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DRUGS ARTICLES (CONT.)

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Cover Art: Rakesh Gudimella, Meds 2017

Description: In 1964, Dorothy Hodgkin won the Nobel Prize for the discovery of the structure of penicillin using the emerging technique of x-ray crystallography. The original x-ray diffraction patterns and the subsequent molecular model she created is shown in the foreground. Although the chemical formula of penicillin was known, its structure was not, making it difficult to produce on a large scale. Her discovery set us on the path to understanding antibiotic mechanisms and opened the door for the synthesis of cephalosporins and other important medications. The background shows the chemical structures of several lifesaving and influential drugs on the WHO List of Essential Medicines.

Knowledge translation and UWOMJ's expanded authorship

> *KT [knowledge translation] is of critical importance to health research, as it has become clear that the creation of new knowledge often does not, on its own, lead to widespread implementation or impacts on health.*
>
> **– Canadian Institutes of Health Research (CIHR)**[1]

CIHR, the largest academic health research funding agency in Canada, defines knowledge translation (KT) as "a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system."[1] Many more interrelated terms are also frequently tossed around and all carry a similar spirit as that of KT, including knowledge transfer, knowledge exchange, and research implementation.[2] Well-intentioned scholars have worked very hard at defining the nuanced semantic differences between these buzzwords, and they would likely scold the notion that any of these terms could be lumped together. To complicate matters even more, the use and popularity of these terms varies across geographic regions. In the interest of simplicity, only KT (a more prominent term in Canada) will be discussed here.[2]

While CIHR may be notoriously buried in obscure lingo, on the matter of KT the message to clinicians can be made plain and simple; the dialogue across all elements of the healthcare system needs to be improved. This means better communication between all knowledge users, which in addition to clinicians includes researchers, administrators, and policy makers. Given all that is at stake in healthcare, we should not rely on serendipity alone to guide vital health research towards clinical practise and public health measures.

Currently, KT involves considerable time lags; 17 years seems to be a common estimate for the time that it takes for research evidence to integrate into clinical practice.[3] If time lags are unavoidable because of the demands of safety and ethics, then it is especially important that KT efforts are initiated by young professionals. Promoting KT early on in a healthcare career will encourage knowledge users to see projects through over the span of their careers. From the perspective of a trainee, it seems clear that greater and earlier emphasis on KT, in the form of curriculum, tools, and resources, would be promising investments in the future of KT.

The UWOMJ team hopes to contribute to KT and towards this aim, we were excited to open up authorship to all healthcare-related graduate students as of this issue. We hope that this expansion might help bring together clinical and research trainees and encourage direct collaboration in the future. It was a great pleasure to see that there was interest in this opportunity and that this new venture proceeded very smoothly. Perhaps it was not by chance that one of the articles in this issue, authored by one of the first research students to publish in the UWOMJ, explicitly stressed the importance of KT. Natalie V. Scime's outstanding article on the use of antidepressant medication during pregnancy concludes that "while continued research on the outcomes and safety of antidepressant use during pregnancy is important, tailored KT efforts should be implemented and prioritized to improve the counselling and decision-making process for everyone involved."[4] Without doubt, this applies to all areas of healthcare.

We hope that you enjoy this issue on the theme of drugs, a topic that so often tugs on KT and inter-disciplinary expertise.

Alexander Levit
Junior Associate Editor

REFERENCES

1. Canadian Institutes of Health Research. Guide to knowledge translation planning at CIHR: Integrated and end-of-grant approaches. Ottawa (ON): Canadian Institutes of Health Research; 2012. 34 p. (Catalogue Number R4-11/2012E-PDF)
2. Graham I, Logan J, Harrison M, et al. Lost in knowledge translation: Time for a map? J Contin Educ Health Prof. 2006;26(1):13-24.
3. Morris ZS, Wooding S, Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. J R Soc Med. 2011;104(12):510-20.
4. Scime NV. Antidepressant use during pregnancy: Current attitudes and knowledge translation efforts. UWOMJ. 2016;85(1):12-4.

A gut reaction

Novel concerns and recommendations to address inappropriate antibiotic use

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ABSTRACT

The development of antibiotics is one of the greatest advances of modern medicine. While antibiotics have dramatically improved morbidity and mortality rates worldwide, current evidence asserts that one should err on the side of caution when prescribing antibiotics. The medical literature is accumulating studies on alarming consequences of inappropriate antibiotic use. Due to antibiotic overexposure, a North American "hypervirulant" strain of *Clostridium difficile* has emerged causing more severe gastrointestinal manifestations than previous strains. More recently, antibiotic overuse has been associated with obesity and diabetes mellitus. Unnecessary antibiotic use has led to increasing rates of bacterial resistance rendering more antibiotics ineffective. We are currently on the brink of an era which could reverse all the progress made with the introduction of antibiotics. The salient health consequences of inappropriate antibiotic prescriptions and the threat of a postantibiotic era command attention to practical initiatives that improve antibiotic prescribing patterns.

INTRODUCTION

The advent of antibiotics revolutionized the way medicine is practiced. Our most effective tools for inhibiting bacterial growth or killing bacteria are these powerful pills. When first introduced in 1928, antibiotics could effectively treat any bacteria they were targeting. These wonder drugs were particularly brilliant alternatives to invasive surgeries. Morbidity and mortality rates have dramatically decreased since the development of antibiotics, increasing life expectancy by 15 years, and saving millions of lives.[1]

Unfortunately, such a radical change in medicine has brought with it many adverse effects. Inappropriate antibiotic prescription is a serious concern as it opens the door to numerous health sequelae. Antibiotics have been known to cause *Clostridium difficile* infections by disrupting the beneficial microbes that protect our gut.[2] Through a similar mechanism, new research has now linked the inappropriate use of antibiotics with increased risk of chronic diseases, such as diabetes mellitus and obesity.[1,3–5] The era of untreatable infections is impending if bacteria continue to become increasingly resistant to first-line antibiotic therapy.[1,6] The Chief Medical Officer for England has described this potential postantibiotic era as "apocalyptical" and "catastrophic."[6]

In light of these findings, this article will bring forth new evidence on the adverse effects of antimicrobials, and advocate for their judicious use with practical recommendations.

ANTIBIOTIC OVERUSE

The evidence of overexposure to antibiotics in Canada is overwhelming. Studies have shown that in Canadian hospitals, only half of antibiotic prescriptions were justifiably used.[7,8] Consequently, a staggering loss of up to $850 million, yearly, is attributed to inappropriate antibiotic use in Canada.[7] In order to address this problem, it is important to recognize why antibiotics are excessively prescribed. In the context of diagnosing lower respiratory tract infections, a study conducted with the College of Family Physicians of Canada examined some possible causes of the misuse of antibiotics.[9] This study determined that physicians were (1) uncertain about the need for antibiotics, (2) conflicted about the clinical diagnosis, (3) concerned that patients could become sicker, and (4) pressured by patients or parents to prescribe antibiotics.[9] This is especially disconcerting as a public opinion poll demonstrated that 50% of Canadians are misinformed about the effectiveness of antibiotics on viruses.[7] The etiology for antibiotic prescribing must be addressed to circumvent alarming health concerns.

HEALTH CONSEQUENCES

Understanding the significance of taking unnecessary antibiotics can help prevent their overuse. An emerging field of microbiology research focuses on the relationship between antibiotics and gut microbiota, the community of bacteria that reside within the gastrointestinal tract (formerly known as gut flora). Gut microbiota are able to counteract infection by playing an essential role in immune system development.[10] Various antibiotics can alter the beneficial microbiota in the colon, leaving it vulnerable to infection.[11] High doses of or prolonged exposure to antibiotics can lead to an increased risk of *C difficile* infections, which range from causing severe diarrhea to life-threatening pseudomembranous colitis.[2] Of note, a major article has recently reported a North American "hypervirulant" strain which causes increasingly severe *C difficile* infections.[12] This is particularly disturbing as *C difficile* is currently a leading cause of nosocomial infection,[11] highlighting the need to correctly monitor antibiotic dosage and duration to maintain the integrity of the microbiota.

A lesser known function of the microbiota is its role in metabolism. Current research has identified additional features to the role of the microbiota in immune defense, including the regulation of fat storage, hormone secretion, and energy expenditure.[1,10] While it is known that antibiotics can suppress or eradicate gut microbiota, their influence on the microbiota's nutrient metabolism has been associated with an increased risk of type 1 and type 2 diabetes mellitus.[1,3] The disturbance in glucose homeostasis and insulin sensitivity has been suspected to be caused by use of oral vancomycin,

bactericidal, and narrow-spectrum antibiotics.[10,13] It is important to note that these are preliminary studies in this field, and further evidence would be needed to make conclusive assertions.

Another chronic disease that has been linked to prolonged antibiotic use is obesity. In mice, exposure to antibiotics has been shown to increase body fat mass due to disruption of the microbiota composition.[14] Antibiotics have also been shown to contribute to the risk of obesity in humans; some studies go on to indicate that people who are obese have lower microbial diversity.[4,5,15] The postnatal period is especially susceptible to disruptions of the microbial environment from antibiotics, as the gut microbiota in infants is still developing.[16] Azad and colleagues observed that boys who took antibiotics before their first birthday were 5 times more likely to become overweight by age 12.[16] The mechanism is believed to be similar to that seen in agriculture where livestock given antibiotics at a young age improve feeding and weight gain due to growth promotion.[17]

The heavy introduction of antibiotics in agricultural practice was one of the first settings to raise a concern for antibiotic resistance.[15] It has been well known for decades that unnecessary antibiotic use can lead to resistance, but the types of bacteria that are evolving to evade the life-saving effects of antimicrobials are increasingly becoming more prevalent. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a Gram-positive bacterium that is the archetype of antimicrobial resistance but there are now new "bugs on the block" that disarm Gram-negative antibiotics. The emergence of Gram-negative antibiotic resistance leads to dire consequences as without effective antimicrobials, they are capable of causing high rates of morbidity and mortality.[18] New Delhi Metallo-beta-lactamase-1 (NDM-1) is a newly discovered enzyme found in Gram-negative bacteria that is able to defy antibiotics which are normally used to target Gram-negative organisms. NDM-1 can be found in *Escherichia coli* bacteria which are becoming more difficult to treat due to the unavailability of alternative antimicrobials.[18] Antibiotic resistance has now become a public health emergency as it is predicted that the role of antibiotics in the eradication of disease will become obsolete in as little as 20 years.[6,16]

PRACTICAL SOLUTIONS

Given the infancy of research on the effect of antibiotics on gut microbiota, mitigating the adverse effects of the specific emerging health consequences discussed above is still a challenge.

The literature indicates that fecal microbiota transplants (FMT), well known for their effective treatment of *C difficile*, are now being piloted as a therapeutic strategy for obesity.[15] Early studies show that this novel approach, involving FMT from lean to obese patients, has been effective in improving insulin resistance.[15] Furthermore, probiotics may be a useful treatment for metabolic diseases like obesity and diabetes as they have been shown to reduce adiposity, body fat, and weight gain.[19] Probiotics may be administered in multiple forms (ie, capsule, sachet, or yogurt), and are currently available in supermarkets for consumption without a prescription.[20,21] Finally, there is a critical need for new and modified forms of antibiotics to treat the diversifying and increasing number of resistant bacteria, particularly targeted at Gram-negative bacteria.[1]

More practical recommendations for physicians to address the inappropriate prescription of antibiotics are numerous; however, 3 specific examples will be discussed. The first, antimicrobial stewardship programs (ASP), are "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration."[22] The implementation of patient and/or provider ASP education programs has led to substantial reductions (up to 35%) of inappropriate antibiotic prescriptions.[23,24] Recent evidence suggests, however, that even simpler and less costly ASP interventions can result in a significant decline in antibiotic prescription.[25] Meeker and colleagues found that physicians who displayed a signed letter of commitment to avoid inappropriate prescriptions of antibiotics in examinations rooms for 12 weeks reduced their antibiotic prescriptions by nearly 20%.[25] While physicians' commitment to ASP is pivotal to their success, their uncertainty in the infectious etiology (ie, bacterial or viral) is a major contributing factor to the inappropriate prescription of antibiotics.[9] To address this challenge, it is recommended that where appropriate, physicians are vigilant about ordering cultures and perform throat swabs and rapid testing to confirm diagnoses.[9] Lastly, physicians should exercise more preventive medicine such as prophylaxis for influenza given that patients who present with influenza-like symptoms are often inappropriately prescribed with antibiotics.[26,27] A study showed that 38% of health care visits for influenza resulted in an antibiotic prescription.[27] Therefore, more efforts in promoting flu vaccinations would decrease the spread of influenza infections altogether, and subsequently reduce the proportion of unnecessary antibiotic use.[26]

CONCLUSION

Cautious and thoughtful use of antibiotics remains paramount to the prevention of antibiotic-acquired illnesses. However, it is now becoming more evident that antibiotics can assault the human microbiome causing a myriad of adverse and potentially chronic health effects. Additional research is necessary to establish alternative evidence-based strategies that foster the maintenance of normal and healthy gut microbiota. More immediately, there is strong evidence supporting tangible initiatives that improve antibiotic prescribing patterns, which can immediately be adopted by physicians for the best practice of care.

REFERENCES

1. Keeney KM, Yurist-Doutsch S, Arrieta M-C, Finlay BB. Effects of antibiotics on human microbiota and subsequent disease. Annu Rev Microbiol. 2014;68(1):217-35.
2. Stevens V, Dumyati G, Fine LS, Fisher SG, Van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of clostridium difficile infection. Clin Infect Dis. 2011;53(1):42-8.
3. Mikkelsen KH, Knop FK, Frost M, Hallas J, Pottegård A. Use of antibiotics and risk of type 2 diabetes: a population-based case-control study. J Clin Endocrinol Metab. 2015 Oct;100(10):3633-40.
4. Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology. 2010;156(Pt 11):3216-23.
5. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, DeRusso PA. Association of antibiotics in infancy with early childhood obesity. JAMA Pediatr. 2014;168(11):1063-9.
6. Viens AM, Littmann J. Is antimicrobial resistance a slowly emerging disaster? Public Health Ethics. 2015 Nov; 8(3): 255-65.
7. Thomas RE. Controlling antimicrobial resistance Health Canada proposes an integrated action plan for Canadians. 1998;44:1901-2.
8. Schollenberg E, Albritton WL. Antibiotic misuse in a pediatric teaching hospital. Can Med Assoc J. 1980;122(1):49-52.
9. McIsaac WJ, To T. Antibiotics for lower respiratory tract infections. Still too frequently prescribed? Can Fam Physician. 2004;50:569-75.
10. Sommer F, Bäckhed F. The gut microbiota — masters of host development and physiology. Nat Rev Microbiol. Nature Publishing Group; 2013;11(4):227-38.
11. Seekatz AM, Young VB. Clostridium difficile and the microbiota. J Clin Invest. 2014;124(10):4182-9.
12. See I, Mu Y, Cohen J, Beldavs ZG, Winston LG, Dumyati G, et al. NAP1 strain type predicts outcomes from Clostridium difficile infection. Clin Infect Dis. 2014;58(10):1394-400.
13. Vrieze A, Out C, Fuentes S, Jonker L, Reuling I, Kootte RS, et al. Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity. J Hepatol. European Association for the Study of the Liver; 2014;60(4):824-31.
14. Cho I, Yamanishi S, Cox L, Methé BA, Zavadil J, Li K, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature. 2012;488(7413):621-6.
15. Konturek PC, Haziri D, Brzozowski T, Hess T, Heyman S. Emerging role of fecal microbiota therapy in the treatment of obesity. J Physiol Pharmacol. 2015 Jul;66(4):483-91.
16. Azad MB, Bridgman SL, Becker AB, Kozyrskyj AL. Infant antibiotic exposure and the development of childhood overweight and central adiposity. Int J Obes (Lond). Nature Publishing Group; 2014;38(10):1-35.
17. Jukes TH. Antibiotics in animal feeds and animal production. Bioscience. 1972;22(9):526-34.
18. Kaye KS, Pogue JM. Infections caused by resistant Gram-negative bacteria: epidemiology and management. Pharmacotherapy. 2015 Oct;35(10):949-62.
19. Mekkes M, Weenen T, Brummer R, Claassen E. The development of probiotic treatment in obesity: a review. Benef Microbes. 2014;5(1):19-28.
20. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. BMJ. 2002;324(7350):1361.

21. Johnston BC, Supina AL, Ospina M, Vohra S. Probiotics for the prevention of pediatric antibiotic-associated diarrhea gastrointestinal and extra-gastrointestinal disease. (Review). Cochrane Database Syst Rev. 2011 Nov 9;(11):CD004827
22. Fishman N. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33(04):322-7.
23. Canadian Antimicrobial Resistance Alliance. Comprehensive overview of antibiotic resistance in Canada. 2006 [cited 2015 Nov 15]. p. 1-27.
24. Roque F, Herdeiro MT, Soares S, Teixeira Rodrigues A, Breitenfeld L, Figueiras A. Educational interventions to improve prescription and dispensing of antibiotics: a systematic review. BMC Public Health. 2014;14(1):1276.
25. Meeker D, Knight TK, Friedberg MW, Linder JA, Goldstein NJ, Fox CR, et al. Nudging guideline-concordant antibiotic prescribing. JAMA Intern Med. 2014;174(3): 425-31.
26. Low D. Reducing antibiotic use in influenza: challenges and rewards. Clin Microbiol Infect. European Society of Clinical Infectious Diseases; 2008;14(4):298-306.
27. Ciesla G, Leader S, Stoddard J. Antibiotic prescribing rates in the US ambulatory care setting for patients diagnosed with influenza, 1997–2001. Respir Med. 2004;98(11):1093-101.

Back to the drawing board

Resistance and its implications for the use of targeted agents in head and neck squamous cell cancer

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ABSTRACT

A significant limitation of genomically-guided targeted cancer therapies is the inevitability of innate or evolved resistance. Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous and anatomically complex cancer in which both the disease and available treatments carry considerable toxicity with lasting effects on patient quality of life; therapies with increased efficacy and decreased toxicity are needed. The therapeutic focus for HNSCC is shifting towards targeted inhibition of specific, frequently altered genes or pathways, including the phosphatidylinositol 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) network, which is the most frequently altered pathway in HNSCC. Agents targeting this network have demonstrated preclinical and clinical efficacy; however, as in most solid tumour malignancies, response to therapy is temporary and systems become refractory following prolonged treatment.

In this review, I examine the role of emerged resistance with particular regard to targeted PI3K inhibitors in HNSCC and describe targetable mutations, pathway reactivation and bypass mechanisms as mediators of resistance. I conclude by emphasizing the value of combinatorial therapies and the value in re-evaluation of response to therapy over time to prevent or delay the onset of resistance. PI3K inhibitors and other targeted therapies have already begun transforming cancer care, providing improved patient responses and quality of life benefits. Characterizing resistance mechanisms will help guide the application of such agents, as well as the design of combination treatments to improve outcomes for cancer patients.

INTRODUCTION

Resistance to drug therapy is a major challenge in modern oncology. Outside of hematologic malignancies, prolonged efficacy of targeted agents has been largely disappointing; emerged resistance to single targeted agent treatments is almost universally inevitable.[1,2] Resistant subclones emerge through 2 mechanisms: (1) innate (intrinsic) resistance whereby a mutation exists before treatment in a select number of cells, or in a minor sub-population of cells that eventually dominate due to selective pressure; or (2) evolved (acquired) resistance resulting from clonal expansion of newly altered cells.[3]

Advancements in next-generation DNA/RNA sequencing (NGS) have prompted an explosion of targeted agents, and mutation-directed therapy has already become standard of care for select cancers. While targeted inhibition of frequently mutated or overactive signalling pathways achieves tumour responses in a portion of cases, these responses have not been durable over time, and clinical application of single-agent targeted therapies has shown only modest benefit.[4] Here I discuss the role of targeted phosphatidylinositol-3-kinase (PI3K) inhibition in head and neck squamous cell carcinoma (HNSCC) and describe mechanisms of resistance to targeted therapies, including targeting key activating mutations and pathway reactivation, before addressing combination therapies as an approach to overcome resistance.

RESISTANCE TO PI3K INHIBITION IN HNSCC

HNSCC is the 5th most common malignancy worldwide with over 550 000 cases diagnosed annually, and is on the rise due to newfound associations with oral human papillomavirus (HPV) infection.[5,6] Despite efforts to improve outcomes, the 5-year survival rate is only about 50% for advanced disease. Toxicity associated with both the disease and available treatments (chemotherapy, radiation, surgery) is high, often permanently altering functional and aesthetic features of the head and neck, including facial appearance, breathing, speech, and swallowing. This treatment morbidity highlights an urgent need for improved therapeutics with increased efficacy and decreased toxicity.[5,7,8]

The first targeted therapy to demonstrate survival advantage in HNSCC addresses epidermal growth factor biology, as the epidermal growth factor receptor (EGFR) is overexpressed in more than 90% of HNSCC cases.[9] Cetuximab (trade name Erbitux) is an EGFR monoclonal antibody and remains the only Food and Drug Administration (FDA)-approved targeted agent for HNSCC. Together with recent multi-platform genomic analyses of HNSCC, the PI3K-AKT-mammalian target of rapamycin (mTOR) network downstream of EGFR is emerging as perhaps one of the most critical pathways in HNSCC. Agents targeting this pathway are at various stages of preclinical and clinical development.[10,11]

The PI3K-AKT-mTOR axis is mutated in 34% of HPV-negative and 56% of HPV-positive tumours and is the only truly targetable pathway in HNSCC, a disease dominated by alterations in tumour suppressors.[10,12] Alterations to PI3K pathway members have been shown to induce cell line transformations and tumorigenesis in transgenic mice, demonstrating the oncogenic potential of the PI3K network.[13-15] Additionally, elevated PI3K signaling following deregulation of upstream mediators (eg, EGFR, FGFR1-3, TSC1-2) or aberrations in downstream effectors (eg, PIK3CA, PIK3R1,

mTORC1-2, PTEN) has been shown to induce cell growth, proliferation, and angiogenesis essential for tumour progression.[14] The prevalence of PI3K pathway alterations and its oncogenic capacity in solid tumours has led to the creation of targeted agents against its major effectors, including the 2-aminothiazole derivative BYL719 (Alpelisib; Novartis).[16]

BYL719 is a p110α-specific PI3K inhibitor equipotent for wild-type and somatic mutant forms of the p110α catalytic subunit of Class IA PI3Ks.[10] Mutations and amplifications in PIK3CA—which encodes p110α—is frequently amplified and is characterized by 3 hotspot mutations (E542K, E545K, and H1047R/L). These genetic changes were found to be the predominant positive predictors for BYL719 sensitivity. Also available are panisoform PI3K inhibitors, dual PI3K-mTOR inhibitors, as well as drugs targeting other pathway members such as mTOR and AKT.[10]

MUTATIONS MEDIATING RESISTANCE

Mathematical models to describe the evolutionary dynamics of cancers in response to targeted agents emphasize that around 50 unique mutations—innate or acquired—may confer resistance to a given drug. As such, single-agent therapy will eventually fail in all cases, even if the lesion recedes to below clinical detection for months before re-emerging. This explains why tumours can recur after long remission periods.[2]

Approaches to overcome such resistance may include designing agents with greater potency—for instance, irreversible inhibitors or mutant-selective drugs.[18] Irreversible PI3K inhibitors, such as wortmannin, covalently bind target residues, blocking ATP competition indefinitely. Such inhibitors, however, may impart high toxicity due to off-target effects.[3,18] With regard to selectivity, most targeted agents—including BYL719—do not specifically inhibit mutant forms of their target. If resistance occurs via a mutation in the original target, it may be effective to replace the drug with a mutant-selective counterpart. For instance, osimertinib targets T790M-mutant EGFR, a primary mediator of resistance for growth factor receptor-targeted agents, such as erlotinib or gefitinib.[10] As our understanding of resistance mechanisms continues to develop, considerations for drug potency and selectivity will become increasingly relevant.

