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CV, cardiovascular; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; SU, sulfonylurea.

References: 1. RYBELSUS® (semaglutide tablets) Product Monograph. Novo Nordisk Canada Inc., March 30, 2020.
2. Rosenstock J, et al. Effect of additional oral semaglutide versus sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: The PIONEER 3 randomized clinical trial. *JAMA*. 2019.
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UPDATE ON THE MANAGEMENT OF HYPERTENSION IN 2023

Introduction

Hypertension is the most common condition managed in the primary care setting. It is a potent but modifiable risk factor for cardiovascular disease (CVD) and premature mortality.[1] Currently, approximately 25% of Canadian adults have a diagnosis of hypertension.[2,3] However, the global community is experiencing challenges with optimizing hypertension management; it is estimated that at least 23% of individuals globally have effectively managed hypertension.[4] Furthermore, if clinicians were able to identify and adequately intervene in these cases, we could prevent 10.8 million deaths per year.[1] This statistic is extremely relevant to Canadian practitioners as our most recent Canadian data suggest that 34% of adults with hypertension are not achieving target blood pressure (BP) due to undertreatment or lack of awareness.[3]

The undertreatment of hypertension is complex. There are a number of structural and environmental drivers of CV risk, and there is increasing recognition that if we are going to be effective at CV risk reduction, we must acknowledge the significant role that social determinants play in the development of risk factors including hypertension, smoking, obesity and diabetes.[5]

The clinical guidance concerning hypertension may inadvertently contribute to the challenges we are seeing globally with hypertension management.[6,7] There are numerous guidelines available to inform clinicians about how to provide supportive care for individuals with hypertension, and discordance between guidelines and the granularity of guidelines make implementation challenging.[7,8] While there is disparity between guidelines, as well as differences regarding hypertension nomenclature, there is unanimous agreement that accurate BP measurement, risk-based thresholds for intervention, simplified approaches to pharmacotherapy, and well-structured care are the foundations of effective hypertension management.[9]

Accurate Blood Pressure Measurement

Accurate BP measurement is critical to the diagnosis of hypertension. While it is a very common clinical procedure, errors in BP measurement are frequent due to a variety of factors including patient preparation and positioning, incorrect use of measurement equipment, and human errors in interpreting and documenting measured results.[10] As quality BP measurement does take some time, measurement quality can also be compromised or neglected in clinical settings where appropriate measurement training and workflows have not been implemented.[11]

Electronic (oscillometric) BP measurement is the preferred method for all office measurements as it is easy to perform and eliminates many of the human factors that contribute to erroneous or inconsistent BP measurement results.[12] *Standardized office BP* measurement (using electronic devices) is currently recommended *for screening adults* for hypertension and for *assessing response to treatment*.

Out-of-office measurements (24-hour ambulatory BP monitoring and home BP measurement [HBPM]) are recommended to *confirm a diagnosis of hypertension* and to identify individuals with white coat and masked hypertension.[12]

Visit-to-visit variability (VVV) in in-office BP measurement is a significant challenge for clinicians. A recent cohort study by Lu et al examined nearly eight million systolic BP (SBP) measurements from just over 500,000 adults and found that the average variation in SBP between visits (≤90 days apart) was +/-12 mmHg.[13] This is concerning, as the magnitude of variation is as significant as a change one might expect to see with initiation or discontinuation of therapy.

The reality of significant VVV in the face of guidelines that recommend standardized in-office BP monitoring be used to determine when therapy should be initiated and how well patients are responding to treatment is a challenging one. Unlike the real-world study by Lu et al, clinical studies that inform the guidelines use a standardized approach to measurement that ensures quality and reproducibility.[11] The study by Lu et al highlights two important points: 1) That every effort must be made to optimize the quality of in-office BP measurements; 2) That there is a role for out-of-office and unattended, automated in-office measures to further inform therapeutic decision-making.

With respect to out-of-office measures, 24-hour ambulatory BP monitoring (ABPM) is the preferred measurement method.[12] While both ABPM and HBPM better predict CV events than in-office BP measurement,[14-16] ABPM has the advantage of providing nocturnal BP measurements and insights into the integrity of BP diurnal variation. Nocturnal BP is a very sensitive predictor of increased CV risk in individuals with known hypertension and among those without it.[17,18] Individuals who have lost diurnal variations in BP have also been found to have a CV event rate that is nearly double that of individuals with normal BP circadian rhythms.[17,19]

Unfortunately, access to ABPM is a challenge in many clinical settings. If it is unavailable, HBPM provides a reasonable and valid alternative for the diagnosis of hypertension, white coat hypertension and masked hypertension. Given the prevalence of hypertension and the importance of valid out-of-office measures, normalizing the presence of a validated HBPM device and familiarizing adults with HBPM are important discussion points at wellness visits in primary care. While there are several emerging technologies that can estimate BP (wrist and watch devices, for example) there is limited use for these tools in a clinical setting. Hypertension Canada recommends that validated wrist cuffs be used solely to *estimate* BP in individuals with a large upper arm circumference.[12] Abnormal levels for each measurement modality are tabulated in **Table 1**.

The Hypertension Canada diagnostic algorithm is displayed in **Figure 1**; it can be divided into four distinct steps: screening visit; BP assessment visit; collection of further BP data; and diagnosis. A diagnosis of hypertension can be made in individuals with highly elevated BP (≥180/110 mmHg) at the time of the assessment visit; however, out-of-office measures are still encouraged for risk assessment and to engage patients in self-monitoring of BP.

Clinical, Biochemical and Risk Assessment of Adults with Hypertension

Following diagnosis, patients should be assessed for conditions that can guide therapeutic decision-making and determine whether any hypertension-mediated organ damage (HMOD) has occurred. Therefore, when a patient is diagnosed with hypertension, the following investigations are recommended:[12,20]

1. Screening neurologic exam
2. Fundoscopy
3. 12-lead ECG
4. Urinalysis
5. Electrolytes
6. Creatinine/eGFR
7. Lipid profile
8. HbA1c and/or fasting glucose (if not already diagnosed with diabetes)
9. Pregnancy test (in individuals with potential for pregnancy)

While not currently recommended at the time of diagnosis, screening for primary aldosteronism (PA) with an aldosterone-renin ratio may be considered. The prevalence of PA among adults with hypertension is currently estimated at 5%; it is as high as 20% among those with resistant hypertension and in the under-diagnosed population.[21,22] As PA is associated with significant and premature CV morbidity and mortality, identifying individuals that could benefit from surgery or early treatment with a mineralocorticoid receptor antagonist is important.

Cardiovascular Risk Assessment

CVD is the leading cause of death among patients with hypertension, and patients should be engaged in regular discussions about their risk.[1,12,20,23,24] Risk assessment provides an opportunity to engage patients regarding how individual risk factors can be modified, in addition to informing therapeutic decision-making. CVD risk (or the presence of clinical CVD) also determines the threshold at which hypertensive therapy is initiated, as well as the therapeutic target (**Table 2**).

Hypertension Canada recommends that the Framingham Risk Score be calculated as this was the tool used to identify high-risk individuals (10-year risk >15%) in the context of the Systolic Blood Pressure Intervention

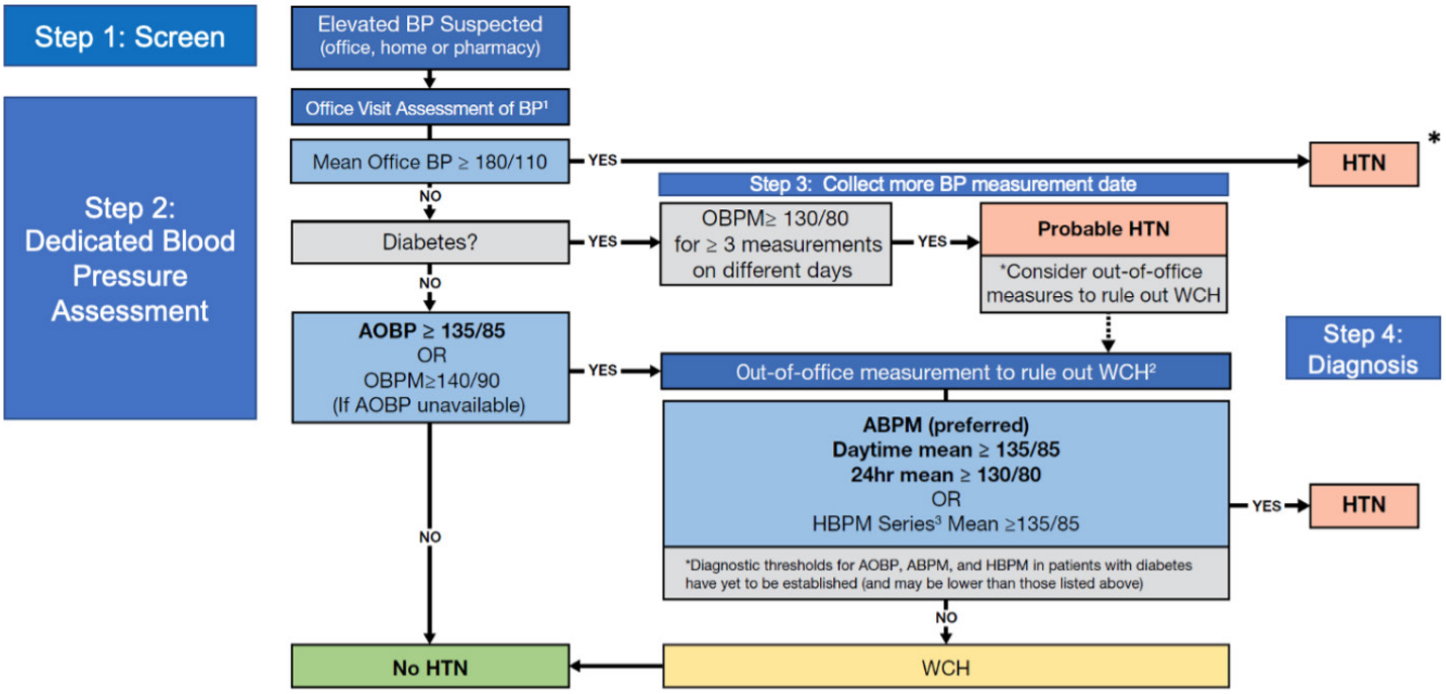

Figure 1: Hypertension Canada diagnostic algorithm.

