Vital Link

The journal of the Canadian Association of Naturopathic Doctors

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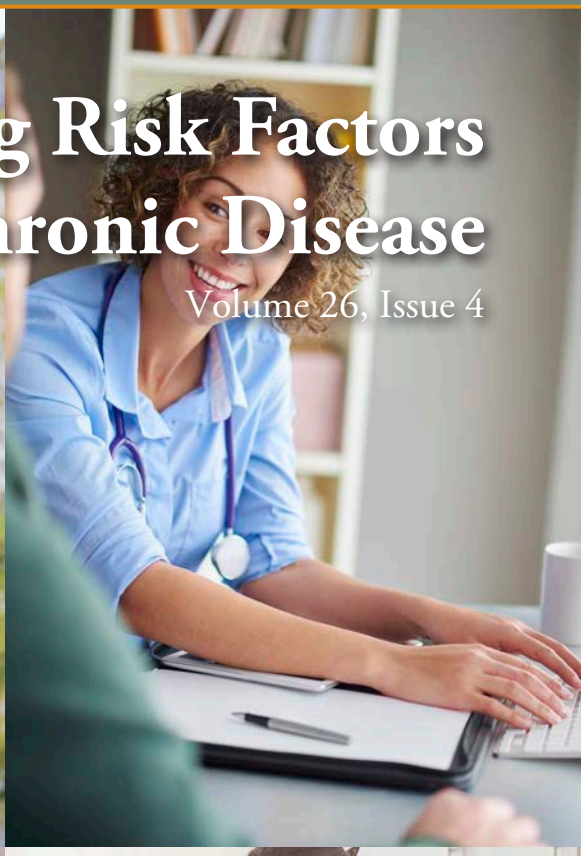

Addressing Risk Factors for Chronic Disease

Volume 26, Issue 4

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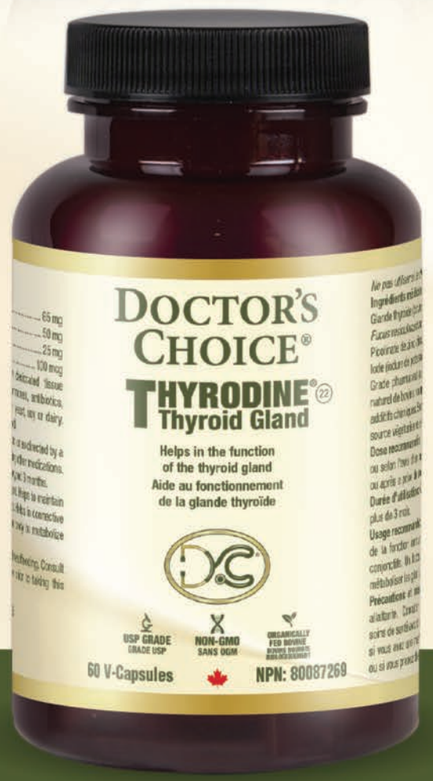

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Contents

Volume 26, Issue 4

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Plus

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Vital Link
The journal of the Canadian Association of Naturopathic Doctors

Volume 26, Issue 4
Addressing Risk Factors for Chronic Disease

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The *Vital Link* is the flagship journal of the Canadian Association of Naturopathic Doctors (CAND). It publishes on a wide variety of topics related to the research and practice of naturopathic medicine in Canada, promoting our profession to Canadians, government, other health care professionals and insurance companies, raising awareness of our unique role in supporting the health of Canadians.

Forthcoming Themes
Vol. 27, Issue 1 Pediatric and Adolescent Health
Vol. 27, Issue 2 Geriatric Health
Vol. 27, Issue 3 Case Report Competition

Submissions
As a general naturopathic journal, we encourage submissions related to themes of our upcoming editions, but also in the core areas of primary care naturopathic practice including: mental health, health of vulnerable populations, community, and planetary health. Contributors should keep in mind that while the main audience for the *Vital Link* is practicing Naturopathic Doctors, we encourage authors from any discipline to submit articles to our editoral team for peer review.
For more detailed submission guidelines please contact our Editor in Chief, Dr. Marianne Trevorrow, ND at drmtrevorrow@cand.ca.

Circulation
The *Vital Link* is published three times per year and is distributed to over 2300 qualified Canadian NDs and students of CNME-accredited naturopathic programs in Canada and the U.S. The *Vital Link* is also distributed to the CAND's corporate members and in our media kit. The journal is available in print and e-formats, by paid subscription. Additionally, the *Vital Link* is a tool promoting qualified naturopathic doctors to corporations, insurance companies, and the provincial/territorial, and Federal branches of government in Canada.

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Naturopathic Notes: Addressing Chronic Disease with Naturopathic Medicine

Dr. Marianne Trevorrow, MA, ND

Our last edition of 2019 is a time of beginnings and endings; for the decade, and for some important staffing changes at the CAND and the *Vital Link*.

Our theme for this edition is managing chronic disease risk. Health Canada statistics tell us that chronic diseases such as cancer, coronary heart disease and type II diabetes are the leading cause of disability and death in Canada and place a significant strain on our publicly funded health care system. Many studies have noted that the prevalence of these conditions falls disproportionately on our more vulnerable populations: indigenous and northern communities, people of lower socioeconomic status, and those struggling with mental health, trauma and addiction issues. These topics will all be the subject of upcoming editions, as we seek to understand areas of health where naturopathic medicine can reach out to these underserved communities and areas of practice.

From a Public Health standpoint, working with modifiable behavioral factors for chronic disease risk is an area where naturopathic doctors are already providing significant benefit to our public system, as well as supporting the increasing numbers of Canadians who are seeking out naturopathic doctors for their care.[1]

Our regular CAND Governmental Relations report leads off this issue from our Executive Director, Shawn O'Reilly, who updates us on CAND strategies to work with the new Federal Health Minister Patty Hajdu, as well as ongoing lobbying efforts to obtain coverage with Indigenous and Veteran's Affairs, and the inclusion of NDs as practitioners able to authorize cannabis for medicinal purposes.

Our feature clinical practice article leads off this edition with Paola Cubillos outlining research on adult use of recreational cannabis, as well as strategies for communicating risks around various methods of ingestion and clinical evaluation of problematic use. Dr. Cubillos is a dually qualified MD/ND, who currently serves as Medical Director for CB2 Insights in Cali, Colombia, where she also maintains a private integrative practice.

Our next two articles address different factors contributing to cardiovascular disease risk with modification strategies. Leigha Saunders first assesses evidence linking disordered sleep to increased CVD risk, possible neuroendocrine mechanisms, and mind-body clinical interventions to improve sleep quality and duration. David Duizer then outlines a personalized clinical CVD prevention framework, focusing on the use of conventional laboratory biomarkers to individualize treatment options. Dr. Saunders is the founder of True Roots Healthcare in Uxbridge, Ontario, while Dr. Duizer is the Director of DAMY Health in Vancouver, BC.

Similarly, James Conway writes on a possible physiologic link between chronic migraine and metabolic syndrome and discusses an evidence-informed lifestyle focused approach to benefit both conditions. Dr. Conway is a practicing clinician in Langley, BC.

Finally, we are adding a new article category in this edition; expert commentary on novel, controversial, or recent studies of relevance to naturopathic practice. Lara Briden leads off with a review of a recent Lancet meta-analysis of Menopausal Hormone Therapy (MHT), which caused considerable controversy on publication. Dr. Briden is the author of the recent book *Period Repair Manual: Natural Treatment for Better Hormones and Better Periods* (2017) and practices in Christchurch, New Zealand.

Lastly as mentioned, we have some changes to our editorial board and staff. Drs. Tanya Lee, Kim Sanders and Nicole Redvers have joined our board as reviewers, and give us a broader pool of clinical and research expertise as we gear up for expanded editions in 2020/21. We are very glad to have them all on board, as well as our returning reviewers, all of whom volunteer their time to help produce great quality professional content for our readers.

As we go to press, we also say goodbye to our longtime Managing Editor and CAND Marketing and Communications Director, Alex McKenna. I have personally worked with Alex for over ten years at the *Vital Link,* as both a contributor and editorial board member. We shared a common vision to make the journal *the* voice for the best content and practices of naturopathic medicine in Canada.

Alex has been synonymous with the *Vital Link* for many years, quietly shepherding new and experienced authors alike through the review process with diplomacy and good humour over the deadlines and last-minute changes inevitable on publishing schedules. During his tenure, he labored tirelessly to transform the journal from its original newsletter format to the fully peer-reviewed and scholarly professional journal our members enjoy now. During this time, he led the ongoing recruitment and management of a volunteer team of

contributors and reviewers and managed the corporate partnerships and marketing that enabled the expansion of *Vital Link*, including several important design improvements over his period in charge.

In 2013, I was delighted to be the co-recipient with Alex of the first CAND *Vital Link* award for our work with the journal, and even more delighted when I was asked to step up and take over as Editor in Chief in 2018. We are still working towards the stated goal of publishing original and online Open Access Naturopathic and CAM-focused research in the *Vital Link*, as well as increasing our international profile and impact, while maintaining our mandate as the voice of the CAND and its members.

I'm sure I speak for the entire Editorial Board and Executive as well as many of you in wishing Alex all the very best with the completion of his Public Policy studies at York and future endeavours.

Sláinte, my friend. We will miss you greatly.

Marianne Trevorrow, Editor in Chief
drmtrevorrow@cand.ca

1. Seely D et al. Naturopathic Medicine for the prevention of cardiovascular disease: a randomized clinical trial *CMAJ* June 11, 2013 185 (9) E409-E416; DOI: https://doi.org/10/1503/cmaj.120567.

Exiting *Vital Link* Managing Editor Alex McKenna (left), in conversation with Dr. Walter Crinnion, ND.

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Government Relations Report

Shawn O'Reilly, CAND Executive Director and Director of Government Relations

On October 21st Canadians elected a Liberal minority government. The Liberal seats in the House of Commons were reduced to 157, while Conservative leader Andrew Sheer increased the Conservative seats to 121 followed by the Bloc with 32, the NDP with 24 and the Greens with 3 (an increase of 2).

Nearly a month to the day Prime Minister Trudeau unveiled his Cabinet for the Liberals second mandate (for a list of Cabinet members go to www.liberal.ca/your-cabinet/). Once again the Cabinet is gender-balanced with only one additional seat. The Prime Minster has chosen to highlight members with genuine roots in Western Canada to offset the Liberals lack of electoral representation in the West. This follows acknowledgement by the Prime Minister that the message from the West was loud and clear, he heard their concerns and now government needed to move forward with addressing them. Jim Carr has been tasked as the Special Representative to the Prairies. To address the challenge of the resurgence of the Bloc in Quebec Trudeau appointed Pablo Rodriquez as his "Quebec Lieutenant". He will have his hands full.

While there are many familiar faces in this new cabinet, such as Lawrence MacAulay who remains Minster of Veterans Affairs, there are several new faces that will play a pivotal role in the work of the CAND at the Federal level. Patty Hajdu (Thunder Bay-Superior North) has been named Health Minister replacing Ginette Petitipas-Taylor who is now Deputy Government Whip. Ms. Hajdu has garnered a reputation as a competent Minister and team player having been promoted twice in the previous Cabinet. Marc Miller (Ville-Marie-Le Sud-Quest-Ile-des-Soeurs) is the new Minister of Indigenous Services. A high achiever and well respected by his caucus colleagues, Miller is most known for delivering a speech in the House in 2017 in the Mohawk language, signaling that he took engagement with Indigenous communities very seriously. Once all Ministers have received their Mandate Letters we will have a better understanding of the Governments plans for each portfolio and will work with our government relations experts at H + K on a strategy to move our agenda forward on the professions behalf. We will continue to push for coverage of the services provided by Naturopathic Doctors for Veterans and Indigenous peoples; the inclusion of NDs on the list of practitioners able to authorize Cannabis for medical purposes; maintain our engagement with the Public Health Agency of Canada on both the Lyme and Opioid files, as well as our work with the Natural and Non-Pharmaceutical Health Products Directorate (NHPD).