PATHWAY ACTIVATION BY UPSTREAM OR DOWNSTREAM ALTERATIONS

Crosstalk between signalling networks is a considerable challenge in designing drugs with specificity and efficacy. For instance, downstream signalling of PI3K is transmitted via several pathways, including the AKT-mTOR network (involved in cell survival) and the MAPK pathway (growth and proliferation) (Figure).[10,21] RAF and MEK inhibitors targeting the MAPK network, as well as mTORC1-2 inhibitors have demonstrated efficacy when prolonged treatment with upstream PI3K inhibitors have resulted in tumour resistance.[19]

A second strategy to mitigate single-agent resistance is to target upstream or downstream effectors of the primary target. Mutations acquired during cell divisions and/or in response to prolonged therapy do not necessarily occur in the targeted gene but rather in

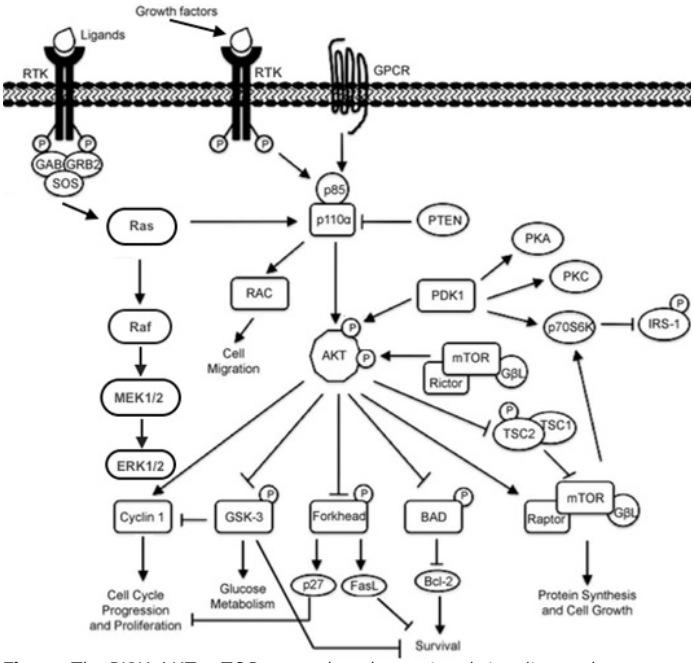

Figure: The PI3K-AKT-mTOR network and associated signaling pathways. Adapted from Castellano & Downward.[21]

a gene elsewhere in the pathway.[18] PTEN loss, for instance, was found by sequencing metastatic lesions from a patient treated with BYL719 who achieved a clinical response but eventually became resistant and died.[17] All lesions resistant to BYL719 showed genetic PTEN alterations not present in the pretreatment tumour, each unique and resulting in loss of PTEN expression.[17] PTEN functions immediately downstream of PI3K, where it acts as a negative regulator, effectively managing network activation. It is evident that alterations in critical effectors up- or downstream of the drug target may be capable of modulating therapy resistance, and alterations to treatment regimens to account for these events may be necessary.

BYPASS MECHANISMS

Increasing evidence supports a role for bypass mechanisms in mediating targeted cancer resistance. This involves pathway reactivation via mediators of a pathway independent of the target of interest.[3] An early in vitro study of prolonged BYL719 treatment in HNSCC found that models refractory to p110α inhibition overexpress AXL, a receptor tyrosine kinase that dimerizes with EGFR, leading to PI3K-independent mTOR activation.[19] In such bypass scenarios, dual inhibition of both pathways (here PI3K and EGFR/AXL) may be a potential strategy to prevent or delay the onset of resistance.

Another bypass-type mechanism takes advantage of the deregulation of cellular metabolism frequent in many cancers. Increased acetyl-CoA production afforded by cancer metabolic reprogramming to favour glycolysis permits increased acetylation of lysine residues in RICTOR, a core component of mTORC2.[20] RICTOR activation is maintained as a result, forming an activation loop for mTORC2 leading to its continued signalling activity, even when other components of the growth factor receptor pathways are inhibited. By removing the dependency of mTOR activation on up-

stream signalling, systems effectively become resistant to EGFR, PI3K, or AKT-targeted therapies. Altered cellular metabolism therefore has been shown to not only be a factor mediating cancer progression, but more recently, also an opportunity for drug resistance to develop.

CONCLUSION

As resistance continues to demand consideration in clinical settings, strategies to prevent or delay innate and evolved resistance are being investigated. These include (1) designing more selective, potent inhibitors, including agents active against presently "undruggable" targets (for instance, oncogenic or hyperactive RAS); (2) identifying effective drug combinations to maintain cancer inhibitory properties for a longer period of time; and (3) developing drug dosing regimens with improved efficacy and durability. Already, next-generation inhibitors have been designed with improved tolerability and specificity, and combination therapies of 2 or more agents appear effective; one example is dual inhibition of EGFR and PI3K in BYL719-resistant HNSCC.[19] Thorough investigation of the relative value of sequential versus simultaneous combinatorial therapy and research into the implementation of repeated noninvasive techniques to monitor treatment response and the status of emerging resistance variants will provide answers to some of these questions.[18]

The ongoing effort to design more specific and potent inhibitors, in combination with continued validation of potential biomarkers identified by NGS of large-scale patient tumour databanks and characterization of resistance mechanisms to targeted agents, is expected to lead to improved design of clinical trials, and ideally, prolonged clinically relevant patient responses. The genetic diversity and complex anatomical location of head and neck cancers make treatment by conventional means challenging; the focus on personalized treatment of genetically-distinct tumours via targeted therapy holds tremendous treatment potential for HNSCC as well as other cancers. Understanding treatment failure due to resistance is critical for the continued development of such therapies and demands preclinical and clinical focus to overcome.

REFERENCES

1. Bozic I, Nowak MA. Timing and heterogeneity of mutations associated with drug resistance in metastatic cancers. Proc Natl Acad Sci USA. 201 Nov 11;111(45):15964-8.
2. Bozic I, Reiter JG, Allen B, Antal T, Chatterjee K, Shah P, et al. Evolutionary dynamics of cancer in response to targeted combination therapy. eLife. 2013 Jun 25;2:1-15.
3. Groenendijk FH, Bernards R. Drug resistance to targeted therapies: deja vu all over again. Molecular Oncology. Elsevier B.V; 2014 Sep 12;8(6):1067-83.
4. Martini M, De Santis MC, Braccini L, Gulluni F, Hirsch E. PI3K/AKT signaling pathway and cancer: an updated review. Ann Med. 2014 Sep;46(6):372-83.
5. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal for Clinicians. 2011 Feb 4;61(2):69-90.
6. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of Clinical Oncology. 2011 Nov 8;29(32):4294-301.
7. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010 Jul;363(1):24-35.
8. Nichols AC, Dhaliwal SS, Palma DA, Basmaji J, Chapeskie C, Dowthwaite S, et al. Does HPV type affect outcome in oropharyngeal cancer? J Otolaryngol Head Neck Surg. 2013 Feb 1;42(9):1.
9. Hansen AR, Siu LL. Epidermal growth factor receptor targeting in head and neck cancer: have we been just skimming the surface? Journal of Clinical Oncology. 2013 Mar 25;31:1-3.
10. Rodon J, Dienstmann R, Serra V, Tabernero J. Development of PI3K inhibitors: lessons learned from early clinical trials. Nat Rev Clin Oncol. 2013 Feb 12;10(3):143-53.
11. Juric D, et al. Phase I study of the PI3Kα inhibitor BYL719, as a single agent in patients with advanced solid tumors (aST). Ann Oncol. 2014 Sept 28;25(suppl 4): abstract.
12. Lawrence MS, Sougnez C, Lichtenstein L, Cibulskis K, Lander E, Gabriel SB, et al. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 28;517(7536):576-82.
13. Carver BS, et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell. 2011 May 17;19(5):575-586.
14. Zhao Y, Adjei AA. The clinical development of MEK inhibitors. Nat Rev Clin Oncol. Nature Publishing Group; 2014 May 20;11(7):385-400.
15. Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. Journal of Clinical Oncology. 2010 Feb 18;28(6):1075-83.
16. Fritsch C, Huang A, Chatenay-Rivauday C, Schnell C, Reddy A, Liu M, et al. Characterization of the novel and specific PI3K inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials. Molecular Cancer Therapeutics. 2014 May 5;13(5):1117-29.
17. Juric D, Castel P, Griffith M, Griffith OL, Won HH, Ellis H, et al. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. Nature. Nature Publishing Group; 2015 Nov 17;518(7138):240-4.
18. Gioeli D, editor. Molecular and translational medicine. New York: Humana Press; 2011. 211 p.
19. Elkabets M, Pazarentzos E, Juric D, Sheng Q, Pelossof RA, Brook S, et al. AXL mediates resistance to PI3Kα inhibition by activating the EGFR/PKC/mTOR axis in head and neck and esophageal squamous cell carcinomas. Cancer Cell. Elsevier Inc; 2015 Apr 13;27(4):533-46.
20. Masui K, Tanaka K, Ikegami S, Villa GR, Yang H, Yong WH, et al. Glucose-dependent acetylation of Rictor promotes targeted cancer therapy resistance. Proc Natl Acad Sci USA. 2015 Jul 28;112(30):9406-11.
21. Castellano E, Downward J. RAS Interaction with PI3K: more than just another effector pathway. Genes & Cancer. 2011 Jul 1;2(3):261-74.

Antidepressant use during pregnancy

Current attitudes and knowledge translation efforts

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ABSTRACT

Antidepressant use during pregnancy is a widely debated and controversial topic among researchers and clinicians. Despite a wealth of studies examining the adverse outcomes and relative safety of these prescription medications, inconsistencies in study design and methodology make it challenging to draw conclusions and translate findings into clinical practice. Consequently, healthcare professionals are often uncertain about how to counsel pregnant women regarding antidepressant use, leading patients to feel unsupported and conflicted about where to receive information and how to make an informed decision. To remedy this clinical issue, many knowledge translation initiatives exist in Canada, including the Motherisk program, patient decision aids, professional handbooks, and critically appraised summaries of evidence published in scholarly journals. These endeavours represent important progress in knowledge dissemination and uptake among patients and healthcare professionals. However, further implementation and evaluation of targeted knowledge translation strategies are warranted to improve the knowledge and support necessary in making decisions regarding antidepressant use during pregnancy.

INTRODUCTION

Depression during pregnancy has been associated with detrimental outcomes for both mother and baby, including preeclampsia, preterm birth, delayed cognitive and emotional development in offspring, and unhealthy behaviours throughout pregnancy,[1] and is a major risk factor for postpartum depression.[2] Thus, treatment of depression is necessary to protect the health of the mother-infant dyad. Given that depression affects approximately 10% of pregnant women in Canada,[3] it is imperative that healthcare professionals appropriately counsel these women on treatment with antidepressants. This is exceptionally challenging considering that this complex topic is met with much controversy in research and healthcare.

Antidepressants are the most widely studied pharmaceutical for use during pregnancy with selective serotonin reuptake inhibitors, a first-line class of antidepressants, having more than 30 000 reported pregnancy outcomes following prenatal exposure.[4,5] Pulmonary hypertension, autism, preterm birth, cardiac defects, and congenital anomalies are among the many medical conditions that have been studied in association with antidepressant use during pregnancy.[6] Conclusions from various studies are inconsistent, likely due to the use of varying study designs,[7] incomplete patient reporting,[8] difficulties translating findings to clinical significance,[4] and the potential for confounding and detection bias.[4,5] Furthermore, appraisal and synthesis of current evidence into clinical practice guidelines does not exist in Canada,[7] leaving the onus on clinicians to navigate through the literature and educate themselves.

ATTITUDES OF HEALTHCARE PROFESSIONALS AND PREGNANT WOMEN

Confusing literature and the lack of authoritative guidelines has led to persistent uncertainty regarding antidepressants and pregnancy among healthcare professionals. One survey of Australian and Canadian primary care physicians found that physicians lacked confidence when facing decisions about antidepressant use during pregnancy.[9] Similarly, a survey of Dutch general practitioners and pharmacists concluded that substantial differences in views exist on the management of depression in pregnant women in addition to a general lack of subject knowledge.[10] This uncertainty might be a product of inadequate coverage of this topic in healthcare training. A study of Saskatchewan pharmacy, nursing, and medical students found that students did not have adequate knowledge about depression and antidepressants during pregnancy.[11] Moreover, students demonstrated some apprehension towards pregnant patients with depression; after reading vignettes, several students agreed with statements about feeling nervous around the patient or finding her difficult to talk to.[11]

It is ultimately pregnant women who suffer from healthcare professionals' lack of knowledge and confidence. Pregnant women have reported a lack of direction and reassurance from their physician on whether to continue antidepressants,[12,13] and have described physicians as appearing uncomfortable during such discussions.[13] It is therefore understandable that pregnant women faced with decisions regarding antidepressant use consult multiple sources before making a decision,[12] with approximately 65% of women retrieving information from the internet.[13] This absence of professional support is particularly alarming given the high decisional conflict attached to antidepressant use during pregnancy.[14] Decision-making is difficult for women because of considerations in weighing their own health versus their infant's health, uncertainty about the impact of antidepressant use on their fetus, negative external influences (ie, unsupportive partners, families, friends), and emotional distress.[14] Additionally, negative or frightening information received early on from professional or lay sources is subsequently hard to erase with more positive, reassuring counselling as evident by mothers' continued feelings of worry and guilt and avoidance of antidepressant use.[12,13] Clearly, a need exists for knowledge translation (KT) activities targeted towards both mothers and healthcare professionals to increase the knowledge and support necessary for informed decision-making.

CURRENT KNOWLEDGE TRANSLATION ACTIVITIES

To address the need for KT in this area, many initiatives are ongoing in Canada. One of these is the internationally renowned Motherisk program established at the Hospital for Sick Children. Motherisk is a teratogen information centre that operates a national telephone hotline, a face-to-face clinic, and a wealth of online resources that provide a distillation of current evidence, available to both the public and healthcare professionals (http://www.motherisk.org). Motherisk receives thousands of calls annually and estimates that 12% of callers inquire about antidepressant use.[12] Women that call this hotline receive evidence-based counselling from trained Motherisk counsellors for free.[15] This service is also cost effective, with an estimated annual savings of approximately $10 million.[16]

Despite receiving evidence-based information about antidepressants, women may still experience high decisional conflict in selecting the treatment for their depression. Recognizing this, Dr Simone Vigod and her colleagues at Women's College Hospital are currently recruiting mothers to evaluate an online decision aid regarding antidepressant use during pregnancy (Permission received from Dr Vigod to describe select details of decision aid in this article). Decision aids help patients make deliberated choices about healthcare options by providing evidence-based information about harms and benefits of each option and assisting patients in clarifying their personal values related to treatment outcomes and adverse effects.[17,18] These aids complement clinician counselling and have been associated with positive effects on informed decision-making in pregnancy care.[18] The decision aid designed by Dr Vigod, in consultation with pregnant women to optimize user-friendliness, provides risks and benefits for taking antidepressants versus stopping antidepressants, asks women to rank and rate benefits and risks in accordance with their values, and allows women to identify people in their lives that make this decision easier or more difficult. Women receive a summary sheet containing this information and their responses, which they may keep to themselves or share with their healthcare provider.[19] The goal of this tool is to reduce decisional conflict and, consequently, promote effective and informed decision-making. While the details of this study have not been formally published, they hold promise for providing nonjudgemental and unbiased support for women facing this decision.

Healthcare professionals are also an important audience for KT activities given their trusted role as an information source. A handbook was created in 2007 by the Centre for Addictions and Mental Health (CAMH) and Motherisk to assist healthcare professionals in providing competent counselling to pregnant women with mental health concerns. *Exposure to psychotropic medications and other substances during pregnancy and breastfeeding* is freely available through the CAMH website and contains gleaned evidence about the potential adverse effects and relative safety of several medications, including antidepressants.[20] To further the professional reach of critically appraised evidence, Motherisk publishes quarterly grand rounds in the *Journal of Obstetrics and Gynaecology Canada* and a monthly column in *Canadian Family Physician*, each of which is circulated to their respective population of Canadian physicians and regularly delves into antidepressant use.[21]

FUTURE DIRECTIONS FOR KNOWLEDGE TRANSLATION

The presented KT activities represent progress in promoting knowledge dissemination and uptake in this area. Nevertheless, additional initiatives likely need to be implemented, monitored, and evaluated to measure successes, determine where gaps exist, and rectify attitudes and experiences regarding antidepressant use during pregnancy.[22]

Continued promotion of Motherisk through media advertising and referral can ensure that expectant mothers consult this comprehensive information source during their decision-making. If proven effective, widespread implementation of Dr Vigod's decision aid may help decrease levels of decisional conflict in these women. This tool is particularly valuable as its web-based nature allows for accessibility regardless of geographic location and the ability to continuously update the information presented as new evidence emerges. Another viable KT approach might include partnerships with online magazines, blogs, or media sources that have large followings of pregnant women or women planning pregnancy to publish evidence-based materials regarding depression and antidepressant use during pregnancy. Since a large proportion of pregnant women seek antidepressant information on the internet, harnessing this mode of dissemination can ensure that accurate information from a high-traffic online source is available. This strategy aligns with several dissemination principles such as tailoring the message and medium to the audience as well as media engagement.[23]

Ensuring that healthcare professionals are comfortable and knowledgeable in providing support to pregnant women facing decisions about antidepressants is critical for improving the decision-making process. Integrating educational curriculum components that address antidepressants and depression during pregnancy as well as introduce strategies for counselling these women might reduce levels of uncertainty, discomfort, and stigma surrounding this topic. Development of clinical practice guidelines or algorithms by professional colleges that provide direction in counselling and treatment with antidepressants during pregnancy may also be useful. Replicating a survey of professionals' attitudes with a focus on Canada and inclusion of all pertinent clinicians such as pharmacists, obstetricians, psychiatrists, and family physicians would provide additional context regarding current attitudes and allow for tracking attitude changes after KT implementation. A survey of this nature is also warranted due to the low response rates (31.5%) for Canadian physicians in a former study, thus limiting the representativeness of results.[9]

The thalidomide tragedy may still have lingering impacts given the heightened awareness of the negative effects of medications during pregnancy. However, when untreated conditions are unequivocally detrimental, as is the case with depression, it is essential that healthcare professionals and women receive timely, evidence-based information. Controversy regarding the data on this topic may hinder KT attempts, and efforts towards promoting sound methodology, critically appraising evidence, and strengthening the knowledge base will assist with more seamless KT. While continued research on the outcomes and safety of antidepressant use during pregnancy is important, tailored KT efforts should be

implemented and prioritized to improve the counselling and decision-making process for everyone involved.

REFERENCES

1. Bonari L, Einarson A, Koren G. Risk of untreated depression during pregnancy. Can Fam Physician. 2004;50(11):37-9.
2. Gaillard A, Le Strat Y, Mandelbrot L, Keïta H, Dubertret C. Predictors of postpartum depression: prospective study of 264 women followed during pregnancy and postpartum. Psychiatry Res. 2014;215(2):341-6.
3. Gavin NI, Gaynes BN, Lorh KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. Obstet Gynecol. 2005;106(5):1071-83.
4. Einarson A. Antidepressant use during pregnancy: navigating the sea of information. Can Fam Physician. 2013;59:941-4.
5. Diav-Citrin O, Ornoy A. Selective serotonin reuptake inhibitors in human pregnancy: to treat or not to treat? Obstet Gynecol Int. 2012;Article ID 698947.
6. Robinson GE. Controversies about the use of antidepressants in pregnancy. J Nerv Ment Dis. 2015;203(3):159-63.
7. Einarson A, Koren G. Prescribing antidepressants to pregnant women: what is a family physician to do? Can Fam Physician. 2007;53(9):1412-4, 1423-5.
8. Einarson A, Egberts TC, Heerdink ER. Antidepressant use in pregnancy: knowledge transfer and translation of research findings. J Eval Clin Pract. 2015;21(4):579-83.
9. Bilszta JLC, Tsuchiya S, Han K, Buist AE, Einarson A. Primary care physician's attitudes and practices regarding antidepressant use during pregnancy: a survey of two countries. Arch Womens Ment Health. 2011;14(1):71-5.
10. Ververs T, van Dijk L, Yousofi S, Schobben F, Visser GH. Depression during pregnancy: views on antidepressant use and information sources of general practitioners and pharmacists. BMC Health Serv Res. 2009;9(1):119.
11. Gawley L, Einarson A, Bowen A. Stigma and attitudes towards antenatal depression and antidepressant use during pregnancy in healthcare students. Adv Heal Sci Educ. 2011;16(5):669-79.
12. Bonari L, Koren G, Einarson TR, Jasper JD, Taddio A, Einarson A. Use of antidepressants by pregnant women: evaluation of perception of risk, efficacy of evidence based counseling and determinants of decision making. Arch Womens Ment Health. 2005;8(4):214-20.
13. Mulder E, Davis A, Gawley L, Bowen A, Einarson A. Negative impact of non-evidence-based information received by women taking antidepressants during pregnancy from health care providers and others. J Obstet Gynaecol Can. 2012;34(1):66-71.
14. Walton GD, Ross LE, Stewart DE, Grigoriadis S, Dennis CL, Vigod S. Decisional conflict among women considering antidepressant medication use in pregnancy. Arch Womens Ment Health. 2014;17(6):493-501.
15. Kim E, Sarkar M, Navioz Y, Koren G, Einarson A. The Motherisk Alcohol and Substance Use Helpline: 10 years of experience and counting. J Popul Ther Clin Pharmacol. 2010;17(2):e269-80.
16. Koren G, Bozzo P. Cost effectiveness of teratology counseling - the Motherisk experience. J Popul Ther Clin Pharmacol. 2014;21(2):e266-70.
17. Vlemmix F, Warendorf J, Rosman A, Kok M, Mol B, Morris J, et al. Decision aids to improve informed decision-making in pregnancy care: a systematic review. BJOG An Int J Obstet Gynaecol. 2013;120(3):257-66.
18. Stacey D, Légaré F, Col N, Bennett C, Barry M, Eden K, et al. Decision aids for people facing health treatment or screening decisions (Review). Cochrane Database Syst Rev. 2014;(1):CD001431.
19. Vigod, Simone (Women's College Hospital, Toronto, ON). Conversation with: Natalie V. Scime (Faculty of Health Sciences, Western University, London, ON). 2015 Oct 13.
20. CAMH, Motherisk. Exposure to psychotropic medications and other substances during pregnancy and lactation: a handbook for health care professionals. Canada: Centre for Addiction and Mental Health; 2007.
21. Koren G. Treating the mother, protecting the unborn: the motherisk approach. J Pediatr Pharmacol Ther. 2013;18(1):4-7.
22. Graham I, Logan J, Harrison M, Straus S, Tetroe J, Caswel W, et al. Lost in knowledge translation: time for a map? J Contin Educ Health Prof. 2006. p. 12.
23. Gagnon ML. Moving knowledge to action through dissemination and exchange. J Clin Epidemiol. 2011;64(1):25-31.