** In individuals with very high blood pressures in office >180/110, a diagnosis of hypertension can be made, however out of office blood pressure measurement can still assist in characterizing hypertension and CV risk prediction*

Standardized Office Measures	**Automated (oscillometric), unattended Office BP measurement (AOBP)**	Displayed mean SBP ≥ 135 mmHg or DBP ≥ 85 mmHg is **high**
	Automated (oscillometric), attended Office BP measurement (AOBP)	Mean SBP ≥ 140 mmHg or DBP ≥ 90 mmHg is **high**
Out of Office Measures	**24-hour Ambulatory BP Monitoring (ABPM)**	Mean awake SBP ≥ 135 mmHg or DBP ≥ 85 mmHG **OR** mean 24-hour SBP ≥ 130 mmHG or DBP ≥ 80 mmHG are **high**
	Home BP Monitoring (HBPM)	mean SBP ≥ 135 mmHg or DBP ≥ 85 mmHg are **high**

Table 1: Identifying abnormally high BP readings by measurement modality.

(SPRINT) trial[25]; however different CVD risk assessment approaches are encouraged by other guidelines in the U.S. and Europe, and newer Canadian population data risk prediction models have been developed.[23,24,26] Regardless of the specific tool used, risk assessment as a practice is universally considered an important activity, particularly in the context of shared decision-making.[20] A thoughtful clinician-patient discussion about CV risk is valuable; clinicians should use the tools they feel are most appropriate to support those discussions.

In addition to risk factor assessment, patients with hypertension must also be screened for evidence of HMOD, including hypertensive retinopathy, nephropathy, and peripheral vascular, CV and cerebrovascular disease. This is particularly important for individuals who have not been identified as having an elevated predicted risk (i.e. lower risk factor burden) for several reasons:

1) Individuals have varying degrees of vascular tolerance for hypertension and the presence of HMOD with low risk factor burden identifies those with particular sensitivity to the vascular effects of hypertension;
2) Individuals with specific patterns of organ injury may have a higher risk for secondary hypertension;
3) The natural history of HMOD can be modified with appropriate treatment; and
4) The presence of HMOD may also influence therapeutic agent selection.[1]

Simplified Approaches to Pharmacotherapy

BP lowering is highly effective in improving health outcomes. All patients should be counselled on healthy behaviours such as engaging in 150 minutes of physical activity per week; reduction of dietary sodium; increased

Patient Population	BP threshold (mmHg) for initiation of therapy	BP target (mmHg) for treatment
Low risk (no HMOD or CV risk factors)	SBP ≥ 160 DBP > 100	SBP < 140 DBP < 90
High risk of CVD*	SBP > 130	SBP < 120
Diabetes mellitus	SBP > 130 DBP > 80	SBP < 130 DBP < 80
All others (HMOD, CV risk factors without CVD)	SBP > 140 DBP > 90	SBP < 140 DBP < 90

Table 2: Hypertension Canada treatment thresholds and targets (OBPM unless otherwise stated).[12]

* *Hypertension Canada defines "High Risk" as a person that is >50 years, a known diagnosis of hypertension and an automated office BP measure of ≥130/80 plus at least one of the following:*

1. *Clinical/sub-clinical CVD*
2. *Non-diabetic, non-proteinuric chronic kidney disease (eGFR 20-59 ml/min/1.73m²)*
3. *Age ≥ 75 years*

consumption of fresh fruits and vegetables; maintenance of a healthy body mass; reduction of alcohol consumption; cessation of tobacco use; and optimizing mental health, as non-pharmacologic interventions are both effective and preferred by patients.[12,27] Reducing BP by 20 mmHg/10 mmHg reduces the risk of adverse CVD events by 50%, which makes efforts to reduce BP in hypertensive patients an extremely cost-effective strategy to lessen the burden of CV disease at a population level.[28-30] In the absence of compelling indications, ACE inhibitors (ACEi's), angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (DCCBs), thiazide (and thiazide-type) diuretics are first-line therapies for most hypertensive individuals.[12,23,24,31] Network meta-analyses suggest that there are no significant differences between the ability of each of these agents to lower BP, and recent evidence has demonstrated that there is significant heterogeneity in the antihypertensive effect of first-line agents at the individual level.[31,32] Therefore, it is perhaps not surprising that within populations, it has been established that using combination therapy achieves better BP lowering than using the maximum dose of a single agent.[33,34] Furthermore, single-pill combination (SPC) therapy (combinations of two or three first-line medications at low doses) is an approach that is both well tolerated and more effective at promoting consistent medication use, lowering BP and achieving improved CVD outcomes.[34]

Guidelines from various organizations have suggested that race/ethnicity be considered in the selection of BP-lowering medication.[12,23,24] Although they are well-intended, specific prescribing patterns based on race can be harmful as they suggest biological differences related to the entirely socially constructed concept of race (i.e., they can perpetuate biological racism).[35] While the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) suggested that individuals who identify as Black experience attenuated BP lowering with lisinopril relative to participants who identify as Caucasian,[36] the nearly 20-year directive to tailor therapy by race has not improved the quality of treatment for racialized patients.[5,37] The reality is that low-dose combination therapy is more effective and better tolerated than standard dose monotherapy, and it is often under-prescribed. Dual combination therapies that include ACEi's, ARBs, DCCBs, or a thiazide (or thiazide-type) diuretic appear similarly effective in reducing CVD risk across patient subgroups.[34] Using race-based approaches to prescribing can contribute to epistemic bias and overly complicated guidelines; single pill combination approaches are highly effective and should be used to a greater degree.

Organization of Patient Care

Community-based healthcare and multidisciplinary care models that support accurate BP pressure measurement in-office and out-of-office; clear treatment protocols for therapeutic management and medication titration; and frequent contact with a healthcare professional (HCP) (physician, nurse and/or pharmacist) are highly effective at promoting BP lowering at a practice and community level.[38-40] The structure and process of patient care are fundamental to the quality of care and are often under-discussed in clinical practice guidelines,[41] even though they are strongly supported by evidence. Funding models, professional regulatory and licensing bodies that determine scope of practice, and health professional education must all align to enable highly functioning multidisciplinary teams. The organization of patient care directly impacts primary healthcare professionals (PCPs), but they have limited power to influence this end result.

When Hypertension Canada's inaugural guidelines were launched nearly 30 years ago, they were just one component of a population-based quality improvement approach to hypertension care optimization. Several implementation strategies were deployed that included empowering hypertension screening within the community (at local fire stations and grocery stores, for example) and using peer champions to facilitate hypertension awareness and participation in screening.[38,39,42] In addition, several continuing medical education (CME) programs and capacity-building initiatives have been developed to help propel Canada

into the position of a global leader in hypertension management.[43] Many of these programs were supported by industry and community partnerships, and they were discontinued when funding was no longer available—even though they were unquestionably impactful.[42] Communities, particularly those in which healthcare professionals are under-represented but in which there is an elevated risk of hypertension and its complications, need to be empowered to care for their population and encouraged to determine how to support high-quality primary care that is trusted by these communities. This has never been more urgent.

Key Messages

- ✓ Hypertension is a clinical challenge with several effective interventions; however, it continues to grow in scale and scope
- ✓ Enabling communities to be active partners in BP screening, education and prevention is urgently needed
- ✓ At the point of care, ensure that BP is consistently and appropriately measured
- ✓ CV risk should be regularly reviewed, discussed and optimally managed
- ✓ Ensure that single-pill combination therapies are prescribed early
- ✓ Plan regular follow-up with a PCP (MD, pharmacist, or nurse)

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Financial Disclosures

None.

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IMMUNIZATION IN MIDLIFE

Introduction

Midlife is often defined as age 50 and above and is a period of life when patients commonly access the healthcare system, having recognized the need for various preventions. The Women's Health Initiative (WHI) identified cardiovascular disease (CVD), cancer and osteoporosis as the most common causes of morbidity, disability, and poor quality of life in post-menopausal women.[1] Healthcare professionals routinely screen patients with risk factors for these diseases and offer prevention and treatment to improve their quality of life. However, recommendations for immunizations are often neglected leading to unnecessary morbidity and mortality in our aging population. In Canada, it is estimated that 20,000 hospitalizations related to influenza occur each year[2] and that 4,000 to 8,000 Canadians die from influenza-related complications alone.[2,3] Vaccines can prevent the debilitating and fatal effects of infectious disease,[4] yet clinical evidence has revealed an adult immunization gap.[5] Midlife screening and intervention should serve as an immunization checkpoint, providing an opportunity for healthcare professionals to optimize quality of care and health maintenance in older patients.

Vaccination Measures and Protocols

Currently, in the midst of a global pandemic, we are also faced with options for vaccination against COVID-19. As patients review their general health and the preventions that are advised by healthcare professionals (HCPs), it is important to understand the newest COVID-19 immunizations that are available and their impact on long-term health.

National immunization standards are established by the Advisory Committee on Immunization Practices in the United States (ACIP) and the National Advisory Committee on Immunizations (NACI) in Canada. In Mexico, the National Immunization Technical Advisory Group (NITAG) establishes standards for infants and adolescents, but not for adults. Although the disease-prevention benefits of various vaccinations have been well-established, several known barriers result in a low prevalence of adult immunization.[6] The United States National Vaccine Advisory Committee (NVAC) updated their vaccine recommendations in 2013 and cited barriers to adult vaccination including lack of patient and healthcare provider knowledge about the need for vaccination; lack of priority given to preventive services; affordability concerns; healthcare insurance coverage and reimbursement; and care by multiple providers, which complicates the coordination of care. Facilitators of adult vaccination include the provider's recommendation and offer of vaccination during the same visit, which has

been shown to predict compliance for meeting adult vaccination recommendations.