The House of Commons returned on December 5, 2019 with a Speech from the Thorne and the election of the Speaker of the House. The House is now adjourned for the Holiday break until January 27th. In the interim staff are being reassigned and/or hired, the MPs are settling into their offices and plans are being made for 2020. As the Liberals are still in power many of the MPs, senior policy advisors and staff are people with whom the CAND has established relationships making it easier to move forward with our work as we do not have to start from the beginning to introduce both our organization and the profession to a whole new group of MPs. Letters of congratulations from the CAND have been sent to the newly appointed Ministers and we encourage NDs to congratulate the successful candidates in their area utilizing the template found on the landing page of the Members Portal.

We thank all of you who downloaded and used the election materials posted by the CAND. We were pleased to hear that you found them valuable and that they were helpful in candidate meetings that were held right across the Country. Thank you for adding your voice and helping us to get the message out during the election on who you are and the difference you are making in the lives of Canadians every day!

Editor's Note: This article pertains to the use of recreational Cannabis. NDs in Canada are reminded that they must follow the policies/guidelines established by their regulator when engaging with patients about recreational Cannabis and that NDs in Canada do not currently have the legal authority to authorize Cannabis for medical use.

Adult-use Cannabis: What a Naturopathic Doctor Should Know

Dr. Paola Cubillos, M.D, N.D, Medical Director – Colombia, CB2 Insights

Canada took a bold step with the legalization of the most widely used illicit substance on the planet: cannabis.[1] The intent of the Canadian government enacting the adult-use regulation is to "keep cannabis out of the hands of youth; keep profits out of the pockets of criminals; protect public health and safety by allowing adults access to legal cannabis".[2]

As of October 17, 2018, Canadians who are 18 years or older (note: age varies by province) are allowed to possess up to 30 grams of dried (or equivalent in non-dried form) cannabis which has been sourced from a legal supplier. Adults are also permitted to share up to 30 grams of legal cannabis with other adults, buy dried and fresh cannabis from a licensed retailer or online from a federally-licensed producer, and grow up to four cannabis plants per residence, from a licensed seed or seedling supplier.[2]

While expanded availability of products under the legal framework was expected to result in increased consumption, recent Health Canada reports show that only 5% more Canadians consumed cannabis in the second quarter of 2019 compared to the second quarter of 2018.[5] Even pre-legalization, Canada has displayed some of the highest rates of cannabis consumption,[4] lower than the USA, which has an annual prevalence of cannabis use of 18.4% but higher than most European countries (reference https://dataunodc.un.org/drugs/prevalence_map_2017)

Now, in what has been dubbed by the media as "Cannabis 2.0", the Federal government has established regulations for the production and sale of edible cannabis, cannabis extracts and topical cannabis. These products are expected to be available for Canadians to purchase in early 2020.[3]

The rapidly changing adult-use cannabis landscape in Canada poses challenges for NDs, as healthcare professionals who focus on health promotion and prevention. While cannabis has been used by humans for thousands of years, given its illegal status worldwide for most of the last century, to date there has been little standardized research to guide NDs to fully understand its impact on human health, both short and long term. That being said, even with current scope prohibitions on authorizing medicinal cannabis, NDs still need to be able to discuss basic aspects of recreational cannabis harm reduction from an evidence-based viewpoint. The intent of this article is to elaborate on the more salient aspects of cannabis effects on human health and harm reduction strategies naturopathic doctors should know as Canada undertakes one of the most important public health experiments in modern history.[6]

Cannabis Use by Canadians

Prior to 2018, national survey data demonstrated high cannabis consumption levels in Canada, with use rising 4-5 years before adult-use legalization, reported across all age groups.[7] Since early 2018, Statistics Canada has also been collecting self-reported consumption and purchasing data, publishing their findings quarterly under the title *National Cannabis Survey*. According to their data, the prevalence of cannabis consumption has remained somewhat unchanged since the legislation came into effect; the second quarter of 2019, for example, reported consumption returned to pre-legalization levels after a slight increase in the first quarter. Males were also twice as likely as females to have used cannabis, were more likely to use cannabis daily or almost daily, and are more likely to use cannabis for non-medical reasons. This report also revealed that about 4.9 million Canadians, or 16% of Canadians aged 15 or older, reported using cannabis post-legalization;[8] the first quarter of 2019, recorded an increase in first-time users, to 646,000 from 327,000 in the first quarter of 2018; however, somewhat surprisingly, over half of these new users were aged 45 and older. Consumption patterns among young people, ages 15-25 remains unchanged, at around 30%.[9] Although this trend has not varied from before legalization, 6.1% of Canadians aged 15 and older (1.8 million) reported using cannabis on a daily or almost daily basis.[10]

Cannabis administration routes

According to the National Cannabis Survey, smoking remains the most common method of consuming cannabis, with approximately two-thirds of male (68%) and female (62%) consumers choosing this method in 2019. Smoking exposes the dried cannabis flower to very high temperatures, which allows for the decarboxylation of the different cannabinoids.[11] Cannabinoids are a group of C21 compounds occurring in resin produced by glandular hairs of C. sativa L. Among the over 420 known constituents of cannabis, more than 60 belong to cannabinoids, which chemically belong to the terpenophenol group of compounds.[12] In their decarboxylated forms, cannabinoids — such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are readily absorbed in the bloodstream via the lungs, and reach different systems to exert their effects through the interaction with endocannabinoid receptors: CB1, which is mainly present in the central nervous system, and CB2, localized in the spleen and other organs associated with immune function.[13] While the two major cannabinoids can be considered "psychoactive" (both impacting brain function) THC is the component more commonly associated with the intoxicating effects of cannabis, while CBD is thought to 'counteract' the effects of THC.[14]

Intrapulmonary administration of cannabinoids by smoking is considered to be an effective delivery method due to the high systemic bioavailability, fast onset of action, short duration of peak effects and limited duration of effects as compared to other administration methods such as ingestion.[15] Vaporization of dry flower or cannabis extracts relies on lower temperatures, while achieving similar results.

Cannabis oils are increasing in popularity, particularly with older adults who are experimenting with cannabis for the first time. These oils are meant to be ingested therefore their pharmacokinetics are influenced by first-pass metabolism. Oral THC bioavailability has been reported to be 10-20%,[16] demonstrating peak plasma concentrations at 4-6 hours after ingestion. Hepatic metabolism of delta-9-THC results in the production of higher amounts of 11-OH-THC, a highly active metabolic compound which has been suggested to have increased psychoactive properties when compared to delta-9-THC.[17, 18, 11]

Oral preparations, commonly known as 'edibles' are an increasing cannabis market segment and products that Canadians will soon be able to legally purchase for recreational use. Under the amendments to the official Cannabis Regulations, which came into effect on October 17, 2019, Health Canada has stipulated a series of requirements that edibles, cannabis extracts and cannabis topicals should meet in order to be allowed for sale.[19] Edible cannabis, either for eating or drinking, can have up to 10 mg of THC per package, and cannabis extracts meant for ingestion can contain up to 10 mg per unit. Other packaging and labeling restrictions are placed on these products to minimize the appeal to children and youth.[3, 19] Consumption of oral preparations follow similar pharmacokinetics and pharmacodynamics as cannabis oils, are subjected to first pass metabolism described above, and demonstrates distinct pharmacokinetics patterns when compared to the inhalation routes of administration. Onset of "drug" effects are generally perceived 30-60 minutes after ingestion, with a sustained peak effect that occurs 90 to 180 minutes after exposure, and a gradual return to baseline 6-8 hours post-administration.[20] Given that onset of symptoms when using cannabis edibles is delayed, over intoxication is more likely to occur with these products. It is recommended therefore that adult users begin with a smaller dose of THC than that permitted by the regulations, particularly for those who are not experienced cannabis users.[21]

While the Canadian regulations specifically stipulate that edibles packaging must be plain, child resistant, and not include elements that may appeal to youth or children, one of the risks associated with these kinds of products is unintentional consumption by children or pets. A review of data from the US National Poison Data System from 2005 to 2011 found that decriminalization of cannabis was associated with increased reports of unintentional exposures in young children up to 9 years of age.[22] A more recent review of National Poison Data System data showed similar increases in edibles-related calls to poison control centers from 2013 to 2015.[23] In Canada, 16 cases of children that have suffered serious adverse events involving cannabis in the months around legalization have been reported, according to preliminary data from the Canadian Pediatric Surveillance Program study.[24]

Short term cannabis effects

Individual susceptibilities and previous cannabis experience influence the effects exerted by cannabis, particularly THC. Acute effects of cannabis use include euphoria, impaired short-term memory, impaired motor coordination which interferes with driving skills, inattentiveness, altered judgement, increased anxiety, challenges in processing and retaining information, and paranoia in extreme cases.[25] On a physiological level, cannabis use may lead to dry mouth, conjunctival injection, tachycardia and hypotension.[26] Hemodynamic changes are implicated as the cause of the different adverse cardiovascular events that have been seen acutely with cannabis use (particularly high THC products) such as arrhythmias and acute myocardial infarction, both in young and adult users with comorbidities.[27, 28, 29]

Long term effects of cannabis use

Long term cognitive effects and challenges for regular cannabis users are of particular importance for adolescents, as early and/or frequent cannabis use is associated with poor long-term outcomes.[30] Limited evidence suggests that frequent cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.[31] While the different methodologies employed to assess the long-term cognitive impact of cannabis, the various types of cognitive measures researched, and variability in length and frequency and exposure studied may lead to discrepancies across the studies that have shed light on the impact of cannabis use, generally speaking, studies agree that chronic cannabis users are at higher risk of suffering various degrees of cognitive impairment that can potentially be long-lasting particularly if use starts early during adolescence, is frequent and persists for years.[32, 33]

The risk of cannabis dependence (defined as lack of control over use despite associated harms) is considered to be approximately 9% among individuals with any lifetime cannabis use.[34] The rate increases to approximately 16% for those who initiate cannabis use during adolescence.[35] Additionally, while most cannabis users do not develop dependence, heavy cannabis use in adolescence is also linked to increased dependence risk.[36]

Connection with mental illness

Although the relationship between cannabis use and mental health issues is complex and generally poorly understood, numerous studies have established a connection between cannabis use and psychotic syndromes and/or schizophrenia. In *The Health effects of Cannabis and Cannabinoids* report by the National Academies of Science, Engineering and Medicines in the US, the authors determined there is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with most frequent users being at highest risk.[31] To date, establishing causality between cannabis use and the development of mental health disorders has been difficult. Both epidemiological and experimental studies consistently suggest a link between heavy cannabis use and risk of psychosis, however one statistic that speaks against this association is the fact that while cannabis use has increased in some populations, the incidence of psychosis has not.[37]

There are consumption patterns that have been associated with higher risk for the development of psychotic illness or schizophrenia, such as earlier onset cannabis use, particularly for those under age 16,[38, 39] and higher frequency use and higher potency products.[40, 41] Considering genetic predispositions is also relevant when discussing cannabis use and mental health issues, as studies have demonstrated that schizophrenia symptoms can be precipitated by cannabis use in those with genetic predispositions,[42] and those cannabis users with a family history of psychosis can be 2.5 to 10 times more likely to develop psychotic disorders compared to non-users with a family history.[43] The relationship between cannabis use and schizophrenia becomes even more complex when the possibility that cannabis use may represent self-medication of early schizophrenia symptom management is considered.[44, 45]

Risks from cannabis use vs. other substances

Cannabis is not a harmless substance, despite the shifting perceptions harbored by the general public, young people in particular.[46] It is useful, however, to contrast the harm associated with cannabis use, both on a societal and individual level, with other legal and illegal recreational substances. Nutt *et al* assessed the harm caused by a variety of substances based on 16 different criteria and reached the conclusion that the most harmful drugs to drug users were heroin, crack cocaine and methamphetamine, while the most harmful to others were alcohol, followed by heroin and crack cocaine. In their scoring system, alcohol was assigned a score of 72 (cumulative for the sum of the weights of all criteria of harm to users and harm to others), cocaine a score of 27, tobacco 26 and cannabis 20.[47] Results from similar analysis undertaken by Lachenmeier and Rehm conclude that "the risk of cannabis may have been overestimated in the past. At least for the endpoint of mortality, the margin of exposure for THC/Cannabis in both individual and population-based assessments would be above safety thresholds. In contrast, the risk of alcohol, may have been commonly underestimated".[48]