"Ow, doc, it hurts"

Management of nonmalignant chronic pain

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ABSTRACT

In a world where medical conditions are increasingly understood, chronic pain remains among the most difficult to diagnose and treat. Current first-line treatment of nonmalignant chronic pain include tricyclic antidepressants and physiotherapy, while topical lidocaine, nonsteroidal anti-inflammatory drugs and other antidepressants serve as appropriate second-line therapy. Opioids, though highly effective analgesics, remain medical options of last resort due to their highly addictive properties. Surgical implantation of nerve stimulators and/or spinal decompression may also be considered for treatment of chronic pain. As a parallel course of treatment, complementary and alternative medicine such as acupuncture may also be considered. Unfortunately, people with pain are among the least anticipated patients that doctors will see, and lack of both patience and expertise often result in cookie-cutter prescriptions and standardized healthcare that do not benefit individual patients. In the ever-evolving field of pain management, recent evidence has shown that a multidisciplinary approach, rather than traditional physician-based management, offers the best long-term results to patients.

Humans have been finding and using ways to manage pain since antiquity, from the Mesopotamians using the "plant of joy" (the opium poppy) to manage basic surgeries to Chinese surgeons putting their patients under general anesthesia for 3 days at a time. Ever since Joseph Priestley's first use of ether in the medical setting, doctors have progressively made advances in pain and sensation management, although advances in management of chronic pain remains slow due to the difficulty with which it can be treated, or even managed.[1]

Part of the difficulty lies in the fact that the umbrella term "chronic pain" gives both a false sense of unity to the myriad of conditions ("oh, my uncle had this too") as well as a false sense of simplicity to the problem ("just give me some pain meds, doc!"). Chronic pain can be broadly characterized as neuropathic versus non-neuropathic and malignant versus nonmalignant. Non-neuropathic pain includes somatic pain such as musculoskeletal pain, and visceral pain such as menstrual cramps, while neuropathic pain derives from faulty nerve signalling and includes conditions like diabetic neuropathy and shingles. Cancer can significantly modulate chronic pain due to its ability to invade multiple tissues and to cause both neuropathic and non-neuropathic pain, often in a progressively worse fashion. Chemotherapy, radiation and surgery can and often do contribute to the profile of pain related to malignancy. This article will address only nonmalignant chronic pain and discuss current treatment methods as well as future directions.

MEDICAL MANAGEMENT

First-line medical management of chronic pain includes antidepressants, anticonvulsants and topical agents. In low doses—lower than those used to treat depression—tricyclic antidepressants have been shown to be effective especially in relieving neuropathic pain, possibly through inhibition of sodium channels unrelated to depression. Anticonvulsant drugs like gabapentin prevent neuronal signalling by blocking calcium channels, and have been shown to be effective as well. Similar efficacy has not been shown in other antidepressant drugs, such as serotonin reuptake inhibitors (SRI) and serotonin noradrenaline reuptake inhibitors (SNRIs), although they can still be considered for second-line therapy.[2,3]

Topical lidocaine and other nonsteroidal anti-inflammatory drugs are second-line options, as well as options for patients who do not wish to consume pills. Topical lidocaine differs from topical opioids in that it functions locally while opioids work systemically through bloodstream absorption. One other topical option is high-strength capsaicin, which works primarily by desensitizing neurons; it is important to note that this method will be extremely uncomfortable for most patients in the first few months.[2,3]

Other medical treatments for pain involve treating or modulating the underlying cause of the pain, but the discussion rapidly becomes nuanced and cannot be generalized to chronic pain in general.

OPIOIDS

First purified in 1803, opioids have always held a fascinating place in society. Equally loved and feared, they were among the first class of compounds identified for their analgesic properties, but also for their mind-altering and addictive properties (morphine was so addictive, in fact, that a less addictive form, diacetylmorphine, was produced and marketed under the brand name "Heroin"). Opioids were avoided in treatment of chronic pain for reasons relating to tolerance, withdrawal and abuse. However, due to evidence from treatment of cancer patients, opioids have been the subject of renewed interest and increasing usage since the 1990s.[1]

Opioids are defined as substances that bind to mu, kappa and delta receptors in the central nervous system, inhibiting neuronal transmission of pain signals. This family of compounds, consisting of agonists, antagonists and partial agonists of opioid receptors, has long been marketed in various combinations and preparations.

These include intravenous hydromorphone (eg, Dilaudid), oral oxycodone (eg, OxyNEO), and topical fentanyl (eg, Duragesic), each route of administration with its own indications and side effects.[1]

In the outpatient setting, physicians have the option of administering oral, transdermal and sublingual preparations. Of these, the oral route is by far the most preferred due to the reduced rate of adverse events (save those of the opioid compounds themselves) and the ability to prescribe slow- and fast-release preparations as required. Patients who do not tolerate oral administration may also use transdermal patches to help maintain a stable plasma opioid concentration, with the risk of both slow onset of relief and longer-lasting effects of toxicity. Sublingual preparations are a third, very rapid onset, option for the chronic pain patient, with minimum adverse effects other than a bitter taste.[4]

Current Canadian guidelines recommend using opioids as a last resort in treatment of chronic pain. This includes conducting a risk assessment for addiction/abuse (including psychiatric status) and exploring other options (such as physiotherapy and NSAIDs) beforehand. Dosage should be titrated to the patient—being especially careful if the patient is already taking benzodiazepines—and shouldn't exceed 200mg/day of morphine or an equivalent dosage. Due to their different potencies and bioavailabilities, the various opioid compounds can be standardized to their oral morphine equivalent. Even after the optimal dosage has been found, the patient should be followed carefully for adverse drug reactions and tolerance/abuse.[3]

In terms of special considerations for certain populations, opioids should be tapered and eliminated in pregnant women. In addition to the titration described above, adolescent and psychiatric patients may be at greater risk of addiction as well, so only prescribe opioid medications for well-defined somatic or neuropathic pain, and monitor carefully for psychological changes. Again, elderly patients, especially those on benzodiazepines, are usually tolerant of opioids, although titration should still be slower and start from a lower dose. Chronic pain patients who are already addicted to opioids may still benefit from treatment, although concurrent rehabilitation treatment plans such as methadone/buprenorphine treatment, structured opioid therapy or abstinence should be provided subject to consultation and physician discretion.[3]

SURGICAL MANAGEMENT

Chronic pain, particularly neuropathic pain, can be treated surgically through direct nerve ablation, chemical sympathectomy (using chemicals to destroy affected nerves) and spinal decompression, although surgical options are often a last-resort method due to the risk of negative sequelae or outcomes. The most common surgical management option for chronic pain is implantation of devices in the body to either electrically or pharmacologically suppress nerve transmission of pain. Intrathecal devices use lidocaine in a "perpetual nerve block," while electrical stimulators aim to desensitize the affected nerves. On a closing note, there has been relatively little research into the long-term effectiveness of surgical therapies, and these procedures may also be much more costly than their medical counterparts.[5,6]

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Given the complex nature of chronic pain, including the psychological factor, alternative medicine is increasingly accepted in its treatment provided that there is no interference with ongoing medical or surgical management. Acupuncture is the poster child for alternative treatments for pain, and there have been studies demonstrating effectiveness, although it should be noted that many of the studies have been shown to be of low quality.[7] Lifestyle changes and exercise have also been cited as key ways to improve chronic pain symptoms in most conditions, not just those from muscular causes.[8]

Medical marijuana has previously been considered for treatment of chronic pain, given that cannabis and hashish have historically been used much like opiates to manage pain. However, there has been little peer-reviewed research on the effectiveness of cannabinoids to date. Perhaps in the coming years, given recent changes in the legal status of marijuana in the US, definitive recommendations will emerge regarding its use in chronic pain.

In the last 10 years, a biopsychosocial model of pain, contrary to the traditional model of pain being purely physiological, has emerged and has important implications on the assessment and treatment of patients with chronic pain. Under this model, and in keeping with the increasingly interprofessional nature of medicine, there are recommendations to include social workers and other community care personnel to address psychological and social factors that may exacerbate or even cause the physiological pain. Under this model, pain clinics have been founded across Canada with interdisciplinary teams to manage patients in a more holistic and effective manner.[9,10]

CONCLUSION

Chronic pain is a difficult condition to treat, especially given the multifactorial causes of many patients' pain under the biopsychosocial model of pain. With the increasing prevalence of interdisciplinary management teams, it is more important than ever for physicians to understand medical and surgical management options and how they may be affected by other therapies. Given all of these complexities, it is hoped that this primer motivates medical trainees to develop a better understanding of chronic pain.

REFERENCES

1. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. Exp Clin Psychopharmacol. 2008 Oct;16(5):405-16.
2. Ashburn MA, Staats PS. Management of chronic pain. Lancet. 1999 May 29;353(9167):1865-9.
3. Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. Canada: National Opioid Use Guideline Group (NOUGG); 2010 [cited 2015 Nov 20]. Available from: http://nationalpaincentre.mcmaster.ca/opioid/.
4. Stevens RA, Ghazi SM. Routes of opioid analgesic therapy in the management of cancer pain. Cancer Control. 2000;7(2):132-41.
5. Singh B, Moodley J, Shaik AS, Robbs JV. Sympathectomy for complex regional pain syndrome. J Vasc Sur. 2003 Mar;37(3):508-11.
6. WebMD. Chronic pain – surgery [Internet]. 2014 [cited 2015 Nov 21]. Available from: http://www.webmd.com/pain-management/tc/chronic-pain-surgery.

7. Ter Riet G, Kleunen J, Knipschild P. Acupuncture and chronic pain: a criteria-based meta-analysis. J Clin Epi. 1990;43(11):1191-9.
8. Griffin RM. Living with chronic pain [Internet]. WebMD. [cited 2015 Nov 25]. Available from: http://www.webmd.com/pain-management/chronic-pain-11/alternative-treatments.
9. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychological Bulletin. 2007;133(4):581-624.
10. Canadian Pain Coalition. Canadian pain clinic listing. [cited 2015 Nov 25]. Available from: http://www.canadianpaincoalition.ca/downloads/pain_clinics.pdf.

Companion diagnostics and the age of personalized medicine in oncology

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ABSTRACT

Companion diagnostics are tests which are used to guide targeted therapies. They represent the application of knowledge of unique sensitivities of hosts or diseases. The FDA approved the first companion diagnostic-related drug, trastuzumab (Herceptin), in 1998. Trastuzumab is specifically effective in human epidermal growth factor receptor 2 (HER2) positive cancers, which are associated with poor outcomes with conventional cytotoxic therapy. Since trastuzumab, many other companion diagnostics have been brought to market. There are both health and economical advantages to developing companion diagnostics. With personalized therapy, patients will experience fewer and less severe side effects, and patients are more likely to have positive outcomes. Companies seeking to approve companion diagnostics will be able to recruit fewer participants for efficacy trials, leading to decreased development costs. Challenges to the future of companion diagnostics include preventing off-label usage of drugs. Additionally, the likely expensive cost of companion diagnostics, as in the example of ivacaftor (Kalydeco), will raise questions on how these drugs will be paid for.

Physicians have long recognized differences in individual treatment responses. As medicine evolves, an emphasis on personalized therapy tailored to patients based on diagnostic testing ensures maximum effectiveness. Nowhere is this trend more evident than in the rapidly evolving field of oncology, where pairings between drugs and corresponding diagnostic tests allows physicians to determine clinical utility. Companion diagnostics are the diagnostic tests employed to identify patients eligible for treatment with targeted therapies. In the case of cancer, these tests can be used to assess susceptibility of the cancer to treatment. Advances in our understanding of pathology has made the development of more specific therapies possible, moving from generalized cytotoxic cancer treatment to targeted drugs. Complementing developments in treatments, diagnostic technologies such as multiplex genotyping and high-throughput genomic profiling by next-generation sequencing now allow us to quickly analyze cancer genomes from biopsy material.

PIONEERING DRUGS

Research on companion diagnostics was first launched with FDA approval of the first companion diagnostic related treatment, trastuzumab (Herceptin), in 1998.[1] By interfering with the human epidermal growth factor 2 (HER2) receptor, overexpressed in around a third of breast cancers, HER2-positive patients went from having some of the worst outcomes to more favorable ones. The commercial success of trastuzumab and the corresponding diagnostic tests required for its prescription helped propel the entire field of personalized medicine forward.[1] Old drugs such as tamoxifen used in estrogen receptor-positive breast cancers patients became re-evaluated. It was found that women with a CYP2D6 gene variant lacked the ability to break down the drug rendering it ineffective.[2] Thus, diagnostics can be used to test not only the genomes of cancers but also of the patients themselves. Another diagnostic, TheraScreen, was launched in 2007. TheraScreen was the first diagnostic for detecting mutations in epidermal growth factor receptor (EGFR), which are known to cause non-small cell lung cancer (NSCLC). Cancers with certain mutations in EGFR are susceptible to tyrosine kinase inhibitor treatment.[3] There are currently a number of Food and Drug Administration (FDA)-approved companion diagnostics (Table).

ADVANTAGES

Companion diagnostics will potentially allow therapy to be given only to the targeted population which will receive the most benefit, thus improving patient outcomes. Likewise, patients who would receive little benefit from a drug, as determined by a diagnostic assay, will not be prescribed drugs which will cause them to needlessly suffer any related drug toxicities. Through increased efficiency, the healthcare system may save costs by avoiding ineffective treatments and managing their associated side effects. A comparison of clinical trials conducted for drugs with and without companion diagnostics found that the presence of a corresponding diagnostic tool decreased the odds of treatment discontinuation as well as moderate adverse events.[4]

From an economic perspective, pharmaceutical companies that push drug-diagnostic pairings only have to prove that the drug is effective in the targeted population. By using only the target subset of patients in clinical trials, companies may potentially reduce development costs since drug effects will be more pronounced and a smaller number of patients will be needed to prove efficacy. The higher chance of regulatory approval significantly lowers the financial risk for pharmaceutical companies engaging in clinical trials and drug development. For example, a study of 199 compounds developed for the treatment of NSCLC found that only 11% passed the entire regulatory process, but drugs that used biomarkers to guide their administration had a 62% regulatory approval success rate.[5]

Table. Current oncological companion diagnostics[6-8]

Indication	Drug (generic name)	Diagnostic device (type)	Diagnostic rationale
Non-small cell lung cancer (NSCLC)	Keytruda (pembrolizumab)	PD-L1 IHC 22C3 pharmDx (Immunohistochemical)	Cancer expressing the inhibitory ligand PD-L1 can supress the immune response, which can be blocked by antibody administration.
	Iressa (gefitinib); Gilotrif (afatinib); Tarceva (erlotinib)	Therascreen EGFR RGQ PCR Kit (Real-time PCR) Cobas EGFR Mutation Test (Real-time PCR)	Exon 19 deletions/exon 21 (L858R) substitution mutations on EGFR gene lead to overactivation of anti-apoptotic pathways. These mutations indicate increased susceptibility to EGFR tyrosine kinase inhibitors.
	Xalkori (crizotinib)	VENTANA ALK (D5F3) CDx Assay (Immunohistochemical) VYSIS ALK Break Apart (FISH)	Around 4% of patients (typically nonsmokers) have a fusion protein that drives malignancy (EML4-Anaplastic lymphoma kinase). This kinase is inhibited by crizotinib.
Colorectal cancer	Erbitux (cetuximab); Vectibix (panitumumab)	The Cobas KRAS Mutation Test (Real-time PCR test) Therascreen KRAS RGQ PCR Kit (Real-time PCR)	Detection of 7 somatic mutations in codons 12 and 13 of the KRAS gene (cell-cycle regulator). These mutations are associated with resistance to EGFR inhibitor therapy. Treatment is only given if KRAS is negative for these mutations
Ovarian cancer	Lynparza (olaparib)	BRACAnalysis CDx (PCR/Sanger sequencing for small variants, multiplex PCR for large deletions/duplications)	Patients with germline mutations in the DNA repair enzymes BRCA1/2 are predisposed to resistant forms of ovarian cancer. These cancers rely on DNA repair from the PARP enzyme to remain viable, which can be inhibited by olaparib.
Breast cancer	Herceptin (trastuzumab)	INFORM HER-2/NEU (FISH) PATHWAY ANTI-HER-2/NEU (4B5) (Immunohistochemical)	Risk stratification and prognostic utility for breast cancer patients. Overexpression of HER2 oncogene occurs in 15-30% of breast cancers, often with more aggressive phenotypes, incurring susceptibility to the HER2 monoclonal antibody.
Breast cancer or metastatic gastric or gastroesophageal junction adenocarcinomas	Herceptin (trastuzumab); Perjeta (pertuzumab); Kadcyla (ado-trastuzumab emtansine)	HERCEPTEST (Immunohistochemical)	HER2 overexpression drives aggressive neoplasia, susceptibility to HER2 interference either by monoclonal antibody (trastuzumab), conjugation of antibody with cytotoxic DM1, or inhibition of dimerization with HER3 (pertuzumab).
Gastrointestinal stromal tumours (GIST)	Gleevec/Glivec (imatinib mesylate)	DAKO C-KIT PharmDx (Immunohistochemical)	Mutation or overexpression in the CD117 proto-oncogene drive certain GIST tumors. These tumors are responsive to receptor tyrosine kinase inhibitors.
Melanoma	Mekinist (tramatenib); Tafinlar (dabrafenib); Zelboraf (vemurafenib)	Melanoma THxID BRAF Kit (Real-time PCR) COBAS 4800 BRAF V600 (Real-time PCR)	These drugs are only effective against tumors expressing the V600E mutation of the proto-oncogene BRAF or the rarer V600K variant.

Abbreviations: CDx, companion diagnostic; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction.

CHALLENGES

Early on there was resistance among pharmaceutical companies against pursuing companion diagnostics since they would restrict the use of the drug to a subset of patients, thereby segmenting the drug market instead of selling to a broader population. Although the regulatory-approval benefits have seemed to assuage some of these concerns, logistical issues still exist in the codevelopment of drugs and diagnostic devices.[7] By adding an additional stakeholder (the diagnostic device company), the issue of negotiating development with pharmaceutical companies is further complicated.[1] The costs associated with research and development of companion diagnostics and the fact that, by their nature, few people will be using the personalized pharmaceuticals means that the drugs are likely to be expensive. For instance, ivacaftor (Kalydeco) is an effective treatment for cystic fibrosis patients with the G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene but costs $300 000 per patient per year.[10] Despite the cost of treatment, ivacaftor became available through Ontario's Exceptional Access Program in 2014. Another consideration is "indication creep," or the usage of drugs beyond their initial indications. For example, the FDA initially approved the use of infliximab in Crohn's disease in 1998, but it has since been expanded to treat other diseases, and there are many who use it off-label.[11,12] Finally, physicians must be educated on the mechanism and clinical indications of these personalized therapies.

FUTURE DIRECTIONS AND CONCLUSIONS

Companion diagnostics may serve to be a powerful therapeutic option in the future of medicine. However, the exorbitant cost of these drugs coupled with the fact that they will be of great benefit to a select population raises questions on how they will be paid for. Although currently approved devices use single biomarkers, future diagnostics may aim to combine several biomarkers for more accurate benefit-to-risk stratification of patients for different treatments.

REFERENCES

1. Agarwal A, Ressler D, Snyder G. The current and future state of companion diagnostics. Pharmgenomics Pers Med. 2015;8:99-110.
2. Schroth W, Antoniadou L, Fritz P, Schwab M, Muerdter T, Zanger UM, et al. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol. 2007;25:5187-93.
3. Soulieres D, Greer W, Magliocco AM, Huntsman D, Young S, Tsao MS et al. KRAS mutation testing in the treatment of metastatic colorectal cancer with anti-EGFR therapies. Curr Oncol, 2010;7 Suppl 1.S31-40.
4. Ocana A, Ethier JL, Diez-Gonzalez L, Corrales-Sanchez V, Srikanthan A, Gascon-Escribano MJ, et al. Influence of companion diagnostics on efficacy and safety of targeted anti-cancer drugs: systematic review and meta-analyses. Oncotarget. 2015;6:39538-49.
5. Falconi A, Lopes G, Parker JL. Biomarkers and receptor targeted therapies reduce clinical trial risk in non-small-cell lung cancer. J Thorac Oncol.2014;9:163-9.
6. Fan YS. Companion diagnostic testing for targeted cancer therapies: an overview. Genet Test Mol Biomarkers. 2013;17:515-23.
7. Duffy MJ, Crown J. Companion biomarkers: paving the pathway to personalized treatment for cancer. Clin Chem. 2013;59:1447-56.
8. U.S Food and Drug Administration [internet]. Silver Spring (MD): U.S Food and Drug Administration;c2015. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). c2015. [cited 2016 Feb 01] Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.
9. Philip R, Carrington L, Chan M. US FDA perspective on challenges in co-developing in vitro companion diagnostics and targeted cancer therapeutics. Bioanalysis, 2011,3, 383-9.
10. Bowen KL, Gleason PP. Cystic fibrosis prevalence and total cost of care in a commercially insured population. Poster session presented at: Academy of Managed Care Pharmacy Annual Meeting, 2015 April 8-10; San Diego, CA.
11. Allen EMV, Miyake T, Gunn N, Behler CM, Kohlwes J. Off-label use of rituximab in a multipayer insurance system. JOP. 2011 Mar 1;7(2):76-9.
12. Sailler L. Rituximab off label use for difficult-to-treat auto-immune diseases: reappraisal of benefits and risks. Clin Rev Allergy Immunol. 2008 Feb;34(1):103-10.

Ethics of recommending natural health products as physicians

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INTRODUCTION

In Canada, pharmaceutical drugs must undergo a rigorous, multiphase clinical trial process to obtain approval by Health Canada.[1] Physicians prescribe these drugs based on their evidence of effectiveness and safety according to a Western scientific framework. This practice of evidence-based medicine (EBM) is coupled with clinical expertise and consideration of patients' values.[2] Although pharmaceutical drugs are considered conventional medicine in Canada, over 70% of Canadians also use or replace these treatments with natural health products (NHPs), such as herbal products, vitamins, traditional medicine and homeopathic medicine.[3,4] NHPs fall under the umbrella of complementary and alternative medicine (CAM), which encompasses natural and traditional therapies such as yoga and acupuncture that have been scientifically verified to varying degrees. NHPs appeal to Canadians based on their non- or minimally invasive nature, to which patients attribute a low-risk profile. Opposition to Big Pharma and scientific reductionism also contribute to NHPs' popularity.[5] However, safety and efficacy are defined more broadly for NHP licensing approval than is the case for pharmaceutical drugs, with textbooks, theories, experiences and beliefs constituting sources of evidence.[6] Proponents of CAM argue that this flexibility is necessary because trial methods of EBM, notably randomized controlled trials (RCTs), are incompatible with evaluating CAM.[7,8] Conversely, sceptics of CAM question the effectiveness of these looser regulations, believing CAM research to be poorly funded, lacking in proper control groups and published in self-referring alternative medicine-specific journals.[5,7,9] In the context of these opposing views, this article will compare definitions of evidence in CAM and biomedicine before exploring legal and moral dimensions around the question of whether it is ethical for physicians to recommend NHPs without conventional scientific evidence of clinical safety and effectiveness.

