variable to include in cardiovascular risk stratification has also come from the study of Boersma et al., wherein an age-adjusted RCRI is proposed.[15] While we found a crude statistical association between gender and postoperative MACE, adjusted results failed to show any difference in risk of postoperative MACE between male and female patients. This finding is in agreement with findings from cardiovascular risk stratification studies, notably the original RCRI study conducted by Lee and colleagues.[13] Of the six established cardiovascular risk factors, only three were crudely associated with postoperative MACE: ischemic heart disease, renal impairment, and major surgery.[13] These three risk factors were subsequently found to be independent predictors of postoperative MACE. There is research that suggests the clinical importance of risk factors comprising the RCRI might vary between different surgical settings,[16] which could explain why we did not observe all RCRI risk factors to be independently associated with a higher risk of postoperative MACE. This is further supported by our finding that while higher RCRI scores (RCRI scores ≥2 points) were crudely associated with postoperative MACE, this variable was not associated with a higher risk of postoperative MACE when it was included in the multivariate analysis.

There were limitations to this research. A more powerful, true matched case-control study was not feasible, as the sample size calculations revealed there was an insufficient number of cases available in the original registry to conduct the research through this approach. However, there was a sufficient number of cases in the original registry to conduct the research through an unmatched study design. Smoking, hypertension, and hypercholesterolemia were not identified as perioperative cardiovascular risk factors in the study of Lee and colleagues, which is why these variables were not included in the original patient registry and were subsequently absent from our statistical analysis.[13] Another potential reason for the lack of association between RCRI score and MACE in our study could be the modest sample size. This study was conducted at a single, tertiary level hospital and our findings might not be generalizable. A larger study that includes several primary, secondary, and tertiary level healthcare facilities is required. Due to the retrospective nature of our study, we were limited to reporting inpatient outcomes and not outcomes at 30 days postoperatively as done in other prospectively-designed studies of cardiovascular outcomes in surgical populations, such as the VISION study.[12] We recommend prospective research be conducted to measure the association between an unknown HIV serostatus and postoperative MACE within 30 days of surgery.

Conclusion

In summary, we found that an unknown HIV serostatus had no impact on the risk of postoperative MACE in South African surgical patients. Our results suggest that HIV serostatus should not be included in cardiovascular risk stratification methods in surgical settings with a high prevalence of HIV. While HIV serostatus might not have been associated with poor outcomes in this study, determination of HIV serostatus in patients where it is unknown remains important as it allows for the identification of HIV-positive patients who might subsequently require antiretroviral therapy. Increasing age and certain established cardiovascular risk factors appear to be associated with a higher risk of postoperative MACE in South African surgical patients. Further research is required to confirm the findings of our study.

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Andreas Vesalius: Leader of the Anatomical Renaissance

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Ad fontes "(back) to the source" is a phrase often used to characterize the renewed vigor with which Renaissance humanists sought and studied the texts of Roman and Greek antiquity. In the field of anatomy, the texts of ancient Greek physician, Claudius Galen (129-c.216 CE), constituted the fund of all Western knowledge on human anatomy for over 1500 years. For centuries, any incongruences between the human cadaver and the authoritative text were attributed to a fault in the eyes of the observer, a malformation of the body, or an error that had been introduced during translation[1] – never was the word of Galen disputed. Unbeknownst to students of anatomy for centuries was the fact that Galen's observations were based on dissections not of human cadavers, but of the carcasses of animals, such as pigs, dogs, and apes. Nevertheless, the work of Galen formed the basis of university curricula well into the sixteenth century. One who embraced the spirit of the Renaissance was Belgian physician, Andreas Vesalius (1514-64), who fervidly returned to the texts of the ancients. However, unlike generations of anatomists before him, Vesalius studied these texts in an effort to engage his contemporaries in the processes of inquiry and discovery and to add to the wealth of knowledge in the field of anatomy. Part I of this article will explore the published works of Vesalius and include a discussion of his teaching activities. In Part II, the role of Vesalius as a forbearer in the restoration of anatomical investigation will be evaluated in the context of the Renaissance.

Born into a wealthy family in Pergamon (present-day Turkey), Galen received a comprehensive education in the fields of medicine and philosophy and eventually settled in Rome. Roman law strongly prohibited the dissection of human cadavers, thus necessitating his use of animal carcasses for anatomical studies. Despite errors that arose from the nature of the anatomical material available to him, Galen was a devoted and highly skilled investigator, publishing hundreds of treatises. His death is said to have marked the end of anatomical investigation in the West.[1] At least part of the reason for the long hindrance to the return to the study of anatomy lay in Galen's doctrine of final cause. This teleological doctrine required that something be philosophical and sometimes religious, before it be considered scientific.[2] A secondly contributing factor, and perhaps a more important one, is the fact that Galen's works were not translated into Latin in the ancient period. Thus, alongside the collapse of the Roman Empire was the decline of the Greek medical tradition.

From approximately the eighth to thirteenth century, intellectual leadership of the West passed to the Byzantine and Muslim civilizations as trustees of the classical heritage. It was during this period that many of the most important Greek medical writings were translated into Arabic to become, in turn, the guide for Eastern medicine.

Between the fourteenth and sixteenth centuries, a growing number of universities, beginning with those of Bologna and Padua, became well known for their demonstrations of human dissections. Two points must be made about this trend. The first of these is a consideration of the utility of the dissections to students. They were performed on an annual or biennial basis, with only a privileged handful of students permitted to attend each.[2] Additionally, each dissection was completed within a matter of days with very few, if any, interruptions. Students were given little opportunity to digest and comprehend what was taking place before them. Secondly, human dissection during this period was performed not as a means of investigation but merely for illustration of the authority, a somewhat diluted Galenism. Toward the end of the fifteenth century, a paucity of Galen's writings became available directly from the original Greek texts, while the majority were recovered as Latin translations from Arabic.[2] A pervasive belief developed that the true answers to all medical questions were to be found in these recovered texts.

Part I: Vesalius the Anatomist

Andreas Vesalius was born in Brussels, Belgium, into a family of eminent medical men who served as apothecaries and physicians to successive emperors of the Holy Roman Empire. Vesalius studied medicine from 1529-1533 at Louvain in Belgium, a university about which he claimed, "doctors had not even dreamed of anatomy."[3] According to his own account, Vesalius inspired its members to "spend great and very serious study in acquiring a knowledge of the parts of man."[3] Vesalius continued his training in Paris from 1533 to 1536 in a medical faculty that also adhered to the Galenic framework of medicine. In fact, Vesalius worked under the supervision of two pre-eminent Galenists, Johann Günther and Jacobus Sylvius, to translate and compile the work of Galen into compendia.[4] These years were vital to the work that Vesalius would later accomplish, as they made him cognizant of the status of anatomy during his time. He became acquainted with the facts of anatomy that had been and continued to be widely circulated and taught.

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On his way to the University of Padua, at which anatomy had been an integral component of medical studies for years, Vesalius befriended artists in the nearby city-states of Venice and Florence. Scholars have suggested that the contact was fostered by apothecary shops, where physicians went for their medicines and artists bought their pigments. It is believed that Vesalius' artistic skills, particularly those in anatomical illustration, were nurtured by these interactions.[5]

Shortly after his arrival in Padua, Vesalius was awarded a doctorate in medicine. According to an oft-repeated legend, the following day, he was appointed Professor of Surgery at the age of twenty three. Vesalius then embarked upon anatomical teaching.[5]

The standard and truly singular practice for conducting anatomical dissections made use of an ignorant barber-surgeon to carry out the physical work of the dissection. Propped atop a chair and far removed from the dissection table was the instructor who looked at the body through the book. In this scenario, the physical aspect of the dissection was viewed as a mere supplement to the reading of the sacred work of Galen. Vesalius believed this practice to be laughable.[1] Not only did he refuse to blindly re-iterate the words of the authoritative text as an instructor, but he took to the knife himself with the intention of stating the facts of the body as they appeared to him in the human cadaver.

Figure 1. Frontispiece of Andreas Vesalius's 1543 *De Humani Corporis Fabrica*.

Vesalius consolidated his findings in two texts. In 1538, Vesalius published his first book, *Tabulae Anatomicae Sex* (Six Anatomical Plates). It was a short book but very popular thanks to its extremely high-quality images. In accordance with long-held tradition, *Tabulae* contained a mere six images and was written in three ancient languages: Latin, Greek, and Hebrew.[5] Historians are particularly interested in this text because of the inconsistencies between the portrayal of certain morphological features and the level of knowledge Vesalius is thought to have acquired by this point in his training. Despite the evident care taken in artistic preparation, the body proportions of some figures are incorrect. The ribs are drawn shortened and the spine too straight.[5] Interestingly, vestiges of Galenic anatomy are also included in this text, such as the five-lobed liver. Some historians believe Vesalius deliberately placed these features in the illustrations of his first text in an attempt to abate the reaction he anticipated to his future work.[5] Copies of *Tabulae* are actually more scarce than original editions of Galen's second and much more famous text.

The culmination of Vesalius' medical career came in 1543 with his publication of the first illustrated and observation-based anatomical textbook: *De Humani Corporis Fabrica* (On The Fabric of the Human Body). The frontispiece (Figure 1) of this seven-volume text is rife with symbolism. In the center, Vesalius is seen surrounded by a large crowd at the medical faculty in Padua. His head is turned towards the reader, at whom he is looking boldly. His hands are in direct contact with the corpse of a woman he is dissecting. Below the table are the squabbling barber-surgeons displaced from their traditional position. Found cast off to the side are the dogs and monkeys of Galen's studies. Finally, in the customary location reserved for the recitation of Galen's text is found nothing more than a skeleton.