NVAC advises that healthcare providers not only educate themselves and their patients about current vaccine recommendations but that that they also include an immunization needs assessment in every clinical encounter. In 2020, a National Vaccine Plan was developed to coordinate immunization objectives and priorities . With the advent of the COVID-19 pandemic and the role of vaccines in its prevention, these objectives and strategies have become even more important in outlining the framework for a robust immunization effort in the general population.[7]

Hepatitis A and Hepatitis B vaccination overview

The hepatitis A virus (HAV) and hepatitis B virus (HBV) cause liver infection with associated morbidity and mortality. Chronic HBV can lead to increased risk of cirrhosis and hepatoma. Multiple vaccines are available as immunization against HAV and HBV. The ACIP recommends the routine vaccination of children aged 12-23 months, and catch-up vaccination for children and adolescents aged 2-18 who have not previously been vaccinated. For unvaccinated adults with risk factors, including illicit-drug users, individuals with chronic liver disease (CLD), and travellers to countries with intermediate or high incidence of HAV, vaccination is recommended. Boosters are not recommended, as IgG anti-HAV antibodies produced post-vaccination confer long term immunity.[8] NACI does not provide guidance for the routine immunization of infants and children, although it has published guidance on post-exposure prophylaxis.[9]

Hepatitis B Vaccine

A universal HBV vaccine for infants and children of all ages has been available since the 1990s in both the United States and Canada. The vaccine is recommended for adults at risk for HBV infection; this includes universal vaccination of adults in settings where a high proportion of individuals have risk factors for HBV infection. In addition, it is recommended in adults requesting protection from HBV without acknowledgment of a specific risk factor. The criteria include adults who have had more than one sex partner in the previous six months, healthcare personnel, patients with end-stage renal disease (ESRD), and adults who have consulted sexually transmitted infection (STI) and HIV testing and treatment facilities. Furthermore, the ACIP recommends the following: testing all pregnant women for hepatitis B surface antigen; administration of the HBV vaccine and hepatitis B immune globulin (HBIG) testing in infants born to HBV-infected women within 12 hours of birth, followed by completion of the vaccine series and post-vaccination serologic testing; universal hepatitis B vaccination within 24 hours of birth, followed by completion of the vaccine series; and vaccination of children and adolescents age <19 years who have not previously been vaccinated.[10] Currently, there is no clinical evidence supporting the administration of a booster dose in healthy individuals in light of the fact that immunological memory is long-lasting.[11]

Human Papillomavirus Vaccine

The human papillomavirus virus (HPV) is associated with cervical, vulvar and vaginal cancer in women; penile cancer in men; and anal and oropharyngeal cancer in men and women. HPV 6 and 11 are also the cause of 90% of genital warts and are included in both the quadrivalent and nonovalent vaccines.[12] Currently, three HPV vaccines are approved for routine vaccination: bivalent, quadrivalent and 9-valent. These vaccines protect against HPV types 16 and 18, the major oncogenic strains of HPV which account for 70% of cervical cancers. The quadrivalent vaccine includes 6, 11, 16 and 18. However, the 9-valent now targets five additional strains which account for an additional 15% of cervical cancers. Vaccination is now recommended for women and men up to age 26, including men who have sex with men and immunocompromised individuals. In Canada, NACI recommends HPV vaccination for at-risk women and men > 26 years of age, with no upper age limit. However, Health Canada has approved the vaccine only up to age 45,[13] reflecting a permissive statement from NACI suggesting that practitioners focus on patient risk, regardless of age past 45.

The recommendation is slightly different in the United States as the Centers for Disease Control and Prevention (CDC) recommends vaccination for men and women up to age 26. For those aged older than 26 years, the CDC does not recommend catch-up HPV vaccination for all adults; however, it does recommend shared clinical decision-making regarding HPV vaccination for adults aged 27 through 45 years.[14] HPV vaccines are not licensed for use in adults older than 45 years of age. Clinicians practicing in the United States do encounter unvaccinated women older than 26 years of age who request immunization. They may be deemed to be at risk or high risk and may choose the protection vaccination provides. In these cases, it is reasonable to offer the vaccine. However, this is a decision for the physician and patient to make together as vaccination in this circumstance is considered off-label.

HPV immunization has been recommended even if an individual has already been infected or has been diagnosed with a cancer or precursor of cancer. The research has demonstrated that by immunizing these women, there is a decreased risk of recurrence of HPV in the original site or in a different location.[15,16]

The HPV 9 vaccine product monograph in the United States and Canada now includes the indication for the prevention of oropharyngeal and other head and neck cancers caused by the types 16, 18, 31, 33, 45, 52, and 58 in both men and women. This is significant as the incidence of oropharyngeal cancers, particularly in

men, has been increasing in both the United States and Canada.[17]

HPV type 16 (HPV16) is the type most often linked to cancer of the oropharynx, especially in the tonsil and base of the tongue. HPV DNA is associated with two out of three oropharyngeal cancers. The number of oropharyngeal cancers linked to HPV has risen greatly over the past few decades. These cancers are becoming more common in younger individuals with a history of multiple sex partners (including the practice of oral sex) and no history of alcohol abuse or tobacco use, previously a common risk factor for these cancers. In midlife, the vaccination discussion should be focused on risk assessment, the likelihood of new exposure, and the understanding that with aging, the immune system is less robust. A previous HPV infection that has been dormant or latent may subsequently become more active, leading to recurrent or new disease in a given patient. Indeed, the statistics for cervical cancer, generally a cancer occurring in younger women, reveal there is a second peak of cancers in older, post-menopausal women. In Canada, HPV incidence peaks among women in their 40s, and then again among women ≥ 70 years of age.[18]

Pneumococcal Vaccines

Streptococcus pneumonia remains a leading infectious cause of serious illness in adults and is responsible for 500,000 cases of pneumococcal pneumonia annually. It is associated with both increased risk of hospitalization and mortality with increasing age.[19] The 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended by the ACIP for all adults >65 years of age, and in younger, immunocompromised and at- risk adults. In 2011, a new 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the Food and Drug Administration (FDA) in the United States for adults aged 50 years and older. In 2014, the ACIP recommended routine vaccination of all adults >65 years of age and adults <65 years of age at risk for invasive pneumococcal disease. However, in 2019, the ACIP stated that PCV13 vaccination is no longer *routinely* recommended for all adults aged 65 and older. Instead, shared clinical decision-making for PCV13 use is recommended for individuals aged 65 years and older who are not high-risk. Shared clinical decision-making considerations may include risk for exposure to PCV13 serotypes and the risk for pneumococcal disease as a result of underlying medical conditions.[20]

Most recently, in 2021, two new vaccines were licensed in the United States, PCV15 and PCV20. These vaccines are conjugated and have a greater number of serotypes, which is likely to translate into reduced disease risk for the patient. In October 2021,the ACIP Working Group reviewed several considerations regarding the use of these vaccines. Their conclusions were both age- and risk-based. The Working Group recommended that patients aged 65 and older who had *not* received a previous pneumococcal vaccine or whose history was unknown should receive either PCV20 alone or PCV15 followed by PPSV23. For those age 19 and older with risk factors, comorbid conditions, and immunologic risk, they also should receive PCV20 alone, or PCV15 followed by PPSV23.[21]

On an individual basis, vaccine decision-making should consider general health factors, including pregnancy; co-morbidities; occupational risks and consequences of disease; loss of work-related productivity; potential loss of daily living capacities; pain resulting from the vaccine; preventable disease complications; and the protection of others (patients, pupils, family).[22]

The vaccination schedule is variable and may depend on a patient's age and underlying risk. In a patient aged 65 and older or in a younger patient with risk, the ideal option is to immunize with PCV13 first, or currently in the United States, PCV15 or PCV20 as they are conjugate vaccines. Immunogenicity studies evaluating responses to PCV13 and PPSV23 administered in series showed an improved immune response when PCV13 was administered first.[23] If PCV13 or 15 is used, it is then followed by PPSV23, the polysaccharide vaccine. The Canadian guidelines suggest that an eight-week interval is sufficient, while ACIP suggests a one-year interval. If PPSV23 has been administered, guidelines in both countries recommend waiting one year before the administration of PCV13.

Pneumococcal Vaccines: Canadian Guidelines Recommendations

It is important to understand the level of recommendation that NACI assigns to any given statement. A strong recommendation applies to most populations/individuals and should be adhered to unless a clear and compelling rationale for an alternative approach is present. A discretionary recommendation may be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

NACI recommends that the pneumococcal conjugate vaccine, PCV20, be offered to pneumococcal vaccine-naïve adults aged 65 and older, and individuals 50-64 years of age with risk factors that place them at higher risk for contracting pneumococcal disease. As well, individuals 18-49 years of age with immunocompromising conditions should be vaccinated. This was a strong NACI recommendation. NACI had a discretionary recommendation for these same cohorts, offering PCV15 as an alternative to PCV20 if needed, but followed by PPSV23, similar to the ACIP recommendation.

NACI recommends that PCV20 be offered to adults 65 and older if they have previously been immunized with PPSV23 alone or, if they have received the series of PCV13 followed by PPSV23 more than five years prior. Once again, this is a strong recommendation. If adults aged 65 and older have received PCV13 alone, they should be reimmunized with PCV20 as early as within one year. This

is a discretionary recommendation.

NACI supports the continued use of PCV13 and PPSV23 in adults only when PCV15 and/or PCV20 are unavailable or inaccessible.

Currently, there are no public health level recommendations on the use of PCV15 or PCV20 in adults 18-49 years of age with non-immunocompromising risk factors that place them at high risk of IPD, as additional analyses on the cost-effectiveness of conjugate PCV15 and PCV20 in this population are needed. PCV15 or PCV20 may be considered for these adults at the clinician's discretion.[24]

Shingles Vaccine

The incidence of herpes zoster, commonly known as shingles, along with the incidence of postherpetic neuralgia, interference with daily activities and hospitalizations, increases with age. To prevent herpes zoster and its complications, the FDA and Health Canada have approved two vaccines for use in individuals over the age of 50: The live virus vaccine (Zostavax®II [Live Zoster Vaccine, LZV]) which has been on the market since 2011, and the newer recombinant vaccine (RZV or Shingrix®) which came to market in 2017. The ACIP has advised that adults > 50 years of age should be immunized regardless of history of shingles, and regardless of whether or not they were previously immunized with the LZV vaccine.[25] The clinical study of the herpes zoster subunit vaccine (RZV) conducted in older adults revealed excellent efficacy of >97% in all age groups. For this reason, this vaccine is has now become the vaccine of choice for herpes zoster. NACI states that while both vaccines remain as options, RZV has longer-lasting efficacy, is more cost-effective and does not have the same contraindications as LZV, including the use in immunocompromised patients. RSV is becoming the standard of care. LZV may be used if RZV is unavailable or contraindicated.[26]

Tetanus (Td) and Tdap Vaccines

A one-time dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) booster (rather than the decennial dose of Td) is recommended for adults who have not previously received Tdap. In 2001, the FDA expanded the age indication for Tdap to include those >65 years of age. Tdap may be administered regardless of the interval since the last tetanus or diphtheria-toxoid vaccine. A single dose of Tdap is recommended for practitioners with direct patient care contact who have not received the vaccine as an adult, and for persons >65 years of age who have or anticipate close contact with an infant less than 1 year old to reduce the transmission of pertussis (e.g., adults who have recently become grandparents) Booster doses of Td vaccine continue to be recommended every 10 years.[27]

COVID-19 Vaccines

Three coronavirus (COVID-19) vaccines are currently authorized for use in the United States. The FDA issued Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine on December 11, 2020, and for the Moderna COVID-19 vaccine on December 18, 2020; each is administered as a two-dose series.[28] The Advisory Committee on Immunization Practices issued interim recommendations for the Pfizer-BioNTech and Moderna COVID-19 vaccines on December 12, 2020,[29] and December 19, 2020.[30] Both of these vaccines, known as mRNA vaccines, are approved by Health Canada and are being administered in Canada.[31]

The Johnson & Johnson/Janssen (J&J/Janssen) vaccine, the third vaccine approved in the United States, was temporarily paused due to concerns of rare blood clots. On April 23, 2021, the CDC and FDA recommended that use of the J&J/Janssen COVID-19 vaccine be resumed in the United States. However, women < 50 years of age should be aware of the rare risk of blood clots with low platelets that can occur post-vaccination. However, these occurrences are extremely rare and are thought to be related to an abnormal reaction of platelets, similar to heparin-induced blood clots. According to the American Society of Hematology, the term now being used to describe these rare events is vaccine-induced immune thrombotic thrombocytopenia (VITT). Its diagnosis is based on four criteria, all of which must be met. These include the administration of the COVID-19 vaccine (Johnson & Johnson and AstraZeneca (AZ) only, to date) 4 to 30 days previously; venous or arterial thrombosis (often cerebral or abdominal); thrombocytopenia; and a positive PF4 "HIT" (heparin-induced thrombocytopenia) ELISA test.[32]

The viral vector vaccines, by AstraZeneca and J&J/Janssen have also been approved for use in Canada, but have various limitations based on age and risk. This is partially dependent on each province as different implementation guidelines exist in various parts of the country.