EVIDENCE IN BIOMEDICINE AND CAM

Evidence includes any information a person uses to determine how likely it is that a given proposition, such as an idea, is true. Epistemology, or theory of knowledge, is defined as the criteria one uses to decide what is acceptable and sufficient evidence to believe a proposition.[10] Although there are many CAMs encompassing a wide variety of belief systems, they are distinguished from biomedicine by their epistemology.[11,12] Fundamentally, biomedical practitioners make diagnoses and provide treatments based on both clinical experience and knowledge that has been verified by the scientific method.[13] Similarly, CAM practitioners practice from their clinical experience and CAM theory. In contrast, theories that underlie CAM are accepted out of tradition, culture, identity, personal narrative or anecdotal evidence of healing, rather than experimental laboratory or population-level science.[12,14,15] Using the results of an RCT, a biomedical practitioner is able to make predictions only about the drug effects and disease symptoms of the theoretical average patient who matches the criteria of the trial. Predictions can only be made for the length of time a participant was studied, which may be relatively short. Understanding of health and illness in CAM is based on the real world experience of the individual patient, considering their entire context and all symptoms from physical to their relationships with family and friends, with information usually collected over a long relationship with the practitioner.[14,16]

When both CAM and biomedicine describe a model of disease in an individual patient and recommend the consequent treatment, the explanation one believes depends on one's particular epistemology. However, mechanisms of action proposed by CAM theory are often epistemologically independent of pathophysiology.[12,17] For instance, some CAMs claim to work by restoring balance to the body's vital energy. Because such an energy field has not been shown to exist using the scientific method, biomedicine finds that explanation highly unlikely.[11] A subjective experience of one's vital energy being restored by a treatment may provide ample evidence to convince one that such a force exists, but it would be a contradiction to accept the scientific account as well.

Though the explanation of how a CAM treatment is effective might differ greatly between a CAM theory and the biomedical model, biomedicine may consider it effective as long as it passes the scientific method. For instance, there is promising scientific evidence of acupuncture's effectiveness on smoking cessation, demonstrated by a meta-analysis of RCTs.[18]

The scientific method strives to provide the most accurate description of reality because it continually compares its descriptions to observations of the external world, rather than a particular cultural narrative or traditional belief. A proper explanation of the myriad reasons why science rarely fully achieves this objective ideal in practice is beyond the scope of this article, but can be summarized by saying that it is conducted by humans with history, culture, motivations and biases, rather than perfect hypothesis-generating and testing machines.[12,19]

Biomedicine remains the description of disease mechanisms and their treatment that is most closely aligned with objective, empirical measurement of reality. However, biomedicine is ill-equipped to determine what being sick means for a patient, or how a treatment may change their whole life. Subjective, holistic experience is used as evidence for determining meaning and purpose, something that most CAMs are adept at facilitating.[12,14]

MORAL CONSIDERATIONS

With regard to Beauchamp and Childress's 4 principles of medical ethics, arguments can be made both for and against recommending NHPs.[20] First, consider autonomy. Discussing NHPs as a therapeutic option allows patients to make an informed decision about their care that includes the full range of options available to them. This empowerment psychologically benefits patients.[5,19] The caveat is that patients may not actually be making informed decisions about their care if all existing evidence on NHPs is not disclosed to them, either due to insufficient research on their effects or if the practitioner is reluctant to reveal that treatments such as homeopathy do not show greater than a placebo effect in scientific trials.[21]

Regarding the principle of nonmaleficence, sceptics of CAM fear that government regulation and physician recommendation of NHPs may provide "undue legitimacy" to therapies not grounded in science.[5,22] This becomes especially worrisome where patients choose to replace rather than complement conventional medicine with alternative treatment.[19,22] For example, in March 2013, Calgarian boy Ryan Lovett died of an easily treatable bacterial throat infection due to his mother's administration of homeopathic remedies instead of antibiotics.[23] Despite this risk, government regulation of homeopathy and other forms of CAM can be viewed as a public safety measure, ensuring a standard of care and creating a formal body for complaints.[22] Furthering this notion of beneficence is the idea of using CAM after attempting conventional therapies, as an "extra safeguard rather than a potential risk."[24]

Considering justice, recommending use of NHPs without scientifically proven effectiveness may be unjust, as these therapies may incur a significant financial burden on patients for no more than a placebo effect.[5]

The utilitarian standpoint also does not present a definite argument, as utility is variably defined. For some, the utility of having control over one's care plan may outweigh the utility of obtaining the outcome of using conventional medicine, even if this means dying versus living.[25] This notion of utility serves the individual; however, Canadian healthcare is publicly funded and thus utility to society must be considered. If a patient, initially using ineffective nonevidence-based therapies, turns to conventional medicine in late-stage disease, society bears the financial cost of this decision.[5] However, this financial cost may be outweighed by the utility of living in a multicultural society that respects other groups' beliefs, even if this means that the economy is not maximized.

Lastly, in deontology, which evaluates morality based on duty, recommending CAM without scientific evidence may be morally right if the practitioner's intent is to help the patient, even if they inadvertently fail to account for potential risks. Nevertheless, physicians have an obligation mandated by the College of Physicians and Surgeons of Ontario (CPSO) to ensure that the care they are providing is grounded in EBM.[5,26] The CPSO requires that all assessments, diagnoses and treatments must be informed by science, and physicians must never recommend therapies that have been proven to be ineffective through scientific study.[26] As such, recommending therapy without good evidence of clinical effectiveness and safety may run counter to both the patient's best interests and a physicians' professional obligations.

LEGAL ARGUMENTS

In accordance with the policy of the CPSO, the Ontario government has committed to scientific, evidence-based medicine with the *Excellent Care for All Act* (2010), which establishes quality committees and the Ontario Health Quality Council that have a mandate to ensure that healthcare is supported by the best available scientific evidence.[27]

The elevated legal status of biomedicine in Ontario is dramatically illustrated by the fact that the *Child and Family Services Act* (1990) may make a child a ward of the Children's Aid Society if parents refuse to consent to a medical procedure that the court deems to be in the child's best interests. However, this legislation does give special protection to the rights of Ontario's indigenous peoples to determine what the best interests of a child are from their own cultural perspective.[28] *Hamilton Health Science Corp v. D.H.* (2015) is a recent case of an application by a biomedical hospital for a court order to give chemotherapy to an 11-year-old girl with leukemia from the Haudenosaunee nation when she and her family chose to use traditional indigenous medicine instead. The application was denied by the Ontario Court of Justice. The court chose to uphold the cultural practices and worldview of the indigenous people, even though it conflicted with the treatment recommended by scientific evidence.[29] This case shows that although the biomedical worldview is privileged in Ontario legislation and official policy, the province's judicial systemcan acknowledge and demonstrate respect for nonscientific views of health and medicine.

CONCLUSION

The major distinction between CAM and biomedicine is the use of scientific evidence to revise theories of disease and treatment. Although a treatment's mechanism of action may differ according to CAM or pathophysiology, if a CAM is found to be effective in an RCT, it can be considered EBM. If a CAM lacks scientific evidence of effectiveness and safety, patients should be given this information before deciding to incorporate this therapy into their care plan, as the treatment may carry risks or confer only placebo effects. Granted, CAMs not yet disproven by the scientific method may one day be accepted by biomedicine. Cases showing promising evidence of CAM's therapeutic effects caution that rejecting CAM, without evidence of harm or lack of benefit, is narrow minded. Additionally, the subjective evidence on which CAM operates may be more useful than scientific data for determining what an event such as a sickness will mean for a patient's life.

This article explored philosophical, ethical and legal considerations surrounding physicians' recommendation of CAM to patients. The authors acknowledge that their views and beliefs have developed within the context of a predominantly biomedical education, which may offer different perspectives than those of individuals with greater exposure to traditional systems of belief.

REFERENCES

1. Health Canada [Internet]. Ottawa: Government of Ganada Publications. Access to therapeutic products: the regulatory process in Canada. 2006 [cited 2015 Nov 10]. Available from: http://publications.gc.ca/collections/collection_2007/hc-sc/H164-9-2006E.pdf.
2. Guyatt G, Cook D, Haynes B. Evidence based medicine has come a long way: the second decade will be as exciting as the first. BMJ . 2004;329(7473):990-1.
3. The College of Physicians and Surgeons of Ontario. Complementary/alternative medicine. Dialogue [Internet]. 2011 Mar [cited 2015 Nov 13];(4):[8 p.]. Available from: http://www.cpso.on.ca/policies-publications/policy/complementary-alternative-medicine.
4. Public Health Agency of Canada [Internet]. Ottawa: Government of Canada Publications. Complementary and alternative health. 2008 Apr 01 [cited 2015 Nov 14]. Available from: http://www.phac-aspc.gc.ca/chn-rcs/cah-acps-eng.php.
5. Smith K. Articles against homeopathy – a utilitarian perspective. Bioethics. 2012;26(8):398-409.
6. Health Canada [Internet]. Ottawa: Government of Canada Publications. Pathway for licensing natural health products making modern health claims. 2012 Dec 27 [cited 2015 Nov 10]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/modern-eng.php.
7. Hammerschlag R, Zwickey H. Evidence-based complementary and alternative medicine: back to basics. J Altern Complement Med. 2011;12(4):2011-2.
8. Jagtenberg T, Evans S, Grant A, Howden I, Lewis M, Singer J. Evidence-based medicine and naturopathy. J Altern Complement Med. 2006;12(3):323-8.
9. Smith K. Homeopathy is unscientific and unethical. Bioethics [Internet]. 2012;26(9):508-12. Available from: http://doi.wiley.com/10.1111/j.1467-8519.2011.01956.x.
10. Fantl J, McGrath M. Evidence, pragmatics, and justification. Philos Rev. 2002;111(1):67-94.
11. Hughes BM. How should clinical psychologists approach complementary and alternative medicine? Empirical, epistemological, and ethical considerations. Clin Psychol Rev [Internet]. 2008;28(4):657-75.
12. Tonelli MR, Callahan TC. Why alternative medicine cannot be evidence-based. Acad Med. 2001;76(12):1213-20.
13. Guyatt G, Haynes B, Jaeschke R, Cook D, Greenhalgh T, Meade M, et al. Introduction: the philosophy of evidence-based medicine. 2005;45(8):77-89.
14. Barry CA. The role of evidence in alternative medicine: contrasting biomedical and anthropological approaches. Soc Sci Med [Internet]. 2006;62(11):2646-57.
15. Ana Ning, King's College at Western University. Personal Communication.
16. Waldram JB. The efficacy of traditional medicine: current theoretical and methodological issues. Med Anthropol Q. 2000;14(4):603-25.
17. Keshet Y. The untenable boundaries of biomedical knowledge: epistemologies and rhetoric strategies in the debate over evaluating complementary and alternative medicine. Health (London) [Internet]. 2009;13(2):131-55.
18. Reiss J, Sprenger J. Scientific Objectivity. The Stanford Encyclopedia of Philosophy (Fall 2014 Edition), Edward N. Zalta (ed.) [Internet]. [updated 2014; cited 2015 Nov 17] Available from: http://plato.stanford.edu/archives/fall2014/entries/scientific-objectivity/.
19. Lui Z, Wang Y, Wu Y, Yang J. Condition and effectiveness evaluation of acupuncture for smoking cessation. Zhongguo Zhen Jiu. 2015 Aug; 35(8):851-7.

20. Beauchamp TL, Childress, JF. Principles of biomedical ethics. New York: Oxford University Press; 2009. 432 p.
21. Shaw DM. Homeopathy is where the harm is: five unethical effects of funding unscientific "remedies." J Med Ethics [Internet]. 2010;36(3):130-1. Available from: http://jme.bmj.com/cgi/doi/10.1136/jme.2009.034959.
22. Mehta D. Ontario regulates homeopathy, greeted with skepticism by critics. The Canadian Press [Internet]. 2015 Apr 1 [cited 2015 Nov 10]. Available from: http://globalnews.ca/news/1915649/ontario-regulates-homeopathy-greeted-with-skepticism-by-critics/.
23. Urback R. Take your kid to a real doctor. National Post [Internet]. 2013 Nov 26 [cited 2015 Nov 10]. Available from: http://news.nationalpost.com/full-comment/robyn-urback-take-your-kid-to-a-real-doctor.
24. Milgrom L, Chatfield K. Is homeopathy really "morally and ethically unacceptable"? A critique of pure scientism. Bioethics. 2012;26(9):501-3.
25. Briggs R. Normative theories of rational choice: expected utility. The Stanford Encyclopedia of Philosophy [Internet]. 2014 Aug 8 [cited 2015 Nov 10]. Available from: http://plato.stanford.edu/entries/rationality-normative-utility/.
26. College of Physicians and Surgeons of Ontario, Policy Statement #3-11
27. Excellent Care for All Act, 2010, S.O. 2010, c. 14.
28. Child and Family Services Act, R.S.O. 1990, c. C.11.
29. Hamilton Health Science Corp. v. D.H. [2015] O.J. 2214.

Is pharmacare the prescription Canada needs?

The debate on universal pharmacare

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CONTEXT

The mounting costs of pharmaceuticals are an emergent concern for Canadians. With the highest per capita drug expenditure in the Organisation for Economic Co-operation and Development (OECD), apart from the United States, the sustainability of Canada's drug coverage system has been called into question. Universal pharmacare, defined as the federal provision of drug coverage for all Canadians, has been suggested as a potential solution to the sustainability issue, which would also help mitigate some of the inequities of the current fragmented system.[1] At present, provincial drug plans cover anywhere between 26% and 45% of prescription drug costs depending on the province while voluntary private insurances cover up to 38% of costs, except in Quebec where insurance is mandatory.[2] Public funding for prescription costs is at most 44% compared to 99% funding for hospital costs and 90% for medical costs.[1] This article will present the benefits and limitations of implementing universal pharmacare in Canada.

THE PRICE IS RIGHT

The largest benefit of universal pharmacare would be the reduction of pharmaceutical costs for insurers and individuals. One strategy used by Australia, New Zealand and several European countries is the negotiation of bulk purchase agreements where federal governments purchase large quantities of pharmaceuticals from a provider pharmaceutical company.[3,4] Savings for individuals and insurers are multifactorial. Decreased redundancy lowers administrative expenses, reduces dispensing fees on large volume orders accepted by provider pharmacies and secures more favourable deals through bulk purchasing agreements.[3,4] The provinces already engage in separate less-efficient bulk purchasing agreements.[5,6] A single unified federal agreement would markedly increase our collective purchasing power, shifting the economic surplus away from producers.[3,4,6,7]

Implementation of universal pharmacare could also result in savings for the federal government. The report entitled *The Economic Case for Universal Pharamacare* projects that Canada could save up to $2.9 billion yearly—about 12% of the federal government's spending on drugs.[4] The April 2015 *Canadian Medical Association Journal* article by Dr Morgan et al argues that universal pharmacare could reduce total spending on prescription drugs by $7.3 billion, with $8.2 billion in savings accruing to the private sector. Government costs were projected to increase by $1.0 billion.[7]

Public funding for subsidizing pharmaceutical costs of individuals is currently administered on a provincial basis. Unfortunately, provinces have disparate coverage plans, which undermine purchasing power, contribute to excessive administration costs and force patients to bear expensive out-of-pocket costs. Ontario's age-dependent drug plan is a fixed subsidy per pharmaceutical for seniors (above the age of 65 years) while nonseniors can register for a drug plan where the deductible is a function of household income. For nonseniors, the government is a payer of last resort, diminishing its purchasing power and leaving uninsured nonseniors exposed to high drug costs. The effects of fragmented financing are worse in British Columbia with its solely income-based drug coverage plan.[8]

Comparing expected out-of-pocket drug costs for median-income seniors (income of approximately $52 000 in 2012) shows that the highest costs are in British Columbia ($1000 deductible and 25% copay) with the lowest in Ontario ($100 deductible and $6.11 copay/prescription).[9-11] For median income (approximately $77 000 in 2012) nonseniors, expected out-of-pocket drug costs are higher in Ontario (deductible 4% of net income and $2.00 co-pay/prescription) than British Columbia ($2250 deductible and 30% co-pay), but costs would be comparable for individuals exceeding Ontario's deductibles.[8,9,11,12] In the end, it is the patient who suffers, with noncompliance rates paralleling the out-of-pocket costs borne.[13] Ironically, noncompliance spurred by excessive drug prices costs the system even more money in the form of unnecessary future hospitalizations.[14] Having a single-payer–funded drug coverage plan would increase the purchasing power of Canada and reduce out-of-pocket drug costs for Canadians.

As it stands, Canadians spend too much money on pharmaceuticals and costs are still growing. From 2000-2010, the drug share of national healthcare costs rose from 15.4% to 16.3%.[1] Implementing universal pharmacare offers a chance to reduce pharmaceutical costs for patients, potentially increase savings for the federal government and resolve the fragmented financing of provincial drug plans in order to ensure fair and equitable access to pharmaceuticals.

LIMITED POLITICAL AND PUBLIC SUPPORT

Canada is a poor performer when it comes to drug spending and population coverage among OECD countries. It is often implied that there is an association between Canada's performance and the fact that it is the only country with universal health insurance that excludes drug coverage.[4] There have been calls for a national drug strategy dating back to 1964, but barriers to implementation have prevented a national strategy from coming to fruition.[15] This section will review these barriers and argue that universal pharmacare may not be necessary to reduce drug expenditures, nor be sufficient to improve coverage.

Evidence is mounting against cost as a barrier to implementation; a number of recent studies claim that universal pharmacare

has the potential to be cost-saving.[4,7] However, these estimates are derived from computer simulations which simplify real interactions in the health system and must be viewed through a critical lens. Furthermore, with a federal government that skirted the issue of universal pharmacare in its platform, it is unlikely that economic evidence will be used to inform decision-making on this front in the near future.[16]

The most significant barrier to implementation has been the reluctance of federal governments to consider a national pharmaceutical strategy.[16] Aside from the upfront costs of reforming the current system, national pharmacare would require that governments that currently maintain heterogeneous formularies agree on which drugs should be covered. Although steps have been taken to standardize drug prices and coverage on a national scale through the Pan-Canadian Pricing Alliance (PCPA) and the Common Drug Review, adherence to these strategies is not uniform across public drug plans.[17] Until Canada can achieve improved participation on such initiatives, it is unlikely that a federal government could successfully negotiate a national system with the provincial governments that hold the health care bargaining power. Additionally, the federal government must consider the interests of stakeholder groups, namely pharmaceutical manufacturers and private insurers, who stand to lose if Canada succeeds in cutting costs and achieving universal coverage.[18] For successful implementation, the government must counter the rhetoric of these groups which has led 61% of Canadians to believe that "no matter what the research shows, a national pharmacare plan will end up costing taxpayers lots of money."[19] Finally, the government faces a lack of constituent support for the potential increases in public spending and the reduced patient choice that would be associated with switching from a predominantly private system to a predominantly public system. The majority of Canadians would oppose increasing the goods and services tax (GST) or income tax by 1% for incomes over $40 000 to achieve the additional $1 billion in public funds needed for pharmacare.[19] Public support may fall even further considering that a universal system would likely mean reduced patient choice and delayed access to new drugs.[20] Depending on the extent to which choice and access are limited, universal pharmacare may not be sufficient to improve inequities in coverage.

CONCLUSION

There is hope for Canada still. Targeted solutions to inefficiencies in the pharmaceutical system minimize the need for complete reform and are therefore more likely to be adopted by federal and provincial governments. Proponents of universal pharmacare claim that savings will be primarily achieved by reducing generic and brand name prices and increasing cost-effective product selection. A national system is not required to improve performance on these indicators. In fact, where we do have a national model for drug provision (fractionated biologics), Canada has not demonstrated that it can achieve prices that are competitive with other OECD countries.[18] Reviewing inefficient drug policy is a key first step. Reduced drug prices could be realized by eliminating the Patented Medicine Prices Review Board policy of artificially inflating drug costs to encourage research and development, and removing the set ceiling on generic prices by switching to the competition model used in comparator countries. Avoiding unnecessary polypharmacy in the elderly and actively deprescribing superfluous drugs could also save Canada up to $1 billion annually.[7] Moreover, the PCPA could expand to include federal and private plans, increasing its negotiating power. Cost effective product selection could be achieved by increasing the prescription rates of off-patent medications and increasing rates of generic substitution, which is a source of significant cost savings in the United Kingdom.[7] Clinical leadership is needed to influence prescribing patterns. It is unlikely that a national formulary would be necessary or sufficient to fulfill this objective.

Fingers often point to the lack of a national pharmacare strategy when considering Canada's international ranking on drug expenditures, but universal pharmacare may not be the magic bullet many perceive it to be. Although it has the potential to be cost-saving, the federal government has not expressed interest in overseeing and funding its implementation. There would be more value in further research investigating the potential costs and benefits of targeted strategies to improve system inefficiencies, which do not have the same political barriers impeding their uptake.

REFERENCES

1. Canadian Institute for Health Information. Drivers of prescription drug spending in Canada [Internet]. Ottawa; 2011 [cited 2015 Nov 22]. Available from: https://www.cihi.ca/en/drug_spend_drivers_en.pdf.
2. Canadian Institute for Health Information. National health expenditures trends, 1975 to 2011 [Internet]. Ottawa; 2011 [cited 2015 Nov 22]. Available from: https://secure.cihi.ca/free_products/nhex_trends_report_2011_en.pdf.
3. Lybecker KM. The bulk purchase of pharmaceuticals: the experiences of the United States, Europe, and New Zealand. Fraser Institute Studies in Health Care Policy. 2013 May.
4. Gagnon MA, Hébert G. The economic case for universal pharmacare.
5. [Internet]. 2010 [cited 2015 Nov 22]. Available from: https://s3.amazonaws.com/policyalternatives.ca/sites/default/files/uploads/publications/National%20Office/2010/09/Universal_Pharmacare.pdf.
6. British Columbia Ministry of Health Services. News Release: B.C. signs health purchasing agreement with Alberta. [Internet] 2009 July [cited 2015 Dec 22]. Available from: http://www2.news.gov.bc.ca/news_releases_2009-2013/2009HSERV0010-000125.htm.
7. Pan-Canadian Pharmaceutical Alliance. Pan Canadian drugs negotiations report. [Internet] 2014 Mar 22 [cited 2015 Dec 22]. Available from: http://www.pmprovincesterritoires.ca/phocadownload/pcpa/pan_canadian_drugs_negotiations_report_march22_2014.pdf.
8. Morgan SG, Law M, Daw JR, Abraham L, Martin D. Estimated cost of universal public coverage of prescription drugs in Canada. CMAJ. 2015 Apr;187(7):491-7.
9. Morgan SG, Daw JR, Law MR. Rethinking pharmacare in Canada. 2013 Jun;384.
10. Statistics Canada. Canadian income survey, 2012. The Daily. 2014 Dec; Statistics Canada Catalogue no. 75-513-X: 3-4.
11. British Columbia Ministry of Health Services. Fair pharmacare assistance levels – families with at least one spouse born in 1939 or earlier. [Internet]. 2009 August [cited 2015 Dec 22]. Available from: http://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/income_bands_fair_pcare_enhanced.pdf.