Vesalius used the preface of *Fabrica* to draw attention to his medical achievements. He differentiates himself from and elevates himself above his peers by claiming to have "trained [him]self without guidance in the dissection of brute creatures"[3] and protesting, rather than accepting dubious information reluctantly. He indicates his detestation of the practice of the day in which a lecturer "perched up aloft a pulpit and with an air of notable disdain, dron[ed] out information about facts they never approached at first hand, but which they merely commit to memory from the books of others."[6] The incongruity between theory and practice exemplified by this scene is what Vesalius sought to eliminate. With complete awareness that he was the first anatomist to physically take to the cadaver for investigation, Vesalius took advantage of each opportunity to educate others. Accompanied by a skeleton and equipped with diagrammatic illustrations and charts for his students,[7] Vesalius' didactic efforts were unique amongst previous anatomists. They were clearly intended to provide his audience members (sometimes made up of over 500 students, physicians, government officials, and distinguished citizens)[6] with an opportunity for further visual analysis.

Fabrica was a "completely fresh arrangement in seven books,"[3] which were presented in the order that Galen himself had written, covering the bones and cartilages, ligaments and muscles, veins and arteries, nerves, the organs involved in

nutrition, the heart, and the brain. Vesalius claimed to have corrected over two-hundred of Galen's mistakes in *Fabrica*.[8] Amongst those errors included the discovery that the mandible is a single bone, not two (an error derived from dog anatomy) and that the sternum has three parts, not seven (an error derived from monkey anatomy). He also gave detailed descriptions of complex abdominal parts, such as the omentum, and suggested that the kidneys filter blood to produce urine (rather than filtering urine as had been previously believed).[1]

Fabrica was copiously illustrated because Vesalius believed that the description of a body structure was inseparable from its corresponding image. In the same way that Vesalius brought diagrams to dissections, he promoted the accessibility of anatomy and "place(d) before the eyes of the student… nature's works, as it were, a dissected corpse."[3] The second book of *Fabrica* features the most famed of Vesalius' illustrations, the muscle men (Figure 2). Commentary accompanied each illustration and explained which muscle origins had been cut and which insertions were left hanging to create each of the successive diagrams. Ironic humor is interwoven throughout the text and its illustrations. As muscle is removed layer by layer, the body of the poor cadaver transitions from one of athletic exuberance to a pitiful sight needing ropes and walls for support. Moreover, the landscape background becomes increasingly barren as summer turns to winter as layer by layer of muscle is removed.[5] In 1996, the late Terence Cavanagh, Professor of Medical Literature at Duke University, placed the reversed muscle figures in a horizontal series to demonstrate that they create a continuous landscape.[9] Some scholars have identified the scenery in the Eugenean Hills near Padua, where physicians have travelled in search of the exact site. Considered the "first great positive achievement of Science itself in modern times"[10] *Fabrica* made nature's handiwork available to a growing literate public and encouraged the widespread practice of dissection.

Part II: Vesalius, Leader of the Anatomical Renaissance

Vesalius' methods, with their apparent disregard for long-held beliefs and his claims, in conflict with those of Galen's, were met with widespread antagonism. Some critics were outraged at the immoral sacrilege of organized dissections which desecrated "God's handiwork."[1] Court physicians and academic professors taunted Vesalius, referring to him as a "mere barber." Some went so far as to call him an "anti-Galenist."[5] Conversely, certain present-day historians have referred to him as "Galen restored to life."[4] How can these two views be reconciled?

In reference to his work at Padua, Vesalius rebutted that one "could not find in [his] procedure anything that fell short of the tradition of the ancients."[3] It is essential that the work of Vesalius be evaluated within the Renaissance context. Anatomical dissections that took place prior to the sixteenth century not aimed not to reveal a hidden truth but rather to confirm and recite facts as Galen had espoused them. The intense study of ancient texts was not undertaken during the Renaissance with an aim to re-install the specific rejections or beliefs of the ancients. Instead, it aspired to appraise ancient texts through a combination of reasoning and empirical evidence, the same methods by which the ancients came to understand their world and explore nature. Vesalius was convinced that "one could with confidence assert that our modern science of anatomy was equal to that of old, and that in this age anatomy was unique both in the level to which it had sunk and in the completeness of its subsequent restoration."[3] Much like the humanists, Vesalius was looking to the past, not to give new life to the presuppositions of the ancients but to emulate their approach to scientific reasoning, an approach that was based entirely on observation and experience.

Almost immediately upon publication, Vesalius faced intense ridicule and derision from his contemporaries. He later wrote in his *China Root* epistle of burning all of his unpublished papers in December 1543: "…as to my notes, which had grown into a huge volume, they were all destroyed by me…"[11] Expressions of sentiment other than awe towards the work and discoveries of Galen were preposterous and considered unacceptable at this time. The examples of John Geynes of Oxford and Thomas Fludd of Cambridge illustrate this. The former was forced to recant his criticisms of Galen, in 1559, before he could be made a fellow of the college. The latter, after having performed poorly on his examinations, was awarded his license to practice after merely reading sections from the work of Galen.[12] Within a short period, Vesalius relinquished his chair at the University of Padua. For reasons unknown, he undertook a pilgrimage in 1564 to Jerusalem. On his return, he was shipwrecked on the island of Zante where he died in October of that year.[2]

William Harvey wrote in the eighth chapter of his book, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (An Anatomical Exercise on the Motion of the Heart and

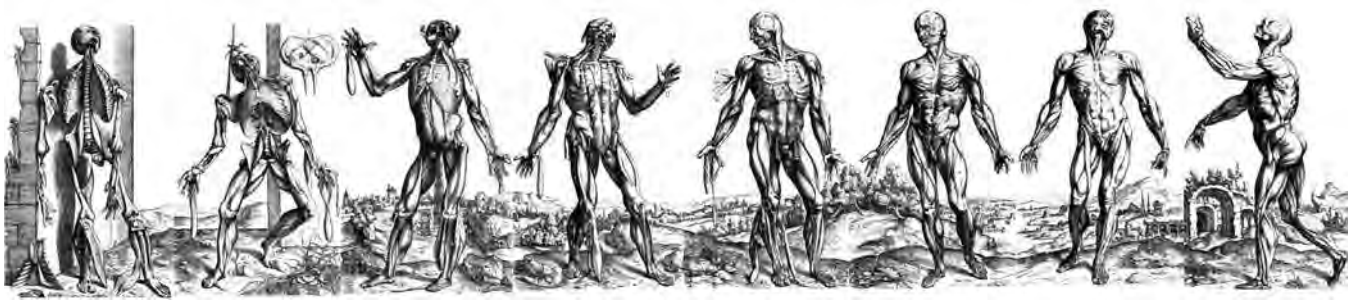

Figure 2. Eight-series landscape panorama of Vesalius' muscle men plates.[9] Reversed muscle figures shown. Paintings are attributed to Jan Stephan Van Calcar.

Blood in Living Beings), that "the die has now been cast, and my hope lies in the lover of truth and the clear-sightedness of the trained mind."[13] The tone had undoubtedly been set for subsequent anatomical investigations in Western medicine. Vesalius' immediate successors at Padua, Matteo Realdo Colombo and Gabriele Falloppio, elaborated and improved upon the work of their predecessor. Vesalius' work was widely copied and plagiarized. One of the best-known plagiarists was Thomas Geminus (c.1510-1562), whose *Compendiosa totius anatomie delineatio, aere exarata* (A complete delineation of the entire anatomy engraved on copper), published in 1545, in London, featured Vesalius' woodcuts finely engraved on copper – the second book in England with engraved plates. Juan Valverde de Hamusco (c.1525-1587), a Spanish anatomist who lived in Rome, was responsible for the introduction of Vesalius' work in Spain. Of the forty-two engravings in his book, *Historia de la composición del cuerpo humano* (Account of the composition of the human body), only four new plates were made – the others were copied from Vesalius' work. His text featured not only observations from his own studies but also a critique of Vesalius'errors.[12] Such was the trend in studies and publications on human anatomy that continued well into the eighteenth century.

Having acquired a firm theoretical foundation as well as skill in dissection early in his medical education, Vesalius was poised to impact the field, most vividly through his debates and demonstrations. He was unique in his inability to accept discrepancies between the authoritative text and the physical embodiment of those texts: the cadaver. As in other areas of Renaissance science, literature, and art, Vesalius' approach and discoveries hastened a break with ancient traditions and long-established but unverified information. Through *Fabrica*, Vesalius pioneered the approach of relying on personal observations and investigations. Returning to the ancients was undertaken in such a way that a new anatomical tradition was created. Going back to the sources (*ad fontes*) resulted in Vesalius' publication of a *new* source to which subsequent anatomists would return for the next several hundred years.

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Neurobiological Underpinnings of Anorexia Nervosa

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Abstract

Anorexia nervosa is an eating disorder characterized by persistent, restricted food intake, which leads to drastic weight loss and has the potential of leading to death. It disproportionately affects young females, with a peak onset age between 14 and 18 years old. Young women with anorexia nervosa have the highest mortality rate in their age group and of those suffering from other psychiatric disorders. Anorexia nervosa, however, presents an enigma for researchers. It has many clinical symptoms, an unknown etiology, and lacks a comprehensive animal model that can be used for therapeutic research. This mini-review presents two animal models that are used by researchers, the diet restriction model and the activity-based anorexia model. The diet restriction model recapitulates physiological and cognitive effects of reduced food intake observed in anorexia nervosa. Activity-based models reflect hyperactivity and self-induced starvation that are characteristic of anorexia nervosa. Currently, there are two competing hypotheses of the neurobiological underpinnings of anorexia nervosa: the reward-centred model and the habit-centred model. The reward-centred model is based on evidence from neuroimaging studies that show increased activity in the mesolimbic reward circuitry in anorexia nervosa patients associated with reduced food intake. The habit-centred model of anorexia nervosa posits that reduced food intake is a learned behaviour mediated by frontostriatal circuitry. Further research is required to gain a better understanding of the neurobiological underpinnings of anorexia nervosa and to better understand the dynamic involvement of mesolimbic and frontostriatal circuitry in the pathogenesis of anorexia nervosa.