According to Thrombosis Canada, a well-respected national guidelines body for thrombosis and the use of anticoagulants, the risk of a significant blood clot with the AZ vaccine is four per one million. By comparison, the risk with the use of birth control pills is 900 per one million. The average Canadian has a thrombosis risk of 1,290 per 1 million, and the risk in a patient hospitalized with COVID-19 is 147,000 per one million.[33] Thrombosis Canada further concludes that a history of blood clot, Factor V Leiden, or the need for ongoing anticoagulant therapies are not contraindications to receiving any of the vaccines.

It must be recognized that as new data emerges, both NACI and ACIP review and update their guidance accordingly. The Vaccine Adverse Event Reporting System (VAERS), is a national passive surveillance system in the United States that accepts reports from healthcare providers, vaccine manufacturers and the public. In

NACI Recommendation		
Population by age	**Primary series**	**Booster dose(s) per recommended interval if not already received**
Adults ≥ 65 years	**Should be** offered	• **At least one** booster dose is recommeneded • **Regardless of previous booster** doses a booster since the start of fall 2022 **should be offered**
Adults 18–64 years	**Should be** offered	**High-risk population** • **At least one** booster dose is recommeneded • **Regardless of previous booster** doses a booster since the start of fall 2022 **should be offered** **Not High-risk population** • **At least one** booster dose is recommeneded • **Regardless of previous booster** doses a booster since the start of fall 2022 **may be offered**
Adolecents 12–17 years	**Should be** offered	**High-risk population** • **At least one** booster dose is recommeneded • **Regardless of previous booster** doses a booster since the start of fall 2022 **should be offered** **Not High-risk population** • **A booster** since the start of fall 2022 **may be offered**
Children 5–11 years	**Should be** offered	**High-risk population** • **A booster** since the start of fall 2022 **should be offered** **Not High-risk population** • **A booster** since the start of fall 2022 **may be offered**
Children 6 months to < 5 years	**May be** offered	No authorized product; not recommended

Figure 1: NACI Guidance on COVID-19 Vaccine Booster Doses (Initial Considerations for 2023)

addition, a safety monitoring system has been established by the CDC specifically for the COVID-19 vaccination program. VAERS reporting has shown extremely reassuring data. Both mRNA vaccines have excellent safety profiles.[27] VAERS has not detected patterns in cause of death that would indicate a safety issue relating to the COVID-19 vaccines.[27]

The current guideline for COVID-19 vaccination, focusing on booster doses, appears in **Figure 1**.

Beginning in the spring of 2023, NACI recommends that an additional booster dose may be offered per the recommended interval to the following individuals who are at increased risk of severe illness:

- Adults 80 years of age and older
- Adult residents of long-term care homes and others in congregate senior living settings, or those with complex medical care need
- Adults 18 years of age and older who are moderately to severely immunocompromised (due to an underlying condition or treatment)
- Adults 65 to 79 years of age, particularly if they do not have a known prior history of SARS-CoV-2 infection
- Individuals who have not previously received recommended doses, including a primary series or Fall 2022 booster dose, are now recommended to receive them[34]

Within the above, however, there are specific details that impact women. First, it is common to develop lymphadenopathy in the region where one has received vaccine, such as the axilla. This has the potential to be read as abnormal in a subsequent mammogram. Therefore, the Society of Breast Imaging suggests conducting routine mammograms before being vaccinated for COVID-19 or waiting four-to-six weeks after the second dose prior to having a mammogram.[35] Lymphadenopathy was noted at 11.6% for the Moderna vaccine vs 5% for placebo. Reported numbers were lower for the Pfizer vaccine; however, unilateral adenopathy revealed in a mammogram is clearly a concern and would warrant assessment, if it was other than reactive.

In general, women tend to experience a greater number of side effects from the vaccines than men, though it is not clear if this is at least partially due to reporting bias. Common side effects include headache, fatigue and dizziness. Anaphylaxis is extremely rare but has been seen more commonly in women than in men.[36]. Biologically, women produce a greater number of antibodies following

flu shots, vaccines for measles, mumps and rubella, and hepatitis A and B. Males and females differ in their immunological responses to foreign and self-antigens and show distinctions in innate and adaptive immune responses. Certain immunological sex differences are present throughout life, whereas others become apparent only after puberty and before reproductive senescence, suggesting that both genes and hormones are involved. These sex-based immunological differences contribute to variations in the incidence of autoimmune diseases and malignancies, susceptibility to infectious diseases, and responses to vaccines in males and females.[37]

Finally, pregnancy has been shown to be associated with a disproportionate risk with respect to COVID-19 infection severity. Severe illness includes illness that results in intensive care admission, mechanical ventilation, or death. Additionally, pregnant women with COVID-19 might be at increased risk of adverse pregnancy outcomes, such as preterm birth, compared with pregnant women without COVID-19.[38] According to the Canadian Society of Obstetricians and Gynecologists (SOGC) and the CDC, while studies have not been completed on pregnant women, given the risk for greater severity of disease and greater risk overall, this cohort of women should be immunized against COVID-19. The SOGC states specifically that all COVID-19 vaccines approved in Canada can be administered in any trimester of pregnancy and during breastfeeding.[39]

Discussion

Patients often seek medical attention in midlife, recognizing that many changes in their physiology that require attention. This is a time to discuss various disease prevention strategies, including immunization. There is significant discussion about barriers to vaccination, as well as hesitancy in the lay press and among clinicians. In Canada, physicians consider financial expense as the chief barrier for patient acceptance of vaccination; it has been rated as the primary concern by 92%-95% of physicians. Perceived barriers of cost may limit recommendations for vaccination, particularly among older women and men.[40] For patients however, the number one reported barrier to vaccination was not having a recommendation from a physician. Cost was seen as a barrier by only 18% (male) and 20% (female) of study participants.[41] Given the importance of immunization and the need to decrease the prevalence of vaccine-preventable diseases, it is our obligation to recommend vaccines, ensuring that patients understand the guidelines and risks, not only of the vaccine but of not being vaccinated for a given disease, and the impact to them personally and to their community. In light of our aging population, this is the ideal time in a patient's life to employ healthy, preventive measures. Our objective is to help make this time of life one of good health, independence, and freedom from vaccine-preventable illness.

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DIAGNOSIS AND MANAGEMENT OF IRRITABLE BOWEL SYNDROME: A PRACTICAL OVERVIEW FOR PRIMARY CARE PROVIDERS

Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder estimated to affect 10% of the Canadian population.[1] Despite its high prevalence, IBS remains a challenging condition to diagnose and manage due to its varied clinical presentations. Patients with IBS often experience a range of distressing symptoms, including abdominal pain, bloating, disordered bowel habits and psychological distress, which significantly impact their quality of life (QOL).[2] As a result, patients with IBS are more likely to be high-frequency medical consulters, leading to an increased burden on healthcare systems.[1] This article aims to provide a practical overview of IBS, including its diagnostic criteria, workup and management strategies.

Clinical Presentation

IBS is considered a manifestation of bidirectional disordered communication within the brain-gut axis that influences GI motility, secretion and sensation. Contributing factors such as genetics, personality traits, alterations in stress-responsive physiologic systems, changes in the microbiota, and sequelae of enteric infections may also play a role in the pathogenesis of IBS.[3]

Due to its complexity, patients with IBS can present with a multitude of varying symptoms. The hallmark characteristic of IBS is recurrent abdominal pain with altered bowel habits. Bloating, nausea and dyspepsia may also be present, and can be seen in up to two-thirds of patients with IBS.[4, 5] In addition, IBS is correlated with other pain syndromes and, therefore, symptoms such as dysuria, widespread musculoskeletal pain, dysmenorrhea, fatigue, anxiety, depression, and headaches may be observed as well.[3,6]

Diagnostic Criteria

The recommended diagnostic criteria for IBS are the Rome IV criteria, which were published in 2016:

Recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following criteria:

1. *Related to defecation*
2. *Associated with a change in frequency of stool*
3. *Associated with a change in form (appearance) of stool*

The Rome IV criteria represent a departure from the historic belief that IBS is a diagnosis of exclusion, and allow clinicians to make a positive diagnosis of IBS based on symptoms and limited testing. The Rome IV criteria also reflect some notable changes from the Rome III criteria, such as removing the term "discomfort" from the diagnostic criteria due to its ambiguity, and modifying the phrase "improvement with defecation" to "related to defecation" to better reflect the experiences of patients with IBS.[2]

IBS Subtypes

IBS can be further classified into four subtypes based on the patient's predominant bowel habits:

1. IBS with predominant constipation (IBS-C): More than 25% of bowel movements are Bristol stool form Types 1 or 2, and less than 25% of bowel movements with Bristol stool form Types 6 or 7.
2. IBS with predominant diarrhea (IBS-D): More than 25% of bowel movements are Bristol stool form Types 6 or 7, and less than 25% of bowel movements with Bristol stool form Types 1 or 2.
3. IBS with mixed bowel habits (IBS-M): more than 25% of bowel movements with Bristol stool form Types 1 or 2, and more than 25% of bowel movements with Bristol stool form Types 6 or 7.
4. IBS unclassified (IBS-U): Patients who meet the diagnostic criteria for IBS, but whose bowel habits cannot be accurately categorized into the above three groups.