Medication Interactions

Regular cannabis use is thought to cause induction of the CYP1A2 enzyme, which may decrease concentrations of 1A2 substrates,[49] including aminophylline, caffeine, clozapine, duloxetine, estradiol, estrogens, lidocaine, melatonin, olanzapine, and zolmitriptan. The CYP3A4 pathway is also involved in the metabolism of the major cannabinoids THC and CBD. 34A inhibitors have been shown to increase serum concentrations of these cannabinoids, while inducers have the opposite effect.[50] Cannabis can also increase the sedative, psychomotor, respirator and other effects of CNS depressant drugs and alcohol.[51, 52] CBD use may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil, antihistamines, haloperidol, antiretrovirals, and some statins, due to its action on CYP3A4.[53] It may also increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone), as it exerts an effect on CYP2D6.[54]

Cannabis effect on driving

Experimental studies suggest that THC predominant cannabis leads to the impairment of cognitive and psychomotor skills required for safe driving.[55] Psychomotor testing performance has been found to decrease for up to five to six hours after smoking cannabis, with the majority of impairment occurring in the first two hours after smoking, although others suggest a window of at least three to six hours after smoking.[56] Meta-analyses have concluded that cannabis use increases the risk of being involved in a motor-vehicle accident, and such risk has been found to be double or more than double in some studies.[57, 58]

Harm reduction strategies

Both federal and provincial agencies in Canada have assessed the evidence to formulate cannabis harm risk reduction strategies. These strategies commonly tackle the issues highlighted in this article, and particularly emphasize the need to prevent early adolescent use.[59, 60] For instance, Canada's *Low Risk Cannabis Use* Guidelines, created by the Canadian Research Initiative on Substance Misuse and the Centre for Addiction and Mental Health provides a set of evidence-based guidelines around abstinence, early initiation of cannabis use, THC content, combusted administration, inhalation practices, frequency and intensity of use, driving, and at-risk populations.[38]

These lower-risk use guidelines (LRUG) include: Abstinence as the best way to avoid cannabis associated risks, delaying taking up cannabis use until later in life, identify and choose lower-risk cannabis products — generally considered to be those with a lower percentage content of THC and a higher percent content of CBD, avoid use of synthetic cannabis products, avoid smoking burnt cannabis, avoiding harmful smoking practices such as deep inhalations or breath-holding, limit and reduce frequency of use, avoid driving or operating machinery for at least 6 hours after using cannabis, avoid combining with alcohol as it can increase impairment, avoid using cannabis if the person is at risk of mental health issues or if they are pregnant, and avoid combining any of the risk factors related to cannabis use.[61]

Currently naturopathic doctors in Canada are not permitted to recommend cannabis- based products to their patients or authorize cannabis for medical use. In BC, NDs with prescribing authority are permitted to prescribe a drug containing cannabis in accordance with the Cannabis Act and regulations. The Standards, Limits and Conditions for Prescribing, Dispensing and Compounding Drugs sets out what is permitted with respect to drugs in BC.[62] Ontario does not include Cannabis in the Prescription Drug List and NAPRA Schedule 1 that Members who have met the standard of practice for prescribing with CONO may prescribe.[63] Nonetheless, as primary care providers, NDs are strongly encouraged to review these resources and to become comfortable discussing the different evidence-based harm-reduction strategies available in order to properly counsel their patients on how to minimize the impact of cannabis use. In its Practice Guideline: *Non-medical (Recreational) Cannabis,* the College of Naturopaths of Ontario (CONO) states that "Members who possess the knowledge, skill and judgment specific to cannabis may where appropriate provide guidance to patients who are interested in incorporating non-medical (recreational) cannabis into their lives".[64]

As cannabis use becomes more prevalent and more accepted in our society, naturopathic doctors should consider routinely screening for cannabis use, particularly groups in which higher use is expected, such as youth and chronic pain patients, and to counsel individuals on how to minimize risk. Naturopathic doctors should also enquire about cannabis use in patients with conditions known to be exacerbated by cannabis use, such as insomnia, mood and psychotic disorders, chronic cough, and for those with impaired performance at school or work.

Additionally, NDs should also learn to distinguish between low-risk and problematic use, based on quantity and frequency of use. Indicators of problematic cannabis use may include daily use, reporting anxiety as primary reason to use cannabis, unsuccessful attempts to quit, and medical, social or financial issues arising from cannabis use.[65] If the suspicion of problematic cannabis use arises, NDs should consider using a validated screening questionnaire, such as CUDIT-R, and refer those patients with problematic use to specialized care, while ensuring that patients stay connected to their trusted primary care provider.

Vaping cannabis – an emerging issue

1479 cases of e-cigarette or vaping product use- associated lung injury (EVALI), and 33 deaths, have been reported in the United States in a span of 4 months in 2019. This illness, that is marked by chest pain, dyspnea and vomiting has affected mainly young people, and the majority of cases have been linked to *illegal* THC vaping cartridges.[66] While the exact cause of these illnesses is not known, it is believed that the lung damage is associated with the use of additives, preservatives and/or heavy metals present in the e-cigarette aerosols, such as vitamin E acetate.[67] No studies have been conducted to determine the short or long term effects of vaporized cannabis extracts (as opposed to the use of devices that rely on dry herb) and while these products were made legal as of October 2019,

THE CANNABIS USE DISORDER IDENTIFICATION TEST – REVISED (CUDIT-R)

Have you used any cannabis over the past six months? YES / NO

If YES, please answer the following questions about your cannabis use. Circle the response that is most correct for you in relation to your cannabis use over the past six months:

1. How often do you use cannabis?

Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
0	1	2	3	4

2. How many hours were you "stoned" on a typical day when you had been using cannabis?

Less than 1	1 or 2	3 or 4	5 or 6	7 or more
0	1	2	3	4

3. How often during the past 6 months did you find that you were not able to stop using cannabis once you had started?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

4. How often during the past 6 months did you fail to do what was normally expected from you because of using cannabis?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

5. How often in the past 6 months have you devoted a great deal of your time to getting, using, or recovering from cannabis?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

6. How often in the past 6 months have you had a problem with your memory or concentration after using cannabis?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

7. How often do you use cannabis in situations that could be physically hazardous, such as driving, operating machinery, or caring for children:

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

8. Have you ever thought about cutting down, or stopping, your use of cannabis?

Never	Yes, but not in the past 6 months	Yes, during the past 6 months
0	2	4

Scores of 8 or more indicate hazardous cannabis use.
Scores of 12 or more indicate a possible cannabis use disorder, for which further intervention may be required.

For further interpretation see: Adamson S, Kay-Lambkin F, Baker A, et al. An improved brief measure of cannabis misuse: The Cannabis Use Disorders Identification Test – Revised (CUDIT-R). Drug Alcohol Depend 2010: (In Press).
www.bpac.org.nz keyword:addiction-tools

such products have yet to reach the licensed Canadian market. Since vaping cannabis has become very prevalent among adolescents,[68] it is important to discuss the unknown health effects of vaporizing cannabis oils with users, and emphasize the potential issues associated with illegal, unregulated market products.

Conclusions

Cannabis use is very common in Canada, chiefly among young Canadians. While its full effects on human health have not been entirely elucidated, there is a good amount of information on evidence-based strategies that can be undertaken by individuals interested in using cannabis to reduce risks and harms. Naturopathic doctors, as health care professionals well trained in engaging with their patients on issues related to disease prevention, are well positioned to counsel on these strategies and to recognize patterns of problematic use and refer to the proper specialties for treatment. With 'Cannabis 2.0', new ways for Canadians to use cannabis have been made legal, therefore health care providers should become aware of the impact the use of these products may have on people's health.

About the Author

Dr. Paola Cubillos, MD, ND received her medical degree from the Universidad del Rosario in Colombia and her naturopathic medical degree from CCNM. Dr. Paola focuses on expanding the knowledge base on evidence-based applications for medical cannabis, spearheading medical cannabis research, participating in international collaborations and creating spaces for training health care professionals on medical cannabis. Dr. Cubillos has lectured on such topics as: common medical cannabis misconceptions; medical cannabis and PTSD and the use of medical cannabis in the treatment of pain. Dr. Paola is currently Medical Director – Colombia for CB2 Insights, a member of the CCNM Research Ethics Committee and Chair of the Research Ethics Board at Clinica Las Américas in Medellin, Columbia.

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Sleep Deprivation & Cardiovascular Risk

Dr. Leigha Saunders, ND

Sleep is a universal experience shared by all humans and is necessary to sustain life.[1] Yet the influence of sleep on other physiological processes is still poorly understood. Increasing evidence is supporting the importance of adequate sleep for overall health, quality of life, decreased risk of disease and all-cause mortality.[2, 3] More recently, the relationship between sleep and cardiovascular disease risk has been investigated and is emerging as an area that deserves increased attention.

The most recent guidelines from the American Academy of Sleep Medicine and Sleep Research Society state that an average adult needs approximately 7 hours of sleep each night for optimal health.[4] Yet, sleep patterns amongst humans are widely variable and are influenced by cultural, social, psychological, behavioural, pathophysiological and environmental factors.[3] Particularly in Western society and developed nations, sleep patterns have drastically changed over the past few decades. With the advent of longer working hours and commuting times, higher rates of shift-work, continuous access to commodities, increased environmental lighting and exposure to LED light sources, regulated indoor temperatures, consumption of caffeine and alcohol as well as the pervasive use of technology, average nightly sleep duration has decreased significantly.[1,3] So much so, the World Health Organization has described a 'global epidemic of sleeplessness' with approximately two-thirds of adults failing to obtain the recommended 8 hours of sleep each night.[5] Alarmingly, only 48% of adults in the USA report regularly sleeping between 7-9 hours nightly, 26% of the population reports sleeping 6-7 hours nightly and 20% have reported to sleep less than 6 hours nightly.[6]

In 2015, an expert panel formed by The National Sleep Foundation conducted a rigorous evaluation of the scientific literature to provide an update to sleep duration recommendations across the lifespan. It was determined that adults aged 18-64 years are recommended to obtain 7-9 hours of sleep nightly.[7] Decreased sleep duration has not only led to increased reports of fatigue and daytime sleepiness, but has also resulted in harmful effects on human physiology with deleterious impacts on metabolic, endocrine, immune and cardiovascular systems.[3] Failing to obtain adequate sleep is associated with increased risk of immune system dysfunction and susceptibility to infection, Alzheimer's disease, reproductive (fertility) challenges, blood sugar dysregulation, obesity, all major psychiatric conditions (including but not limited to depression, anxiety and suicidality) as well as cardiovascular disease and all-cause mortality.[1,3]

With increasing rates of inadequate amounts of sleep in the adult population, the cardiovascular consequences alone are substantial and highly significant.[6] Specifically, short sleep duration has been identified as an independent marker for morbidity and mortality associated with cardiovascular disease, mainly from coronary artery disease, arrhythmias and hypertension.[8] This is of high clinical significance as following cancer, cardiovascular disease is the second leading cause of death in Canada and is estimated to cost the Canadian economy more than $20.9 billion dollars annually.[9, 10]

Cardiovascular disease encompasses a variety of disorders that affect the heart and blood vessels, but for the purposes of this research paper, the risk of hypertension, coronary heart disease, myocardial infarction, cerebrovascular disease and metabolic disorders in relation to sleep deprivation will be explored. The intent of this paper is to review the available data regarding the relationship between inadequate sleep duration (qualitative and quantitative) and cardiovascular disease outcomes and risk, including the importance of screening for sleep as a risk factor for CVD, potential pathophysiologic mechanisms underlying the relationship and potential sleep-related interventions to reduce CVD risk.