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Introduction

Anorexia nervosa is an enigmatic eating disorder that is characterized by the maintenance of a malnourished, starved state and long-term restrictive eating that pose a threat to a healthy body weight. The importance of studying this disorder is highlighted in the fact that mortality among young women due to anorexia nervosa is the highest of any psychiatric disorder for their age group.[1] This disorder presents an enigma to researchers due to the heterogeneity of its clinical manifestations, diversity of symptoms and their neurobiological underpinnings, and the lack of a comprehensive animal model that can recapitulate the various aspects of this disorder. Neuroimaging studies on anorexia nervosa patients have provided us with important insights into neural circuits that show greater activity and have allowed identification of neural circuits that are active in response to reduced food intake. These studies led to the development of reward-centred and habit-centred models of anorexia nervosa.

This mini-review presents two animal models that are currently used by researchers, the diet restriction model and the activity-based anorexia model, and aims to examine the advantages and limitations of each. This review also presents evidence from various neuroimaging studies and analyzes it with respect to the reward-centred versus habit-centred models of anorexia nervosa to better understand the neurobiological underpinnings of this disorder. It draws on both human and animal studies to illustrate the complexity of this disorder, competing explanations for its neurobiology, and emphasizes the need for development of better animal models that can provide evidence for reward-centred and habit-centred models in animals. Development of animal models will allow for testing of potential therapeutic drugs that can help in treating patients with anorexia nervosa in the future.

Animal Models of Anorexia Nervosa

Diet Restriction Model

The diet restriction model of anorexia nervosa implements significant food restriction in animals, that is, less than half of the daily food intake. While it has previously been shown that reduced caloric intake can extend the lifespan of an animal, excessive caloric restriction can serve as a model for anorexia nervosa.[2] An important limitation of this model is that unlike the clinical manifestation of anorexia nervosa, the food restriction in the animal model is not voluntary. Nonetheless, the advantage of the diet restriction model lies in the opportunity it provides to elucidate the physiological, cognitive and neuro-endocrine effects of reduced food intake observed in

anorexia nervosa. A study by Avraham et al. investigated the effects of varying levels of food restriction on young female mice.[3] Results illustrated that while 60% diet restriction improved performance in the 8-arm maze, 40% diet restriction was associated with reduced performance in the 8-arm maze and greater mortality. Cognitive function measured by performance in the Morris water maze was also found to be lower in the 40% diet restriction mice than both control and 60% diet restriction mice. Interestingly, treatment with tyrosine mitigated these adverse effects: for instance, cognitive function improved in 40% diet-restricted mice to the level of 60% diet-restricted mice without any accompanying changes in body weight. These findings from a diet restriction model of anorexia nervosa are important because nutritional rehabilitation is a pre-requisite to any benefit that patients can gain from psychological treatment. This creates a barrier in commencing treatment because patients resist nutritional rehabilitation due to fear of weight gain.

In a later study, Avraham et al. go on to demonstrate that anorexia is associated with elevated hypothalamic serotonin levels and that tyrosine intake normalizes these levels.[4] In doing so, tyrosine improves cognitive performance, food intake, and activity performance. More recently, Hart et al. have demonstrated the validity of tyrosine supplementation as an adjunct treatment in anorexia nervosa.[5] This stems from the hypothesis that noradrenergic dysregulation is observed in anorexia nervosa, and tyrosine supplementation mitigates noradrenergic dysregulation, as tyrosine is a precursor for dopamine, serotonin, and noradrenaline synthesis. Hence, tyrosine supplementation as a strategy might have important implications to help with initiating treatment in patients with anorexia nervosa to improve their mood, lessen anxiety around re-starting food intake, and improve cognitive performance.

Activity-Based Anorexia Model

A defining characteristic of anorexia nervosa is self-motivated restricted food intake, a characteristic that is difficult to recapitulate in animals as food intake is usually controlled by experimenters. To overcome this limitation, Routtenberg and Kuznesof developed the self-starvation or activity-based anorexia (ABA) model where rats are placed in conditions where they have a choice between food intake and another rewarding condition such as exercise.[6] It is important to note that individuals with anorexia nervosa have high activity levels, even with restricted food intake and accompanying weight loss, and they compulsively engage in excessive exercise. Hence the ABA model recapitulates not only self-induced starvation but also hyperactivity that is characteristic of anorexia nervosa. Routtenberg and Kuznesof illustrate that self-starvation can be induced by exercise in rats using activity-wheels.[6] In this study, active rats consumed less food than control rats and eventually starved to death due to the inability to compensate for energy lost during exercise. In contrast, control rats on a feeding schedule of 1 hour/day maintained their body weight. This study established that the ABA model can reproduce some main characteristics of anorexia nervosa as hyperactivity, self-induced starvation, and weight loss. Furthermore, it has also been shown that female rats exercise significantly more than male rats, a finding that strengthens the ABA model and its clinical relevance, as it reflects the sex distribution of anorexia nervosa in humans.[2] This finding also raises important questions for future research to further investigate the underlying reasons of differences in sex.

A study by Pare compared the effects of high running activity and associated reduced food intake in younger versus older rats.[7] Interestingly, results showed that younger rats with high activity levels had a higher mortality rate than older rats with low activity levels. This finding is of significance, as anorexia nervosa disproportionately affects young females, and mortality among young women due to anorexia nervosa is the highest of any psychiatric disorder for their age group.[1]

Anorexia Nervosa and Reward Processing

Neural systems of reward processing entail the ventral striatum, nucleus accumbens, midbrain and ventral tegmental area, and the orbitofrontal cortex. The nucleus accumbens and ventral striatum are involved in the control of food intake energy balance and taste perception.[8] Previous animal studies have shown that restricted food intake heightens sensitivity of reward circuits.[1] Neuroimaging studies have analyzed neural substrates of reward processing in anorexia nervosa patients compared to healthy controls, using structural and functional MRI as well as positron emission tomography (PET). Fladung et al. conducted a fMRI study in which they recorded neural activity in healthy individuals and anorexia nervosa patients in response to images of under-weight, normal-weight, and overweight females.[9] The study illustrated that individuals with anorexia nervosa had decreased activity in the ventral striatum in response to normal-weight stimuli when compared to healthy controls, who show greater activation of ventral striatum when exposed to normal-weight stimuli. Titova et al. conducted structural MRI on anorexia nervosa patients and found that volumes of regions involved in reward processing, particularly the orbitofrontal cortex, are abnormal in anorexia nervosa.[10] While this study reported decreased volumes of reward-sensitive regions in anorexia nervosa patients, a later study by Frank et al. contradicted these findings and reported an increased volume in anorexia nervosa patients compared to healthy controls.[11] Frank et al. utilized a more accurate analysis software, and the patients taking part in the study were inpatients and had normal food and fluid intake for a week before brain imaging.[11]

Furthermore, task-based fMRI studies have been employed to elucidate how responses to taste rewards differ in anorexia nervosa. A study by Fladung et al. showed that individuals with anorexia nervosa have heightened activity in the orbitofrontal cortex and nucleus accumbens in response to taste rewards.[12] Taken together, the structural MRI and fMRI studies provide evidence for the involvement of reward circuitry in the neural underpinnings of anorexia nervosa.

In addition to the starvation-induced sensitization of reward circuitry, another reason reward circuitry is central to understanding the neurobiology of anorexia nervosa lies in adolescent reward circuitry, where rewards have an increased salience.[1] Galvan et al. conducted a fMRI study where they

compared activity in the nucleus accumbens and orbitofrontal cortex in children, teens, and adults in response to a monetary reward.[13] The results showed that adolescents had the strongest activity levels in nucleus accumbens in response to a monetary reward. This finding supports the notion that adolescents experience increased salience of rewards.

Taken together, these studies suggest two main ideas, that food restriction sensitizes the mesolimbic reward circuitry and that adolescents show increased nucleus accumbens activity. Given that anorexia nervosa is characterized by decreased food intake and has a peak onset age between 14 and 18 years, these studies suggest that anorexia nervosa is associated with abnormalities in reward circuitry, also known as the reward-centred model of anorexia nervosa.

Anorexia Nervosa and Neural Circuits Underlying Habit Formation

Habit formation describes a process by which a behaviour is paired with a reward and when repeated several times, the behaviour becomes automatic and persists in the absence of the reward.[14] Studies show that as a behaviour undergoes the shift from intentional to habitual, the neural systems regulating the behaviour shift as well. Findings from animal and human studies show that when the behaviour becomes a habit, it comes under the control of the dorsal striatum. The dorsal striatum is composed of the putamen, basal ganglia, and caudate. The dorsal striatum is part of the frontostriatal circuitry, and this circuitry plays a role in maladaptive behaviours characteristic of various psychiatric disorders.[1] Delvenne et al. conducted PET studies of anorexia nervosa patients and showed elevated metabolic activity in the caudate.[15]

A central question in better understanding the underlying neural mechanisms mediating anorexia nervosa is why do people make maladaptive choices? In anorexia nervosa, persistent maladaptive food choices cause weight loss and can be accompanied by mortality. Individuals with anorexia nervosa repeatedly and persistently choose low fat foods over high fat foods.[16] This pattern of food choice continues when individuals change their goals (i.e. enter treatment) and hinders progress on weight gain. In this manner, anorexia nervosa can be viewed as an excellent model of persistent maladaptive behaviour. In a study by Steinglass et al.,[17] women with anorexia nervosa and a group of healthy female controls participated in a food choice task, where they were asked to choose food items from a list that contained both low fat and high fat food items.[1] Results showed that anorexia nervosa patients were less likely to choose high fat foods compared to healthy females. The study then examined if the results from the food choice task correlated with eating behaviour. It was found that the eating behaviour of anorexia nervosa patients was significantly correlated with the foods they chose in the food choice task.