It is important to recognize that IBS subtypes can only be established when patients are evaluated in the absence of any medications that can affect bowel habits.[2] The prevalence of IBS-C, IBS-D, IBS-M, and IBS-U are 20.0%, 27.8%, 33.8%, and 14.1% respectively.[7]

IBS Workup

The diagnosis of IBS requires a comprehensive medical history, physical examination and limited diagnostic tests. Clinicians should take a thorough medical history to understand the frequency, severity and localization of a patient's abdominal pain. It is also important to identify whether or not a patient has a history of disordered bowel habits and to determine the temporal association with episodes of abdominal pain. IBS is a chronic pain disorder, and the presence of disordered bowel movements in the absence of abdominal pain is inconsistent with IBS. Identifying a patient's predominant symptom (pain, constipation or diarrhea) is critical as it will impact treatment selection. Clinicians should carefully review the patient's medication and diet to identify triggers that may mimic or exacerbate IBS symptoms. A brief

psychosocial assessment should be performed in patients with suspected IBS, as stress can be a contributor to IBS symptomatology. A pertinent family history for GI disorders, such as celiac disease, should also be obtained. Finally, clinicians should identify any alarm features that require further investigation or referrals to rule out more insidious conditions. These alarm features may include a family history of colorectal cancer or inflammatory bowel disease (IBD), new onset of symptoms after the age of 50, unintended weight loss, GI bleeding, constitutional symptoms, or iron deficiency anemia.

A physical examination should be performed in all patients being evaluated for IBS to exclude any organic etiologies of symptoms which may warrant further investigations or referrals (e.g., the presence of ascites, organomegaly, masses or cachexia).

A complete blood count (CBC) should be ordered for patients with suspected IBS, as the presence of anemia or leukocytosis may warrant further investigation.[2] The Canadian Association of Gastroenterology (CAG) also recommends that IBS patients have serological testing to exclude celiac disease, given the frequent overlap between celiac disease and IBS (GRADE: Conditional recommendation, low-quality evidence).[8] Routine thyroid tests are not indicated, but can be performed if clinically warranted. Infectious stool studies for bacteria, parasites and ova may be useful if diarrhea is the primary symptom, or if the patient has recently travelled/lived in an area where infectious diarrhea is prevalent.[2] The CAG recommends against routine c-reactive protein (CRP) and fecal calprotectin testing unless there is high suspicion for IBD (GRADE: Strong recommendation, very low-quality evidence). Routine use of food allergy testing, lactose hydrogen breath tests and glucose hydrogen breath tests in evaluating IBS patients is also not recommended (GRADE: Strong recommendation, very low-quality evidence). Patients who experience new-onset IBS symptoms after the age of 50 are recommended to have a colonoscopy to exclude alternative diagnoses (GRADE: Strong recommendation, very low-quality evidence) , while routine colonoscopy is not recommended for IBS patients under age 50 in the absence of alarm symptoms (GRADE: Strong recommendation, very low-quality evidence). Full recommendations from the CAG, including a concise algorithm summarizing consensus-guided approach to management of IBS patients, can be found in the "Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS)", published in 2019.[8]

General Principles of IBS Treatment

Clinicians should provide education and reassurance to patients regarding the benign natural history of IBS, while also establishing realistic treatment goals. Lifestyle modifications, such as exercise, stress reduction and attention to impaired sleep, should be recommended to all patients.[2] In addition to lifestyle modifications, the CAG recommends offering IBS patients a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, polyols) diet based on evidence from four randomized controlled trials (RCTs) demonstrating its efficacy.[8-12] Increased dietary intake of soluble fibre (such as psyllium) also has a significant effect on the treatment of IBS symptoms.[8]

Probiotics should be offered to patients with IBS, as clinical studies have shown the superior efficacy of combination probiotics vs placebo. However, there is significant heterogeneity between studies and insufficient evidence to support any particular species of probiotics.[8] In contrast, a systematic review of three eligible RCTs failed to demonstrate any clear benefit of prebiotics in the treatment of IBS.[13] In addition to these interventions, the CAG recommends considering peppermint oil, cognitive-behavioral therapy (CBT) and hypnotherapy as alternative treatment options for IBS patients.[8]

Treatment of Abdominal Pain in IBS

It is important to consider that while disordered bowel movements can be treated with medications, IBS is a chronic pain disorder and clinicians should place an equal emphasis on treating patients' pain. Antispasmodics, low-dose tricyclic antidepressants (TCAs), and selective serotonin receptor inhibitors (SSRIs) are commonly used to treat abdominal pain in IBS. In Canada, the three available antispasmodics with proven efficacy are hyoscine, pinaverium and dicyclomine. However, the evidence for their effectiveness is generally weak, and there is a potential for anticholinergic side effects. Peppermint oil also has antispasmodic properties and, although the evidence is of low quality, it should be offered to patients with abdominal pain (**Table 1**).[8]

TCAs and SSRIs have good-quality evidence demonstrating efficacy in improving IBS-associated abdominal pain. TCAs, such as amitriptyline, desipramine, doxepin, imipramine, and trimipramine, are known to prolong gut transit times and can cause constipation. Therefore, they may be more effective in IBS-D. In contrast, SSRIs, including citalopram, fluoxetine and paroxetine, may decrease transit time and are preferred in IBS-C.[8]

Treatment of IBS-D

Loperamide is a μ-opioid receptor agonist that decreases colonic transit and can be used to treat diarrhea. However, its prolonged use should be avoided as it may lead to constipation. Loperamide may be beneficial in patients with IBS-D as a prophylactic or as-needed treatment before social situations or travel. It is important to recognize that while loperamide is effective in treating diarrhea, it does not improve other IBS symptoms such as abdominal pain. Eluxadoline is a synthetic opioid receptor modulator approved by Health Canada in 2017 for the treatment of IBS-D and has demonstrated moderate-quality evidence of efficacy. However, it is contraindicated

Abdominal Pain	IBS-D	IBS-C
Hyoscine • 10–20 mg TID • Up to 60 mg/day	**Loperamide** • 2–4 mg daily as needed	**Polyethylene glycol** • 17 g daily as needed
Pinaverium • 50 mg TID • Up to 100 mg TID	**Eluxadoline*** • 100 mg BID	**Prucalopride** • 2 mg daily
Dicyclomine • 20 mg QID	**Rifaximin*** • 550 mg TID x 14 days	**Linaclotide*** • 290 µg daily
Peppermint oil • 0.2 to 0.4 ml TID		**Plecanatide*** • 3 mg daily
Amitriptyline • 10–25 mg QHS • Up to 100 mg/day		**Lubiprostone** • 8 µg BID
Citalopram • 10-20 mg daily • Up to 40 mg/day		**Tenapanor*** • 50 mg BID

Table 1: Pharmacologic treatments for abdominal pain, IBS-D, and IBS-C.
** Medications approved by Health Canada for the treatment of IBS.*

in patients with biliary duct obstruction, cholecystectomy, pancreatitis, and hepatic impairment.[8] Clinicians should carefully consider the potential risks of eluxadolin before prescribing it to patients with IBS-D. There is also emerging evidence supporting the use of rifaximin, a non-systemic antibiotic, in managing IBS-D. A 14-day course of rifaximin has demonstrated moderate-quality evidence of efficacy in reducing symptoms. Additionally, bile acid sequestrants have shown promise as a second-line treatment option for IBS-D options.[6] Eluxadoline and rifaximin are the two medications currently approved by Health Canada for the treatment of IBS-D (**Table 1**). In order for medications to be approved by Health Canada, they must improve both disordered bowel movements and abdominal pain.

Treatment of IBS-C

The importance of adequate soluble fibre and water intake should be emphasized to all patients with IBS-C, alongside pharmacologic therapies. Polyethylene glycol is an osmotic laxative which has beneficial effects for constipation, but limited effects in treating other IBS symptoms.

Linaclotide and plecanatide are guanylate cyclase-C agonists that are effective in improving both abdominal pain and diarrhea. Despite its relatively expensive cost, the CAG has made a strong recommendation in favour of using linaclotide in IBS-C patients. Similarly, lubiprostone is a chloride channel activator with proven efficacy in treating both abdominal pain and constipation. While lubiprostone is also recommended in the treatment of IBS-C, it is generally more expensive than similar medications.[6,8] Tenapanor is a locally acting inhibitor of the sodium/hydrogen exchanger 3 (NHE3), which increases water secretion and accelerates intestinal transit. Tenapanor has been shown to have improved IBS-C symptoms in RCTs and is generally well tolerated by patients.[14] Linaclotide, plecanatide, and tenapanor are the three medications currently approved by Health Canada for the treatment of IBS-C (**Table 1**).

Treatment of IBS-M/U

Managing IBS-M and IBS-U can be challenging due to their sporadic and varying symptoms. In addition to pharmacologic therapies, dietary modifications and lifestyle principles are important in managing these subtypes of IBS. Efforts should be made to identify common food triggers and remove these from the patient's diet. The use of a food diary and referral to a registered dietician can be helpful to support dietary changes. Soluble fibre supplementation and adherence to a low FODMAP diet should also be emphasized to patients.

Regular exercise is recommended for patients with IBS-M/U, as accumulating 150 minutes per week of aerobic physical activity has been shown to be an effective strategy for stress reduction.[15] In addition, counselling and reassurance are key to long-term effective management of IBS-M/U, and referral for CBT should be considered.

Pharmacologic management of IBS-M/U is challenging

due to the limited available evidence to guide treatment. Medications such as TCAs, secretagogues (lubiprostone, linaclotide) and antispasmodics are often used, but clinicians must remain aware of their potential side effects.

Conclusion

IBS is a highly prevalent and often debilitating GI disorder that affects a significant proportion of the Canadian population. In recent years, there have been significant advancements in our understanding of IBS, including the development of the Rome IV diagnostic criteria. These criteria help reduce unnecessary investigations and improve the subtyping of patients with IBS to better guide treatment. The management of IBS involves a multidisciplinary approach that includes dietary modifications, pharmacological and non-pharmacological interventions, and psychological support. This approach can be effective in reducing symptoms and improving the QOL of individuals with IBS.

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PRINCIPLES OF ANXIETY MANAGEMENT FOR FAMILY PHYSICIANS

Introduction

Family practitioners (FPs) play an essential role in mental healthcare delivery, providing triage, diagnosis, patient referral, and treatment. They are usually are patient's first—and often their only—contact with mental healthcare services, due to the lack of access to psychiatric care. As such, FPs are commonly tasked with collecting and evaluating a broad range of symptoms that can be categorized as anxiety. The symptoms of anxiety have become increasingly ubiquitous, particularly due to the impact of the COVID-19 pandemic, leading many front-line providers to understandably feel anxious concerning optimal methods to assess and support these patients.

This article provides clinical pearls, supported by current empirical research, for assessing, diagnosing and treating patients presenting with anxiety.