12. Ontario Ministry of Health and Long-Term Care. Ontario's drug plans: how much do I pay? [Internet]. 2008 [cited 2015 Dec 22]. Available from: http://www.health.gov.on.ca/en/public/programs/drugs/programs/odb/opdp_pay.aspx.
13. British Columbia Ministry of Health Services. Fair pharmacare assistance levels – regular. [Internet]. 2009 August [cited 2015 Dec 22]. Available from: http://www2.gov.bc.ca/assets/gov/health/health-drug-coverage/pharmacare/income_bands_fair_pcare_regular.pdf.
14. Beardon PH, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. BMJ. 1993 Oct;307(6908):846-8.
15. Saoy LJ, Zed PJ, Wilbur K, Balen RM, Abu-Lanam RB, Roberts M. Drug-Related Hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a prospective study. Pharmacotherapy. 2006; 26(11): 1578-86.
16. Goldman, B. National pharmacare? Not a chance! [Internet]. Toronto: White Coat, Black Art; 2015 [cited 2015 Nov 23]. Available from: http://www.cbc.ca/radio/whitecoat/blog/national-pharmacare-not-a-chance-1.2996922.
17. Liberal Party of Canada: The platform [Internet]. Ottawa: Liberal Party of Canada; 2015. A New Health Accord; 2015 [cited 2015 Nov 23]. Available from: http://www.liberal.ca/realchange/a-new-health-accord/.
18. Morgan SG, Daw JR. Canadian pharmacare: looking back, looking forward. Healthcare Policy. 2012 Aug;8(1):14-23.
19. Morgan SG, Brougham M. IHSPR Policy rounds – pharmacare in Canada [Internet]. 2014 [cited 2015 Nov 22]. Available from: http://www.cihr-irsc.gc.ca/e/45645.html.
20. Angus Reid Institute. Prescription drug access and affordability an issue for nearly a quarter of all Canadian households. [Internet]. 2015 [cited 2015 Nov 23]. Available from: http://angusreid.org/wp-content/uploads/2015/07/2015.07.09-Pharma.pdf.
21. Rovere M, Skinner BJ. Access delayed, access denied. Fraser Institute [Internet]. 2012 [cited 2015 Nov 23]. Available from: https://www.fraserinstitute.org/sites/default/files/access-delayed-access-denied-2012.pdf.

The Trans-Pacific Partnership

Challenges for the Canadian health care system and developing world

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A NEW TYPE OF TRADE AGREEMENT

Free trade agreements are often lauded by economists. Excessive tariffs, subsidies and regulations distort international and domestic markets. It is the lifting of restrictions on imports and exports that allows countries to trade more easily and realize economic efficiencies that benefit all parties involved. The Trans-Pacific Partnership (TPP), signed on 4 February 2016, is a free trade agreement of tremendous scope, yet experts are wary of the agreement's implications on the sovereignty of its signatories.[1] Unlike other free trade agreements, the TPP does not seek to dismantle regulations, but rather to harmonize domestic policy between nations.[2] The TPP seeks to achieve "free trade" not through the elimination of regulations but through international conformity in regional legislation.[2] The lowering of trade barriers seems almost incidental.

When the TPP enters into force, it will eliminate tariff and nontariff barriers to trade while introducing stringent regulations on environmental protection, minimum working conditions, intellectual property and quality control of food and drug products. Prospective signatories are Australia, Brunei, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, the United States (US) and Vietnam, but the agreement is structured such that other countries may sign on at a later date.[3] The TPP will be the largest trade agreement ever attempted, and the seminal trade deal of the 21st century. The TPP countries have a combined gross domestic product (GDP) of over US$26 trillion and US$5 trillion in goods and services. This is over 40% of the world's GDP and includes almost 800 million people.[4] The significance of this agreement should not be understated.

Critics of the TPP are particularly suspicious of its implications for intellectual property and privacy. The intellectual property provisions in particular could have far-reaching ramifications for health care in Canada, other developed nations and the developing world. In Canada, the TPP may limit the ability of federal and provincial governments to legislate public health efforts when those efforts clash with the interests of industry.[5] Additionally, the TPP may drive up the cost of pharmaceutical products by enshrining special legal protections for pharmaceutical companies and decreasing the Canadian government's ability to effectively regulate them.[6] The plight of the developing world is even worse. Increases in patent term length, drug cost and decreased availability of generic drugs will likely deny millions of people access to essential lifesaving medications.[7]

HEALTH CARE IN CANADA

The Canadian health care system may not be perfect, but it is a far cry from the inefficiencies of the US system. Even after accounting for differences in the strength of the Canadian and US dollars, drug prices in the US are approximately 32% greater than in Canada.[8] This gap could be widened further with the introduction of a national Canadian pharmacare plan.[9] The TPP may expose Canada to the same inefficiencies experienced by the US and limit our ability to change health policy going forward, such as creating any kind of unified national pharmacare strategy.[6]

The TPP limits the ability of Canadian and provincial governments to legislate public health efforts. In chapter 16, "Competition Policy," the TPP directly limits the regulation of consumer products. Any law that limits the competitiveness of a corporation would be discouraged or forbidden by the TPP.[10] This could have broad implications for: product labelling, advertising, nutritional requirements, quality control, and taxation (especially for excise taxes).[11] Though the TPP would allow for certain exemptions from its competition clause, it is unclear how and where they would apply.[10] In chapter 26, "Transparency and Anti-Corruption," the TPP enshrines the right of industry to contribute to national nutrition policy thereby increasing the lobbying power of large corporations.[11,12] These sections undermine Canada's mission to combat chronic noncommunicable diseases like diabetes and heart disease and severely limit the options available to regulators and health policy experts.

The investor-state dispute settlement mechanism outlined in chapter 28, "Dispute Settlement," creates an internationally recognized panel whereby private institutions can pursue legal action against countries.[13] This chapter vastly increases the legal powers of corporations and gives pharmaceutical companies a powerful piece of leverage, which may be used to extract economic rents in court or during the bargaining phase of contract negotiation. The Canadian government is already being sued by US drug company Alexion Pharmaceuticals, who alleges that the Canadian government unfairly lowered the cost of their drug Soliris.[14] Even if the Canadian government wins this lawsuit, the Canadian public will have lost. Money that could have been spent on public health projects by Health Canada or research and development by Alexion Pharmaceuticals will have been wasted in the courts. The new anticompetition clauses of chapter 16 coupled with the easily accessed dispute settlement mechanism of chapter 28 will likely see such lawsuits become more commonplace. Moreover, even if this policy does not encourage increased legal action in Canada, the mere threat of legal action may prompt a rise in drug prices.

HEALTH CARE IN THE DEVELOPING WORLD

The humanitarian organization Doctors Without Borders/Médecins Sans Frontières (MSF) has publicly condemned the TPP for what they view as an agreement that places dangerous restrictions

on medications in the developing world.[7] Lack of access to essential medicines is estimated to result in over 40 million deaths in the developing world.[15] Policies that raise the cost of drugs through increasing the enforceability and length of patents will only see this number rise.[16]

Chapter 18 of the TPP, "Intellectual Property," has been the document's most contentious area. It introduces a number of policies that define the minimum length of patent protection and outlines mandatory criteria for patent extension, including a 3-year extension for a new indication and a 5-year extension for a change in chemical structure.[17] In Canada, the length of a pharmaceutical patent is already 20 years, but the duration is considerably lower in a number of developing countries if protections exist at all. Many developing nations have intentionally loose patent regulations so that they can produce or purchase generic alternatives to brand name drugs that are beyond the financial reach of many of their citizens.[18]

MSF purchases over 80% of their antiretroviral drugs (drugs used in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome) from India, a country famous for skirting US patent law. India has a history of ignoring the validity of US patents and producing their own generics long before patent expiry.[7] Like MSF, many developing nations rely on India as a cheap source of life-saving medications.[19] Though India is not a signatory of the TPP, signatories that continue to purchase protected drugs from India will face steep fines for violating the "Competition Policy" and "Intellectual Property" chapters of the TPP.[10,17]

Biologics and biosimilars (their generic counterparts) are large complex molecules that are manufactured in the living system of a microorganism. These drugs are becoming increasingly important in the creation of vaccines, blood components, allergenics, gene therapy and in the treatment of a host of immune-mediated disorders including some cancers, rheumatoid arthritis, inflammatory bowel disease and many others. Due to the incredible complexity of these drugs, manufacturers of biosimilars rely on data from the clinical trials of the original biologic and still require 7 to 8 years and between US$100-US$250 million USD to bring products to market.[20] The barriers to entry for the biosimilars market are already tremendous, yet the TPP mandates 10 years of data exclusivity for biologics.[17] Brunei, Peru, Vietnam, Malaysia and Mexico currently have 0 years of data exclusivity while Japan has 8.[7] The TPP will likely markedly increase the cost of such drugs in the developing world, limiting the treatment options available to all but the richest segments of the population.

A WOLF IN SHEEP'S CLOTHING

The TPP is the most ambitious free trade agreement ever attempted. It opens the borders between 12 countries across North America and the Asia-Pacific region while instituting mandatory statutes for worker safety and environmental protection. This trade agreement could be a revolution in global commerce, but the TPP is so much more than just a free trade agreement. Its 30 chapters introduce a host of regulations that restrict certain domestic policies while mandating the legislation of others. The regulations it introduces and the precedent it creates will steer international markets as well as individual countries and guide their future development for years to come. Unfortunately, the agreement seems to sacrifice the global health care system on the altar of economic progress. Increased pharmaceutical costs, decreased autonomy in legislating public health solutions and decreased access to generics and biosimilars, particularly in the developing world, is a price that seems too great to bear.

The TPP is perhaps the greatest trade agreement ever created, but it is an agreement ruled by its subtexts.

REFERENCES

1. Baldwin RE. 21st Century Regionalism: Filling the gap between 21st century trade and 20th century trade rules. Available at SSRN 1869845. 2011 Apr.
2. Fergusson IF, Cooper WH, Jurenas R, Williams BR. The Trans-Pacific Partnership: negotiations and issues for congress. Digital Commons. 2013 Aug.
3. Williams BR. Trans-Pacific Partnership (TPP) countries: comparative trade and economic analysis. Digital Commons. 2013 Jan.
4. Schott JJ, Kotschwar B, Muir J. Understanding the Trans-Pacific Partnership. Peterson Institute. 2013 Jan.
5. Kapczynski A. The Trans-Pacific Partnership—is it bad for your health? N Engl J Med. 2015 Jul;373(3):201-203.
6. Thow AM, Gleeson DH, Friel S. What doctors should know about the Trans-Pacific Partnership agreement. Med J Aust. 2015 Mar;202(4):165-166.
7. MSF. Trading Away Health. [Internet]. New York (USA); MSF; 2012 [cited 2015 Nov 19]. Available from: http://www.msfaccess.org/sites/default/files/MSF_assets/Access/Docs/Access_Briefing_TPP_ENG_2012_update.pdf.
8. Danzon PM, Kim JD. International price comparisons for pharmaceuticals. Pharmacoeconomics. 1998 Nov;14(1):115-128.
9. Morgan SG, Daw JR, Law MR. Rethinking Pharmacare in Canada. 2013 Jun;384.
10. Office of the United States Trade Representative. TPP Chapter 16; Competition. [Internet]. United States; 2015 [cited 2015 Nov 19]. Available from: https://ustr.gov/sites/default/files/TPP-Final-Text-Competition.pdf.
11. Thow AM, Snowdon W, Labonté R, Gleeson D, Stuckler D, Hattersley L, et al. Will the next generation of preferential trade and investment agreements undermine prevention of noncommunicable diseases? A prospective policy analysis of the Trans Pacific Partnership Agreement. Health Policy. 2015 Jan;119(1):88-96.
12. Office of the United States Trade Representative. TPP Chapter 26; Transparency and anti-corruption. [Internet]. United States; 2015 [cited 2015 Nov 19]. Available from: https://ustr.gov/sites/default/files/TPP-Final-Text-Transparency-and-Anti-corruption.pdf.
13. Office of the United States Trade Representative. TPP Chapter 28; Dispute Settlement. [Internet]. United States; 2015 [cited 2015 Nov 19]. Available from: https://ustr.gov/sites/default/files/TPP-Final-Text-Dispute-Settlement.pdf.
14. CBC News. U.S. drug company sues Canada for trying to lower cost of $700K-a-year drug. Canada; 2015 [cited 2015 Nov 19]. Available from: http://www.cbc.ca/news/health/u-s-drug-company-sues-canada-for-trying-to-lower-cost-of-700k-a-year-drug-1.3242172.
15. World Health Organization. WHO model list of essential medicines: 19th list (updated) April 2015. 2015 Apr.
16. Attaran A. How do patents and economic policies affect access to essential medicines in developing countries? Health Affairs. 2004 May;23(3):155-66.

17. Office of the United States Trade Representative. TPP Chapter 18; Intellectual property. [Internet]. United States; 2015 [cited 2015 Nov 19]. Available from: https://ustr.gov/sites/default/files/TPP-Final-Text-Competition.pdf.
18. Luo J, Kesselheim AS. The Trans-Pacific Partnership agreement and implications for access to essential medicines. JAMA. 2015 Oct.
19. Lynch S, Ford N, van Cutsem G, Bygrave H, Janssens B, Decroo T, et al. Getting HIV treatment to the most people. Science. 2012 Jul;337(6092):298-300.
20. Blackstone EA, Joseph PF. The economics of biosimilars. AHDB. 2013 Sep;6(8):469.

Addressing the diverging public and physician perceptions on the topic of antibiotic resistance

A review of current progress and future directions

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ABSTRACT

Antibiotics are a powerful tool in fighting bacterial infections but with overuse and misuse, resistance is emerging at an alarming rate. To better understand the root causes of resistance, studying the perceptions of both physicians and the general populace may prove beneficial from a health promotion standpoint. Research reveals that diverging views of these 2 groups remain significant, which proves concerning especially in the face of increasingly resistant bacteria and associated mortality. The issue at large, therefore, requires a better understanding from both parties with regard to antibiotic guidelines, prescription habits and public awareness campaigns.

INTRODUCTION

The world we live in today is built, in part, upon the shoulders of antibiotics. They represent our strongest tool against bacterial infections and are arguably one of the greatest successes in public health. However, exploitation of this valuable resource has led to an uphill battle in the quest for new antibiotics since the 1960s.[1] At this rate, a world in which lethal bacterial infections are the norm may once more become a grim reality. According to the US Centre for Disease Control and Prevention (CDC), in 2013 alone, roughly 2 million people fell victim to highly resistant bacteria, which subsequently led to over 23 000 casualties.[2]

As indicated by the Government of Canada, some of the currently rampant drug resistant bacteria include multidrug-resistant (MDR) *Escherichia coli*, vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).[3] Some of the statistics also proved worrying—for instance, rates of gonorrhea infection have been steadily climbing since the late 1990s, coupled with the emergence of multidrug-resistant strains that present significant therapeutic challenges.[3] At the same time, resistant *Salmonella* accounted for 759 of the 2987 total *Salmonella* reports in 2013,[4] more than a quarter of all cases.

Not surprisingly, antibiotic resistance is currently an urgent concern to Canadian healthcare providers. The issue at hand is intricately complex and requires in-depth understanding of both public perception as well as approaches aimed at increasing public awareness, both of which will be addressed in greater detail in subsequent sections.

PUBLIC PERCEPTIONS OF ANTIBIOTIC RESISTANCE: THE PATIENT AND PHYSICIAN PERSPECTIVES

A greater understanding of laypeople's perceptions may offer significant insights into determinants of misuse, as proposed by numerous epidemiological studies.[5] A large study conducted in the early 2000s (n = 5379) revealed that as many as 11% resorted to overstating their clinical symptoms in order to get an antibiotic prescription from their physicians. According to Haynes et al, there also seems to be confusion among the general public regarding the specific therapeutic indications for antibiotics, as their studies show that the majority consider antibiotics to be effective in the context of common colds, with 79% of patients reporting utilization when "discolored nasal discharge" was present (P = 0.001).[5] Meanwhile, those who display avid aversions to antibiotic usage seem to do so for the wrong reasons. Based on another study more centered on narratives, many of those interviewed showed reluctance because antibiotics "upset the body somehow," and others admit to being common users of alternative medicine such as homeopathy, believing that antibiotics are the cause of increasing incidences of illnesses in the current generation.[6]

Furthermore, there are also studies that seek to understand exactly how patients interpret the term *antibiotic resistance*. A survey conducted in 9 countries across Europe (n = 121) found that virtually all patients associated resistance with antibiotic use, but not to a point deemed to be considered an "accepted scientific view." Instead, most (median 88% [interquartile range (IQR) 86%-89%], n = 2 studies) resort to the vague concept of *resistant body* for their explanations and were incapable of explaining antibiotic resistance in any greater detail. Another significant percentage (median 70% [IQR 59-77%], n = 11 studies) believed that excessive use and failure to complete treatment courses are the drivers of resistance.[7] From their perspective, antibiotic resistance develops not due to mutations in bacteria but the human body gradually mounting tolerance, meaning every antibiotic can only be used for a limited time period before it becomes obsolete. The above observations have been replicated in many other studies as well,[8-10] suggesting that we are still far from reaching an adequate understanding in the general populace, and initiatives designed to raise greater awareness in this subject area should be more extensively implemented and promoted.

It is also noteworthy to address the two-sided nature of this issue. Patients aside, a meta-analysis conducted this year suggests

physicians also played a significant role in exacerbating the situation. A systematic review of 57 studies involving over 11 000 physicians, mostly across North America, show that while most admit to being aware of antibiotic resistance as a serious global health issue, a significant number of respondents also designated short treatment courses, low dosage and patient noncompliance as contributing factors.[11] This shows evidence for diffusion of responsibility amongst physicians, and suggests that in order for the concern to be properly addressed in the foreseeable future, the combined contributions from both the patients and physicians are required.

ADDRESSING THE ISSUE: WHAT CAN BE DONE TO INFLUENCE PUBLIC PERCEPTIONS

A number of measures have been suggested by the Canadian Government to combat this trend, keeping in mind that both Canadians and healthcare professionals alike should play their part. Some general recommendations include maintaining good hygiene, ensuring proper sneezing methods to prevent bacterial host transfer, practicing safer sex and keeping up with current vaccinations. Physicians and other healthcare professionals share the added responsibility of preventing the spread through suboptimal dispensing practices. Whenever possible, antibiotic stewardship should be employed and clinical practice guidelines should be strictly adhered to.[12] The World Health Organization (WHO) also publishes its own sets of standards regarding approaches to control antimicrobial resistance. It implements many surveillance programs, such as the Global Antimicrobial Resistance Surveillance System (GLASS), that provide an internationally standardized approach for collecting relevant data on the most resistance-prone bacterial species worldwide,[13] making it much easier to track resistance progress. Finally, they publish reports that outline practical guidelines such as rational drug use, which physicians can access and consult either for their own professional development or for promoting these practices in the community at large.

Historical polling reveals that while public faith in the healthcare system has significantly fluctuated over time (as low as 23% in 2014), trust and confidence in the physicians' knowledge and personal values has remained overwhelmingly positive.[14] It is no surprise therefore that respondents in a randomized survey admitted that if a physician prescribed them antibiotics for a certain condition, they would be much more inclined to request antibiotics when the same condition re-emerges, irrespective of the actual nature of the condition.[15] Consequently, physician prescribing habits are a key element in the containment of excessive antibiotics use, and they should be the first subpopulation targeted for appropriate education and should also be encouraged to self-educate in this subject area.

It is also interesting to point out that those with a greater educational background were no less likely to be prescribed antibiotics, and individuals with higher perceived knowledge about antibiotics were in fact more likely to self-medicate and keep leftover antibiotics.[15] The implications of this finding are not entirely clear, but does seem to suggest that changing physician and public perceptions alone is by no means an exhaustive approach to combat antibiotic resistance. The overarching scheme should be multidisciplinary in nature and include a combination of epidemiological studies, population surveys, pharmaceutical research, dispensing practices by health professionals and government intervention (eg, limiting antibiotics use by placing quotas).

Meanwhile, for the lay public, raising awareness should be much less resource-intensive and should instead take the form of public health campaigns. Campaigns have often been an effective medium to relay important messages. For instance, there are currently many campaigns directed at raising awareness about the various cancer screening programs such as colorectal cancer, as demonstrated by the Canadian Cancer Society.[16] An article published in the UK reported that a pilot colorectal cancer screening awareness campaign resulted in a 10% increase in participation within a single month.[17] Greater emphasis should also be placed on educating the public on the importance of their own contributions. A large portion of the public consider their role in antibiotic resistance to be minimal, and believe the root of resistance lies with unsanitary hospitals. Many also resort to popular media as their primary source of information on these topics.[18] One way to approach this would be to urge patients to acquire their information from more reputable sources, and assist them in the process by providing examples of databases known to contain more reliable information. The alternative would be to actually harness the power of the media, and generate campaigns compatible with multiple media sources so that they are more widely received by the public.

CONCLUSION

Our paper discussed antibiotics resistance as one of the forefront concerns in healthcare, one that is bound to be exacerbated if the government, physicians and the public fail to react promptly and implement appropriate strategies. The current landscape is deteriorating rapidly as spine-chilling cases of resistant bacteria, with the potential to kill many millions, make routine headlines.[19] Improving physician and patient understanding of the underlying basis of antimicrobial resistance currently takes precedence, but a truly multidisciplinary strategy is required to pave the way for a new era, where antibiotics can once more be the symbol of a successful public health story, for now and for many years to come.

REFERENCES

1. Lewis K. Recover the lost art of drug discovery: bacterial evolution is overwhelming our antibiotic defences. Nature. 2012 May 24;485(7399):439-40.
2. Frieden T. Antibiotic resistance threats in the United States, 2013. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014 Jul. 113p. Report No.: CS239559-B.
3. Antibiotic-resistant illnesses and bacteria [Internet]. Centre for Communicable Diseases and Infection Control. 2014 July 10 [updated 2015 Aug 21; cited 2015 Nov 9]. Available from: http://healthycanadians.gc.ca/drugs-products-medicaments-produits/buying-using-achat-utilisation/antibiotic-resistance-antibiotique/illnesses-maladies-eng.php.
4. Canadian antimicrobial resistance surveillance system report 2015. Ottawa (ON): Centre for Communicable Diseases and Infection Control. 2014 Jul. 53p. Catalogue No.: HP37-21E-PDF.
5. Pechere JC. Patients' interviews and misuse of antibiotics. Clin Infect Dis. 2011 Sep 15;33(S3): S170-3.