In a following study, Foerde et al. (2015) used a similar food choice task and conducted imaging of anorexia nervosa patients and healthy controls as they chose low versus high fat foods.[16] Similar trends as observed in the study by Steinglass et al. (2015) were seen in the food choice task: anorexia nervosa patients were significantly more likely to choose low fat foods.[17] More importantly, significantly greater neural activity in the dorsal striatum of individuals with anorexia nervosa during the food-choice task was observed than in healthy controls where there was no difference in activity in the ventral striatum. These results suggest that specifically the dorsal striatum, and not the ventral striatum, is a neural substrate of persistent maladaptive choices observed in anorexia nervosa. In addition, Foerde et al. also conducted a functional connectivity analysis to elucidate the role that frontostriatal circuits play in food choice decisions made by anorexia nervosa patients.[16] Results showed that food choice is associated with functional connectivity between the striatum and the dorsolateral prefrontal cortex (dlPFC). Analysis of differential connectivity between these areas showed that anorexia nervosa patients show greater connectivity for low fat foods, whereas the opposite is seen in healthy controls. These results suggest that a neural circuit between the dorsal striatum and the dlPFC may be important in the underlying neural mechanism mediating persistent maladaptive food-intake choices characteristic of anorexia nervosa. The results from this study have important implications towards improving our understanding of the neurobiological substrates and circuitry underlying anorexia nervosa. Some recent studies have proposed a role for neural circuitry involved with habit formation in anorexia nervosa. This habit-centred model of understanding anorexia nervosa views restrictive dietary intake in anorexia nervosa as a habit, one that is learned, not innate and elicited by specific stimuli. The involvement of frontostriatal neural circuitry in food choice decisions by anorexia nervosa patients, as shown in this study, strengthens the habit-centred model of anorexia nervosa, as dorsal striatum is associated with habit formation.

Conclusion

Anorexia nervosa is defined by persistent, self-motivated starvation that leads to reduced food intake and is accompanied by excessive exercise.[16] Anorexia nervosa, however, is difficult to study due to its complex etiology and the lack of a comprehensive animal model that can be used for therapeutic research. This mini-review evaluates the diet restriction and the activity-based anorexia animal models. There is a need for further research to develop an animal model for anorexia nervosa that can not only recapitulate the clinical symptoms but also allow researchers to study decision-making in food choices and study the underlying reward circuitry and habit-formation circuitry as the animals engage in these tasks. Recent technological advancements in neuroscience such as the ability to do live calcium imaging in vivo are promising ways through which such investigations can be done. For instance, in vivo circuit and cellular level functional imaging as described by Gulati et al. can help to better understand the role of mesolimbic and frontostriatal circuitry in animal models of anorexia nervosa.[18]

Despite the evidence from fMRI studies of neural circuits linked with habit formation in anorexia nervosa, behavioural studies need to be done to establish that restricted food intake is in fact a habit. In addition, studies in animal models are also needed to examine whether animals can develop the habit of restricted food intake. This will help to confirm if

similar neural circuitry is involved in anorexia nervosa in animal models. In addition, it is unknown if the circuits engaged by individuals who diet but do not develop anorexia nervosa are the same as, or differ from, the neural circuits associated with anorexia nervosa. Structural and functional imaging studies will help to address this question. It is also unknown how neural circuits change over time as an individual has anorexia nervosa for longer durations or as a patient recovers from anorexia nervosa. In the future, this knowledge will be essential to find treatments for anorexia nervosa. Furthermore, while studies show that cues can impact food restriction in anorexia nervosa, more work needs to be done on how cues and emotional factors influence neural circuits linked with food choice.

In future studies, animal models of anorexia nervosa should be used to study changes in the mesolimbic reward circuitry and the frontostriatal circuitry associated with habit formation. This will facilitate better understanding of the currently-competing hypotheses of the neurobiological underpinnings of anorexia nervosa: reward-centred versus habit-centred models. The reward-centred hypothesis argues for the involvement of the ventral striatum, whereas the habit-centred hypothesis argues for increased activity of the dorsal striatum in anorexia nervosa patients. Animal research will also make it possible to test therapeutic drugs that may help with treating anorexia nervosa in humans.

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Expediting a Changing Attitude: Technology in Medicine

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As recent as a decade ago, physicians did not routinely implement basic technological (tech) tools that are considered indispensable today.[1] Devices such as portable ultrasounds are a case in point: considered by some to be a recent feat and an essential office tool, they have been available since the mid 1970's.[2] Efforts that have increased the uptake of technology in medicine focus on addressing challenges that healthcare providers face in its implementation.[1] It is incumbent on the doctors of today to stay current with new technologies in order to be aware of the out-of-clinic information platforms being used by their patients. This is an opportunity for the healthcare provider to serve as both a guide and a collaborator.

We are in the age of technology and, as advances are being made in every field, it follows that we would see an increased use in the realm of medicine. Nonetheless, it seems there are as many counter arguments as there are documented benefits to furthering the use of technology in medicine.[3,4] One frequently-referenced barrier to the adoption and recommendation of technology-driven interventions from the perspective of some physicians is endangering the physician-patient relationship.[4] Through holistic electronic access, the physician may become privy to medical information previously unmentioned by patients. Physicians may also face patient dissent following unauthorized information disclosures secondary to ethical obligations.[4] This can create a precarious situation of newfound transparency between practitioner and patient.

The emerging domain of e-health encompasses technologically savvy concepts applied to tackling every day health challenges.[5] Current and coming examples include facilitating video-chats between physicians and their remotely situated patients and equipping healthcare users with mobile devices for receiving appointment alerts, respectively.[6,7]

Presently, the healthcare system regularly employs only the aforementioned e-health tools and such portable devices as mobile ultrasounds.[2,7,8] An up-and-coming phase of tech in medicine revolves around online applications (apps) as well as attachable gadgets, such as smartphone glucometers, for the purpose of monitoring and maintaining health by giving charge to the patient.[9,10]

Though the technological advances outlined in this paper are by no means exhaustive, they allude to a plethora of functional possibilities. Indeed, each one of these technologies is amenable to a multitude of permutations and hence patients and physicians alike gain enormous functionality from a single smartphone.[10]

Notably, however, patients have access to potentially false or misleading information online, whether or not physicians condone it. By being a part of changing times, however, physicians can help guide patients to appropriate sources and, through such regulation, are better positioned to assess patient-collected data and provide informed care.[9,11]

The present opportunity to bring to fruition an era of research in health technology is an exciting time for both physicians and patients. Some of the more prominent benefits of deploying such tools as smartphone glucose monitors include patient empowerment, increased accessibility, better primary prevention, and decreased cost in providing health care.[7,9] In the case of the aforementioned aid specifically, patients are able to track and view their glycemic indices over time and enter meals to record the subsequent impact on blood-glucose. In this way, patients become both learners and stewards in their own health.[5,9,10]

A major aspect of technology in medicine is facilitation of data tracking from the comfort of patients' homes, ushering in a generation of truly patient-centred care. In the process, individuals are empowered to be frontrunners in monitoring their health.[9] This in turn reduces reliance on health care authorities, potentially bolstering patients' sense of self as partners in their health while reducing the time burden on physicians.[4,9] The grandfathered trend of physicians as decision makers is in fact being phased out due to growing awareness of patient autonomy and its contribution to beneficence of care.[4] In effect, through supporting use of technology in medicine, we may simply be accelerating a happening shift from physician paternalism to patient empowerment.[2,4,9]

Technologically-driven interventions are also generally immune to the dilemma of accessibility being limited by patient ability, time, or location.[7,9] For example, people with disabilities may be confined to their homes, but with newer technology, they may be able to communicate to a health care provider without the burden of commuting. Telehealth may be a means of improving the availability of health care services for people limited by residences in remote communities as well.[7] We must, of course, factor into consideration the cost of setting up tele-health sites, financial compensation for the involved medical personnel, and a tech maintenance budget. Technology may also enhance efficiency further for the growing number of patients whose schedules are more amenable to typing in data on their smartphones than to planning health care visits.