Understanding the medical pathology of anxiety

While terms such as anxiety and depression are commonly employed, their meaning often varies between individuals. When a patient reports they are experiencing anxiety, their clinicians should ask, "What does anxiety mean for you?" Clinicians should then determine whether the anxiety symptoms are impairing the individual's ability to function in their usual roles—at work, home, and school—and whether they are severe enough to require treatment.

It can be challenging, particularly in the age of social media, where clinical terms have been integrated into everyday language, to differentiate between normal worries and anxiety symptoms that require medical intervention. Parents, in particular, are struggling with the term anxiety, because it has become a catch-all phrase for every unpleasant sensation their child may be experiencing.

An example of normal worry is captured in the statement, "My school exams make me anxious"; examinations are designed to prompt individuals to master new material in a limited amount of time. Some young people, however, exhibit symptoms of anxiety that are extremely severe, impacting their ability to attend school, seek employment, or develop relationships. Anxiety symptoms might also be a harbinger of another serious mental illness, such as clinical depression, bipolar disorder or schizophrenia.

The Fear Response versus Pathological Anxiety

Fear is a normal response to a concrete threat, and it is critical for individuals' safety. When confronted by a threat, the brain transmits sensory information via neuronal pathways from the thalamus to the amygdala, which orchestrates an appropriate response to the perceived threat, known as the fight, flight, or freeze response. The amygdala provokes an increase in norepinephrine, leading to heightened arousal, sharpened attention, and greater sensory acuity. This surge of norepinephrine

increases the heart rate and blood pressure via the lateral hypothalamus. When a threat is perceived, blood is rapidly directed away from less vital organs, toward body sites necessary to adopt evasive coping measures.

The sensation of fear provokes the hypothalamic-pituitary-adrenal axis (HPAA) to increase the release of corticotropin-releasing hormone (CRH), subsequently provoking the pituitary glad to release adenocorticotropic hormone (ACTH), which ultimately triggers the release of cortisol. Cortisol is a critical stress-response hormone that protects the body from stress-related tissue and nerve damage and, in the context of normal functioning, returns an individual's body to homeostasis. If, however, the level of cortisol remains excessively high for a prolonged period of time, as sometimes occurs with chronic depression or anxiety, it can provoke an inflammatory cascade, increasing pro-inflammatory cytokines and altering brain structure and functioning. This can ultimately lead to greater symptom severity and chronicity, treatment resistance, and functional impairment.

Individuals with pathological anxiety experience fear that is excessive, unwarranted, inappropriate, and impairing. Rather than reacting to an obvious threat such as an aggressive, barking dog, pathological anxiety is a response to a threat that is vague, unclear, and at times of unknown origin.

Anxious Distress versus Anxiety Disorders

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) has added the "anxious distress specifier" to the major depressive disorder (MDD) and bipolar disorder diagnoses to highlight the important clinical impact of anxiety associated with mood disorders.[1] Approximately three-quarters of patients with MDD meet the criteria for the anxious distress specifier.[1] Anxious distress typically resolves with the appropriate management of the primary disorder. The presence of anxiety commonly implies that the disorder is more severe,[2] more challenging to treat,[3] and will take longer to resolve.[4,5] In cases where medication is required, the patient may require higher doses and more medications than those required to treat the mood disorder in the absence of anxious distress. In addition, anxiety is associated with poor functioning and reduced quality of life.[6] Anxiety significantly heightens the risk of suicidal ideation and suicide attempts associated with mood disorders.[7–10] Furthermore, anxiety may provoke self-medication, including the excessive use of alcohol or cannabis.[11]

Anxiety disorders are distinct psychiatric disorders, each with a unique constellation of symptoms. As with all DSM-5 diagnoses, to meet the criteria for an anxiety disorder the symptoms must impair social, occupational or other important areas of functioning, and cause clinically significant distress. DSM-5 anxiety disorders include separation anxiety, social anxiety disorder (SAD), generalized anxiety disorder (GAD), panic disorder (PD), and specific phobia.

While previously considered anxiety disorders, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) have been reclassified under separate categories in the DSM-5, together with other similar diagnoses. The purpose of grouping similar disorders into two new categories, Trauma- and Stressor-Related Disorders, and Obsessive-Compulsive and Related Disorders, was to reflect the current clinical evidence that these diagnostic groups are related through their unique neurobiology and treatment response patterns.[12]

Anxiety Screening

Any patient presenting with a mood disorder should be screened for anxiety, due to the heightened morbidity and mortality associated with anxious distress. Likewise, because anxiety can worsen the outcome of any psychiatric disorder, it is important to screen all patients with a psychiatric diagnosis, including ADHD, psychotic disorders, eating disorders, and dementia.

For those patients who have chronic anxiety or a suspected anxiety disorder, a few targeted questions can help to hone in on a specific anxiety disorder diagnosis, which can then be confirmed using DSM-5 criteria.

Individuals with GAD frequently ask themselves, "What if." Commonly, their worries are focused on everyday issues like health, relationships, or finances. Someone with GAD might repeatedly worry "What if my partner gets sick and we can't pay the mortgage?" even though their partner is in good health and their family is financially stable. Occasional worries of this nature are not unusual, particularly if they rooted in legitimate concerns, but they rarely cause a significant impact on functioning. However, those living with GAD are unable to cease worrying about everyday matters. In fact, they worry about their worry. Their worry consumes their entire life, their relationships, and their ability to function in their usual roles. GAD commonly presents co-morbidly with MDD, so both should be considered for screening.

Patients with SAD experience intense discomfort when they are the centre of attention, particularly in social settings with people they do not know well. Additionally, they often feel that they have missed out on important life experiences as a result of their anxiety.

The diagnosis of panic disorder is usually straightforward, although patients sometimes complain of days-long panic attacks. While they have clearly experienced extremely unpleasant and intense anxiety, they are not experiencing a true panic attack. A panic attack is a discrete episode of intense fear or discomfort that emerges very suddenly, peaks over several minutes (usually within 10 minutes), and then slowly resolves. A panic disorder diagnosis requires repeated *unexpected* panic attacks and a pattern of post-panic concern about having a subsequent attack and/or maladaptive behaviour as a result of the panic attack, including functional impairments such as being

unable to venture to the grocery store. Panic attacks are not necessarily associated with a psychiatric disorder; approximately 30% of panic attacks occur in individuals who do not have a psychiatric diagnosis.

Diagnosing Anxiety

The anxious distress specifier cited in the DSM-5 includes:

1. Feeling keyed up or tense
2. Feeling unusually restless
3. Difficulty concentrating because of worry
4. Fear that something awful may happen
5. Feeling like one might lose control

Severity-based symptom number and type:

1. Mild: Two symptoms
2. Moderate: Three symptoms
3. Moderate-to-Severe: Four or five symptoms
4. Severe: 4 or 5 symptoms accompanied by motor agitation

The Generalized Anxiety Disorder Scale-7 (GAD-7) is a critical self-reporting tool for evaluating the presence and severity of generalized anxiety disorder. Additionally, it has been shown to have moderate sensitivity and specificity for screening PD, SAD, and PTSD. Patients can complete the GAD-7 as part of an initial evaluation and at follow-up appointments to assess treatment response (**Figure 1**).[13]

Validated self-report scales have been developed for the majority of mental health disorders. Patients can be assessed for SAD by using the Liebowitz Social Anxiety Scale.[14] A rapid screening tool for OCD, the Obsessive-Compulsive Inventory-Revised (OCI-R) scale, has now been validated as a four-item version self-report tool (OCI-4).[15] This concise version can identify OCD in settings where it is not possible to access an in-depth assessment. There were three version of the PTSD Checklist (PCL) for the DSM-4: PCL-M (military), PCL-C (civilian) and PCL-S (specific). The PCL-5 is a 20-item self-report questionnaire corresponding to the updated DSM-5 criteria for PTSD. There are no longer military or civilian versions.[16]

The impact of a patient's symptoms on their functioning is a critical aspect of any DSM-5 diagnosis. The Sheehan Disability Scale (SDS) was developed to assess functioning in three domains: work/school, social life, and family life (**Figure 2**). This self-report, concise scale requires patients to rate the extent to which their functioning is impaired as it relates to their psychiatric symptoms, on a 10-point visual analog scale. The SDS can be employed at the time of diagnosis and with each follow-up appointment to assess the patient's response to treatment in terms of functional recovery. It has been validated for use in several mood and anxiety disorders, including MDD, GAD, OCD, and PD.[17]

It is important to note that a positive result on a clinical screening tool should be considered in combination with a clinical interview to confirm the diagnosis.

Treatment of Anxiety Disorders

Anxiety disorders tend to be chronic as well as highly recurrent. One clinical study of 643 women with no history of depression found that during the three-year study period, 35% experienced a new onset of an anxiety disorder, and 65% reported a recurrence of anxiety.[18]

Generalized Anxiety Disorder 7-item (GAD-7) Scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score (*add your column score*) =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____