Sleep, the Sleep Cycle & Disordered Sleeping

Simply defined, sleep is the prolonged period of unconsciousness that typically occurs for several hours each night. Sleep is clinically and objectively identified and defined by polysomnography (PSG), which records specific brainwave, eye movement and muscle activity by the placement of electrodes on the head and body. With the development of the PSG in the 1950s, sleep was originally divided into two stages, non-rapid eye movement (NREM) and rapid eye movement (REM). In following years, NREM was further sub divided into four separate stages (NREM Stage 1 through 4), with stages 3 and 4 being the deepest states of sleep in which it becomes increasingly difficult to wake an individual.[1]

Interruption in the quality and/or quantity of sleep that allows an individual to transition through continuous sleep cycles may be secondary to environmental or organic causes. The Diagnostic and

Statistical Manual of Mental Disorders (DSM-5) has identified 10 sleep-wake disorders, which include individual disorders as well as several disorder groups. In the past number of years, the relationship between disordered sleep and risk of cardiovascular disease has been investigated by a number of studies.[11]

DSM-5 SLEEP-WAKE DISORDERS

- Insomnia disorder
- Hypersomnolence disorder
- Narcolepsy
- Breathing-related sleep disorders
  - Obstructive sleep apnea
  - Central sleep apnea
  - Sleep-related hypoventilation
- Circadian rhythm sleep-wake disorders
  - Delayed sleep phase type
  - Advanced sleep phase type
  - Irregular sleep-wake type
  - Non-24-hour sleep-wake type
  - Shift work type
- Non-rapid eye movement sleep arousal disorders
- Nightmare disorder
- Rapid eye movement sleep behavior disorder
- Restless legs syndrome
- Substance/medication-induced sleep disorder

The Association Between Sleep & CVD Risk

In a recent meta-analysis (2017) of more than 5 million participants from 153 studies, short sleepers (those sleeping <6 hours nightly) had a relative risk of increased mortality of 1.12 (this translates to a 12% absolute increase). With regards to outcomes related to cardiometabolic disease, the review reported a point estimate of an absolute increase of 37% for diabetes mellitus, 17% for hypertension, 16% for cardiovascular disease, 26% for coronary heart disease and 38% for obesity.[12] An exploration of the relationship between specific cardiometabolic conditions and sleep follows.

Hypertension

In 2012-2013, hypertension (defined as blood pressure ≥ 140/90 mmHg) affected 22.6% of the Canadian adult population and the lifetime incidence of developing hypertension is estimated to be 90%[13, 14]. The prevalence of self-reported hypertension has nearly doubled in the past two decades and the annual cost attributed to managing hypertension in Canada is forecasted to reach $20.5 billion by 2020[15]. Hypertension is a clinically relevant and significant risk factor for developing other cardiovascular disorders, such as coronary artery disease, congestive heart failure and cerebrovascular disease (stroke).[16] Epidemiological evidence has reported a U-shaped relationship between extremes of sleep duration and the risk of hypertension, and in corroboration of this, a recent meta-analysis has indicated that short sleep is an independent marker for the incidence of hypertension.[17–19]

An epidemiologic and experimental evidence review completed by Covassin and Singh in 2016 identified that the risk of hypertension is lowest in those sleeping 7 to 8 hours nightly with progressive increases in risk with extremes of sleep length distribution[6]. The greatest risk is seen in those sleeping less than 6 hours nightly; it is estimated that these individuals are 20-32% more likely to develop hypertension in comparison to those obtaining 7-8 hours of sleep. This review also highlighted a 60% increased likelihood of an individual developing hypertension if they are sleeping ≤5 hours and are between 32 to 59 years old.[6]

Interestingly, different populations may be more greatly affected by the curtailing of sleep. Women appear to be more susceptible to developing hypertension due to sleep restriction; the Whitehall II study identified a higher prevalence and incidence of hypertension in middle-aged women sleeping <5 hours nightly compared to those sleeping 7 hours. This was not observed in men.[20] In a study by Stranges et al., the authors found a 66% higher prevalence of hypertension in women who were sleeping less than 6 hours nightly compared to those sleeping 6 hours or more. This study was the first to identify that the effect of short sleep duration on hypertension was more than doubled in premenopausal versus postmenopausal women (OR 3.25 versus 1.49).[21] The impact of sleep duration may also differentially affect various ethnicities. Both white and black individuals sleeping less than 6 hours have a greater likelihood of reporting hypertension; however, hypertension rates were reportedly higher in African-American subjects who were sleeping less than 6 or more than 8 hours nightly as compared to White subjects in the National Health Interview Survey (NHIS), even after adjustment for confounding factors.[6]

The U-shaped relationship between hypertension and sleep hours is most robust for systolic values. Both short and long, typically defined as less than 6 or more than 8 hours respectively, sleep durations have been correlated with loss of nocturnal reduction in blood pressure, a sensitive prognostic marker for CVD.[6]

PRACTICE | **Sleep Deprivation & Cardiovascular Risk** – cont'd

Coronary Heart Disease

Coronary heart disease (CHD), includes a spectrum of acute and chronic cardiovascular conditions and is one of the leading causes of death worldwide.[6] CHD is caused the atherosclerosis of the coronary vessels, which can lead to ischemic heart disease, the underlying cause of angina pectoris, myocardial infarction and cardiac arrest.[22] Numerous studies have identified the negative correlation between sleep duration and coronary heart disease, demonstrating an increased risk of coronary artery calcification, myocardial infarction and heart failure highest in those with short sleep duration.[8] Furthermore, the recurrence of cardiac events is strongly associated with disturbed sleep patterns and disturbed sleep is now known to be an independent prognostic marker for cardiac prognosis.[23]

In similarity to hypertension, epidemiologic studies show a U-shaped curve with respect to sleep duration and risk of CHD; prevalence of CHD is higher in those sleeping <6 hours/night or >9 hours/night.[6] The incidence of fatal and non-fatal CHD events follows a similar pattern; greatest risk of CHD occurs in those with regular sleep duration above or below 7-8 hours nightly. A 10-year follow up with the participants in The Nurses' Health Study reported a 1.39 relative risk in women reporting <5 hours of sleep each night and a 1.37-fold higher relative risk in those sleeping >9 hours nightly compared to those sleeping 8 hours.[6] A meta-analysis in 2014 identified a 45% increased risk of morbidity and/or mortality from cardiovascular disease in subjects who reported difficulty initiating and maintaining sleep or experienced disturbed sleep during the night in comparison to subjects who reports good sleep quality.[11]

In a 2019 systematic review investigating the relationship between sleep and coronary heart disease, Madsen et al completed a review of 64 articles. The authors reported that both disturbed sleep architecture and amount of sleep are commonly experienced by those with CHD, with sleep disturbances being most aggravated in relation to an acute coronary event.[23] Importantly, this systematic review was the first to account for CHD and sleep disturbances in patients with anxiety, depression and sleep-disordered breathing, as these are known to co-occur. The authors also noted that the majority of literature investigating sleep disturbances and CHD is in relation to sleep disordered breathing (SDB).

Sleep-disordered breathing

Diagnosed with overnight polysomnography, sleep disordered breathing (SDB) is "characterized by repetitive episodes of shallow breathing or apnea during sleep", resulting in intermittent hypoxemia.[24] In a vicious cycle, the risk factors for developing and the sequelae of SDB include sympathetic nervous system activation, metabolic abnormalities (insulin resistance and dyslipidemia), systemic inflammation and increased oxidative stress, obesity and cardiovascular dysfunction (hypercoagulability, uncoupling of myocardial workload, vascular endothelial dysfunction and arteriosclerosis). SDB is in return associated with a high risk of CVD, including sudden death, atrial fibrillation, stroke, coronary heart disease and heart failure.[24]

SDB encompasses obstructive sleep apnea (OSA; characterized by the cessation or reduction of airflow still in the presence of respiratory effort) and central sleep apnea (CSA; in which both the airflow and respiratory effort stop during sleep). The gold-standard treatment for SDB is continuous positive airway pressure (CPAP) therapy, which attenuates apneic and hypoxic episodes by preventing collapse of the pharynx and reducing the cessation of airflow and oxygen desaturation. Treatment with CPAP therapy has been reported to improve sleep quality, heart rate variation, daytime sleepiness and overall quality of life.[24] However, the effect of CPAP therapy on various cardiovascular conditions is mixed.

A 2015 review highlighted that the strongest evidence of CPAP use is for the reduction of hypertension.[25] A 2018 review reported that observational studies indicate CPAP therapy is effective at reducing the incidence of hypertension, nonfatal cardiovascular events in men and fatal cardiovascular events in men, women and the elderly.[26] However, the authors noted that more recent randomized trials failed to demonstrate benefit for secondary prevention of cardiovascular events. It is noteworthy that this discrepancy may be due to the failure to adjust for confounding variables unknown in observational studies as well as poor CPAP adherence and compliance in randomized trials.[25] Given the nature of the device, users often remove their CPAP machine over the course of the night, particularly in the early hours of the morning during REM sleep periods.[26] This is of additional significance, as REM sleep is already associated with an increased cardiometabolic demand and occurs when noncompliant individuals have removed their CPAP. However, numerous studies have indicated that the longer the duration of use of a CPAP machine on a nightly basis, the more benefit on CVD.[26]

Metabolic Disorders

Several epidemiological studies have demonstrated the relationship between short sleep duration, circadian rhythm disruption and metabolic derangement, including insulin resistance, glucose intolerance, changes in leptin and ghrelin hormone release and negative alterations in lipid profiles.[16] These metabolic changes, although not described in detail here, can lead to an increased risk of obesity, hypercholesterolemia, metabolic syndrome and type 2 diabetes mellitus, further increasing the risk of CVD in the presence of prolonged sleep deprivation.[16]

Pathophysiological Mechanisms

The underlying mechanisms relating the increased risk of CVD and sleep complaints have been investigated by both epidemiologic and experimental studies, but remain incompletely understood. [11] This is complicated by the fact that there is considerable heterogeneity in experiments investigating the effects of short sleep time in humans and population-based studies have associated limitations. Regardless, epidemiological observational findings are accompanied by experimental and laboratory-based evidence, which provide some insight into the mechanisms of increased CVD risk due to inadequate sleep.

Inflammation – Considered to be one of the most important underlying pathophysiological mechanisms in the development of CVD, the creation of a pro-inflammatory state in short sleepers has been proposed as a possible mechanism increasing the risk of CVD in these individuals. Although conclusive evidence is lacking, several studies consistently report a pro-inflammatory state after both partial and total sleep deprivation. This pro-inflammatory state is thought to play into the increased oxidative stress, endothelial dysfunction, release of prothrombotic factors and ultimately, the development of atherosclerosis, increasing the risk of CVD. Exactly how an inflammatory state develops after sleep deprivation is not fully understood, but it appears that increased sympathetic nervous system activation plays a role.[16]

Autonomic Nervous System Dysfunction – In studies in both humans and rodents, sleep deprivation and sleep restriction are associated with increases in sympathetic nervous system (SNS) activity and the hypothalamic pituitary adrenal (HPA) axis dysfunction.[27] Activation of these systems in the presence of an acute or chronic stressor results in the release of catecholamines (adrenaline and noradrenaline) and glucocorticoids (cortisol). Under normal circumstances, these hormones have pronounced diurnal variation and rapidly decline during sleep, as sleep has suppressive effects on these systems.