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Primary prevention would be boosted since apps on phones and computers could fill the void between health care visits, improving monitoring of health data and potentially significant adverse events.[9,10] Those with chronic health issues can receive reminders for information such as appointments and treatment adherence.[6,8] Early diagnosis is not only more cost-effective but also a patient's right. Withholding or even neglecting to offer such potentially life-saving amenities as health data tracking applications compromises the standard of care for patients. In the world of controlled trials, it is in fact considered unethical to continue experimentation once a given treatment arm has benefited from the intervention being tested.[12] This furthers the case for why technology-driven advancements aimed at disease prevention should transcend provider biases. The number of studies supporting the greater efficacy of technology are only increasing.[4,13]

Technology allows healthcare providers to save time from making large differential diagnoses. They may focus on aggregates of symptoms that patients record on smartphone apps regarding exercise habits, for instance. Such holistic, objective data can also decrease the financial strain associated with initiating costly and ineffective health treatments and investigations.[14]

Mobile health exemplifies the application of a simple, affordable technology in combatting a once challenging medical dilemma: treatment adherence.[8] This has particular utility through its application in marginalized populations like individuals with HIV.[15] Poor medication adherence, accessibility, and improper clinical follow-up invariably result in increased morbidity and mortality. Tech interventions such as e-health provide a patient-friendly text message interface that helps manage treatment regimens, minimizing avoidable health adversities.[15,16]

Nonetheless, user and provider hesitancy in uptake and promotion of technology in medicine is not uncommon. Reasons for this apparent reluctance will be discussed next and include safety, cost, practicality, and accessibility. In general, electronic health data across North America has seen a steady rise in annual hacking breaches, reaching over 20 per annum in the recent years – constituting up to 1 in 3 patient records being transiently exposed.[17] Health applications catering to a select number of users may be able to curb such breaches through appropriately budgeting for out-sourced app security IT. Industry standard does not suffice when it comes to storing people's health information.[4,17]

Implementing online systems to access electronic data can also pose the risk of internally compromised privacy and confidentiality.[3,4] Although legislation exists to protect those seeking insurance, many unaware citizens may fear that data sharing could generate such consequences as restricted coverage by insurance companies.[4]

The cost of initiating and managing an electronic system in a care home or hospital may be unnecessary as well since the vast majority of smartphone apps are often gratis or associated with a nominal fee.[10] Nevertheless, it is inappropriate to assume that all patients are able to afford a smartphone or computer.[3] Without the device itself, the issue of promoting a system of online health management is irrelevant.

Leaving aside the issue of cost and security, there is the question of practicality. For instance, how may the health care provider assure themselves of the accuracy and reliability of the data? Is it practical for the health care provider to synthesize and aggregate data from the various sources the patient has used in managing their health? Of utmost concern and perhaps what most conflicts with current physicians is the threat that this movement poses to their role as health leaders. Physician services may seem to be rendered dispensable with the implementation of apps that track health data and potentially diagnose.[4]

We have briefly touched upon the positive value of online data in increasing accessibility for those limited by ability, location or time. We must, however, consider the level of literacy required to use these systems. Implementation and uptake of such technology platforms necessitates and presumes a proportionally literate population: it would be imperative to consider user ability amongst all potential users of tech platforms – be they geriatric, indigenous, or immigrants.[5,18,19]

It is upon the doctors of tomorrow to be aware of newer devices and, if relevant, advocate for the application of such readily available technologies. From a medical student perspective, it is almost daunting to see the volume of generational patients who reference smartphone apps or online health aids to senior physicians. Without familiarity or personal usage, it is challenging to provide advice regardless of the credibility of such e-health tools. Despite this apparent ubiquity of electronics, though, not every person in this technological age is "tech savvy."[5] Consequently, this may raise the question of equitability.

Hence, it is imperative to the success of a technological initiative to ensure that it suits the demands and preferences of both the users and providers. To this effect, it may be useful to generalize such guidelines as the HIV Engagement Interventions Criteria, which were designed to summarize the ideal characteristics of a technological approach to enhancing HIV care.[20,21] According to these criteria, it is pivotal to the success of an e-health initiative to maintain a patient centered approach while still being cognizant of the feasibility of the given intervention.[20,21] For instance, an idealistic focus on patient preference over feasibility could pose an insurmountable challenge come time to implement the technology. It would instead be more constructive to gauge the overall value that said intervention holds to the population in question, its acceptability based on the beliefs of the community, and the accessibility for all eligible individuals.[20,21] Feasibility more specifically entails an examination of the affordability by the responsible governmental body as well as the intervention's scalability. These tenets must be met for a truly measurable impact on community health.[20,21]

The era of prescribed smartphone apps and data tracking is fast approaching, and although not every technological intervention is equally effective, they all have the potential to supplement existing health care practices. As the next generation of physicians and patients alike make conscious efforts to gain comfort with the surging tech age, they will be in a better position to appraise the growing utility of new and developing devices. Clinical technology is indeed a rapidly growing sector of health care and one that is likely to see fortification in the near future.[4]

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Psoriasis: Treating the Skin and the Mind

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Abstract

Psoriasis is a debilitating autoimmune disease defined by erythematous, pruritic, and scaly plaques. Yet, this disease also has numerous extracutaneous associations including depression, heart disease, arthritis, and inflammatory bowel disease. The combination of physical and mental manifestations of psoriasis can be explained, respectively, by inflammatory cytokines that act on skin cells to create scaly patches and brain cells to alter one's mental state. In light of such discoveries, this paper discusses the novel use of psoriasis medications such as tumour necrosis factor-α blockers, anti-interleukin-1β antibodies, and anti-interleukin-6 antibodies to address mood and anxiety disorders.

Introduction

Named after the Greek word for "scaly," psoriasis is marked by raised, erythematous plaques covered with silvery paches.[1] It primarily affects flexural skin surfaces such as elbows and knees, but can also affect other parts of the body such as nails, joints, and the brain.[1] Moreover, this chronic disease affects overall quality of life, thus necessitating examination of both psychosocial and physical aspects of the disease for management.[2-5]

Numerous topical and systemic therapies are tailored towards the cutaneous manifestations of psoriasis, with treatment options depending on disease severity, individual patient response, and efficacy.[2] As an autoimmune skin condition, psoriasis is currently managed with topical steroids that dampen the inflammatory response. However, topical steroids are not selective for the disease-causing cells and thus produce various side-effects such as atrophy, striae, and hypopigmentation.[6] Furthermore, systemic therapy and phototherapy are available for moderate and severe cases of psoriasis, defined as involvement of more than 5-10% of the body surface area, or involvement of the face, palm, sole, or other body parts that are otherwise disabling.[2] However, these treatment options are costly, inconvenient, and prone to severe side-effects.[6] In fact, patient dissatisfaction is evident through the analysis of surveys performed by the National Psoriasis Foundation, showing that 52% of 5604 survey respondents with psoriasis expressed dissatisfaction with their treatment.[7]

Biologic agents used in the treatment of severe psoriasis include anti-tumour necrosis factor (TNF) agents as well as anti-interleukin (IL) antibodies.[2] It is possible to approach disease management by targeting inflammatory cells that are pathognomonic of psoriasis. In fact, immune modulators involved in the cutaneous pathogenesis of this disease also act on the central nervous system, contributing to increased rates of depression and anxiety in psoriasis patients.[1,8]

Understanding how cytokines distribute in the body provides further clues as to how they affect inflammation and depression. This process starts when stress signals induce the release of modulators such as corticotropin-releasing hormone (CRH) and substance P, which trigger mast cells to start the inflammatory process.[9] In turn, peripheral inflammatory cytokines such as TNF-α, IL-1β, and IL-6 induce microglial inflammation in the brain while promoting apoptosis via receptor binding in the skin.[10,11] Furthermore, stress signals also travel from the brain and spinal cord to the peripheral nervous system. Given the involvement of the central and peripheral nervous system in psoriasis, recent studies have investigated the cross-utilization of medications for psoriasis and mental disorders.[1,9] These studies include the use of TNF-α blockers and anti-IL antibodies for the treatment of psychoactive disorders such as major depressive disorder, bipolar disorder, and generalized anxiety disorder.

TNF-α Blockers for Anxiety, Depression, and Bipolar Disorder

With the understanding that inflammatory cytokines can lead to physical and emotional symptoms in psoriasis, there is work underway to develop new medications that can stop inflammation, stress, and depression altogether. At the same time, it is important to note that pre-existing treatments for each of these conditions can also be used to target this common route of pathogenesis. For instance, certain TNF-α inhibitors such as etanercept and infliximab that are currently used to treat psoriasis can also alleviate depression through serotonin disruption in the brain and activation of hypothalamo-pituitary-adrenocortical (HPA) axis.[12-14]

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Pro-inflammatory cytokines such as TNF-α influence affective disorders by up-regulating serotonin transporter (SERT) activity, activating the enzyme indolamine-2,3-dioxygenase (IDO) as well as the HPA axis.[10,14] Both SERT and IDO reduce serotonin availability, while HPA activation leads to the release of CRH, adrenocorticotropic hormone (ACTH), and cortisol.[14] In addition, IDO activation leads to serotonin depression by converting tryptophan in kynurenine, which is further converted to the N-methyl-D-aspartate receptor agonist, quinolinic acid. Quinolinic acid, in turn, induces lipid peroxidation and oxidative stress, thus leading to a self-propagating cycle of neurodegeneration involving IL-1β, TNF-α and IFN-γ cytokines.[15]

Studies have supported the anti-depressant effects of etanercept on patients with major depressive disorder (MDD) and bipolar disorder (BD).[12] In one study, depression was measured via the Hamilton Depression Rating Scale (HAMD-21) and self-rated Beck Depression Inventory (BDI-II). Following a wash-out period of 14 days, depressive symptoms were quantified after 7, 14, and 21 days of etanercept monotherapy. The results demonstrated that TNF-α blockers reduced the prevalence of both major depressive disorder and bipolar disorder, reducing HAMD-21 score by 25 points and BDI-II score by 13 points after merely 7 days.[12]

Anti-TNF-α therapy has also been used in 83 consecutive rheumatoid arthritis patients to alleviate mood and anxiety disorders.[13] In one study, psychiatric disorders were defined using the Structural Clinical Interview for DSM-IV.[13] Similar to psoriasis, rheumatoid arthritis is an inflammatory disorder associated with depressive (34.9% of patients) and anxiety disorders (22.9% of patients).[13] TNF-α antagonists like etanercept and inflixumab also reduced the prevalence of psychiatric conditions in rheumatoid arthritis patients.[13]

Anti-IL Antibodies for Anxiety and Depression

In addition to TNF-α, there are numerous ways in which inflammatory cytokines can alter brain activation and behaviour.[16] Cytokines like IL-6 and IL-1β can cross the blood-brain-barrier using saturable transport mechanisms and act directly on microglia, astrocytes, and neurons throughout the CNS. This further affects physiological processes such as neuronal differentiation and survival as well as astrocyte proliferation. Furthermore, microglia activation stimulates the surrounding glia to allow inflammatory monocytes to enter the affected brain regions. Once inside the brain, these monocytes differentiate into microglia and produce local inflammatory responses that contribute to anxiety. Furthermore, interleukins also modulate astrocyte receptors. Astrocytes typically line the blood-brain-barrier, thus preserving the integrity of the barrier and acting as a filtering agent. Increasing peripheral cytokines changes the transcriptome profile of astrocytes and further upregulates the cytokines that are released into the central nervous system.[16] Interestingly, chronic stress acts by decreasing astrocytic volume and branching pattern as opposed to reducing the overall number of astrocytes.