Somewhat difficult _____

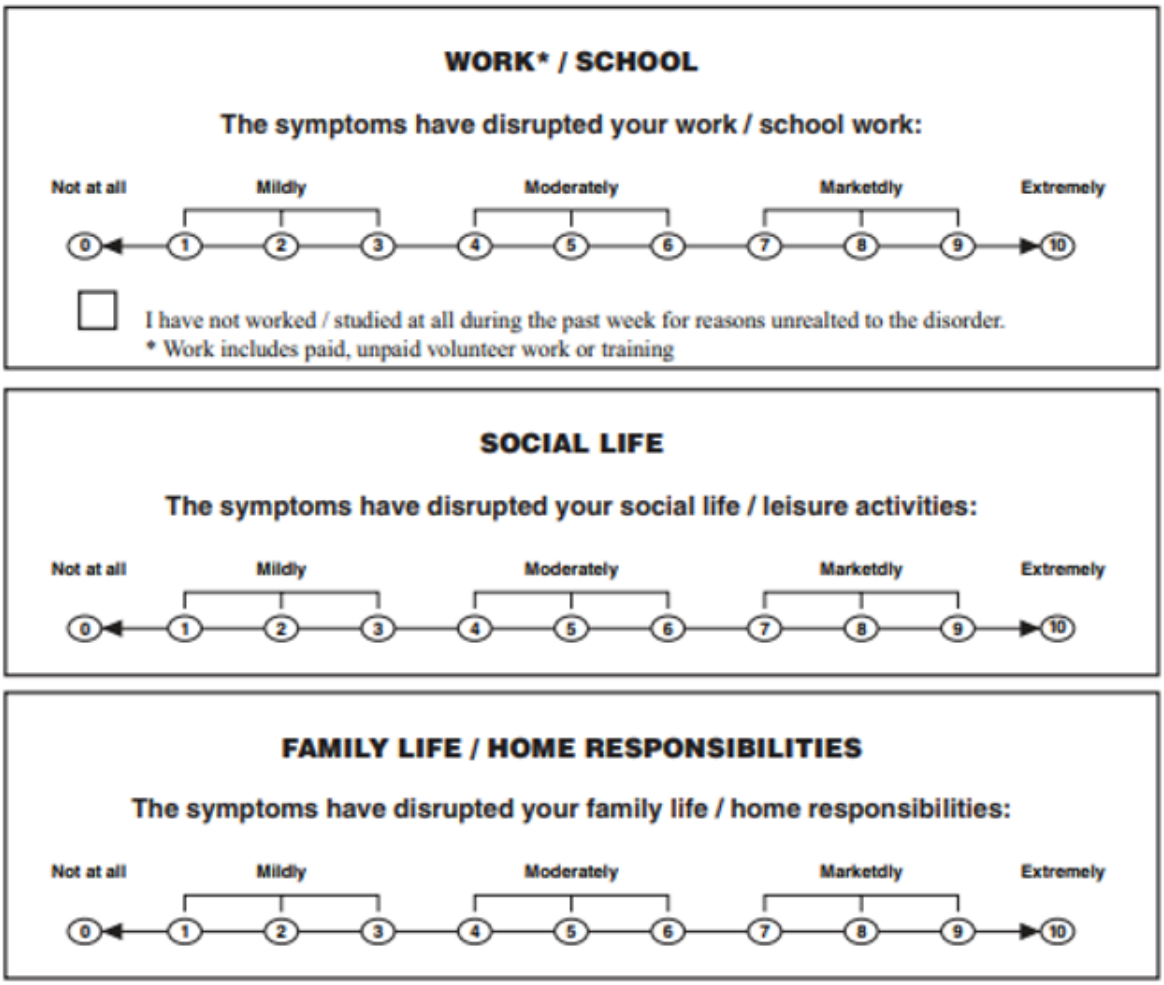
Very difficult _____

Extremely difficult _____

Figure 1: GAD-7 Scale. Adapted from Kroenke et al, 2007.

A brief, patient rated, measure of disability and impairment.

Please mark ONE circle for each scale.



Days Lost

On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

Days Unproductive

On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced? _____

Figure 2: Sheehan Disability Scale. Adpated from Sheehan DV et al, 1996.

When anxiety disorders are recurrent, approximately 33% of patients will present with a different anxiety disorder.[19] For this reason, the goals of anxiety treatment should include complete symptom remission and full functional recovery.

A biopsychosocial approach to anxiety management is most likely to provide enduring benefits to the patient. The psychological therapy with the greatest empirical evidence demonstrating its value for treating anxiety and anxiety disorders is cognitive-behavioural therapy (CBT).[20] While CBT can be expensive and difficult to access, clinical evidence supports its value when it is delivered from multiple modalities: bibliotherapy, group therapy, virtual CBT, and one-on-one therapy are all known to provide therapeutic value.

Prior to suggesting CBT, it is critical to consider whether the patient is cognitively able to benefit. If short-term memory or concentration are severely impaired, it will be very difficult for them to focus and practice to learn new skills, which are the cornerstones of CBT. In such cases, it may be necessary to initiate medication prior to initiating formal CBT. While the medication is helping to manage cognitive symptoms, patients generally benefit from supportive therapy and a compassionate approach.

Mindfulness meditation, yoga, and regular mild-to-moderate exercise are complimentary therapies that support anxiety management, which has been confirmed by clinical research.

Pharmacotherapy for Anxiety Disorders

The pharmacotherapy guidance provided herein is based on treatment guidelines, as well as a long history of clinical experience.[21] As the Canadian guidelines[22] are outdated, and it is exceedingly rare for pharmaceutical companies to pursue formal regulatory indications for anxiety disorders, the guidance offered below is largely based on off-label use.

The effectiveness of pharmacotherapy is dependent on patient compliance. Identifying a treatment to which a patient is willing to adhere depends on its effectiveness and tolerability. Critical side effects with the greatest impact on adherence include weight gain, sexual dysfunction, excessive daytime sedation, and "zombification". This term refers to the unpleasant experience of feeling emotionally blunted, apathetic or unmotivated, and occurs in approximately 30% of patients prescribed a selective serotonin reuptake inhibitor (SSRI) or low-dose serotonin and norepinephrine reuptake inhibitor (SNRI).

Patient education regarding psychopharmacology is imperative. Patients commonly under-value the importance of treating their anxiety symptoms fully. They may benefit from gentle reminders regarding the value of full symptom remission and functional recovery. Engaging their primary support person—for example, a close friend or family member—can have a significant impact on treatment adherence and helping the patient remain patient during the treatment process.

Fortunately, numerous antidepressants are available and most have been proven helpful in managing moderate-to-severe anxiety. Managing anxiety disorders typically requires augmenting serotonin levels, which involves employing an SSRI, SNRI or multimodal antidepressant.

It is critical to remember that while all antidepressants are effective, not all of them are effective for every patient. Treatment of psychiatric illness requires a trial-and-error approach, and it is important to inform patients about what to expect at treatment initiation.

Patients struggling with anxiety may be highly sensitive to side effects and the initial weeks of treatment are often the most challenging. The majority of early side effects, such as headache and nausea, resolve completely within the first two weeks of treatment. Minor changes, such as dose timing and administration with food, can have a significant impact on tolerability. Sensitivity to side effects makes it even more imperative to initiate an antidepressant at a low dose, titrate slowly and only when the initial side effects have resolved, and continue to optimize the dosage until full remission is achieved.

In some cases, a short-term benzodiazepine, such as low-dose lorazepam or clonazepam, can make a significant difference in tolerability at treatment initiation. Alprazolam should be avoided because it is difficult to taper. Likewise, avoid diazepam, which has active metabolites that accumulate, heightening or prolonging side effects.

Recommended choices for the treatment of anxiety disorders:

SSRIs: escitalopram, sertraline

SNRIs: duloxetine, desvenlafaxine, levomilnacipran

Multimodal agents: vortioxetine, vilazodone

While bupropion XL is very well-tolerated, with clinical data supporting its value in treating anxious distress and GAD, there is a paucity of favourable data supporting its use in other anxiety disorders. Mirtazapine can be helpful for some anxiety disorders, but consistent weight gain and excessive sedation make it a less desirable first-line choice of treatment.

Antidepressants previously considered mainstays for the treatment of depression and anxiety are not cited above due to their considerable side effect burden. For example, paroxetine and venlafaxine XR are effective, but both carry the risk of severe discontinuation syndrome. Paroxetine is known to cause significant weight gain and both agents carry a high risk of sexual dysfunction. In general, SNRIs and multimodal agents have more favourable side effect profiles, particularly concerning weight gain and sexual dysfunction, compared to SSRIs.

Treatment augmentation for severe anxiety may include combining two antidepressants with distinct mechanisms

of action, such as combining an SSRI, SNRI or multimodal agent with bupropion XL or mirtazapine. However, adding an atypical antipsychotic with empirically validated antidepressant benefits, as well as a Health Canada/FDA indication, is more likely to be beneficial than an antidepressant combination. These medications include brexpiprazole, aripiprazole, cariprazine and quetiapine. The first three of these are D2 partial agonists and are less likely to promote weight gain or metabolic syndrome, although every medication in this class carries some risk.

Alternatives to antidepressants and atypical antipsychotics include pregabalin and beta- blockers. Pregabalin is commonly used to treat anxiety, however, its benefits are inconsistent. It has been associated with unfavourable side effects, including weight gain and cognitive impairment. Beta-blockers treat only the physical manifestations of anxiety. They may be helpful for patients who have intense performance anxiety and can be used on a PRN basis for that purpose.

Conclusion

While anxiety is often viewed as less severe and less worthy of clinical concern than MDD, clinical research highlights its significant impact on patient functioning, suicide risk and quality of life. It is incumbent on mental health care providers to assess the presence and severity of the patient's anxiety, measure it using validated clinical scales, treat it to complete remission, and monitor the patient's treatment progress.

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ACUTE AND PROPHYLACTIC TREATMENT OF MIGRAINE: 2023 UPDATE

Introduction

Migraine is a chronic neurological disorder that causes significant disability in patients and has a substantial economic impact in Canada. Effective treatment for migraine will improve our patients' quality of life; additionally, it will reduce the economic burden generated by healthcare visits and employee absenteeism.

The novel treatments in migraine target calcitonin gene-related peptide (CGRP), a neuropeptide which plays a role in the initiation of a migraine attack.[1] Although our current understanding of migraine pathophysiology is incomplete, it is believed to involve the trigeminal nerve and its connections with the cerebral vasculature with nociceptive signals activated through a variety of neuropeptides including CGRP, substance P and nitric oxide.[1]

As a result of an improved understanding of migraine pathophysiology, the past several years have seen the advent of a variety of new therapeutic options in both the acute and prophylactic management of migraine. Although these agents represent additional options in the clinician's arsenal, they have, in addition, introduced challenges in determining their cost-effectiveness. In this review, we provide an update on new acute and prophylactic migraine therapies and how they integrate into current practice from a primary care perspective.