6. Mainous III AG, Zoorob RJ, Oler MJ, Haynes DM. Patient knowledge of upper respiratory infections: implications for antibiotic expectations and unnecessary utilization. J Fam Practice. 1997 July;45(1):75-83.
7. Brookes-Howell L, Elwyn G, Hood K, Wood F, Cooper L, Goossens H, et al. 'The body gets used to them': patients' interpretations of antibiotic resistance and the implication of containment strategies. J Gen Intern Med. 2011 Nov 8;27(7):766-72.
8. Fredericks I, Hollingworth S, Pudmenzky A, Rosato L, Syed S, Kairuz T. Consumer knowledge and perceptions about antibiotics and upper respiratory infections in a community pharmacy. Int J Clin Pharm. 2015 Sep 21;37(6):1213-21.
9. Wiklund S, Fagerberg I, Ortgvist A, Vading M, Giske CG, Broliden K, et al. Knowledge and understanding of antibiotic resistance and the risk of becoming a carrier when travelling abroad: a qualitative study of Swedish travellers. Scan J Public Health. 2015 Feb 23;43(3):302-8.
10. Gualano MR, Gili R, Scaioli G, Bert F, Siliguini R. General population's knowledge and attitudes about antibiotics: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2014 Sep 24;24(1):2-10.
11. McCullough AR, Rathbone J, Parekh S, Hoffmann TC, Del Marr CB. Not in my backyard: a systematic review of clinicians' knowledge and beliefs about antibiotic resistance. J Antimicrob Chemother. 2015 June 20;70(9):2465-73.
12. Prevention of antibiotic resistance [Internet]. Centre for Communicable Diseases and Infection Control. 2014 Sep 30 [cited 2015 Nov 9]. Available from: http://healthycanadians.gc.ca/drugs-products-medicaments-produits/buying-using-achat-utilisation/antibiotic-resistance-antibiotique/prevention-eng.php.
13. Antimicrobial use [Internet]. World Health Organization. 2015 [cited 2015 Oct 25]. Available from: http://www.who.int/drugresistance/use/en/.
14. Blendon RJ, Benson JM, Hero JO. Public trust in physicians – US medicine in international perspective. N Engl J Med. 2014 Oct 23;371(17):1570-2.
15. McNulty CA, Boyle P, Nichols T, Clappison P, Davey P. The public's attitudes to and compliance with antibiotics. J Antimicrob Chemother. 2007 Aug;60(1):i63-8.
16. Screening of colorectal cancer [Internet]. Canadian Cancer Society. 2015 [cited 2015 Nov 4]. Available from: http://www.cancer.ca/en/prevention-and-screening/early-detection-and-screening/screening/screening-for-colorectal-cancer/?region=pe.
17. Whyte S, Harnan S. Effectiveness and cost-effectiveness of an awareness campaign for colorectal cancer: a mathematical modeling study. Cancer Causes Control. 2014 Mar 29;25(6):647-58.
18. Hawkings NJ, Wood F, Butler CC. Public attitudes towards bacterial resistance: a qualitative study. J Antimicrob Chemother. 2007 Apr 21;59(6):1155-60.
19. Lauren W. This disease could kill 75 million people by 2050 [Internet]. The Huffington Post. 2015 Oct 23 [cited 2015 Nov 4]. Available from: http://www.huffingtonpost.com/entry/tuberculosis-mdr-tb-treatment_56211f2be4b06462a13bc8fd.

Pain, prejudice, and prohibition

The history of opioid drug policy in Canada

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INTRODUCTION

Historically, the use of drugs has been a part of every society, consumed for ritual or religious purposes, for pleasure, to enhance performance, or as a means to cure ailments or relieve symptoms. In the 20th century, a distinction has arisen between legal drugs which are prescribed and administered by medical professionals, and illegal drugs which are subject to state regulation and suppression. In particular, opium derivatives and related semisynthetic and synthetic compounds including morphine, heroin, codeine, hydrocodone, oxycodone, and methadone have been subject to numerous restrictions in prescription, possession, and distribution internationally. The history of opioid regulations in Canada and the criminalization of its use is a story of complex socioeconomic and cultural factors, navigating the elements of otherness and threat associated with the opioid drug user, from the Chinese opium den to the criminal addict. As stakeholders in this discussion, physicians have been both the regulators and the regulated with respect to the availability and accessibility of opioids. An examination of this history can be instructive in reflecting on our approach to drug policy today.

HISTORICAL USE OF OPIATES

Sir William Osler feted it as "God's own medicine," and indeed opium has been one of the most widely used and extolled drugs throughout history. Derived from juices of the poppy plant harvested in central Asia, opium has been used as early as 3100 BC for its potent anesthetic and euphoric effects. The drug was well known in ancient Greece, introduced to China by Arab traders by the 10th century AD, and spread onwards to all parts of Europe.[1] In the 16th century, the number of medical recipes using opium began to increase, with Paracelsus creating a tincture for which he coined the word "laudanum."[1] Laudanum, which came to mean a solution of opium in alcohol, was widely prescribed by physicians for any number of illnesses including pain, sleeplessness, diarrhea, convulsions, delirium, and nervous disorders.[1] With the widespread use of opiates, the problems of dependence and addiction too became known. The 17th century English physician Thomas Willis warned against the "dazzlingly seductive Opium" which could bring "destructive Tragedies" with an excessive or unreasonable dose.[1] The largest burden of addiction was in China, with widespread use despite a ban by imperial edict due to an influx of opium trafficked by the British East India Company; this triggered the First (1839-1842) and Second Opium Wars (1856-1860).[2]

EARLY LEGISLATION: THE RACIALIZATION OF OPIUM AND THE NARCOTICS DIVISION

Morphine was purified from opium in 1804, and greatly utilized in the American Civil War (1861-1865);[2] heroin was synthesized in 1874.[1] Their addictive potential was recognized and documented, but addiction was regarded as an unfortunate consequence and not a threat to society at large; consumption of medicinal opioids was not uncommon as Canadians could purchase them readily at the local pharmacy. In contrast, opium smoking was closely identified with the Chinese immigrants who started arriving during the 1850s to build the Canadian Pacific Railway. Public anti-Chinese sentiment led the government to impose a $50 head tax on all Chinese immigrants, which was raised to $500 by 1904.[3] Events culminated with a rally in Vancouver in September 1907, which exploded into violence and vandalism as the rioting mob of thousands destroyed numerous Chinatown properties.[4] Deputy Minister of Labour William Lyon Mackenzie King was charged with the on-site investigation; appalled by circulating reports that opium smoking was seducing and corrupting young Caucasian women of good social standing, he drafted the "Report on the Need for the Suppression of Opium Traffic in Canada."[4] Within a month of its release, Canada passed federal legislation prohibiting the importation, sale, and manufacture of opium for nonmedical purposes.

Opium use and possession became criminalized under the Opium and Drug Act of 1911. Subsequent amendments reduced the legitimate scope of medical opium, increased penalties to include significant jail time, increased police powers of search and seizure, and added cocaine and marijuana.[5] The image of the nefarious Chinese drug menace was further promoted to the Canadian public by magistrate Emily Murphy in a series of articles in *Maclean's* magazine and in her 1922 book *The Black Candle*.[4] Drug use and addiction was seen as a contagion, and users as both victims of injury to the self, and criminals in causing injury to others.[5] The new legislations were implemented through the creation of the Narcotics Division, while the professional autonomy of physicians to prescribe and administer opioids became severely restricted. Law enforcement was positioned as the highest authority on the legitimate and illegitimate uses of opioids, and what constituted sound medical practice. The narcotics purchases of physicians were scrutinized through the newly introduced licensing system. Additionally, the classification of drug users as criminal addicts was used to delegitimize the few physicians who called for the extension of treatment beyond arrest and confinement.[5]

GLOBAL INFLUENCES: THE VIETNAM WAR & INTERNATIONAL TREATIES

Canadian opioid regulations changed little in the subsequent decades. By the 1930s, there were few Chinese drug users left due to deportations and the restriction of immigration by the Chinese Immigration Act of 1923.[4] For Caucasian drug users, criminalization and harsher penalties made opioid use an increasingly dangerous activity. The poor economic conditions of the Great Depression and the shortage of anesthetics during World War II made it difficult for users to obtain opioids.[4] In addition, opioid production and trade were being increasingly regulated by international treaties. The landmark charter was the 1961 United Nations Single Convention on Narcotic Drugs, which created 4 schedules of controlled substances and a process for additions to keep pace with accelerating advances in chemistry without the need to ratify amendments.[6] Stating that "addiction to narcotic drugs constitutes a serious evil for the individual [...] fraught with social and economic danger to mankind," the goal was the global prohibition of all nonmedical and nonscientific use of narcotic drugs, a category under which cannabis was included for the first time in international regulations.[6] By signing this treaty, Canada took on an international responsibility to prohibit narcotic production, possession, distribution, and consumption.

The Vietnam War (1963-1975) began just as the convention was adopted. Military conflict and substance use have always had a synergistic relationship, with drugs used to relieve the pain of war and stimulate troops to fight. At the height of the Vietnam War, heroin produced in the Golden Triangle of Southeast Asia became widely available amongst the troops in Vietnam and civilians in America.[2] In 1971, President Richard Nixon declared drug abuse "public enemy number one."[1] Drug use became framed administratively and socially as a threat to national security, with the response phrase "War on Drugs" equally militaristic. The legacy of Nixon's Drug Enforcement Administration has been one which further entangled war and drugs, as American covert operations entwined with Afghan and Pakistani drug traffickers during the Soviet-Afghan war (1979-1989); Afghanistan, Iran, and Pakistan became opium's new empire, the Golden Crescent.[2] The billions of dollars generated by the illicit narcotics trade continue to contribute to international civil and political unrest, and thereby to the perpetuation of the prohibitionist approach to opioid drug regulations.

THE MEDICALIZATION OF OPIOID USE: TOWARDS HARM REDUCTION

The treatment-based paradigm for drug abuse emerged in the 1950s, as medicine became a more powerful and prestigious profession than ever before. The quality of medical care had improved significantly with the development of germ theory, antisepsis, and antibiotics. It seemed reasonable that the ability of modern medical practice to heal could extend to include drug addiction. Of particular significance was the report penned by Dr Lawrence Ranta, chair of an independent committee appointed by the Community Chest and Council of Greater Vancouver (a forerunner to the United Way). The report made only 2 recommendations, yet fundamentally challenged Canadian approaches to illicit drug use at the time. The first called for a pilot medical treatment and rehabilitation centre for drug users. The second advocated for provincial narcotics clinics where users could receive maintenance doses.[5] In 1958, the first methadone program in Canada opened in Vancouver, initially for the treatment of withdrawal symptoms from morphine or heroin and later for maintenance.[4] In 1961, the Narcotic Control Act granted physicians more professional autonomy, as the regulation of prescription practices shifted from the purview of law enforcement to provincial licensing bodies.[5]

In 1969, the Commission of Inquiry into the Non-Medical Use of Drugs, better known as the Le Dain Commission, was established to gather data and to make recommendations to the federal government on the phenomenon of nonmedical drug use, particularly of cannabis.[7] In describing and analyzing the social and individual costs of the criminalization legislation, the Commission was an important step in the development of a policy of harm reduction in Canada; the report recommended a gradual withdrawal from criminal sanctions.[8] The harm reduction approach has since been repeatedly validated for its safety, efficacy, and cost-effectiveness.[9] The human immunodeficiency virus (HIV) epidemic of the 1980s and the rise of infection among injection drug users, mainly of heroin, prompted the expansion of harm reduction efforts. The first syringe exchange program started in Toronto in 1988, with many following in communities across Canada.[10] Despite numerous efforts aimed at decriminalization, the current federal drug legislation, the Controlled Drugs and Substances Act enacted in 1994, remains soundly prohibitionist.[11] The National Anti-Drug Strategy implemented by the Harper conservative government in 2008 further emphasized the criminal nature of drug use, with 70% of funding allocated to law enforcement and only 17% to treatment programs.[12]

CONCLUSION

While physicians have been leaders in advocacy for harm reduction and decriminalization, the role of physicians in the prescription opioid addiction epidemic must also be acknowledged. Nonmedical use of prescribed opioids is now the 4th most prevalent form of substance use in Canada, behind alcohol, tobacco, and cannabis.[13] In Ontario, the number of fatal opioid overdoses has increased 242% between 1991-2010, to approximately 550 deaths each year.[14] With the blurring line between licit and illicit opioid drug use, and the role of physicians as gatekeepers, an understanding of the history and context of opioid drug regulations is increasingly important. As part of a strategy to combat this crisis, some have proposed establishing prescription monitoring programs and increasing physician adherence to prescribing and dispensing guidelines;[15] it is not difficult to recall similar regulations on physician actions pre-1961. Simultaneously, it is a time of great potential. Physicians can play a major role in shaping the development of legislation to reduce barriers to effective opioid addiction treatment and prevent the harms of opioid use.

REFERENCES

1. Davenport-Hines R. The pursuit of oblivion: a global history of narcotics. New York, NY: Norton & Company; 2002.
2. Bergen-Cico DK. War and Drugs: The role of military conflict in the development of substance abuse. Boulder, CO: Paradigm Publishers; 2012.
3. Calgary Chinese Cultural Centre. A history of exclusion [Internet]. Calgary, AB: Calgary Chinese Cultural Centre; 2008 [cited 2015 Dec]. Available from: http://www.culturalcentre.ca/chinese_albertan_history/policies.htm.
4. Carstairs C. Jailed for possession: illegal drug use, regulation, and power in Canada, 1920-1961. Toronto, ON; University of Toronto Press; 2006.
5. Grayson K. Chasing dragons: security, identity, and illicit drugs in Canada. Toronto, ON: University of Toronto Press; 2008.
6. United Nations. Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol [Internet]. Vienna, Austria: International Narcotics Control Board; 1972 [cited 2015 Dec]. Available from: http://www.incb.org/documents/Narcotic-Drugs/1961-Convention/convention_1961_en.pdf.
7. Martel M. Not this time: Canadians, public policy, and the marijuana question 1961-1975. Toronto, ON: University of Toronto Press; 2006.
8. The report of the Canadian Government Commission of Inquiry into the Non-Medical Use of Drugs [Internet]. Ottawa, ON: Schaffer Online Library of Drug Policy; c2006. Conclusions and Recommendations; c2006 [cited 2015 Dec]. Available from: http://www.druglibrary.org/schaffer/library/studies/ledain/ldctoc.html.
9. Ritter A, Cameron J. A review of the efficacy and effectiveness of harm reduction strategies for alcohol, tobacco and illicit drugs. Drug Alcohol Rev. 2006 Nov;25(6):611-24.
10. Weekes J, Palmer D. Needle exchange programs (NEPs) [Internet]. Ottawa, ON: Canadian Centre on Substance Abuse; 2004 [cited 2015 Dec]. Available from: http://www.ccsa.ca/Resource%20Library/ccsa-010055-2004.pdf.
11. Minister of Justice. Controlled drugs and substances act [Internet]. Ottawa, ON: Minister of Justice; 2015 [cited 2015 Dec]. Available from: http://laws-lois.justice.gc.ca/PDF/C-38.8.pdf.
12. Debeck K, Wood E, Montaner J, Kerr T. Canada's new federal 'National Anti-Drug Strategy': an informal audit of reported funding allocation. Int J Drug Policy. 2009 Mar;20(2):188-191.
13. Fischer B, Argento E. Prescription Opioid related misuse, harms, diversion and interventions in Canada: a review. Pain Physician. 2012 Jul;15(3 Suppl):ES191-203.
14. Carter CI, Graham B. Opioid overdose prevention & response in Canada [Internet]. Vancouver, BC: Canadian Drug Policy Coalition; 2013 [cited 2015 Dec]. Available from: http://drugpolicy.ca/wp-content/uploads/2014/07/CDPC_OverdosePreventionPolicy_Final_July2014.pdf.
15. National Advisory Council on Prescription Drug Misuse. First, do no harm: responding to Canada's prescription drug crisis [Internet]. Ottawa, ON: National Advisory Council on Prescription Drug Misuse; 2013 [cited 2015 Dec]. Available from: http://www.ccsa.ca/resource%20library/canada-strategy-prescription-drug-misuse-report-en.pdf.

A review of housing-first strategies in reducing rates of substance use amongst people experiencing homelessness

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ABSTRACT

Substance use is a serious and prevalent health challenge among people who are homeless. The rate of alcohol use is 6 to 7 times more common in people experiencing homelessness than the general population, while approximately a quarter of all homeless individuals exhibit disordered use of one or more substances other than alcohol. Substance use is recognized as a significant risk factor for becoming homeless and is thought to complicate rehousing efforts and contribute to decreased adherence to rehabilitation programs that were and continue to be traditionally a requirement of rehousing. While studies have largely shown that housing-first strategies result in increased rates of retention in permanent housing compared to more established treatment-first strategies, it is less established whether housing-first strategies are equally successful among those homeless individuals with substance use challenges. In this review, we examine the available evidence on the efficacy of housing-first strategies in rehousing individuals with substance use challenges and in reducing the rates of substance use among people experiencing homelessness. We conclude that while housing-first strategies have not been shown to reduce rates of substance use compared to treatment-first strategies, both types of programs result in a comparable level of decrease in substance use rates despite treatment-first strategies mandating rehabilitation prior to rehousing. Finally, we provide a number of guidelines for an interdisciplinary approach to rehousing homeless individuals with substance use disorders through a housing-first strategy.

INTRODUCTION

Homelessness is a significant and growing problem in Canada. Homeless individuals are at greater risk of developing health problems and have significantly higher rates of early morbidity and mortality, all while having fewer resources and avenues to access necessary medical care.[1] Management of homeless patients is complicated by a lack of identification and of permanent address,[2] frequent loss to follow-up[3] and especially higher rates of mental illness and substance use challenges.[1,4,5]

Epidemiology of homelessness in Canada

Homelessness has become an epidemic in Canada. To give one example of many, more than 4000 people sleep in shelters every night in Toronto.[1] Experts estimate that the number of homeless individuals in Canada in 2013 numbered approximately 235 000.[6] A further 1 in 7 households in Canada face problems of housing affordability, with housing costs in excess of 30% of the annual household income.[7] The demographics of homelessness has also changed significantly in the past 2 decades, from mostly single adult men with alcohol use disorders to a diverse population including adolescents, single mothers, the under- and unemployed, the elderly and recent immigrants.[4]

The relationship between homelessness and substance abuse

Substance use is a disorder diagnosed on the basis of recurrent use of a substance leading to impaired control, social impairment and risky use.[8] It is well established that homelessness and substance use exhibit a bidirectional relationship, with substance use both being more prevalent among people experiencing homelessness[4,5] and being an independent risk factor for homelessness.[9] Alcohol use among people experiencing homelessness is estimated to be 6 to 7 times that of the general population.[10] A 2008 meta-analysis of alcohol use among homeless adult men found that approximately 38% had some form of alcohol use disorder. The same meta-analysis found that 24% of homeless men had a substance use disorder involving one or more substances other than alcohol.[11]

REDUCING HOMELESSNESS THROUGH A HOUSING-FIRST STRATEGY

Housing-first strategies

A housing-first strategy to reduce homelessness was first conceived and implemented by clinical psychologist Sam Tsemberis in 1992. This program, called Pathways to Housing, was aimed at increasing rehousing rates for homeless individuals with psychiatric disabilities in New York City.[12]

Housing-first strategies mandate the provision of immediate housing, choice and self-determination in rehousing, a focus on recovery, individualized and person-driven supports and social and community integration of the rehoused individual.[13] Whereas more established treatment-first strategies have stipulated that the individual must be "housing ready" by completing rehabilitation programs aimed at treating substance use and other health challenges, housing-first strategies provide stable, private housing with concurrent, optional rehabilitation programs and other social support services.[14]

Efficacy of housing-first strategies in reducing homelessness

In one American study of the outcomes of a housing-first intervention in reducing homelessness, researchers found that 57% to 78% of people rehoused through housing-first programs remained

in stable housing after 47 months.[15] Housing-first strategies also reduce the costs associated with homelessness. In a study by the Mental Health Commission of Canada, a 5-year housing-first strategy resulted in cost savings of between Can$3.42 to Can$9.60 for every Can$10.00 invested. This was achieved through a reduction of utilization of other services by rehoused individuals.[13]

When compared to treatment-first strategies, housing-first strategies have been shown to result in greater housing stability in the first 24 months of starting the program[16] and overall longer lengths of stay in housing[17] when compared to treatment-first strategies.

EFFICACY OF HOUSING-FIRST STRATEGIES IN REDUCING SUBSTANCE USE RATES

Whereas housing-first strategies demonstrate higher overall rates of housing retention, the benefits of a housing-first strategy for rehousing of homeless individuals with a substance use challenge are less clear.

In short-term studies of the efficacy of housing-first strategies in reducing rates of substance use in homeless populations, researchers have found that programs that employ a housing-first strategy actually have greater reductions in rates of alcohol use and relapse into substance use than programs that employ treatment-first strategies.[18,19] In a review of 29 studies from around the world, Collin et al found that there was a 3% decrease in overall and peak alcohol consumption in individuals rehoused through a housing-first strategy compared to those rehoused through a treatment-first strategy.[18] Additionally, Padgett et al showed that participants of a housing-first program were 3.4 times less likely to relapse into substance use than participants of a treatment-first program within the first year.[19]

However, longer-term studies of the efficacy of housing-first programs have largely failed to replicate these promising early results. A 2010 study of the efficacy of housing-first programs across 11 communities across the United States did not identify a significant difference in rates of substance use between housing-first and treatment-first participants after 2 years.[17] Similarly, a direct comparison between a housing-first intervention and a treatment-first intervention in a homeless population in New York City failed to show improvement in rates of alcohol and substance use with housing-first compared to treatment-first.[20] The 2014 Canadian At Home/Chez Soi study also found no significant difference between rates of substance use between participants of housing-first versus treatment-first programs, although it also noted an overall improvement in substance use rates amongst both groups.[13]

Despite the lack of long-term improvement in rates of substance use when compared to treatment-first programs, it is important to note that housing-first programs showed equivalent levels of overall reduction in substance use despite not mandating that rehabilitation programs be completed.[20] In combination with the fact that the overall outcomes are better in housing-first programs than treatment-first programs, it must be concluded that housing-first programs are more effective, or at least not any less effective, than traditional treatment-first programs in rehousing homeless individuals with substance use challenges.