In addition to their effect on astrocytes and microglia, IL-6 and IL-1β can also act directly on neurons to alter brain plasticity. In fact, an intracranial infusion of IL-6 and administration of IL-1β into the hippocampus increases depression-associated behaviour and reduces neurogenesis. To alter brain plasticity, the cytokines can either act on serotonin neurons via the kynurenine pathway or directly on glutaminergic neurons in the frontal cortex and hippocampus.[16] Therefore, IL-6 and IL-1β antibodies can prevent cytokines from altering neuronal plasticity, thereby reducing the potential for development of depressive behaviour.

Various studies have demonstrated that the differences in the innate peripheral immune response can predict susceptibility or resilience to repeated social defeat stress (RSDS).[16] It has been observed that prior to stress exposure, animals that later became susceptible had a higher IL-6 count prior to stress. Furthermore, Hodes and colleagues demonstrated a causal relationship between IL-6 counts and RSDS susceptibility.[16] To do this, the team removed hematopoeitic stem cells (HSCs) from IL-6 +/+ and IL-6 -/- mice and transplanted these HSCs into wildtype mice that had their peripheral immune cells irradiated. The results showed that stress-susceptible IL-6 +/+ chimeras developed susceptibility to RSDS, whereas IL-6 -/- chimeras became resilient to RSDS.[16] Therefore, it is apparent that a dysregulated inflammatory response can induce susceptibility to RSDS and contribute to the development of depressive symptoms. As such, anti-IL-6 antibodies such as tocilizumab, which are currently FDA-approved for the treatment of inflammatory diseases like arthritis, can be considered for the symptomatic treatment of psychiatric diseases.[16] Similarly, current psoriasis therapeutic agents like anti-IL-12/23 antibodies (e.g. ustekinumab), and anti-IL-17A antibodies (e.g. secukinumab) have also been shown to reduce the prevalence and severity of depression.[17-21]

Future Outlook

Similar to the way in which psoriasis medications treat mood and anxiety disorders, psychoactive drugs have also been suspected to help treat psoriasis in patients. Reducing anxiety can reduce the release of stress compounds, thus reducing body's inflammatory reaction. In fact, stress signals such as CRH and substance P contribute to the release of inflammatory cytokines such as TNF-α and interleukins.1 Therefore, a potential avenue of exploration is to determine whether anti-anxiolytic medications can also be used for psoriasis management. It is yet to be determined whether these medications can help alleviate psoriatic symptoms, or whether they in fact aggravate psoriasis further. Thus, further examination of the interplay between stress and inflammation can shed further light on this matter.

Conclusions

Psoriasis provides evidence for the connection between the psychological symptoms caused by changes in the brain as well as cutaneous symptoms caused by changes in the skin. The bidirectionality of these interactions is used to alleviate mood and anxiety disorders with psoriasis medications. In particular, TNF-α blockers such as etanercept and infliximab can reduce depressive behaviour by inhibiting serotonin deprivation and HPA-axis modulation. In addition, anti-IL-1β and anti-IL-6 antibodies such as tocilizumab can reduce

anxiety and depression symptoms by inhibiting astrocyte and microglial modulation and by preventing cytokine-mediated alterations in brain plasticity. Future studies can aim at determining the efficacy of anti-anxiolytic medications for treatment of psoriasis.

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Brain Machine Interfaces using Operant Conditioning of Neural Activity

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Individuals with sensorimotor deficits resulting from disease, cardiovascular injury or traumatic injury are often unable to effectively interact with the world around them. This dramatically reduces their quality of life as they are unable to perform their activities of daily living (ADLs).[1,2] Brain machine interfaces (BMIs) and brain computer interfaces (BCIs) are an emerging set of technologies that aim to provide these individuals with a novel way of interacting with their environment. BMIs and BCIs (hereafter referred to collectively as BMIs) function by converting neural activity from the brain into various forms of output commands that can be used to control external devices (such as robotic arms, computer cursors, wheelchairs, etc.) or neuroprostheses.[3,4]

The source of the neural activity determines its spatial and temporal specificity. Non-invasive imaging techniques such as near infrared spectroscopy (NIRS) decode neural activity by observing changes in metabolic activity but provide low spatial and temporal resolution.[5,6] Non-invasive electromagnetic recording techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) provide greater temporal resolution. As a result, these techniques can record temporally precise population activity and whole-brain oscillatory rhythms that have significant motor and behavioural correlates. For instance, novel work by Marquez-Chin and colleagues has shown that EEG signals can be used to predict specific hand movements with high accuracy, by observing desynchronization of neuronal oscillations above the sensorimotor cortices of the human brain.[7] The limitation of EEG and MEG recording techniques is that they provide poor spatial resolution and have a lower signal to noise ratio, making it impossible to accurately localize the source of specific neuronal activity.[8] Since the brain is known to function with high spatial specificity (i.e. specific foci of the brain are known to be responsible for specific behavioural and motor correlates), it becomes necessary to record activity at the spatial resolution of the brain using invasive techniques such as intracranial electroencephalography (iEEG). iEEG provides access to local field potentials and activities of single neurons, which can then be used to decipher more specific intents from neuronal activity.

Traditional invasive BMI systems function by correlating a specific pattern of neural activity to an overt behavioural or motor intent. A mathematical model is then developed based on this correlation, to convert the neural activity into a desired control signal, which can in turn be used to control an actuator (any kind of electrical device, for example a computer cursor, a robotic arm, or a neuroprosthesis). However, the underlying assumption made in this approach is that a specific pattern of neural activity is responsible for a specific motor or behavioural intent, and the goal of the mathematical model is to decipher and decode this neural activity in order to extract that specific intent. Through training, participants learn to volitionally drive and adapt these existing neuronal circuits in order to obtain effective control over the actuator. For the past two decades, BMI research has mainly focused on recording from ever larger populations of neurons and improving the mathematical algorithms used to decode this activity into useful commands. And while there is ample evidence of volitional modulation of cortical neuron activity in human and animal models, BMI systems have limited performance for reasons that are not well understood. For example, a study found that the prediction accuracy of movement parameters increased with the number of neurons included in the decoding algorithm; however, accuracy plateaued below 100%. Extrapolating these prediction accuracy curves shows an asymptotic trend for an infinite number of neurons, even when recording from motor-related areas.[9]

While the prevailing view in BMI research is to assume that the motor cortex encodes static movement parameters,[9-11] which can be extracted and decoded with high density neural interfaces and improved mathematical algorithms, an alternative approach has been proposed based on research from the early 1970's involving operant conditioning of neural activity. A series of studies by Fetz and colleagues provided some of the first evidence for the volitional modulation of single neuron activity using biofeedback.[12,13] In these experiments, the activity of a single cortical neuron was explicitly reinforced every time the firing rate surpassed a threshold, in this case by giving a food reward to a monkey. After a few minutes, the activity of the neuron changed drastically from baseline levels. Interestingly, the monkeys would quickly learn to modulate newly isolated neurons, even when two contiguous neurons (recorded from by the same electrode) would be trained to perform opposing tasks (upregulation vs. downregulation). If the selected cortical neuron happened to be the primary motor cortex, upregulation of the activity of this

neuron was typically accompanied with a physical movement (corresponding to the somatotopic location of the neuron) in the early experiments. As the animal practiced and became more proficient at modulating the activity of this neuron, the physical movements disappeared. This meant that the animal learned to dissociate the activity of a neuron from an explicit motor task that it was previously involved in, and associated it with a completely new motor representation, i.e. using the neuron to control a non-physiological actuator. This dissociation has been documented in multiple BMI experiments,[4,9,14] which shows the flexibility of the motor system in solving complex problems (e.g. controlling a real and an artificial limb with the same neuronal population).

In recent years, Moritz and colleagues utilized a similar approach of operantly conditioning neural activity to train monkeys to control a simple grasping neuroprosthesis.[15] They implanted functional electrical stimulation (FES) electrodes in a transiently paralyzed monkey's hand flexor and extensor muscles, which generated torque when stimulated. Impressively, the monkeys gained control of the stimulation to acquire torque targets only within minutes using single cortical neurons, making virtually no errors during peak performance, with nearly a four-fold increment from initial performance.