There is now evidence that clearly illustrates the effect of sleep loss on our neuroendocrine system. Almost all the data investigating the mechanisms of increased risk of CVD risk and sleep deprivation indicate that any form of sleep disruption is associated with sympathetic nervous system activation.[16] Understandably, the relationship between stress and sleep is bidirectional, as increased stress may lead to insufficient and/or poor quality sleep and vice versa.[27] However, studies investigating heart rate variability (HRV), a marker of the response of the SNS on cardiovascular function, demonstrate that SNS activity is indeed affected by sleep, and lack thereof.[27] HRV is an independent risk factor for morbidity and mortality; accumulating evidence is identifying the relationship between HRV and modifiable and non-modifiable CVD risk factors. Interestingly, increasing HRV (by decreasing sympathetic activity and increasing parasympathetic dominance), lowers CVD risk profiles.[28]

While there is reported variation on the degree to which SNS activation occurs after sleep deprivation, increases in sympathetic outflow can in turn increase coronary vasomotor tone, blood pressure and heart rate, ultimately affecting the supply and demand of oxygen, even in healthy individuals.[1, 8] The result of chronic sympathetic activation is endothelial dysfunction, compromising the oxygenation of the myocardium, increasing the risk of atherosclerosis and platelet activation. Accompanying this chronic activation of the SNS are changes in other neuroendocrine pathways, including the renin angiotensin system, the thyroid and leptin/ghrelin release.[8] Figure 1, from Cappuccio and Miller (2017) eloquently illustrates the interconnectedness of sleep deprivation and possible pathological mechanisms affecting the cardiovascular system.[29]

Clinical Significance

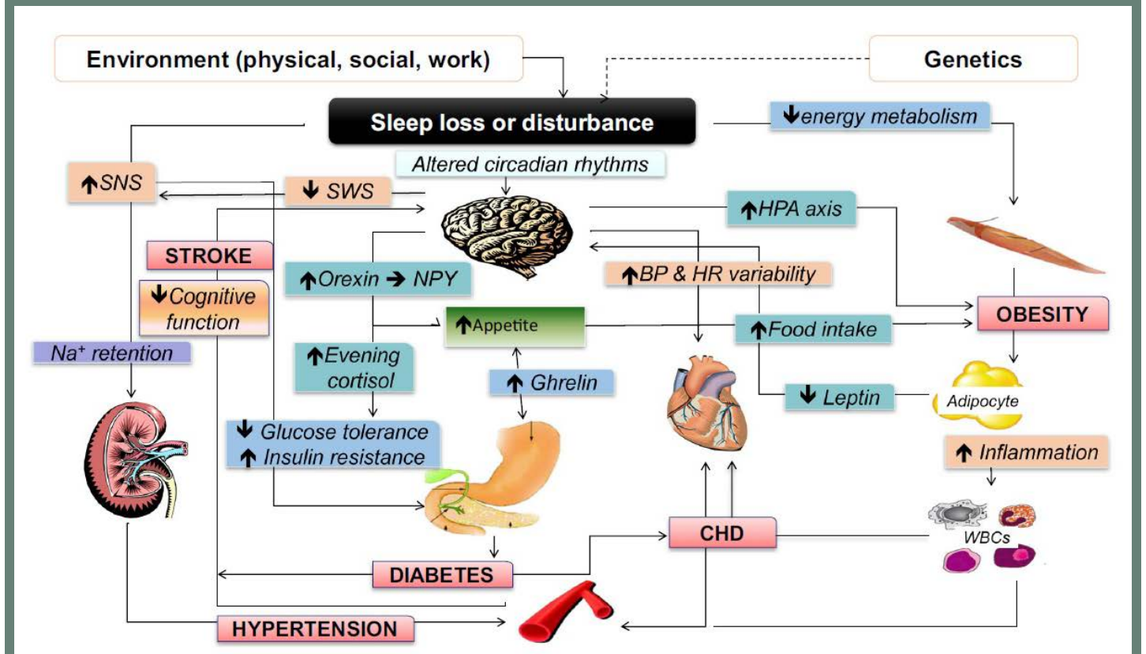
The pathophysiological outcomes associated with short sleep duration are established major risk factors for the development of cardiovascular and metabolic disease.[16] The complex interplay and combination of metabolic and circulatory abnormalities can contribute to the development of cardiovascular diseases, however, there is still debate over whether the relationship between these outcomes and risk factors are mono- or bidirectional.[12, 16] Due to the limitation of the fact that the majority of clinical evidence investigating short sleep duration and the increased risk of cardiovascular disease comes from cross-sectional studies, a causal link cannot be confirmed. However, experimental evidence does support this hypothesis.[16]

Regardless, the clinical significance of disturbed sleep and its negative impact on cardiovascular disease is well-established. Therefore, it is important that clinicians, especially in the primary care setting, screen for sleep disorders, yet data suggests this is not routinely the case.[30] Considering the presented information, primary care providers should take into consideration the power of and importance of sleep on overall health, particularly related to the risk of cardiovascular disease. Primary care providers are at the epicenter of this process, as the screening for cardiovascular risk factors and the development of CVD is widely implemented in Western medicine to identify high-risk individuals and implement risk reduction. A recent 2016 systematic review of guidelines for cardiovascular risk assessment included the review of 21 sets of guidelines, 5 of which were specific to total cardiovascular risk. Sleep was not identified as a recommended risk factor to screen for.[31]

A number of ways to increase the screening of sleep disorders have been proposed, including raising awareness through improved communication and educational measures, incorporating chart reminders as well as providing sleep intervention support.[32] As Mollayeva *et al.* report in a systematic review and meta-analysis of 37 studies, the Pittsburgh Sleep Quality Index (PSQI) is the most commonly used subjective assessment of sleep in the clinical and research settings and is currently the only standardized clinical instrument that covers a wide range of factors relevant to sleep quality.[33] Together with a detailed clinical history of the patient, other factors not included on the PSQI may also be identified, including circadian rhythm disruption and medication effects. It is important to note that to date, there is no agreed upon method among clinicians in assessing quality of sleep in a patient, nor has a study to investigate this been completed.[33]

Despite the fact that primary care physicians find screening for sleep disorders and the implementation of preventative strategies to reduce the risk of CVD challenging, approaches to improve the quality and duration of sleep are worthwhile considerations for both the primary and secondary prevention of CVD, as management of those with increased risk of CVD remains suboptimal.[31] While there is plenty of evidence and studies investigating the impact of lifestyle interventions like physical activity, diet, alcohol, smoking

FIGURE 1



and body composition on CVD risk modification, there is limited evidence available including sleep duration.[34] However, despite the lack of volume, the existing evidence is promising and many authors investigating the relationship between short sleep duration and CVD risk emphasize the need and importance of future studies in this area.

In the first study of its kind to identify the impact of sufficient sleep in addition to four other well-established lifestyle factors that reduce the risk of CVD (adequate physical activity, consuming a Mediterranean diet, appropriate alcohol consumption and non-smoking), sufficient sleep (≥ 7 hours nightly) was shown to significantly reduce the risk of CVD.[34] The study involved tracking 10,571 adults aged 20-65 years free of CVD at baseline over 10-14 years. Compared to those who did not implement any or implemented only one of the healthy lifestyle factors, those who implemented all four had a 57% lower risk of CVD (HR 0.43, 95% CI) and a 67% lower risk of fatal CVD (HR 0.33, 95% CI). When sufficient sleep was added to these four healthy lifestyle factors, there was a 65% lower risk of CVD and an 83% lower risk of fatal CVD. This translated to a theoretical prevention of 36% reduction in the number of CVD cases when either all four or five lifestyle factors were implemented and a 46% and 57% reduction in the number of fatal CVD events with adherence to all four or five factors, respectively. Withstanding limitations of the study, this equates to the possible prevention of 14 fatal CVD events amongst the study participants.

Interventions to Improve Sleep & Reduce CVD Risk

With the demonstrated relationship between sleep disturbances and increased risk of cardiovascular disease, the clinical relevance lies in whether improving sleep quality and duration decreases CVD risk. Although limited, there are studies targeting CVD risk reduction with sleep interventions that show promising results.

Cognitive behavioural therapy (CBT) is an evidence-based intervention that teaches cognitive restructuring and behavioural modification to improve mental and physical health outcomes. CBT for insomnia (CBT-I) is considered the gold standard therapy for insomnia recommended by the American College of Physicians and the American Academy of Sleep Medicine. CBT-I focuses on sleep hygiene principles with individualized recommendations for the patient, after accounting for their sleep challenges and lifestyle. CBT-I appears to have more long-lasting benefit than sleeping medications, provides substantial benefit with minimal risk, can address comorbid conditions (i.e. depression and anxiety, which are often present in individuals with CVD) and can be combined with pharmacotherapy for increased efficacy.[35]

Individuals with CVD who receive CBT have been shown to improve health behaviours and positively modify their lifestyle to reduce their overall CVD risk.[36] Although limited, available evidence

does suggest that CBT-I improves biomarkers related to CVD risk, insomnia, sleep patterns and daytime symptoms.[37] In the first of its kind, a recent 2019 study that tailored CBT-I to patients with CVD reported significant improvement in sleep outcomes (duration, continuity, efficiency, latency and quality) while also reporting significantly fewer symptoms of anxiety, depression and insomnia (p value <0.05).[38] The authors, Heenan et al (2018) highlighted the need for randomized trials further investigating CBT-I specific for the CVD patient population.

Furthering the mind-body connection and its implication on reducing risk of CVD, decreased Heart Rate Variability (HRV) (governed by the sympathetic nervous system) is an established risk factor for CVD, and interventions to increase HRV are worthwhile considering. Modifiable factors such as smoking cessation, physical exercise and weight loss are associated with increased HRV.[39] There is also some evidence that suggests that dietary changes (the consumption of fruits and vegetables, moderate alcohol consumption and intake of omega-3 fatty acids and vitamin D) may also increase HRV. Mindfulness and meditation may also reduce stress and worry through the modulation of HRV.[39]

Conclusion

Accumulating evidence is demonstrating a profound relationship between sleep disturbances and the risk of cardiovascular disease, including a clinically significant risk of hypertension, diabetes mellitus, myocardial infarction and coronary heart disease. Short sleep duration is also associated with activation of the sympathetic nervous system, impairing heart rate variability, while also increasing the activity of the HPA axis, leading to elevated secretion of catecholamines and glucocorticoids. The result is a negative cycle in which sleep disturbances may be exacerbated, further increasing the risk of CVD.

The screening for sleep disorders is insufficient in the primary healthcare setting, but may easily be introduced by simply inquiring about sleep habits and administering the PSQI. The importance of identifying sleep disturbances as a significant risk factor for CVD should not be overlooked; in a systematic review and meta-analysis with over 5.1 million cumulative participants from 153 studies, short sleep is significantly associated with mortality (RR 1.12, 95% CI, 1.08-1.16), hypertension (1.17, 1.09-1.26), CVD (1.16, 1.10-1.23) and coronary heart disease (1.26, 1.15-1.38).[12]

With this significant increase in CVD risk associated with short sleep duration, multiple studies emphasize the existing positive evidence as well as the need for future investigation on psychosocial interventions to ultimately lower CVD risk. As naturopathic doctors, we are well positioned within the healthcare system to identify, assess and address sleep disturbances to not only improve the overall quality of life of our patients, but also to reduce the risk of CVD.

About the Author

Dr. Leigha Saunders, ND is a graduate of the Canadian College of Naturopathic Medicine and the owner and founder of Uxbridge, Ontario's premiere wellness clinic, True Roots Healthcare. Dr. Saunders maintains a private practice with a special interest in sleep medicine and the impact sleep has on all aspects of heath. She believes that when you have your health you have everything. Dr. Saunders holds general, IVIT and therapeutic prescribing certification with the College of Naturopaths of Ontario and is a member of the CAND and the OAND.

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Naturopathic Primary Care Cardiovascular Disease Risk Reduction Model

Dr. David Duizer, ND

It is a privilege to be able to provide personalized holistic medicine at a time with reliable, efficient assessment tools, well-tested therapeutic programs and a renewed societal acceptance that "prevention is the best medicine". With greater public knowledge of the role for a healthy diet and lifestyle in cardiovascular disease (CVD) risk reduction, naturopathic doctors have been able to position themselves as the developers and managers of detailed patient heart-health wellness plans.

This service of assessing, treating and tracking using well established biomarkers, naturopathic therapies and a foundational holistic approach promotes health span and lifespan while addressing patient desire for a reduction in the use of pharmaceutical interventions and the side effects that accompany them.

This article will outline such a plan to be adapted and used freely with the goal of improving longevity and health span through reduced cardiovascular events and impairments to activities of daily living.