RECOMMENDATIONS FOR REHOUSING OF HOMELESS INDIVIDUALS WITH SUBSTANCE USE CHALLENGES

Stably rehousing homeless individuals with substance use challenges is a complex task that demands an interdisciplinary case management team. In studies of best practices in the management of homelessness, researchers have identified 6 features of successful case management strategies: client identification and outreach, assessment of needs, planning of treatment and services, linking the client to necessary resources, monitoring progress and client advocacy. Existing studies on the management of this sub-population of patients have emphasized adoption of assertive community treatment (ACT) teams.[21]

The ACT team model was developed for treatment of individuals with severe mental illness, and includes a physician or nurse experienced in the diagnosis and management of mental illness and substance use challenges, a psychiatrist to manage symptoms of mental illness and monitor effectiveness and adherence to medications, social services to help with social reintegration (including support for obtaining education and/or employment, a personal support worker to assist with activities of daily living and a peer specialist who acts as a counselor to facilitate the treatment process).[22]

Based on the findings presented in this review, we propose that the following guidelines be followed when considering the approach to rehouse homeless individuals with substance use challenges:

1. A housing-first strategy is equally viable to a treatment-first strategy in rehousing of homeless individuals with substance use challenges.[20]
2. Rehoused individuals with known substance use challenges should be identified and support should be offered in the form of an interdisciplinary team of healthcare providers, including a physician, nurse, psychiatrist, personal support worker and peer specialist; care should be provided using a client-centred model and should include a case manager who can coordinate the team's actions.[21,22]
3. The interdisciplinary team providing care for rehoused individuals with known substance use challenges should continue working with those individuals for a period of several years to ensure long-term retention in stable housing.[17,20]

CONCLUSION

The implementation of housing-first strategies has the potential to make a real positive impact on homelessness in Canada. In this review we examined the efficacy of housing-first strategies in rehousing individuals with substance use challenges and in reducing rates of substance use among rehoused individuals. Although we found an initial improvement in reduction of substance use in individuals rehoused through a housing-first strategy compared to those rehoused through a treatment-first strategy, current available evidence does not support the existence of any significant long-term reduction in rates of substance use beyond what is achieved with treatment-first strategies. However, we found that housing-first strategies provided a number of other advantages over

treatment-first strategies. We conclude that housing-first strategies are slightly better or at least not worse than treatment-first strategies in rehousing those homeless individuals with a substance use challenge.

REFERENCES

4. Hwang SW. Mental illness and mortality among homeless people. Acta Psychiatr Scand. 2001;103:81-2.
5. Khandor E, Mason K, Chambers C, Rossiter K, Cowan L, Hwang SW. Access to primary health care among homeless adults in Toronto, Canada: results from the Street Health survey. Open Med. 2011;5(2):e94.
6. Conwell DS, Mosher A, Khan A, Tapy J, Sandman L, Vernon A, et al. Factors associated with loss to follow-up in a large tuberculosis treatment trial (TBTC study 22). Contemp Clin Trials. 2007 May;28(3):288-96.
7. Hwang SW. Homelessness and health. CMAJ. 2001;164(1):229-33.
8. Turnbull JS, Muckle W, Masters C. Homelessness and health. CMAJ. 2007 Oct;177(9):1065-6.
9. Gaetz S, Gulliver T, Richter T. The state of homelessness in Canada 2014. Toronto: The Homeless Hub Press; 2014. 73p.
10. Laird G. SHELTER: homelessness in a growth economy: Canada's 21st century paradox. Calgary (AB): Sheldon Chumir Foundation for Ethics in Leadership; 2007 p.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington: American Psychiatric Association; 2013.
12. Dixon L. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophrenia Res. 1999;35:S93-100.
13. Webb GR, Redman S, Gibberd RW, Sanson-Fisher RW. The reliability and stability of a quantity-frequency method and a diary method of measuring alcohol consumption. Drug Alcohol Depend. 1991 May;27(3):223-31.
14. Fazel S, Khosla V, Doll H, Geddes J. The prevalence of mental disorders among the homeless in Western countries: systematic review and meta-regression analysis. PLoS Med. 2008 Dec;5(12):1670-81.
15. Tsemberis S, Eisenberg RF. Pathways to Housing: supported housing for street-dwelling homeless individuals with psychiatric disabilities. Psychiatr Serv. 2000 Apr;51(4):487-93.
16. Goering P, Veldhuizen S, Watson A, Adair C, Kopp B, Latimer E, et al. National At Home/Chez Soi final report. Calgary (AB): Mental Health Commission of Canada.
17. Pleace N, Bretherton J. The case for housing first in the European Union: a critical evaluation of concerns about effectiveness. Eur J Homelessness. 2013 Dec;7(2):21-41.
18. Stefancic A, Tsemberis S. Housing first for long-term shelter dwellers with psychiatric disabilities in a suburban county: a four-year study of housing access and retention. J Primary Prevent. 2007
19. Tsemberis S, Gulcur L, Nakae M. Housing first, consumer choice, and harm reduction for homeless individuals with a dual diagnosis. Am J Public Health. 2004 Apr;94(4):651-6.
20. Tsai J, Mares AS, Rosenheck RA. A multi-site comparison of supported housing for chronically homeless adults: "housing first" versus "residential treatment first." Psychol Serv. 2010;7(4):219-32.
21. Collins SE, Malone DK, Clifasefi SL, Ginzier JA, Garner MD, Burlingham B, et al. Project-based housing first for chronically homeless individuals with alcohol problems: within-subjects analyses of 2-year alcohol trajectories. Am J Public Health. 2012 Mar;102(3):511-9.
22. Padgett DK, Stanhope V, Henwood BF, Stefancic A. Substance use outcomes among homeless clients with serious mental illness: comparing housing first with treatment first programs. Community Ment Health J. 2011 Apr;47(2):227-32.
23. Padgett DK, Gulcur L, Tsemberis S. Housing first services for people who are homeless with co-occurring serious mental illness and substance abuse. Res Soc Work. 2006 Jan;16(1):74-83.
24. Morse G. A review of case management for people who are homeless: implications for practice, policy, and research. In: Fosburg LB, Dennis DL, editors. Practical Lessons: The 1998 National Symposium.
25. Bond GR, Drake RE, Mueser KT, Latimer E. Assertive community treatment for people with severe mental illness: critical ingredients and impacts on patients. Dis Manage Health Outcomes. 2001 Mar;9(3):141-59.

The digital pill

Tracking medication adherence through electronic modalities

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ABSTRACT

Compliance with prescription medication regimens is poor in patients who suffer from chronic conditions as well as from diseases that affect public health. It is thought that improving medication adherence can have a profound effect on patient health, though medication compliance remains a problem despite the availability of many modalities. Recently, digitalizing medication adherence was made possible by Proteus Digital Health, Inc using an ingestible sensor that emits an electric field upon digestion. This signal is detected by an externally worn adhesive monitor, which records the time at which the signal is received, along with other biometric markers such as heart rate. This system is currently under United States Food and Drug Administration (FDA) review for use in a combination pill that also contains aripiprazole, a partial dopamine agonist used for the treatment of certain serious psychiatric conditions. Digitalizing medication adherence can have tremendous applications in all fields of medicine, though issues of drug costs, patient privacy, and patient autonomy may need to be addressed.

INTRODUCTION

Lack of adherence to prescription oral medication is an alarming problem in our healthcare system. Studies in the past decade have shown that approximately 50% of patients with chronic illness do not take their medications as prescribed.[1] Being forgetful is the commonest reason for poor adherence, though some patients may voluntarily choose not to take their medications, perceiving medication as unnecessary, or being fearful of any associated side effects.[2] The latter is a cause for concern for public health, particularly with communicable diseases such as tuberculosis that can be effectively managed through medication.[3,4] Poor compliance to prescription medication regimens puts a tremendous burden on the medical system, as noncompliant patients are more likely to be readmitted to the hospital or clinic, and possibly be prescribed more and/or more potent medication that they may not otherwise need. This ultimately leads to poorer health outcomes, and it has been argued that increasing the effectiveness of adherence interventions may have a far greater impact on patient health than any improvement in specific medical treatments.[5] This problem therefore compels the need to identify modalities to accurately ensure medication compliance in at-risk patients.

CURRENT MODALITIES TO IMPROVE MEDICAL ADHERANCE

The issue of medication nonadherence has been tackled on various fronts to varying degrees of success. Physicians and pharmacists can play an essential role by simplifying regimen characteristics, making the regimen compatible with the patient's lifestyle and daily schedule, and educating patients about their medications and why they are taking them.[1,6] Additionally, a variety of adherence aids are available to patients including pill organizers, blister packs, and reminders/alarms.[7,8] For instance, electronic reminders in the form of pagers, cellphones, and text messages have been shown to improve medication refill adherence in type 2 diabetes mellitus patients.[9] Another approach to improving medication compliance is directly observed therapy (DOT), which arose from the need for strict medication compliance in managing tuberculosis to limit the spread of the infectious agent.[10] DOT involves a healthcare worker or designated individual watching the patient swallow all doses of their medications. DOT is currently the World Health Organization standard for ensuring medication compliance for tuberculosis. Although this approach should theoretically be entirely effective in ensuring tuberculosis medication compliance, the literature suggests that DOT is no better than standard approaches in many communities globally.[10] These results may reflect the fact that DOT is a time- as well as resource-intensive procedure that requires efficient and properly trained staff, which is unavailable in many communities.[10] Furthermore, the process of being regularly monitored can be demeaning to some patients, who then may be reluctant to complete their medication regimen.[10] Despite a plethora of modalities aimed to improve medication adherence, not one of them has demonstrated complete medication compliance. An ideal modality for ensuring medication compliance would be one that not only is highly accurate in detecting if the medication has been taken, but also does not require many resources.

DIGITALIZING MEDICAL ADHERENCE

Monitoring medication adherence through electronic means was recently made possible through the works of Proteus Digital Health, Inc This FDA-approved modality uses an ingestible sensor the size of a grain of sand that is incorporated into a pill. Upon entry into the stomach, the electrolytes found on the sensor's surface (copper and magnesium) react with the electrolytes found in gastric acid to form a biogalvanic-like battery.[11] The sensor utilizes this current to generate an electric field, which is detected by an externally worn adhesive monitor called the Proteus Personal Monitor.[11] The ingestible sensor is capable of communicating with the mon-

itor for 5 to 10 minutes before the sensor subsequently becomes inactivated, passes through the rest of the gastrointestinal tract, and is excreted together with feces. Along with recording when the ingestible sensor signal is detected, the monitor is also capable of recording other parameters such as heart rate and physical activity, making it a helpful tool for both clinicians and researchers.[11] Data from the monitor are encrypted and transmitted to the patient's mobile device via Bluetooth technology, and are subsequently uploaded to a central server, making it possible to integrate data collected by the monitor into electronic medical records.[11] This system has demonstrated high accuracy in detecting the ingestible tracer, low adverse effects in patients (limited to skin rash and 1 case of nausea), and a high rate of patient acceptance.[12] It also requires minimal training, making it an optimal candidate for monitoring medication adherence.

In September 2015, Proteus Digital Health, Inc filed a joint FDA application with Otsuka America Pharmaceutical, Inc for approval of a combination pill that included both an ingestible sensor and aripiprazole (trade name Abilify). Aripiprazole is a partial dopamine agonist that has been shown to be effective in the management of psychiatric diseases including schizophrenia, bipolar disease, and depression. This application, the first of its kind, hopes to demonstrate the potential of digitalizing medication adherence for patients experiencing psychiatric illnesses, where noncompliance rates to medication therapy can be high. Moreover, the outcome of this FDA application, if successful, will undoubtedly influence other fields of medicine. Though not currently approved for clinical use, Belknap et al utilized an earlier prototype of the system designed by Proteus Digital Health, Inc to demonstrate markedly improved medication compliance for the management of tuberculosis disease.[12] Digitalizing medication compliance can also have a tremendous impact in the field of cardiovascular diseases, where nonadherence to medications has been shown in 60% of patients, as well as in a variety of other chronic conditions including rheumatoid arthritis, diabetes mellitus, and sickle cell anemia.[13-15]

Despite the potential to revolutionize healthcare, there are several important limitations and concerns to consider with digitalizing medication adherence. The design of this particular ingestible sensor limits its application to drugs taken orally at the present time. Secondly, there are concerns that incorporating an ingestible sensor into current medication will significantly increase drug costs. As medication affordability is another barrier with medication adherence, particularly for patients without drug insurance coverage, this may make this medication adherence strategy unaffordable for the patients who need it the most. Patient privacy is another concern with digitalizing medical adherence, as there are risks with recording and storing personal health information onto a central server not owned by the patient. However, Proteus Digital Health, Inc has advertised its product as utilizing industry-standard encryption techniques to allow for the secure collection and storage of personal health information.[11] Similar to patient privacy is the issue that some patients may view this strategy of monitoring medication compliance as unnecessary, excessive, and an act of healthcare provider paternalism. These feelings will need to be addressed by the healthcare provider prior to initiation of therapy. Lastly, while this technology effectively monitors medication adherence, it must be supplemented by appropriate and effective patient counseling in order for it to be truly effective in improving patient compliance to medication.

SUMMARY

Digitalizing medication adherence is a very promising modality for improving medication compliance. Compared to other existing modalities, the ingestible sensor accurately records the time at which patients ingest their medications, providing healthcare providers with longitudinal data that they can use to effectively counsel patients about medication compliance. Currently, an FDA application has been filed for use of this technology with aripiprazole, though it would not be surprising if the ingestible sensor were to be incorporated into other medications in the future. Despite the benefits, issues of drug costs, patient privacy, and patient autonomy may need to be addressed before it can be widely used in a clinical setting. However, the "digital pill" offers an innovative solution to a longstanding problem in healthcare, and may be an essential tool in the future physician's toolbox in improving patient health outcomes.

REFERENCES

1. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc. 2011 Apr;86(4):304-14.
2. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009 Jun 16;119(23):3028-35.
3. Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med. 2007 Jul 24;4(7):e238.
4. Tang Y, Zhao M, Wang Y, Gong Y, Yin X, Zhao A, et al. Non-adherence to anti-tuberculosis treatment among internal migrants with pulmonary tuberculosis in Shenzhen, China: a cross-sectional study. BMC Public Health. 2015;15:474.
5. Sabaté E. Adherence to long-term therapies: evidence for action. WHO. 2003;1-194.
6. Jimmy B, Jose J. Patient medication adherence: measures in daily practice. Oman Med J. 2011 May;26(3):155-9.
7. Huang HY, Maguire MG, Miller ER, Appel LJ. Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplementation trials. Am J Epidemiol. 2000 Oct 15;152(8):780-7.
8. Petersen ML, Wang Y, van der Laan MJ, Guzman D, Riley E, Bangsberg DR. Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis. Clin Infect Dis. 2007 Oct 1;45(7):908-15.
9. Vervloet M, van Dijk L, Santen-Reestman J, van Vlijmen B, van Wingerden P, Bouvy ML, et al. SMS reminders improve adherence to oral medication in type 2 diabetes patients who are real time electronically monitored. Int J Med Inform. 2012 Sep;81(9):594-604.
10. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane database Syst Rev. 2015;5:CD003343.
11. DiCarlo L, Moon G, Intondi A, Duck R, Frank J, Hafazi H, et al. A digital health solution for using and managing medications: wirelessly observed therapy. IEEE Pulse. 3(5):23-6.
12. Belknap R, Weis S, Brookens A, Au-Yeung KY, Moon G, DiCarlo L, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. PLoS One. 2013;8(1):e53373.

13. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy. 2008 Apr;28(4):437-43.
14. Baroletti S, Dell'Orfano H. Medication adherence in cardiovascular disease. Circulation. 2010 Mar 30;121(12):1455-8.
15. Creary SE, Gladwin MT, Byrne M, Hildesheim M, Krishnamurti L. A pilot study of electronic directly observed therapy to improve hydroxyurea adherence in pediatric patients with sickle-cell disease. Pediatr Blood Cancer. 2014 Jun;61(6):1068-73.

The future of personalized medicine

Interview with Dr Richard Kim

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Faculty Reviewer: Richard Kim, MD, FRCPC (Division of Clinical Pharmacology)

Dr Richard Kim is currently a professor and the chair of the Division of Clinical Pharmacology at Western University and the Director for the Centre for Clinical Investigation and Therapeutics at the London Health Sciences Centre (LHSC). He also holds the Wolfe Medical Research Chair in Pharmacogenomics and is at the forefront of advancing the specialty of clinical pharmacology—a growing field that promises to change the way we deliver healthcare in Canada and abroad. Dr Kim shared his insights into the future of personalized medicine and his roles as a clinician, researcher, administrator, and teacher.

UWOMJ: Tell us a bit about yourself and how you came to be a clinical pharmacologist.

Richard Kim: I grew up in Saskatchewan and graduated in 1987 from medical school at the University of Saskatchewan. I then did a rotating internship and 3 years of internal medicine, both in Saskatoon, where there were good role models in the field of clinical pharmacology. In 1991 I received funding for a 3-year research fellowship at Vanderbilt University in clinical pharmacology. Along with my wife and our 2-year-old, we put everything in our minivan and drove from Saskatoon to Nashville, Tennessee. I didn't know what kind of experience it would be, but looking back, it was one of the best decisions I've made.

My research dealt with interpatient molecular determinants of variation in drug response; we wanted to find out why people vary in their drug exposure response when prescribed the same dose and medication. By 1994 our research was looking pretty promising, and I was offered a faculty position. I stayed as a faculty member there for 12 more years.

By the mid-2000s I had a very large program with multimillion-dollar grants and a very large number of trainees, both MDs and PhDs. We had to decide if we wanted to continue to grow in that setting or try something different. I was passionate about translating our research to patient care, so along with 2 faculty members and 3 postdoctoral fellows, we took the chance to come to Western in 2006. I had no idea what would happen leaving a well-established institution, but coming back to Canada and to a city such as London had the potential of making a more immediate difference in patient care.

Here, we worked with the hospitals to create the first personalized medicine clinic. We started doing pre-emptive genetic testing of relevance to drug response as a way of preventing adverse drug reactions. We first focused on warfarin and later expanded to cardiovascular drugs, statins, antiplatelet drugs, anti-inflammatory drugs, immunosuppressants, and breast cancer drugs like tamoxifen. In pediatrics, we have had significant ongoing efforts in using pharmacogenomics and personalized medicine. We also hope to further enhance the benefits and safety of mental health medications known to be affected by genetic differences. In early 2016, we will introduce a hospital-wide personalized medicine approach, starting with the oral anticoagulant warfarin, to further demonstrate feasibility of our approach as well as objectively demonstrate cost-effectiveness through reduced length of stay, better discharge planning, reduced readmission rates, and better patient outcomes.

What sorts of challenges do clinical pharmacologists deal with?

There are variations of responses, gene products, age, gender, diet, complex drug interactions, and genomic differences that must be further integrated into delivery of care. Many patients are very different from the patients in randomized drug trials, so we have to do our best to identify and rescue them from lack of benefit.

We can use technology like genomics and mass spectrometry to measure drug levels and provide better care for our patients. We try to optimize drug dosages for our patients, even if that means administering a nonstandard dose. This is done with full permission and consent from the patients and their families, as well as other physicians and pharmacists involved in the care of such patients. This takes a bit of guts, specialty training, clinical judgment, and ability to document nonstandard dosages that other groups would not use.

Can you talk about the clinical pharmacology program for medical residents as well as for graduate students?

Western now has the largest clinical pharmacology program in the country, and the second largest in North America. We look for candidates who have an unbridled enthusiasm for translational research and patient care. We have partnered with other subspecialties to offer combined 3-year subspecialty residency programs after 3 core years in internal medicine or pediatrics. We provide training related to pharmacotherapy, pharmacokinetics, and pharmacogenetics while tailoring our program to each resident's intended scope of practice.

Graduate students are also an important part of our personalized medicine program, particularly in terms of innovative technologies and bench-to-bedside research. In addition, interaction with other faculties at Western has been a major benefit; we are already working with the Ivey School of Business on how to scale up our model of personalized medicine to other centers, and are working with the engineering faculty to use smarter technology in data encryption, confidentiality, bioinformatics, and data mining.

Can you describe a day in your life as a clinical pharmacologist?

During the day I put in a significant amount of effort into our program of personalized medicine–based patient care. We have daily rounding with residents, pharmacists, and other trainees who participate in the care of inpatients who are consulted to us. I also hold 2 weekly half-day personalized medicine clinics. Since starting our personalized medicine clinic at LHSC in 2008, we have looked after over 3000 patients through the clinic and inpatient consultation service.

We see personalized drug therapy as its own speciality that provides outstanding multidisciplinary patient care. For example, even though I hold a half-day clinic at the London Regional Cancer Program, I'm not an oncologist by training. However, we are experts on some of the drugs they use and we are able to provide genomics-guided dosing. Our clinical pharmacology residents see many patients on the wards, and every day we are consulted by different subspecialties for whom we do timely genotyping to provide drug therapy recommendations and follow-up care. We accurately estimate safe and effective drug dosages for various patients, rather than using the traditional iterative approach of slowly increasing the dose from a low baseline dose, which does not work well in conditions where optimized treatment is urgently needed.

At night and on weekends, I spend time writing papers and working on research grants, which extends the 40-50 hour work week closer to 70-80 hours per week for me. All physicians must balance their number of academic and clinical activities. Since there is no other clinic in the country that has a similar model of care, in a way our clinic can be viewed as research. But it is foremost patient-centred care. Creating that model of care is what our team is really doing, and we hope that our approach can be used throughout Canada and beyond.

Every time we help prevent a near-death situation using genomics technologies, it is one of the most comforting thoughts for me. We see clear patient benefits, and that is why I have become such an advocate of innovation in health care such as our personalized medicine program that I am so passionate about.

How can we adopt personalized medicine to improve the efficiency in our healthcare system?

Physicians tend to be very cautious in adopting new frameworks, but if we do not leverage new technology and teaching capabilities to provide better care, we run the risk of doing more of the same things faster, which may not be sustainable in terms of health care expenditure.

Since it is actually cheaper to prevent severe toxicities and improper dosing than to treat the adverse drug events when they happen, our approach, which focuses on "the right dose of the right drug for the right patient," has great potential to reduce overall healthcare costs. This is especially true for the increasing number of elderly patients who are often admitted into hospitals due to drug-related issues. We can prevent hospitalizations by providing genomics-guided advice through pharmacists or physicians who look after those patients in long term care facilities using on-demand telemedicine capabilities that already exist in Ontario.

How can clinical pharmacology be integrated into the current healthcare system?

For personalized medicine as a patient care model to really take off, we need to better understand what works or does not work in a real-world clinical setting. There is little doubt we have to generate robust and objective data on the cost-benefit trade-off of our approach to gain the support of provinces and regulatory agencies such that all healthcare providers are more able to adopt this new framework. We hope to show that this is an economically sustainable model. Our efforts in personalized medicine–based care have been nearly a decade in the making. Our goal is to do the right thing in a titrated and systematic fashion so that we don't overpromise and underdeliver.

Our team is also thinking about how we can help other centres adopt our model of care, but also help them accelerate instead of redoing what we've done from the beginning. We can provide further guidance and logistics support through teleconferencing and consultations. The good thing is that our approach was recognized in an advisory panel on healthcare innovation led by Dr David Naylor, former president of the University of Toronto, for consideration by the federal minister, tasked with what Canada should do to be excellent in healthcare for the next decade. The recommendations urged the government to invest an additional $1 billion per year in healthcare focusing on 5 initiatives, one of them being personalized medicine and pharmacogenomics approaches that teams like ours have been initiating. That gave us further confidence. We now have the national visibility to say we are being recognized as making a difference.

Can you speak to the future employment prospects in clinical pharmacology?

Although we can't predict the future, I'm confident that the field of personalized medicine is where the next wave of long-term innovative careers will be heading. We're going to generate the next versions of physicians, and there is a huge potential for doing something that ignites passion and innovation in this field. I don't see why physicians who can use technology and can integrate more complex clinical information of relevance to patient care would be disadvantaged.