Although both of these approaches rely on establishing a relationship between a specific pattern of neural activity and a behavioural intent, the primary difference is that instead of decoding an existing correlation between neural activity and an observable behavior, the operant conditioning approach allows the brain to utilize its existing plasticity mechanisms to learn a new motor (or abstract) skill. By doing so, the operant conditioning approach empowers the brain to be the primary learning entity, instead of having a complex algorithm learn to decipher existing neural activity.

So, if the brain has an enormous amount of processing power for solving complex motor problems and performing intricate tasks with ease, what is stopping us from developing high performing BMI systems? It is a well-known fact that sensory and proprioceptive feedback is essential for learning and executing new motor skills.[16-20] Hence, a potential roadblock to further developing these operant conditioning-based BMIs may be the inability to provide rich sensory feedback. On this end, there have been efforts to provide feedback by electrically stimulating afferent sensory pathways, or directly stimulating the brain using intracortical microstimulation (ICMS) to provide rich sensory feedback.[16,21-24] Although early results are promising, this still remains an area of active research. Another potential limiting factor for existing operant conditioning BMI studies may be that different cortical neurons have different efficacies with which they can be volitionally controlled. For instance, in our lab, we have found evidence of specific neuron types that are easier to volitionally control and would facilitate BMI implementation,[25] even for actuators with multiple degrees of freedom.

BMIs are typically developed and operated under a neuroprosthetic definition, in which neural activity is used to control an extrinsic or prosthetic device. However, the implications of these operant conditioning-based BMIs extend far beyond this neuroprosthetic definition. As Moxon and Foffani recently pointed out, operant conditioning-based BMIs enforce a truly causal relationship between a specific neural activity (such as the firing rate of a single neuron or the power of a cortical oscillation), and an observable behaviour (such as the movement of a cursor or a robotic arm).[26] Since operant-conditioning-based BMIs require participants to learn a new procedural skill, this causality can be used to study the underlying plasticity mechanisms that are essential for acquiring new skills. For instance, inspiring work by Koralek and colleagues has shown that plasticity in the cortico-striatal networks is essential for operantly conditioning the activity of neurons in the motor cortex, which also happens to be the network responsible for acquiring new motor skills.[19,20]

Operant conditioning-based BMIs also provide us with an alternative perspective on an individual's ability to regulate their own neuronal activity, down to a single neuron. Large bodies of work have been dedicated to using biofeedback, or neurofeedback, when the feedback constitutes some form of neural activity, to help train individuals to regulate their own neural activity, from a single neuron all the way up to large-scale cortical oscillations.[27] Many neurological conditions present with alterations in specific types of neuronal activity. For instance, individuals with epilepsy often present cortical hyperexcitability (and a corresponding loss of inhibitory activity), which can lead to recurrent epileptic seizures that can be truly debilitating. A potential treatment for these individuals who do not respond well to medications is to provide neurofeedback training in which their neural activity is operantly conditioned to upregulate inhibitory oscillations in the brain, such as the sensorimotor rhythm (SMR) and slow cortical potentials (SCP).[28] There is evidence that such neurofeedback therapy can potentially reduce seizure frequency and improve one's control over their own seizure activity.[28-30] Similar neurofeedback training approaches have been studied extensively in the treatment of ADHD[31-33] and have also been investigated for auditory dysfunction,[34,35] insomnia,[36] autism spectrum disorder,[32] schizophrenia,[37] and Parkinson's Disease.[37]

Thus, BMIs, and specifically those that utilize operant conditioning of neural activity have the potential to not only provide individuals with sensorimotor deficits new and more effective ways of interacting with the environment around them, but also serve as new scientific tools that unlock new possibilities for basic brain research. These novel BMIs also have the potential to modulate neural activity to obtain volitional control over certain neurological disease states, potentially improving clinical outcomes and overall quality of life.

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Concurrent Disorders: A Cat Chasing Its Tail

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Abstract

Dual disorders manifest as a social problem of high prevalence and great importance. The stigma associated with mental illness and substance use has been well documented and conceptually distinguished from physical disease. Those who suffer from mental health and substance use disorders recognize this sense of opprobrium, and their illness inevitably leads to social ostracism, self-deprecation, repeat or chronic self-harm experiences, the fear of being judged by authority figures, and the danger of suicide. Individuals with concurrent disorders often end up in acute care facilities, with inadequate follow-up, at great expense to the healthcare system. Despite the burden of concurrent substance use and mental illness, there is a lack of consensus on how to best identify and treat this pathology. These gaps in our knowledge base need to be addressed. It is mandatory that additional research be conducted to identify and engage the large number of individuals affected by both psychiatric and addictive disorders in a therapeutic manner. These realities highlight the need for the intelligent rationing of resources.

Patients suffering from co-occurring mental health and substance use problems, concurrent disorders, represent a heterogeneous and vulnerable population that faces unique challenges, including frequent relapse and rehospitalization as well as misdiagnosis and mistreatment.[1-5] Many of these individuals struggle to cope with deconditioning and insults to their overall well-being, most prominently including the risk of HIV and hepatitis C infection.[1,3,6] As a consequence, persons with concurrent disorders often experience higher rates of unemployment, incarceration, relationship difficulties, homelessness, and an increased risk of suicide, victimization, and social marginalization.[1,3,7] To further complicate matters, Canada's mental health and addiction systems primarily function independently of each other, and patients are often subject to a "one size fits all" treatment strategy that fails to appreciate their duality and does not address their diagnostic complexity.[1,5,8] Although the mental health and addiction systems in Ontario recognize individuals with concurrent disorders as a priority population, there is currently no standardized, province-wide system of evidence-based performance measurement for the mental health and addictions sector.[5,9] These therapeutic barriers prejudice this undertreated population and society as a whole. This apparent gap in the knowledge base of clinicians, the associated consequences for patients in terms of the implementation of policy and eligibility for services, and future directions will be reflected on in this paper.

There is no consensus among the various health service providers regarding the inclusion criteria for "concurrent disorders." The discrepancies in definition extend from process addictions, such as gambling, shopping, and sex, and go so far as to include tobacco use disorder.[5] In general terms, the working definition of the term "concurrent disorders" refers to patients experiencing a combination of mental or psychiatric illness coincident with the abuse of alcohol and/or other psychoactive drugs.[1] From a diagnostic perspective, this descriptive refers to any combination of mental health and substance use disorders, as outlined in the DSM-V.[2]

The causes of addictive behaviours are complex, involving both innate and social forces.[3] The bio-psychosocial-spiritual model suggests that people with a concurrent disorder are not a homogeneous population in terms of etiology but rather a group of heterogeneous subpopulations with vulnerability to disease.[1-4] That is to say, their pathologies stem from variable genetic loading, the biological impact of progressive physical illness, psychosocial disintegration, cultural disruption, and access to substances of abuse. From this perspective, one can more easily refer to a set of diverse "concurrent disorders" rather than a solitary disease entity.

From a diagnostic viewpoint, the relative proportion of the mental health as opposed to the substance-induced component of concurrent pathology is based on a "chicken and egg" chronology, with primary and secondary designations being determined by history.[1-3,10] In reality, the typical real-world clinical presentation of co-occurring disorders is more nuanced – and in need of diagnostic clarification over time. Healthcare professionals must investigate the relationship between the mental health and substance use problems and

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examine the intersection between these disease processes.[1-3,10] Failing clear evidence of causation, it is most useful to presume that an individual suffers from separate substance use and mental health problems that interact with each other and require personalized treatment.[3]

It follows that the prevalence of concurrent disorders varies depending on the substance of abuse and the particular mental health diagnosis in question.[5] Regier and colleagues noted that 37% of individuals diagnosed with an alcohol use disorder are likely to also suffer from a co-occurring mental health disorder during their lifetime, whereas the likelihood of co-morbidity for those using substances other than alcohol was approximately 53%.[11,12] On the other hand, it was found that 29% of people diagnosed with mental health disorders will also have a substance use disorder during their lifetime.[11,12] O'Campo and colleagues have suggested that 10 to 20% of the homeless population in North America have co-occurring mental health and substance use disorders, and other experts believe that the true prevalence of these maladies is much higher.[13] Despite the perverseness of this pathology, there is a lack of knowledge and training around how to best identify and treat concurrent substance use and mental illness.[1,3,5]

It is not surprising that this burden of pathology has an economic price and that mental illness in Canada is estimated to cost up to $51 billion per year.[14] Pan-Canadian data suggests that individuals diagnosed with concurrent mental health and substance use problems constituted approximately one third of psychiatric inpatients.[15] Individuals hospitalized with dual disorders were more likely to be readmitted within 30 days and one year of discharge (62% to 53.2% increased likelihood, respectively) as compared to individuals with the single diagnosis of schizophrenia or psychotic disorder.[15] During the year following discharge, those with co-morbid disorders were expected to remain in hospital 19% longer than those without either a mental health or substance use diagnosis.[15] It follows that targeted investment by the Canadian Federal and Provincial governments in the integration of hospital-based and outpatient services, particularly community and home care services, when combined with diagnostic acumen, has the potential to repurpose scarce economic and human resources with great social benefit.