Non-Pharmacological Management

Despite the availability of novel medications, non-pharmacological approaches continue to play a role in migraine management. Patients should be counselled on lifestyle measures they can adopt to help mitigate attacks. This includes adequate sleep hygiene with regular sleep patterns such as sleeping and waking at the same time each day. Regular exercise can also be recommended as a reduced level of activity is associated with more frequent migraines.[2] Obesity has a known association with poor migraine control, including increased frequency and severity which further supports regular low-level physical activity.[2] Finally, supplementation with Vitamin B, CoQ10, magnesium and Vitamin D may confer additional benefit.[3]

Acute Migraine: Therapeutic Approaches

The objective of therapy for acute migraine is to provide a prompt reduction in pain and associated symptoms without recurrence, with minimal need for repeat dosing and minimal or no side effects.[3] All patients with a diagnosis of migraine should be counselled on acute and abortive treatments.[4]

Despite the introduction of new migraine medications, first-line therapies have not changed. For patients with mild-to-moderate attacks, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, acetaminophen, and caffeinated analgesic combinations (i.e. acetaminophen and caffeine combination) are recommended.[4,5] The use of triptans with NSAIDs (such as sumatriptan plus naproxen) can be more effective than monotherapy for some patients.[6] For attacks that are more severe (moderate-to-severe), migraine-specific abortive therapies including triptans and small molecule CGRP receptor antagonists (gepants) can be effective **(Figure 1).**[4,7]

Approximately 30% of patients provided a prescription for triptans may have a poor response.[7] Newer therapies such as gepants offer a targeted mechanistic abortive and prophylactic treatment of migraine.[8] Ubrogepant was approved by Health Canada for the acute treatment of migraine in 2022 and rimegepant is pending approval. Considerable evidence has demonstrated that gepants represent efficacious and well-tolerated therapy for acute migraine.[5,9,10] Ubrogepant can be administered at a dose of 50 mg to 100 mg as a single dose with a repeat dose that may be administered if recurrent symptoms persist after two hours (up to a maximum dose of 200 mg/day). Rimegepant can be administered as a single oral 75 mg dose. Both of these agents have been demonstrated to work in patients who have previously failed with or been intolerant to triptans.[11] Both ubrogepant and rimegepant are metabolized by CYP3A4. Drug interactions with agents that are strong CYP3A4 inhibitors (ketoconazole and verapamil) and CYP3A4 inducers (phenytoin) have been observed.[11] Side effects associated with the gepants have been minimal; these include nausea, somnolence and dry month.[12]

Use of prophylactic medications in migraine

The objectives of prophylactic migraine therapy are to reduce the frequency, duration and severity of attacks; improve the response to therapy; reduce the likelihood of escalation to acute migraine; reduce overall disability; and improve function.[4] Patients with both episodic and chronic migraine can benefit from prophylactic medications. Indications to begin prophylactic therapy include both long-lasting migraine headaches that impact the patient's quality of life, and frequent migraines. Prophylactic therapy should be considered if attacks (even if infrequent) interfere with a patient's daily routine, regardless of abortive treatment, and in patients who experience frequent attacks as defined by four or more moderate headaches per month.[5] In addition, patients who experience significant adverse effects with acute treatments can be considered for the administration of a prophylactic agent.[4]

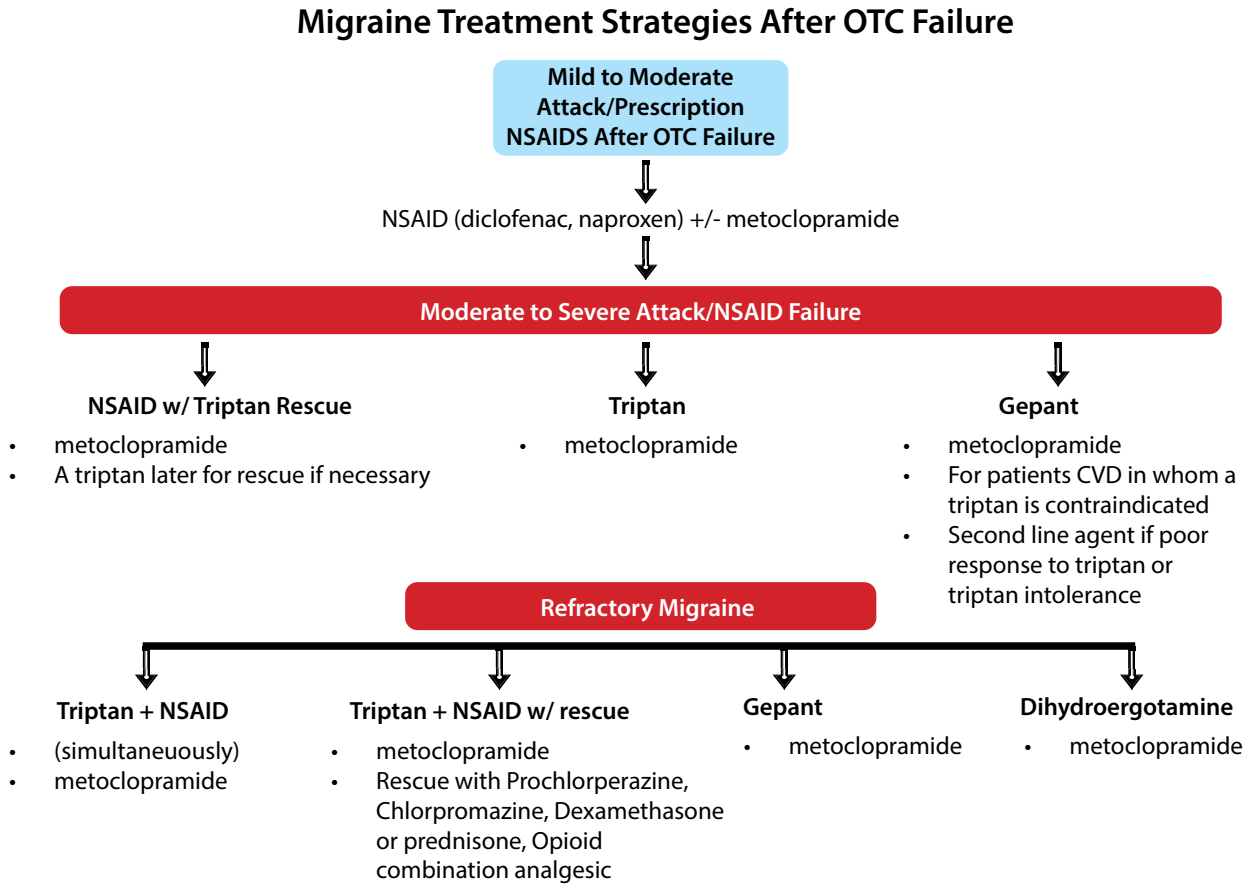

Figure 1: Acute Migraine Treatment Strategies. Adapted from Worthington et al, 2013.[5]

First-line prophylactic therapy is initiated with the traditional oral migraine agents. These should be initiated at low doses and titrated gradually until the desired outcome or maximum medication dosage is achieved. The treating clinician should ensure an adequate trial of the prophylactic medication, typically defined as treatment for a minimum of 12 weeks. If the desired response is not achieved at an adequate dose following 12 weeks, switching to a different prophylactic medication can be considered. Several lines of prophylactic migraine medications are available including antihypertensives (i.e., metoprolol, propranolol, candesartan); antiepileptic agents (i.e., topiramate, valproate); and antidepressants (amitriptyline, venlafaxine)[3,4] **(Figure 2)**. Key patient characteristics should be considered in selecting prophylactic agents, including comorbidities, pregnancy and the potential for pregnancy. In addition, botulinum toxin injections can also be effective prophylaxis for chronic migraine and used in place of or concurrently with other pharmacological agents. Ultimately, patient preference should be strongly considered.

The past several years have seen the introduction of new injectable migraine medications that can be used prophylactically **(Figure 2)**. The CGRP monoclonal antibodies mAbs have shown favourable efficacy in migraine management through targeting of the CGRP ligand or CGRP receptor, and have been shown to be safe in episodic and chronic migraine. They are quite safely tolerated in most patients but significant cardiac history or peripheral vascular disease are relative contraindications. Generally, the evidence from clinical trials suggests an approximately 50% reduction in mean headache days per month for patients treated with these agents.[12] The lack of a need for gradual dose titration, relative quick onset of therapeutic action, a more favourable side effect profile, and favourable tolerability are all advantages of the new CGRP monoclonal antibody treatments. The most reported side effect is injection site reaction (swelling, pain, redness) with subcutaneous administration.[4] Other reported side effects are constipation, upper airway symptoms, sinusitis, and flu-like symptoms. Hypertension has been reported with the CGRP receptor mAbs. Rare cases of Reynaud's phenomenon exacerbations have been reported in the literature in association with CGRP monoclonal treatments.[13]

The gepants are not only effective in aborting migraines; there is now clinical evidence for their use in migraine prophylaxis.[14] Atogepant has been approved by Health Canada for migraine prophylaxis with a recommended dose of 10 mg, 30 mg or 60 mg/day. It is expected that Health Canada approval will be sought for rimegepant for migraine prophylaxis as it has already received FDA approval for this indication. Both atogepant and rimegepant have been shown to be safe and well tolerated even up to a year of use; primary side effects

Drugs with strong recommendations	Quality of evidence
Topiramate	High
Propanolol	High
Metoprolol	High
Amitriptyline	High
Nadolol	Moderate
Gabapentin	Moderate
Candesartan	Moderate
Butterbur	Moderate
Riboflavin	Low
Coenzyme Q10	Low
Magnesium citrate	Low

Drugs with weak recommendations	Quality of evidence
Divalproex	High
Flunarizine	High
Pizotifen	High
Venlafaxine	Low
Verapamil	Low
Lisinopril	Low

New agents not yet included in Canadian guidelines

- Onabotulinum toxin type A (since 2010) is for chronic migraine only, so not in the guidelines for episodic migraine
- Calcitonin Gene Related Peptide (CGRP) antibodies arrived in Canada in 2018
- Atogepant recieved Health Canada approval 2022

Figure 2: Canadian Guidelines: Prophylactic Options Recommended for Use in Episodic Migraine. Adapted from Pringsheim T et al.[3]

include nausea, fatigue and constipation.[14]

As with traditional oral prophylactic migraine medications, clinicians need to monitor and measure patient response to the new CGRP-targeted drugs with similar metrics including days with migraine and headache, migraine-related disability and functional impairment. A 50% or greater reduction in mean headache days per month is a marker of therapeutic benefit.

The primary anticipated barriers for patient access to the gepants and CGRP mAbs are cost and insurance coverage. Currently, the majority of insurance companies and provincial pharmaceutical formularies require a patient to have failed two traditional oral prophylactic medications from two different therapeutic classes before being eligible for a CGRP mAb trial or gepant.

Recommendations for Incorporation of Novel Migraine Therapies into Primary Practice

The Canadian guidelines on the novel migraine therapies have not yet been updated. Based on the current data available for the treatment of acute migraine, the gepants are a good first-line option following NSAID failure in patients with cardiovascular disease (CVD) who cannot use a triptan. The efficacy of gepants is similar to that of triptans, with a superior side effect profile; however, gepants are more expensive. In patients without extended healthcare coverage, gepants can be considered for second-line therapy following triptan failure or intolerance. As clinicians' experience with gepants continues, we may find the superior side effects profile of this medication justifies use as first-line therapy. In migraine prophylaxis, both the CGRP mAbs and the gepants have demonstrated favourable efficacy and side effects profiles. Based on their costs and limitation of access by insurance companies and provincial formularies, we recommend a trial of two traditional oral medications prior to the initiation of these novel therapies.

Conclusion

Migraine is a significant contributor to patient disability and burden of disease globally, including in Canada. Over the past several years, numerous therapies have become available in Canada for both the acute and prophylactic treatment of migraine, including the gepant class of medications, as well as the CGRP mAbs, which are injectable prophylactic agents. Their relative ease of use and favourable side effects profile position them as an excellent option in the treatment of migraine. Potential patient barriers to these medications include cost and health insurance coverage.

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Financial Disclosures

None to report.

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