For medical students, sometimes training related to personalized medicine doesn't seem as relevant at the moment and may seem too futuristic, but I'm sure people said the same thing about smartphones 10 years ago.

Drugs as diagnostic tools

Dexamethasone and Cushing syndrome

Nicole Arseneau, Carlos Muzlera

Faculty Reviewer: Stan Van Uum, MD, PhD, FRCPC (Department of Medicine; Division of Clinical Pharmacology; Division of Endocrinology and Metabolism)

MR SIMON

Mr Simon, age 36, presents to his family physician with concerns about his weight. He has gained 20 kg in the past 4 months, and has developed purple striae on his abdomen. His body mass index (BMI) is currently 34, and on physical examination, he is found to have a rounded face, a large dorsal fat pad, and a waist circumference of 112 cm. His blood pressure is elevated at 145/95 mmHg, while all other vitals are normal. He also mentions worsening acne on his face, shoulders, and upper back, as well as mild depression for the past 3 months. His past medical history is significant only for an appendectomy at age 10. He has no family history of diabetes, obesity, or cardiac disease. The only medication he has been on for the past 3 years is a multivitamin supplement. He does not smoke, drinks approximately 5 alcoholic drinks per week, and does not take any illicit drugs.

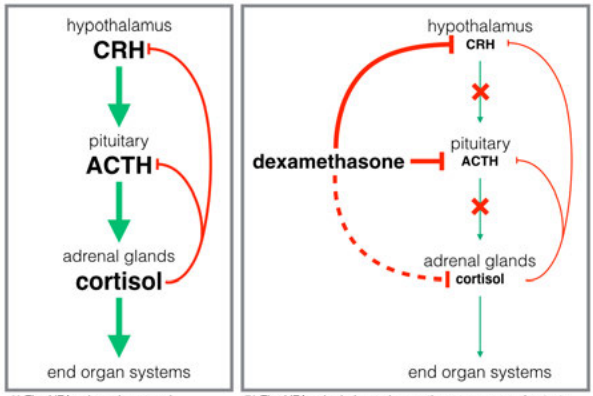
INITIAL INVESTIGATIONS

Mr Simon is presenting with the classic fat redistribution pattern indicative of Cushing syndrome, a pattern of signs and symptoms which can occur after chronic exposure to excess glucocorticoids (hypercortisolism).[1] The most common cause of Cushing syndrome is exogenous glucocorticoid administration, usually due to chronic steroid use for inflammatory, neoplastic, or autoimmune disorders. In these cases, supraphysiologic doses of exogenous steroids will both cause Cushingoid features as well as suppress endogenous corticosteroid production.[2-4] Thus, when treating these patients, it is necessary to remove the offending drug slowly by tapering doses down over weeks or even months to ensure that no withdrawal occurs, as adrenal hormone insufficiency is deadly in its own right.[2,5] In Mr Simon's case, exogenous glucocorticoid administration is unlikely as he has no history of taking steroids for any condition, thus his physician must search for other causes of his symptoms. It is possible that Mr Simon's weight gain and hypertension could be a result of a sedentary lifestyle, however the rapidity of the weight gain, other classic Cushingoid features (moon facies, increased dorsal fat pad, purple striae), and androgenic features (worsening acne) still strongly suggest Cushing syndrome.[1,3] In order to confirm her suspicions, Mr Simon's physician orders a 24 hour urinary free cortisol measurement as well as midnight salivary cortisol tests to confirm hypercortisolism. The physician also orders a fasting blood glucose measurement as well as a lipid panel to investigate for diabetes mellitus and metabolic syndrome.[4,6]

Mr Simon's 24 hour urinary free cortisol level is elevated at 872 nmol/d (normal 30-300 nmol/d). A repeated measurement is also elevated at 931 nmol/d. His midnight salivary cortisol levels are both also elevated at 11.2 nmol/L and 10.7 nmol/L (normal 3.0-4.0 nmol/L). Both blood glucose and lipids are within normal limits. He is referred to an endocrinologist for diagnosis and treatment of hypercortisolism.

DETERMINING THE SOURCE

With hypercortisolism confirmed, the endocrinologist's task is to determine the source of the excess cortisol. As discussed previously, exogenous glucocorticoid administration has been excluded based on the patient's history, so endogenous causes must be considered. In a healthy person, cortisol secretion is regulated by the hypothalamus and the pituitary through the hypothalamic-pituitary-adrenal (HPA) axis (Figure). In times of stress, the hypothalamus secretes corticotropin-releasing hormone (CRH) which acts on the pituitary to stimulate adrenocorticotropic hormone (ACTH) secretion. ACTH then acts on the adrenal cortex to stimulate cortisol release. When there is cortisol in the blood, it acts on both the hypothalamus and pituitary to suppress the release of any further CRH or ACTH, thus acting as negative feedback and inhibiting its own release.[6,7] However, if any of these regulatory mechanisms fail, a disease state such as Cushing syndrome can result. Endogenous Cushing syndrome can thus be classified into ACTH-dependent (80% of Cushing syndrome cases) or ACTH-independent (20%) subtypes. In ACTH-dependent disease, the excess amounts of ACTH are released by the pituitary or another tumor, which stimulates the adrenal glands to produce excess cortisol. The most common cause is Cushing's disease, in which a pituitary adenoma secretes the excess ACTH. In ACTH-independent disease, most



A) The HPA axis under normal physiologic conditions. Green arrows indicate a stimulatory effect, and red flat-headed lines indicate an inhibitory effect.

B) The HPA axis during a dexamethasone suppression test. Solid red flat-headed lines indicate a direct suppression of the hypothalamus and pituitary by dexamethasone. This results in a secondary inhibitory effect (shown as a dashed red line) on cortisol production.

Figure. Hypothalamic-pituitary-adrenal axis.

commonly due to an adrenal adenoma, one or both adrenal glands functions autonomously to produce excess cortisol regardless of ACTH stimulation.[3,4,6]

In order to test whether these regulatory mechanisms are intact, the endocrinologist performs a low-dose dexamethasone overnight suppression test (LDDST). In this test, 1 mg of dexamethasone, an orally administered corticosteroid medication, is given to the patient at bedtime, and serum cortisol is measured the next morning.[1,4,8,9] This is an example of a unique subset of tests where medications are used to mimic endogenous compounds to elicit expected results. In a healthy patient, the dexamethasone should act like cortisol to suppress CRH and ACTH, which should result in reduced cortisol secretion overnight, and thus a serum cortisol level of < 50 nmol/L the next morning. If the cortisol level is suppressed the next morning, this suggests that the source of endogenous cortisol is ACTH-dependent and nonautonomous. If no suppression occurs, the source is more likely to be autonomous and non–ACTH-dependent.[1,4,8,9] Caution must be used when performing the LDDST, as common medications such as estrogen supplementation (in oral contraceptive pills) can affect total cortisol levels, and drugs such as carbamazepine and rifampin can increase metabolism of dexamethasone itself, such that it insufficiently suppresses cortisol. Use of these medications during the test or in the weeks prior to it could result in an inaccurate test.[6,8] A high-dose dexamethasone test can also be performed in certain clinical scenarios when a low-dose test is inconclusive.[9,10]

In some centres, a direct analysis of serum ACTH is also available, which can help further differentiate ACTH-dependent and -independent sources of cortisol.[4] For example, if there is a pituitary abnormality resulting in increased ACTH production (which in turn causes increased cortisol secretion), serum ACTH levels would be high (or inappropriately normal for the high cortisol secretion). If there is an adrenal source of cortisol that is autonomous while the pituitary remains normal, high serum levels of cortisol would suppress ACTH production, thus it would be measured low in the serum. To be thorough, Mr Simon's endocrinologist orders both a low-dose dexamethasone test as well as a serum ACTH level.

Mr Simon's serum cortisol fails to suppress after a LDDST, indicating that cortisol secretion is no longer regulated by the HPA axis. His serum ACTH level is undetectable. His endocrinologist concludes that the patient's Cushing's syndrome is ACTH-independent, and therefore suspects an adrenal source. Mr Simon is sent for an abdominal computed tomography (CT) scan, which identifies a well defined, noninvasive 4.6 cm mass in his left adrenal gland, while the right adrenal gland appears atrophic.

MANAGEMENT OF CUSHING SYNDROME

Mr Simon is diagnosed with an adrenal cortical adenoma. The endocrinologist consults the imaging studies and concludes that, as there is no local invasion or evidence of metastases, the mass is benign. Since the laboratory investigations indicated that the mass is hormonally active and is producing symptoms, Mr Simon is scheduled for surgical removal of the mass in 6 weeks. If the severity or progression of his symptoms is worrisome, he may be prescribed an inhibitor of glucocorticoid synthesis, such as ketoconazole, to reduce his cortisol production while he waits for surgery. If he is not a surgical candidate, glucocorticoid synthesis inhibitors may be continued as treatment.[11,12]

The best course of action for Mr Simon is to remove the mass in his adrenal gland that is producing cortisol.[11,12] Meanwhile, his contralateral adrenal gland has become atrophic from lack of stimulation, as the excess cortisol produced by the tumor is suppressing ACTH at the pituitary level. Thus, when the adrenal cortical adenoma is removed, the contralateral adrenal gland will not be able to function adequately until it can recover from atrophy. For this reason, it is necessary to give Mr Simon oral corticosteroid therapy postoperatively so that he does not experience an adrenal insufficiency crisis, which can be life threatening. Generally, this therapy must continue for weeks to months, based on his recovery, and he must be weaned off the medication slowly to further reduce his risk for adrenal insufficiency. Thus, while surgery is the preferred treatment option for a patient with an adrenal cortical adenoma, medications play an extremely important role in ensuring good outcomes for the patient. Postoperatively, he must be monitored closely to ensure that no other complications of his surgery arise, and that his other concerns (weight gain, acne, depression) resolve with treatment.[3,6,11,12]

Mr Simon successfully undergoes a unilateral left adrenalectomy. Postoperatively he is given 50 mg of hydrocortisone intravenously trice daily, which is gradually changed to oral administration and tapered to 40 mg daily. He is followed closely, and his steroid medication is further tapered successfully at 6 months with no medications being taken at 9 months. At 1 year after surgery, Mr Simon has a BMI of 25, a waist circumference of 88 cm, blood pressure of 125/85, and reports that his depression has improved greatly.

REFERENCES

1. Nieman LK. Cushing's syndrome: update on signs, symptoms and biochemical screening. Eur J Endocrinol. 2015;173(4):M33-8.
2. Hopkins RL, Leinung MC. Exogenous Cushing's syndrome and glucocorticoid withdrawal. Endocrinol Metab Clin North Am. 2005;34:371-84.
3. Nieman LK, Feelders RA, Kennedy E. Cushing's syndrome: epidemiology and developments in disease management. Clin Epidemiol. 2015:281-93.
4. Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Steward PM, et al. The diagnosis of cushing's syndrome : an endocrine society clinical practice guideline. 2008;93(May):1526-40.
5. Fraser LA, Van Uum S. Work-up for Cushing syndrome. CMAJ. 2010;182(6):584-7.
6. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006;367(9522):1605-17.
7. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of cushing's syndrome and pseudo-cushing's states. Endocr Rev. 1998;19(5):647-72.
8. Hempen C, Elfering S, Mulder AHL, van den Bergh FAJTM, Maatman RGHJ. Dexamethasone suppression test: development of a method for simultaneous determination of cortisol and dexamethasone in human plasma by liquid chromatography/tandem mass spectrometry. Ann Clin Biochem. 2012;49(Pt 2):170-6.

9. Reimondo G, Allasino B, Bovio S, Saba L, Ardito A, Angeli A, et al. Pros and cons of dexamethasone suppression test for screening of subclinical Cushing's syndrome in patients with adrenal incidentalomas. J Endocrinol Invest. 2011;34(1):1-5.
10. Grossman R. Dexamethasone Suppression Test Findings in Subjects With Personality Disorders: Associations With Posttraumatic Stress Disorder and Major Depression. Am J Psychiatry. 2003;160(7):1291-8.
11. Bittner IV JG, Brunt LM. Evaluation and management of adrenal incidentaloma. J Surg Oncol. 2012;106(5):557-64.
12. Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-31.

Cisplatin-induced change in moral conscience and behaviour

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INTRODUCTION

Cisplatin is a commonly used chemotherapeutic agent, which has been declared an essential medicine by the World Health Organization.[1] Cisplatin was the first compound approved for use in what is now a class of platinum-containing chemotherapeutic drugs which exert their anticancer effect by cross-linking DNA, leading to cell death by apoptosis.[2] Health Canada has approved cisplatin for use in treating advanced bladder cancer, metastatic ovarian cancer, and metastatic testicular cancer, but it is also commonly used to treat head and neck cancers, germ cell cancers, and small cell lung cancer.[3] Like many chemotherapeutic drugs, cisplatin has many well documented side effects including nephrotoxicity, ototoxicity, and peripheral neuropathy.[4]

Neurotoxicity within the central nervous system (CNS) is not a recognized side effect of platinum-containing drugs. It has been suggested that the selectivity cisplatin demonstrates for damaging the peripheral nervous system is due to an inability of the drug to penetrate the blood brain barrier.[5] This is due to the polar nature of platinum-containing compounds. A recent study in shrews showed that although platinum was detectable in the brain up to 72 hours after injection, the concentrations were at least 20 times lower than concentrations in plasma.[6] This may help explain why CNS complications are not common with cisplatin use, even though peripheral neuropathy is seen in up to 50% of patients receiving treatment.[7] However, a recently reported case by Barlinn et al suggested that cisplatin may in fact be able to cause CNS impairment in rare cases, and may have been responsible for major neurological and behavioural changes in a man undergoing cisplatin treatment for tonsillar cancer.[8]

SUMMARY OF CASE REPORT[8]

A 66-year-old man with tonsillar cancer was treated surgically with a tonsillectomy and radical neck dissection. Four weeks after the surgery, a regimen of targeted radiation and cisplatin chemotherapy was initiated. In the following 4 weeks of treatment with cisplatin, the patient displayed progressive personality changes including increased aggression, violence, and irritability. This resulted in the patient vandalizing his neighbour's house with an axe following an argument. The patient had also expressed suicidal thoughts to his wife. After threatening to push his wife down the stairs, police were called and the patient was ultimately brought to the hospital's emergency department.

The initial mental exam was unremarkable; the patient was properly oriented to time, place, and person. His demeanor was calm and cooperative. Additionally, there was no evidence of elevated mood or euphoria. He had no deficits in global cognitive functions. He had full recollection of his actions but did not express any remorse as he did not believe he had acted inappropriately. On history, the patient had been a chronic alcohol consumer until his cancer diagnosis, with no occurrence of alcohol withdrawal symptoms. No other pertinent medical or psychiatric history was reported. The family was adamant that this was not typical behaviour for the patient. Routine blood tests and brain computed tomography (CT) were unremarkable, and the patient was initially well-behaved. However, after perceived provocation, he became violent and destructive on the ward, destroying a radio which he believed was too loud, and assaulting a fellow patient and a nurse. The patient had to be restrained and treated with lorazepam and risperidone. The man remained unapologetic, insisting that his response was normal for a person who had been disturbed.

While admitted, chemotherapy was halted because of the "unpredictability" of the patient's behaviour, but radiation therapy continued. After stopping the cisplatin treatment, the patient's behaviour progressively improved, and 3 weeks after his last cisplatin dose, he returned to his original personality. Interestingly, he now expressed regret for his previous actions. He did not experience any memory loss, and was no longer irritable or violent.

DISCUSSION

The timing of symptom onset and recovery in this case strongly suggests cisplatin was responsible for the patient's neurological symptoms, demonstrating an extremely rare adverse effect of cisplatin treatment. There are no other reported cases of patients having cisplatin-induced aggression with moral conscience changes similar to the patient in this case. It has been shown that cisplatin can cause certain neurological complications. However, there are only a limited number of cases which report patients using platinum-containing drugs with solely psychiatric symptoms (ie, lacking any identifiable underlying conditions).[9] These cases, although similar with regards to the psychiatric symptoms reported, have been diagnosed as both hypomania and acute psychosis.[10-13] All such cases had side effect onsets between 2 to 5 weeks after starting treatment with platinum-containing drugs. None occurred from the use of cisplatin therapy alone, but instead occurred in patients on multidrug regimens which including either cisplatin or carboplatin.

Although psychiatric changes induced by platinum-containing drugs are rare, neurological changes are not uncommon during chemotherapy with other cytotoxic agents. "Chemo brain" is one of the most frequently reported side effects of chemotherapy treatment for breast cancer, affecting up to 50% of patients.[14] This condition is characterized by impairments in memory, attention, or other aspects of cognitive function, and its etiology is poorly understood.[14] Neurological effects can also be much more severe including acute

encephalopathy and seizures. Cisplatin is one of the many chemotherapy drugs which has been noted to cause posterior reversible encephalopathy syndrome (PRES), characterized by headache, seizures, confusion, and vision loss.[9] Other anticancer drugs that have also been associated with PRES include methotrexate and enzalutamide,[15,16] as well as both oxaliplatin and carboplatin.[17]

There are inherent difficulties with determining the cause of neurological symptoms in patients undergoing chemotherapy. Firstly, cancers are known to cause obscure neurological effects in some cases, even without chemotherapy. Neurological presentations of paraneoplastic syndromes are mediated by the immune system, which can affect the CNS of cancer patients without tumor invasion into the CNS. These syndromes can have a wide range of symptoms depending on the region of the brain affected.[18] Thus, the symptoms of paraneoplastic syndromes can overlap with neurological symptoms of adverse chemotherapy reactions, making them difficult to differentiate. Secondly, many cancers are treated with fixed drug regimens, which can make it difficult to ascertain which drug is responsible for the neurological effect. For example, of the 3 cases of acute psychosis in patients treated with cisplatin, 2 of the patients were on the BEP regimen (bleomycin, etoposide, cisplatin),[11,12] and one patient was treated with a combination of paclitaxel and cisplatin.[13] One case suggested the psychosis was caused by the stress of having cancer and undergoing treatment in combination with other social factors,[11] another attributed the psychosis to chemotherapy drugs without specifying which drug caused the effects,[12] and the third believed that paclitaxel was responsible.[13] The wide array of psychological effects which can be caused by cancers or the drugs used to treat them make it difficult to conclude that a chemotherapeutic agent was responsible for the symptoms.

Although there are inherent challenges with isolating chemotherapy drugs as the cause of neurological symptoms in cancer patients, especially if the onset of symptoms is gradual, it is important to keep drugs in the differential diagnosis until they can be ruled out. In the case by Barlinn et al, cisplatin therapy was stopped due to the uncooperative nature of the patient. It was not until the patient's behaviour improved that cisplatin was suspected as being responsible for the symptoms.[8] The outcome of this case was positive, with the patient seeing a full return to his normal function. However, it seems that the patient's aggressive behaviour was the main reason cisplatin treatment was stopped. In future cases with CNS or psychiatric symptoms in a cancer patient, it is important to consider the possibility of drug reactions, since the patient may not be so aggressive that they are forced to discontinue chemotherapy.

CONCLUSION

This case of a cancer patient with changes in behaviour and moral conscience highlights not only a very atypical side effect of cisplatin therapy, but also some of the inherent difficulties in attributing CNS or psychiatric symptoms to chemotherapy drugs. In the present case, the patient's chemotherapy was stopped because of his uncooperative behaviour, and his symptoms improved dramatically. This case had a favorable outcome; the patient was discharged on risperidone but had generally recovered his personality. It is important that drugs be considered in the different diagnosis of chemotherapy patients with new onset symptoms. Many chemotherapeutic drugs have an array of associated side effects, with some being quite common, and others very rare. To recognize these rare "zebra" cases, one must be willing to think beyond the common causes, and consider what other possibilities could exist.

REFERENCES

1. World Health Organization. Geneva, CHE. WHO model list of essential medicines (19th Ed.) [Internet]. World Health Organization; 2015 Apr [cited 2016 Feb 1]. Available from: http://www.who.int/medicines/publications/essentialmedicines/en/.
2. Dasari S, Tchounwou P. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 2014 Jul;740:364-78.
3. Cisplatin Drug Monograph. Toronto (ON): Cancer Care Ontario Formulary; 2015 Feb. 11 p.
4. Hartmann J, Kollmannsberger C, Kanz L, Bokemeyer C. Platinum organ toxicity and possible prevention in patients with testicular cancer. Int J Cancer. 1999 Dec;83(6):866-9.
5. Englander E. DNA damage response in peripheral nervous system: coping with cancer therapy-induced DNA lesions. DNA Repair. 2013 Aug;12(8):685-90.
6. Eiseman J, Beumer J, Rigatti L, Strychor S, Meyers K, Dienel S, et al. Plasma pharmacokinetics and tissue and brain distribution of cisplatin in musk shrews. Cancer Chemother Pharmacol. 2014 Jan;75(1):143-52.
7. Hoop R, Van Der Burg M, Huinink W, Houwelingen J, Neijt J. Incidence of neuropathy in 395 patients with ovarian cancer treated with or without cisplatin. Cancer. 1990 Oct;66(8):1697-702.
8. Barlinn K, Lehrach H, Siepmann T, Braeuer D, Buntrock U, Sassim N. Temporary loss of moral behavior in a patient undergoing chemotherapy with cisplatin - breaking bad. BMC Psychiatry. 2015 Feb;15(9).
9. Simkens G, Hanse M, Hingh I. Acute neurological disorders following intraperitoneal administration of cisplatin. Int J Gynaecol Obstet. 2012 Mar;120(3):291.
10. Matsunaga M, Onishi H, Ishida M, Miwa K, Araki K, Kaneta T, et al. Hypomanic episode during recurrent gastric cancer treatment: report of a rare case and literature review. Jpn J Clin Oncol. 2012 Oct;42(10):961-4.
11. Campbell B, Panicker J. New onset psychosis in an adolescent during treatment of testicular germ cell tumor. J Pediatr Hematol Oncol. 2011 Apr;33(3):125-6.
12. Puangthong U, Pongpirul K. Chemotherapy-induced acute psychosis in a patient with malignant germ cell tumour. BMJ Case Rep. 2015 Apr;2015.
13. Ahmed N, Usmani S, Jabbour N, Hegde U. Acute psychosis after paclitaxel infusion. Conn Med. 2011 Sep;75(8):465-6.
14. Staat K, Segatore M. The phenomenon of chemo brain. Clin J Oncol Nurs. 2005 Dec;9(6):713-21.
15. Aradillas E, Arora R, Gasperino J. Methotrexate-induced posterior reversible encephalopathy syndrome. J Clin Pharm and Ther. 2011 Aug;36(4):529-36.
16. Crona D, Whang Y. Posterior reversible encephalopathy syndrome induced by enzalutamide in a patient with castration-resistant prostate cancer. Invest New Drugs. 2014 Jun;33(3):751-4.
17. Skelton M, Goldberg R, O'neil B. A case of oxaliplatin-related posterior reversible encephalopathy syndrome. Clin Colorectal Cancer. 2007 Jan;6(5):386-8.
18. Martel S, Angelis F, Lapointe E, Larue S, Speranza G. Paraneoplastic neurologic syndromes: clinical presentation and management. Curr Probl Cancer. 2014 Jul-Aug;38(4):115-34.