Cardiovascular Disease Risk

Cardiovascular disease (CVD) is the second leading cause of mortality in Canada and cerebrovascular disease is the fourth.[1] These two groups of conditions have held positions similar to these for many years even though prevention tools have been well studied, documented, funded, promoted and thoroughly adopted. Personalized prevention program management may be the missing link in primary and secondary risk reduction.

The term cardiovascular disease refers to ischemic heart disease and/or coronary artery disease.[2] The consequences of this condition include heart attack, heart failure and death. As a group, these conditions account for major suffering amongst our population, needless loss, trauma and disability. It is estimated that 80% of all cardiovascular disease is preventable.[3]

This objective approach to assessment uses tools commonly available to most naturopathic doctors with laboratory access. Naturopathic therapeutics and pharmaceutical prescribing protocols are available for each one of the biomarkers listed. Research for nutraceutical and dietary plan effectiveness through biomarker modulation is growing daily with a focus on CVD and all-cause mortality as endpoints. This review focuses on helpful laboratory biomarkers and is not inclusive of all assessment tools. It is simply a framework to build upon and adapt as necessary.

Naturopathic Approach Principles

While sitting down with a patient at the beginning of this process it is helpful to review our approach. We are able to use naturopathic principles to outline where we are coming from:

- First, do no harm - we will not make the situation worse and will have a procedures/alternatives/risks/questions conference before applying therapeutics.
- Doctor as teacher – through in-office graphics of CVD we can review important mechanisms in disease processes and treatment methodology.
- Prevention - we can quantify risk and take action to modify risk immediately.
- The healing power of nature - natural substances can positively impact biomarkers to reduce risk.
- Identify and treat the cause - we are able to review factors associated with hard and soft plaque including environmental, dietary, genetic and lifestyle mediated.
- Treat the whole person - applying the holistic approach to CVD management is one way we set ourselves apart and go above and beyond for patients. This is a powerful way to improve compliance.

To begin personalization we need to set an objective standard. Assessment and therapeutic cycles of 12 weeks can be useful. Initially we gather information, quantify risk and provide a detailed approach.

Quantify Cardiovascular Disease Risk

This approach to CVD risk reduction starts with our initial visit with a patient. First we must determine if we are attempting primary or secondary risk reduction, review past medical history and family history pertaining to the heart/metabolic syndrome and collect laboratory records from previous medical practitioners.

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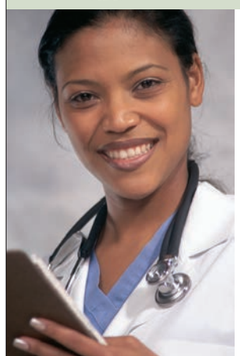

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Our objective approach to CVD risk reduction relies on a risk calculation. A commonly used, easy, quick tool most medical professionals are familiar with is the Framingham Risk Score.[4] Other options include the ASCVD[5] and QRisk.[6] Most of these models require basic inputs including total cholesterol, HDL cholesterol, smoking status, diabetic status, average blood pressure and age.

Most calculators will classify patients into low, intermediate and high-risk categories. A common threshold to use for example could be: Framingham Risk Score (10 year risk of heart attack and stroke) of <10% as low risk, 11-19% intermediate risk and >20% as high risk. Using a risk categorization we can then set goals for biomarkers and subsequent renewed categorization.

We can then do better for our patients and further quantify risk by going beyond basic biomarker assessments and use personalized risk qualification biomarkers as outlined below. For many there is value in the details. For some, depending on financial ability and willingness, the basics could provide adequate information. Finally, if therapeutic routine wouldn't be altered by an unexpected result, further testing might not be warranted.

Advanced Cardiovascular Assessment Tools

Once categorized, the determination for further assessment can be made. Most often further workup is warranted in the intermediate and high-risk classifications. Exceptions are for low risk individuals with a significant family history of CVD. Building a personalized plan in these cases requires personal detail.

This is where the holistic approach to case management can be most obviously applied. The cardiovascular system is influenced and interacts with all other organ systems. The rationale behind the holistic approach is easy to justify using epidemiologic studies and biochemical pathway instruction. Our role is to optimize the body's ability to heal through supportive, non-invasive intervention when possible. For example, observational studies have shown that both low levels of serum testosterone and high levels of serum testosterone have been associated with increased CVD risk.[7] Taking this biomarker into the normal range through lifestyle improvements, dietary recommendations and herbal prescribing could provide a beneficial vasodilatory effect, positive cardiac and skeletal muscle strength and improved insulin sensitivity.[7] This is the kind of detail personalized risk management we can facilitate. If our therapeutic approach provides the time and resources for such detailed analysis we have a duty to provide it.

The following list and review provides a series of testing options to further quantify and qualify risk. This tool kit takes intermediate and high-risk individuals and allows us to qualify them with one or multiple tendencies. Is this picture an inflammatory one, hormone imbalance, nutrient deficiency or excess, genetic, exposure mediated, autoimmune, etc? It also informs us to what we should be tracking long term and what other conditions could be concomitant.

Finally, we can act in a way that is objective, holistic, evidence-based and rational. If CVD is the "silent killer", prevention of CVD requires as much detail as possible. This process is the gamification of biomarker management. We can use our toolkit to improve these biomarkers and thus decrease risk.

Biomarkers of Consideration

As previously described a consult begins with a review of lipids (LDLc, HDLc and triglycerides), HbA1C, fasting plasma glucose and blood pressure. Before moving forward there can be value in providing the triglyceride:HDL ratio as a high number has been associated with insulin resistance and cardio/cerebrovascular disease.[8] Next a determination for appropriate laboratory workup can guide requisition choices. Here are a few examples of categories for testing:

Inflammatory:

- CRP - c-reactive protein - a nonspecific, acute-phase reactant protein commonly used to diagnose bacterial infections and inflammatory disorders. CRP is made in the liver and produced in response to antigen-immune complexes, bacteria, fungi and trauma. As a complement activator CRP plays an important role in promoting an immune response to foreign invaders. We are interested in this molecule for its ability to induce genetic expression of genes required for adhesion of monocytes and the recruitment of intracellular molecules such as E-selectin and monocyte chemoattractant protein-1 (MCP-1) in atherogenic plaques.[9] It is elevated in inflamed plaques and thus is a helpful tool in CVD assessment.

- LP-PLA2 - lipoprotein associated phospholipase A2 - an enzyme involved in the hydrolysis of oxidized LDL within the intima used to determine the inflammatory activity of an atherogenic process. This measure is highly predictive of coronary artery disease mortality indicating it is of highest importance in determining severity of illness.[10] The benefit of adding LP-PLA2 to a risk stratification program is that it is predictive independent of CRP and elevation confirms a doubled event risk.[10]

- Fibrinogen - another acute-phase reactant, fibrinogen is elevated at times of inflammation and tissue necrosis. Its role is as part of the clotting cascade as it is converted to fibrin by thrombin during coagulation. Fibrinogen is helpful as a screening tool to assess increased thrombotic risk.[11]

- Myeloperoxidase - a heme peroxidase responsible for the formation of reactive oxygen species within atherosclerotic lesions and is now known as a role player in both promotion and propagation of atherosclerosis through lipid peroxidation.[12] This enzyme is a predictor of cardiovascular risk independent of Framingham score or CRP.[12]

Metabolic:

- Fasting Insulin and HOMA-IR - the acronym HOMA-IR stands for Homeostatic Model Assessment of Insulin Resistance and is a simple method for estimating insulin sensitivity and pancreatic function. This tool requires a fasting insulin and fasting glucose test and is determined using a calculation found online.[13] In non-obese, non-diabetic patients this measure can help predict risk of CVD thus making it a great tool for prevention and longevity workups in a healthy population.[14]

- OGTT - oral glucose tolerance test - achieving an OGTT with insulin measurements can provide detailed insight into insulin sensitivity and beta cell function. This test adds another metabolic tool to our toolkit for non-diabetics looking to predict their CVD risk. If they do not reach pretest glucose levels after the 2 hour mark of the OGTT they are at higher risk of mortality from cardiovascular disease and all-cause mortality.[15] Compared with fasting glucose this test better predicts coronary heart disease and ischemic stroke.[16]

- TSH - thyroid stimulating hormone - the holistic approach to CVD risk assessment allows us to look at all organ systems. It is important to note with patients how thyroid function impacts the cardiovascular system. In hypothyroidism cardiac output is reduced, arterial stiffness is increased, diastolic blood pressure increases and pulse pressure narrows resulting in sodium sensitive diastolic hypertension.[17] When evaluating Framingham score for hypothyroid patients it is important to note decreased hepatic clearance of LDLc as well as elevations of CRP and homocysteine.[17] Untreated hyperthyroidism is a risk factor for left ventricular hypertrophy, atrial fibrillation and heart failure.[17]

Toxicity:

- Cadmium - well-controlled epidemiologic studies show a correlation between chronic cadmium exposure and CVD.[18] Blood and urine assessments can determine body burden. Cadmium is found in cigarette smoke, air pollution and in certain foods.

- Lead - in 2018 The Lancet Public Health published a study quantifying the contribution of lead exposure to CVD risk. Their conclusion was that even low level environmental lead exposure is an important marker for CVD risk and promoting its avoidance should be addressed at a public health level.[19] The mechanism of impact for lead is multifold and includes its ability to promote oxidative stress, limit nitric oxide availability, impair nitric oxide signaling, augment adrenergic activity, increase endothelin production, alter the renin-angiotensin system, raise vasoconstrictor prostaglandins, lower vasodilator prostaglandins, promote inflammation, disturb vascular smooth muscle Ca2+ signaling, diminish endothelium-dependent vasorelaxation, and modify the vascular response to vasoactive agonists.[20]

Lipid/Vascular microenvironment:

- APOB100 - as a protein constituent of both low-density lipoprotein and very low-density lipoprotein (VLDL) APOB100 is a recognition signal for cellular binding and internalization of LDL particles.[21] There is one APOB100 per LDL particle and therefore it is a highly accurate, less expensive proxy for the LDL particle measurement. The fatty streak phase of atherosclerosis is initiated by APOB containing LDL and VLDL particles. This assay is of highest use in the setting of high triglycerides to further determine the extent of LDLc suppression required.[22]

- APOA1 - this protein constituent lives in the high-density lipoprotein (HDL) molecule and therefore is involved in the cycle of HDL redistribution of cholesterol to the liver for recycling. APOA1 helps to quantify HDL capacity and can be compared to APOB100 using the ratio APOB/APOA1 providing a superior predictor of cardiovascular events compared with simple HDLc and LDLc management.[23]

- Oxidized LDL - although long studied, the measure of oxidized LDL in clinical practice is relatively new. As a key stimulus for inflammatory and immunologic mechanisms leading to endothelial dysfunction, foam cell formation and induction of platelet adhesion and aggregation this assay could provide added detail to a clinical workup beyond that of LDLc.[24]

- Lp(a) - a separate lipoprotein similar to LDL but with increased prothrombotic and anti-fibrinolytic effects and the ability to accelerate atherogenesis through intimal deposition of Lp(a) cholesterol.[25] This measure is an independent risk factor for cardiovascular event risk and elevation is mostly genetically determined.[26]

- PULS - the Protein Unstable Lesion Signature is a group of tests estimating traces of proteins leaking from inflamed vessel plaque in an attempt to determine the severity of atherosclerosis and plaque rupture potential. The PULS protein biomarkers include HDL, HbA1C, Fas ligand, HGF, Eotaxin, CTACK, MCP-3, IL-16 and sFas.[27] The test provides a personalized 5-year diagnosis and prognosis of unstable cardiac lesion and rupture risk as well as a calculated "Heart Age" comparing their risk score relative to their age and gender group.

Nutritional:

- Homocysteine - as an intermediate in the metabolism of methionine, homocysteine should not remain in circulation long. When it does it acts as a diagnostic tool given its label as an independent risk factor for ischemic heart disease, cerebrovascular disease and peripheral arterial disease. Mechanistically, homocysteine is damaging to endothelium, promotes low-density lipoprotein deposition and increased vascular smooth muscle growth. It is known as a risk factor for stroke, dementia and Alzheimer's disease. The two main causes of homocysteine elevation are genetic risk and B12, B6 and folate deficiency.