From a therapeutic perspective, psychiatric disorders are negatively associated with the outcome of substance use treatment and particularly with the ability of patients to withdraw from opioids, benzodiazepines, cocaine, and even alcohol.[1,16-18] Concurrent mental health and substance use disorders increase the probability that patients will relapse, manifest noncompliance, and prematurely abandon treatment.[1,19-21] These individuals often have difficulty establishing a therapeutic alliance and have been reported to experience intense transference and counter-transference reactions limiting their therapy.[1,3,10,22] For this reason, it has been suggested that "retention and treatment" is the best predictor of therapeutic success. The doctor-patient relationship must thus be nurtured by means of a nonjudgmental "don't ask, don't tell" stance that is intended to reduce harm while directing the patient toward more definitive treatment.[23]

The definition of harm reduction remains a matter of ongoing debate, but most experts accept as its core principal "any policy or program designed to reduce drug-related harm without requiring the cessation of drug use."[23] This concept of harm reduction has been endorsed as a pragmatic set of practices within a continuum of care geared to the stabilization of psychiatric or acute substance use symptoms. However, prior to making a psychiatric diagnosis and developing a long-term treatment strategy, the clinician must observe the patient substance free for a minimum of three to six weeks, and sometimes for much longer periods, particularly given the protracted withdrawal syndromes that patients can experience with opioids, benzodiazepines, and even stimulant drugs.[1,3,4] Inpatient treatment pending stability is the ideal, with care provided by means of a single most responsible physician, within a single program. The effective treatment of both concurrent conditions, sequentially or in tandem, is the key, or neither will improve.[1,3,4] At the same time, although relapse to substance use has usually been considered a treatment failure when managing single disorders, this approach has not been the case in the therapy of duly disordered patients.[1,3,4]

Instead of one unified system of care, there are currently two fiefdoms in the form of a mental health system and a substance abuse system, each having its own set of stakeholders and power structure.[1,5,24] Patients have reported being forced to comply with the divergent rules of psychiatric and addiction facilities and with therapeutic discharge to the street rather than to an alternative level of safety.[1,5,24,25] A 2017 Health Quality Ontario (HQO) report highlighted this disparity in access to treatment.[25] In fact, first contact visits to emergency, hospital readmissions, and follow-up visits with primary care doctors or psychiatrists for this cohort varied significantly between Ontario's Local Health Integration Network (LHIN) regions in 2015.[25] HQO examined more than 1,000 organizations in Ontario, but a failure to focus on the mental health and addictions sector has limited the ability of regulatory authorities to accurately evaluate quality of care.[9,25]

The ensuing lack of therapeutic direction in Ontario resulted in a fragmentation of services and in the paradoxical belief that we are saving money in primary and secondary healthcare sectors while actually losing it within our tertiary system. The Concurrent Disorders Ontario Network (CDON) administered through the Centre for Addiction and Mental Health in Toronto was active from 2005 until 2010 and was intended to promote system coordination and integration, with the goal of developing a seamless continuum of services to patients with concurrent disorders.[5] Today, "Open-Minds, Healthy Minds – Ontario's Comprehensive Mental Health and Addiction Strategy", conceived in 2011, is intended to support mental health throughout life, from childhood to old age, and to provide integrated services directed at dual disorders.[9] The implementation of a mental health and addictions data and quality strategy, including the formulation of performance measures, will enable the standardization of care across hospitals and community-based mental health and addiction organizations for the benefit of this patient population.[9]

It is clear that strong linkages across mental health and substance use agencies are a necessary prerequisite in the treatment of dual disorders. Human oversight is the tie that binds treatment and outcome. A truly patient-centred system will require a care facilitator, who, like the conductor of an orchestra, will act as an interface between the patient and treatment team.[3,26] Care facilitators can be non-clinicians or healthcare professionals who provide a central point of contact in this therapeutic process, with a view to monitoring compliance and promoting treatment retention. This arrangement mandates further training, which will allow for a focused multidisciplinary team that addresses the needs of a complex patient population whilst avoiding splitting.[1,3,5,26] A parallel redistribution of disability supports addressing issues such as childcare, housing, transportation, and education, along with outreach and intervention, will convince patients that the cost-benefit of recovery is worth their time and effort.[1,24,27] Health Canada has now acknowledged that new funding sources will be required in order to accommodate the multiple mergers across provinces that are necessary to implement this new model of unitary care for concurrent disorders.[1,5] Some provinces and territories have already begun the process of amalgamating their mental health and substance use systems based upon this understanding of a difficult problem. The process of integration should continue because the associated cost of turnstile admissions to psychiatric emergency departments or detoxification facilities is prohibitive, but also because it is the right and humane thing to do.[5,25]

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Targeting the Immune System in Depression: Promising and Primetime

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As the leading cause of disability worldwide, depression affects greater than 350 million people globally.[1] Currently available pharmacological treatments are associated with high rates of treatment-resistance, mood episode relapses, residual symptoms (e.g., cognitive dysfunction), persistent functional impairments, and poor quality of life.[2] As per the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, approximately one quarter of patients will fail to achieve remission after numerous adequate antidepressant medication trials and combinations are attempted.[2] As such, there continues to be a desperate need to identify novel pharmacological treatments for depression that may improve remission rates and decrease the global burden of depression.

Over the past 60 years, pharmacological treatments for depression have focused on targeting the monoamine system after serendipitously identifying the antidepressant effects of monoamine oxidase inhibitors (MAO-Is).[3] Targeting the monoamine system has yielded great benefits. However, has also been detrimental in shifting the focus of drug development solely on this system, leaving research in other effected systems to be neglected.[4] For example, prior to the discovery of MAO-Is, Julius Wagner-Jauregg suspected that inflammation may be involved in the development of mental illness. As one of the only psychiatrists in history to ever win a Nobel Prize, his research was recognized as important and promising, prior to the discovery of MAO-Is.[5] However, the role of the immune system in depression was largely ignored, as the pursuit for new monoaminergic drugs dominated antidepressant drug development for five decades.[3]

Over the past decade, the role of the immune system in depression has been revisited. Numerous lines of evidence now support a bidirectional interaction between depression and immune dysfunction.[6] Epidemiological evidence has shown a strong association between mood disorders and autoimmune disorders (e.g., rheumatoid arthritis, psoriasis, lupus).[6-10] Furthermore, immune boosting treatments used to treat certain types of cancer and hepatitis C are strongly associated with depression.[11-13] These findings are of particular interest as these medications lead to the resolution of medical illness (e.g., treatment of cancer or hepatitis) but cause patients to develop depression.[11-13] This important finding is helpful to disprove the common misconception that patients with medical illness are only depressed because they are sad about being sick. Certainly, the psycho-social factors of depression are important to consider in the medically ill; however, the important biological role of immune dysfunction should not be discounted. Also of note, induction of an inflammatory state in animal and healthy human models (through injection of pro-inflammatory agents such as vaccines or cytokines) has also been shown to consistently cause significant depressive symptoms, sometimes referred to as "sickness behavior."[14]

In addition to these findings, numerous studies have also shown the strong association between elevated peripheral (i.e., serum) and central (i.e., cerebrospinal fluid) pro-inflammatory cytokines in bipolar and unipolar depression.[15-17] eripherally produced cytokines may traverse the blood-brain barrier and lead to inflammatory changes in the brain. These inflammatory changes have been shown to cause destruction of key neural circuits involved in mood and cognitive function.[18] Numerous pathways have been identified that link immune dysfunction with depression including but not limited to microglial over-activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, cytokine induced monoamine changes, oxidative stress, and gut-microbiota-brain axis dysfunction, all ultimately leading to destruction of key neural circuits, which subsequently leads to depressive symptoms.[6,19] Notably, immune dysfunction may affect certain domains of depression, such as anhedonia and sleep dysfunction, more significantly.[19,20]

Given the strong evidence to support a causal role of immune dysfunction in depression, the immune system presents as a novel target in the treatment of depression. Over the past decade, numerous proof-of-concept randomized controlled trials (RCTs) have repurposed anti-inflammatory medications to treat bipolar and unipolar depression. Meta-analyses have now demonstrated a medium-to-large effect size of adjunctive anti-inflammatories in the treatment of bipolar and unipolar depression.[21,22] More recent studies have used a stratified ap-

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proach, assessing anti-inflammatory treatments specifically in depressed patients with evidence of immune dysfunction (as determined by inflammatory markers), as evidence and logic have suggested that anti-inflammatory treatments are likely only beneficial for this subset of patients.[23,24] This stratified approach is also a step forward for psychiatry, moving to a more precision-based medical approach (as seen in other specialties, such as when selecting chemotherapy regimens or antibiotics). Of the anti-inflammatories evaluated, N-acetylcysteine (NAC),[25] minocycline[26] and omega-3 polyunsaturated fatty acids[27] show the most promise as adjunctive treatments for depression. These agents also have the benefit of excellent tolerability and safety with minimal adverse effects. As these studies were mostly small proof-of-concept RCTs, further larger studies are still required prior recommending these agents routinely in clinical practice.

Taken together, replicated evidence has demonstrated that immune dysfunction is involved in the etiology and pathophysiology of depression. Numerous mechanisms have been identified that subserve the immune-mood pathway. Targeting these mechanisms presents a novel, biologically-informed, and hypothesis-driven strategy that may advance the treatment of depression and yield improved outcomes beyond what may be achievable through solely targeting the monoamine system. Proof-of-concept studies have already yielded promising results in support of adjunctive anti-inflammatories in the treatment of bipolar and unipolar depression. Future, larger studies using a stratified approach are merited to determine which specific anti-inflammatory agents should be recommended.

Conflicts of Interest

JDR has no conflicts of interest to declare. RSM has received research grant support from Lundbeck, Astra Zeneca, Pfizer, Shire, Otsuka, Bristol Myers Squibb, National Institute of Mental Health, Stanley Medical Research Institute, Canadian Institutes for Health Research, and The Brain and Behavior Research Foundation. RSM has also received speaker/consultant fees from Lundbeck, Pfizer, Astra Zeneca, Elli Lilly, Janssen Ortho, Sunovion, Takeda, Forest, Otsuka, Bristol Myers Squibb, and Shire.

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