- Omega 3 Index - the assessment of omega 3, 6 and 9 is now widely available via a simple blood test. The omega 3 index has been validated as a risk marker for CVD mortality with the risk reduction in the highest levels of omega 3 index achieving greater prevention than those with the lowest concentrations of CRP.[28] Intervention trials show omega 3 supplementation reduces risk of sudden cardiac death and can be helpful in secondary prevention of CVD.[28] This assay's sensitivity to diet allows further determination for omega 3 requirements.

- Vitamin D3 - deficiency in this vitamin has been linked to the following cardiovascular outcomes; congestive heart failure, impaired systolic and diastolic function, myocardial infarction, peripheral vascular disease, abdominal aortic aneurysm in older men, nonvalvular atrial fibrillation and hypertension.[29] Low levels of vitamin D3 trigger increased renin and angiotensin II synthesis, inhibition of the pathways necessary for intracellular glucose transporter, thus the development of insulin resistance, and calcium homeostasis disruption impacting smooth muscle calcification and proliferation.[29]

Hormonal:

- Cortisol - elevated hair cortisol is associated with increased incidence of CVD, poorer recovery and treatment outcomes.[30] Excess cortisol over time can induce hypertension, hyperinsulinemia, hyperglycemia, truncal obesity, insulin resistance and dyslipidemia.[31] The impact of cortisol on the cardiovascular system seems to be mainly mediated through its inhibition of nitric oxide therefore promoting vasoconstriction.[31]

- DHEA - an adrenal prohormone that declines with age. Low levels of DHEA-S have been associated with CVD mortality in postmenopausal women and all-cause mortality, CVD and ischemic heart disease in men independent of other CVD risk factors.[32]

- Testosterone - with a favorable role as a direct vasodilator of coronary arteries and through easing peripheral vascular resistance, adequate testosterone levels have proven useful in cardiovascular risk management. Low levels of this hormone have shown to increase CVD risk and controversy remains with hyper-physiologic levels through exogenous testosterone use as a potential for worsening CVD risk is possible. With its impact on the blood vessels and potential for improving insulin sensitivity, exerting a positive effect on cardiac and skeletal muscle maintaining normal testosterone levels has proven essential on a holistic risk management plan.[7]

- Estrogen - a decline in estrogen during menopause is associated with increased CVD risk although hormone replacement therapy has shown an increased stroke risk in certain populations and is not considered a solution to this deficiency for the purpose of CVD risk reduction.[33]

- Melatonin - circadian rhythm optimization is important for managing CVD risk and the main hormone involved in this process is melatonin. Low levels of melatonin are associated with increased CVD risk, hypertension and heart failure. Likelihood of adverse cardiac events, including myocardial infarction, sudden cardiac death and cardiac arrhythmias increases in the early morning, when circulating melatonin levels are lowest.[34]

Genetics:

- 9p21 - also known as the "Heart Attack Gene" this gene risk variant confers a 40% increased risk of coronary artery disease when a patient has two copies.[35]

- APOE4 - commonly known as the "Alzheimer's Gene" this gene risk variant predisposes patients to hypercholesterolemia and increased CVD risk.[35]

- APOC3 - the unfavorable variant of this gene predisposes patients to hypertriglyceridemia and increased CVD risk.

Imaging tools:

Finally, to quantify and qualify risk even further, cardiac imaging can be done using ultrasound, X-ray, MRI and/or CT. Common names for these assessments include echocardiogram, ECG, angiogram and coronary calcium scan. The goal here is to pinpoint inflamed plaque for assessment and to determine the value of invasive treatments such as stenting.

Therapeutic options:

We have made it. We have been able to take a patient from low, intermediate or high risk to a personalized medicine track with an ability to focus on one or more categories of overall wellness. This is when we access our therapeutic toolkit.

A well-rounded approach to CVD risk reduction might include fasting, hydrotherapy, exercise, sleep support, stress reduction and/or nutrition therapy with personalized dietary modifications and meal planning. Advanced treatments directed at biomarker manipulation through the use of nutraceuticals, herbal remedies and low dose pharmaceuticals give us the ability to offer evidence-based protocols to address single physiologic mechanisms. We have the ability to spend time, teach and promote optimal metabolism, nutrient status, organ function, stress response, circadian rhythm management, hormone synthesis, inflammation reduction, and so on. This is our core strength.

Tracking, Treating & Re-assessing Cardiovascular Disease Risk

The "silent killer" becomes very loud when you have the amount of detail outlined above. It can be overwhelming if improperly presented. As an approach it is the opposite of simply addressing high LDLc with a statin drug. It is to say yes, we have an inflamed plaque issue brewing in the cardiovascular system. The environmental factors, external and internal, that brought us to this situation can be clearly defined through our test results.

Is there a genetic influence? Is diet impacting metabolic function? Are we seeing an increase in inflammation and oxidative stress because of a lack of one nutrient such as omega 3 or an increase in immune activity such as in rheumatoid arthritis (and accompanying high c-reactive protein)?

Map the outcomes and apply your toolkit. Common follow up times are 12 and 24 weeks to reassess and refine. After biomarker improvement is met, a new Framingham score can be presented outlining an updated 10-year CVD risk.

Happier and healthier years with family and friends are possible with a balanced approach providing this level of personalized care. As leaders in preventative medicine we are primed for this role.

About the Author

Dr. David Duizer is the co-founder of DAMYHealth.com, co-developer of The Healthy Rebel App and the Medical Director at the Finlandia Health Center in Vancouver, BC where he practices full time. His clinical focus is chronic disease management and integrative cancer care. He completed his Bachelor of Science in Chemistry and Psychology as part of the Regular Officer Training Program (ROTP) at the Royal Military College of Canada in 2008 and graduated from the Boucher Institute of Naturopathic Medicine (BINM) as a Doctor in Naturopathic Medicine in 2014. Dr. Duizer is currently serving a second term as a Director on the Board of Governors at BINM.

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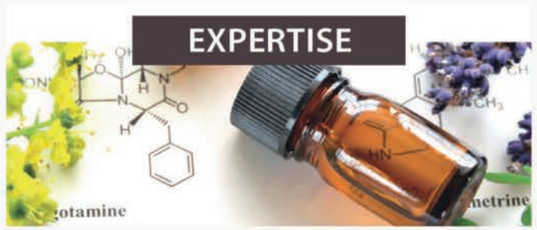

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The Migraine-Metabolic Connection: Screening for and Addressing Metabolic Syndrome in Patients with Migraine

Dr. James R. Conway, ND

Patients presenting with migraine may benefit from screening for insulin-related comorbidities such as metabolic syndrome. Proper assessment optimizes patient care by simultaneously addressing migraine symptoms and offering therapeutic options that can collectively benefit both conditions and improve not only quality of life but risk factors of cardiovascular disease.

The Crisis of Cardiometabolic Conditions

The growing prevalence of chronic health conditions in Canada is alarming with a need for proficient primary care assessment and intervention. Nationwide, metabolic syndrome (MetS) and related cardiometabolic conditions contribute to 17% of all health care costs and more alarming, 43% of all deaths. According to a 2014 study, nearly 1 in 5 individuals (19.1%) meet the diagnostic criteria for MetS—and often without awareness of their risk factors or the implications thereof.[1] Addressing the risk factors associated with chronic health conditions can be challenging for both the patient and the clinician. Developing a therapeutic alliance where patients are informed *and* motivated can be frustrating when the modifiable outcome for patients is often an abstract and fearful endpoint in the future (i.e. mortality and the risk of heart attack or stroke). Addressing tangible symptoms can inspire patients while simultaneously decreasing their risk profile. Improving the risk factors of MetS unfortunately does not always correlate with improved symptomatology. Subtle improvement in triglycerides and blood pressure, for example, is unlikely to significantly alter daily experience. However, improving prominent symptoms that impact the patient regularly may result in therapeutic compliance and long-term success. Migraine is known to coexist with MetS and insulin resistance (IR), though the pathophysiological processes are not entirely known.[2, 3] Patients presenting with a chief concern of chronic migraine may benefit from naturopathic medical treatment not only to alleviate the discomfort but also to screen for and address cardiometabolic conditions such as MetS.

The Migraine-Metabolic Connection

There are multiple theoretical etiologies of migraine. A misinformed concept is the "vascular theory of migraine" that originated due to the pulsatile nature of the pain. This perspective was adopted due to certain vasodilators (e.g. nitric oxide) triggering migraines and vasoconstrictive therapies (e.g. triptans) proving to be effective abortive agents. However, clinical data has revealed that the painful pulsations have a lower frequency and are not synchronized with cardiac rhythm.[4] Intracranial vessel dilation during migraine is slight and is unaffected by sumatriptan (which has also been shown to have neural effects). Though appealing, the vascular theory has been proven obsolete[4]. Current research suggests that migraine is more fittingly a disorder of neurological processes. Neurological hyperexcitability—an over-response to sensory stimuli—has been hypothesized as a key feature of migraine. There are several mechanisms explaining the excitatory neuronal cascades leading to migraine including metabolic influences.[3,4]

Insulin metabolism and activation has been implicated in migraine. A contributing factor to changes in blood glucose levels are appetite-related neuropeptide signals in the hypothalamus. Prodromal migraine symptoms (e.g. fatigue and food cravings) implicate the involvement of the hypothalamus in addition to other brain areas such as the brainstem, cortex, and limbic system.[3] Orexigenic (stimulating food intake and decreasing energy expenditure) and anorexigenic (inhibiting food intake and increasing energy expenditure) neuropeptides are regulators of energy homeostasis in specific hypothalamic nuclei. Neuropeptide Y (NPY) and agouti-related peptide (AgRP) are orexigenic peptides that are inhibited by peripheral insulin and leptin. Insulin levels have been found to be consistently higher in migraineurs compared with controls—implicating the role of IR in migraine. Hypoglycemia from a fasted state is a trigger associated with initiating migraine. In susceptible individuals, low insulin receptor activation—through fasting—may trigger a migraine.[4] Genetic polymorphisms related to insulin receptor function may be a confounding factor.[5] There are many metabolic pathways which have been posited as the formal mechanism linking IR and migraine.[3, 4] Research continues to offer more details on relevant pathophysiology but more importantly shows consistent correlations that warrant judicious and novel approaches to treating migraine and comorbidities collectively.

MetS exhibits a broader range of symptoms than IR alone. Migraine with aura (MA) has a positive association with low HDL-cholesterol, hyperglycemia, and abdominal obesity. MA may contribute to a

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higher risk of MetS and should undergo appropriate screening.[6] Obesity is not considered a risk factor for migraine but is, however, associated with higher incidence and severity of symptoms.[4] There is a link between medication overuse headache (MOH) and MetS. A clinic-based study revealed that comorbid analgesic overuse may be the risk factor for MetS in female migraineurs and is associated with central obesity and hypertension.[7] Appropriate screening and treatment of migraine necessitates a full work up and health inquiry including (1) proper diagnosis of migraine; (2) clinically relevant assessments; (3) evidence-informed treatment strategies; and (4) and a strong therapeutic alliance.

Assessing Migraine Headaches and Screening for Metabolic Conditions

The proper assessment of migraine headache is the clinician's primary duty before considering comorbid metabolic influences. The features of migraine headache are unilateral, pulsating pain of moderate to severe intensity that lasts 4 to 72 hours and typically results in avoidance of normal physical activities (e.g. walking). Migraine is usually associated with nausea and/or vomiting as well as photophobia and phonophobia. Migraine with aura has precipitating symptoms of vision changes (e.g. scotomas), unilateral numbness or tingling, muscle weakness, or speech changes which typically occur less than 60 minutes before the onset of head pain. Migraine can be episodic or chronic.[8] The Migraine Screen Questionnaire (MS-Q) is a self-administered checklist consisting of a mere 5 questions and has been shown to be useful in the primary care setting for early detection and assessment of migraine.[9] A headache diary may be a useful tool to clarify symptoms and to determine possible triggers.[10] Intracranial and emergent conditions such as temporal arteritis, acute glaucoma, and meningitis must be excluded when working up acute migraine.[8] To ensure the safety of patients, the clinician should be satisfied with a non-emergent diagnosis of migraine before pondering specific triggers or coexisting concerns such as food sensitivities, hormonal influences, and IR. Vital signs and a focused neurological examination are non-negotiable.

If risk factors supporting a diagnosis of MetS are present, then a thorough metabolic screen is indicated. The diagnostic criteria for MetS is the presence of 3 of the following features: visceral obesity, low HDL-cholesterol, high triglycerides, hypertension, and insulin-resistance.[1] Evaluating MetS requires diligent observation, physical examination, and laboratory investigations. Querying current pharmacologic intervention is important as some patients exhibit normal blood pressure or lab values due to effective medication use. Medication, genetic, and lifestyle factors may contribute to features associated positively with MetS (e.g. statin medications may increase blood glucose[11] and idiopathic hypertension has a familial component[12]). Inquiry about specific analgesic medications used to treat the migraine—including dose and frequency—helps to rule out MOH as part of the differential diagnosis (recall that MOH can also increase the risk of MetS[7]). Additional physical exam and observations include weight tracking, body measurements, calculation of body mass index (BMI), and possibly bio-electrical impedance analysis (BIA). Cardiopulmonary and vascular health should be examined. If there are prominent features of overt diabetes, then distal extremity, ophthalmoscopic, and nervous system assessment is needed. Laboratory investigations should include basic bloodwork (complete blood count (CBC), cholesterol panel and triglycerides, and a comprehensive metabolic profile (CMP)) to assess the presence and/or progression of MetS. Glucose metabolism can be screened with HbA1c or fasting insulin, but detailed blood insulin and glucose assessment with a 2-hour insulin tolerance test should be considered. Proactive and functional testing considerations are the Kraft Prediabetes Profile; the Protein Unstable Lesion Signature (PULS) Cardiac Test; the CardioMetabolic Profile; Advanced Lipoprotein Testing; and possibly testing that may reveal non-metabolic origins of migraine such as food sensitivity testing and comprehensive hormone analysis.[13]

Naturopathic Approaches to Treatment

Treatment approaches should be evidence-informed and should emphasize development of a therapeutic alliance that is rooted in informed consent, especially when discussing the risks associated with MetS. Patients presenting with a chief concern of chronic migraine require careful management and intervention should not withhold conventional treatments if required: abortive therapies to address acute migraine (NSAID combination medications and triptans) and migraine prophylaxis. If MetS is a suspected comorbidity, then keystone interventions are preventative in nature: diet modification, sleep hygiene, medications, and exercise.[8] The foundations of health—breath, hydration, whole foods, social connection, movement and rest—foster balance and are proactive recommendations that may serve patients well. Therapies such as vitamins, minerals, nutraceutical formulations, herbal preparations, and physical therapies are all on the table when treating migraine and metabolic dysfunction cohesively. Though the link between metabolic conditions and migraine has been established, supporting blood sugar homeostasis does not guarantee mitigation or resolution of migraine-related symptoms. Open and honest discussion around expectations of treatment is needed.

Therapies that simultaneously address IR and migraine can be considered. Interventions include but are not limited to alpha-lipoic acid, magnesium, riboflavin, coenzyme Q10, vitamin D, and therapeutic ketosis. Alpha-lipoic acid (ALA) has evidence in improving IR and may additionally decrease the number of migraine attacks and days of treatments, a 6-month cohort study revealed.[14] Hypomagnesemia has been associated with migraine and IR. Intravenous magnesium significantly relieved acute migraine up to 24 hours after the initial infusion. Oral supplementation with magnesium alleviated the frequency and intensity of migraine.[15] In the context of IR, magnesium supplementation positively effects fasting insulin and glucose levels.[16]

Riboflavin (vitamin B_2) has implications for prophylactic migraine therapy based on a randomized control trial (RCT)[4] and a Korean study showed insufficient riboflavin intake may increase the risk of

developing cardiometabolic disorders—particularly in women.[17] Coenzyme Q10 supplementation is indicated for migraine treatment[17] and may slow the progression of prediabetes to overt diabetes.[19] An RCT showed that the simultaneous use of simvastatin plus vitamin D resulted in improvement in migraine at 12 and 24 weeks compared to placebo.[20] Hypovitaminosis D can hasten the development of IR.[21] Therapeutic ketosis has implications for both blood sugar control and migraine. Elevated ketone bodies (specifically D-β-hydroxybutyrate) are associated with improved migraine symptoms with evidence that a ketogenic diet may be a credible treatment approach. The therapeutic benefit of ketone bodies is attributed to the influence on physiological processes such as inflammation, oxidative stress, and mitochondrial function.[22] Hypoglycemia from fasting is a known trigger for migraines and distinct from glucose and insulin changes in nutritional ketosis. Utilizing therapies that benefit MetS while decreasing migraine duration and frequency can improve quality of life while decreasing risk factors that contribute to morbidity and mortality.

Conclusion

Migraine management requires thorough assessment; exclusion of life-threatening conditions; and openness to conventional therapies. It is prudent to include MetS in the differential diagnosis of migraine when applicable features are present. Though mechanisms are not entirely understood, migraine is a neurological condition that may benefit from metabolic regulation—especially when MetS is noted as a comorbid condition.

About the Author

James R. Conway, ND is a primary care provider in Langley, BC, where he has a family practice with a clinical focus in men's, children's, and cardiometabolic health. Dr. Conway obtained his naturopathic medical training from the Boucher Institute of Naturopathic Medicine and was the recipient of the Clinical Excellence Award on graduation. He has a fascination with languages and he and his wife have dedicated to raising their two young children in a multilingual home.

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New Lancet MHT Study May Not Be Relevant to Modern Body-Identical Formulas

Dr. Lara Briden, ND

Reference

Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *The Lancet* 2019. Epub 2019 Aug 29.

Design and participants

A meta-analysis of epidemiological studies and randomized trials on long-term follow-up of post-menopausal women prescribed menopausal hormone therapy (MHT). The analysis looked at 58 studies published between 1992 and 2018 and more than 100,000 women who received a breast cancer diagnosis during that time. The majority of the data was derived from prospective studies.

Key findings

A slight but statistically significant increased risk of breast cancer was detected for every type of MHT except vaginal estrogen. For a woman of average weight who has never used MHT, the absolute risk of breast cancer in the age range of 50 to 69 years is 6.3%. According to this analysis, that risk increases to 6.8% for estrogen-only MHT; 7.7% for formulations with intermittent progestin; and 8.3% for formulations with daily progestin.

Practice implications

The first takeaway is that no cancer risk was detected for topical vaginal estrogen, a reassuring finding for patients who require vaginal estrogen for dryness and other symptoms of the genitourinary syndrome of menopause (GSM).

The second takeaway is that the highest cancer risk was for estrogen plus progestin, suggesting that at least some of the risk is attributable to the progestin. Given the duration of MHT before diagnosis (average of ten years) and the timing of the diagnoses (median-year of 1999 for North America participants and 2007 for European participants), most of the participants were exposed to estrogen in the form of oral conjugated equine estrogen and progestins such as medroxyprogesterone acetate and norethisterone. The higher risk associated with such formulations may not be relevant to MHT in the form of body-identical transdermal estradiol and oral micronized progesterone — a combination increasingly preferred by clinicians and recommended by expert MHT prescribing guidelines.[1, 2]

Oral micronized progesterone (OMP) is different from progestins in that it is identical to the body's progesterone. OMP is available in Canada as Prometrium® (not accessible by all ND prescribers) or as a compounded capsule. It can be prescribed together with estrogen or *on its own*, a treatment strategy proposed by Canadian researcher Jerilynn Prior. In two randomized controlled trials,[3, 4] Professor Prior found that OMP-alone may relieve the symptoms of both perimenopause and menopause. Both studies were small and of short duration and did not assess for the long-term safety of progesterone.

To understand the safety of OMP, we have to look to other studies such as the 2018 systematic review "The impact of micronized progesterone on breast cancer risk."[5] Conducted by an international expert panel, the review acknowledged the relative scarcity of data for body-identical progesterone and did not conduct a meta-analysis. Instead, they reviewed the data of 19 studies and made the following recommendations: "(1) estrogens combined with oral (approved) or vaginal (off-label use) micronized progesterone do not increase breast cancer risk for up to 5 years of treatment duration; (2) there is limited evidence that estrogens combined with oral micronized progesterone applied for more than 5 years are associated with an increased breast cancer risk; and (3) counseling on combined MHT should cover breast cancer risk - regardless of the progestogen chosen." They found no evidence for the effectiveness or safety of transdermal progesterone.

In conclusion, the new *Lancet* study demonstrates that non-body-identical types of MHT such as oral conjugated equine estrogen and medroxyprogesterone acetate probably do increase the risk of breast cancer, albeit slightly. We should, of course, advise patients of that risk within the broader conversation of risks versus benefits. We should also make patients aware that other types of MHT, such as body-identical transdermal estradiol and OMP, may not carry the same risk. Finally, we could inform patients of the work of Professor Prior, and her recommendation that OMP can be used on its own, without estrogen.

About the Author

Dr. Lara Briden, ND graduated from CCNM in 1997. She is author of the bestselling book "Period Repair Manual" and is a passionate communicator about women's health.

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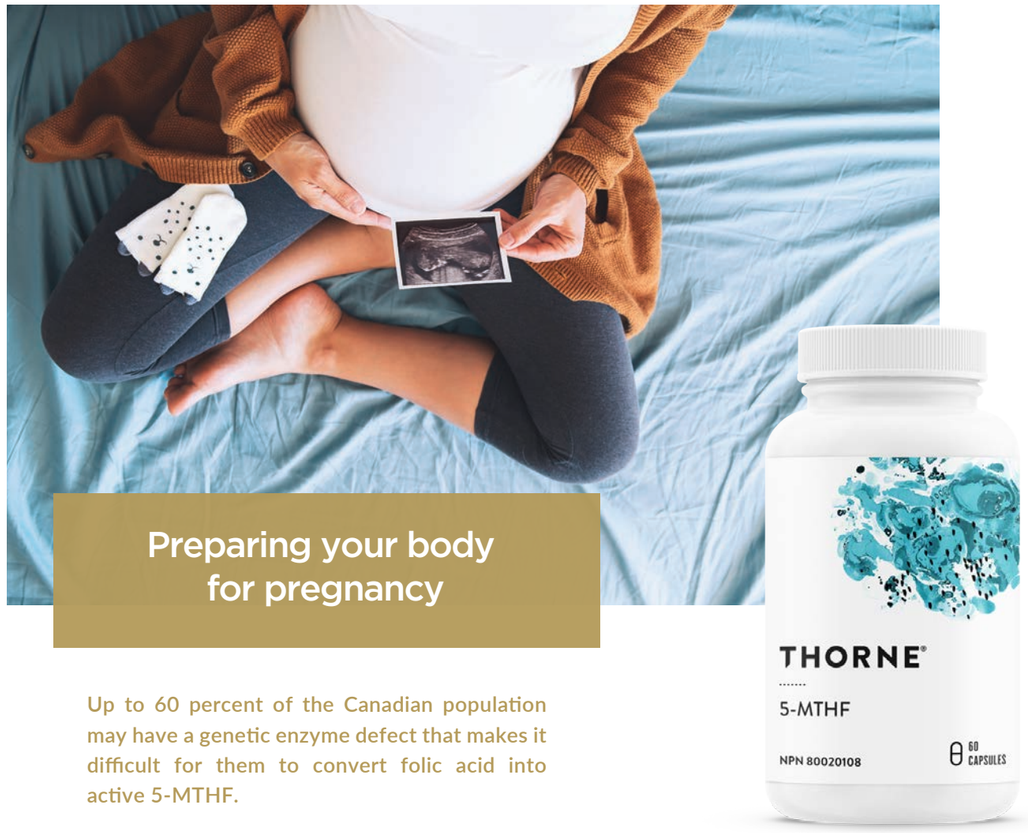

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