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CANADIAN PRIMARY CARE TODAY

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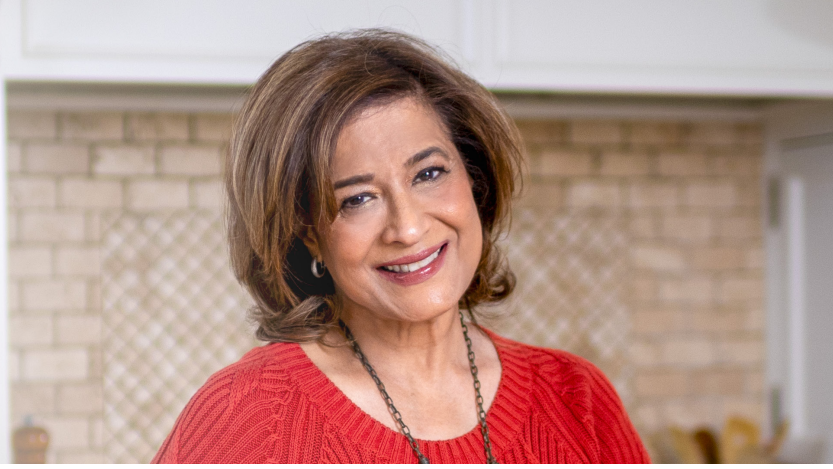

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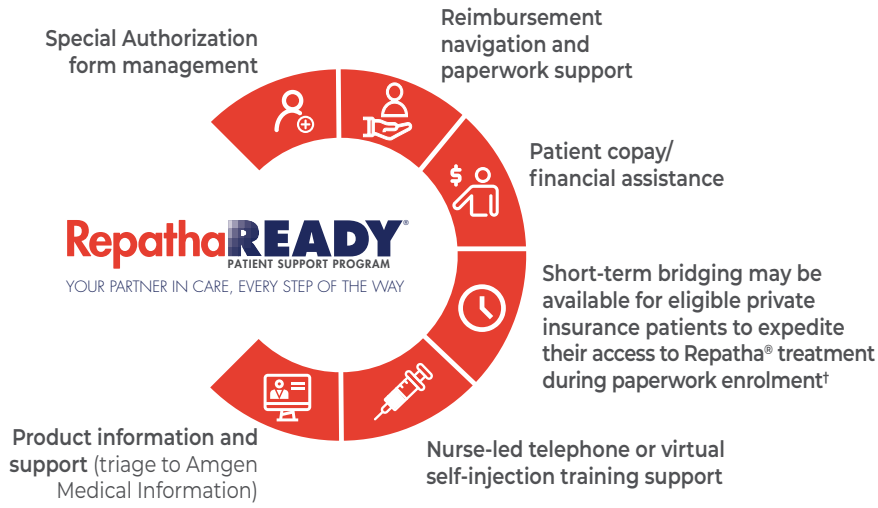

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References:
1. Amgen Data on File. **2.** Repatha® (evolocumab injection) Product Monograph. Amgen Canada Inc., September 27, 2023.

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THE EVOLVING APPROACH TO BREAST CANCER SCREENING AND TREATMENT IN CANADA: IMPLICATIONS FOR PRIMARY CARE PROVIDERS

Introduction

Nearly 30,000 Canadians are diagnosed with breast cancer annually, and while its mortality has decreased by over 55% since the 1970s due to modernized screening technologies and advances in systemic therapy, 5,500 Canadians are estimated to die of the disease every year.[1,2] Primary care providers are critical through all steps of a patient's breast cancer journey, from facilitating routine screening, to identifying breast cancer risk factors, ensuring expedient referrals, and recognizing acute or chronic treatment toxicities and their impact on overall physical and psychological health.

Breast Cancer Risk Factors

While prevention remains a pillar of cancer care, many breast cancer risk factors are unmodifiable, with female gender and age representing the greatest risks. Inherited breast cancer risk, including family history or a known high-risk gene mutation and ductal or lobular carcinoma *in situ*, are less common non-modifiable risks. The total cumulative exposure, either endogenous or exogenous, to ovarian hormones is also associated with an elevated breast cancer risk. As such, early menarche, late menopause, nulliparity or older age at first pregnancy, absence of breastfeeding, oral contraceptives, and hormone replacement therapy all affect risk. Further, history of thoracic radiation, body mass index (BMI) ≥30, and even light alcohol consumption, defined as less than one standard drink per day, are known to increase the risk of breast cancer.[3-5] While recognition of breast cancer risk factors is prudent, of the aforementioned determinants, only a strong family history, *in situ* carcinoma, chest wall irradiation, and a known mutation in high-risk genes such as breast cancer gene (*BRCA*)1, *BRCA2*, and *PALB2*, lead to modified screening recommendations across Canadian jurisdictions.

Updates to Breast Cancer Screening Guidelines and Implementation of Novel Imaging Modalities

For over a decade, the Canadian Task Force on Preventative Health Care (CTFPC) has been consistent in their stance that among individuals with an average risk of breast cancer, those aged 50 to 74 years should be systematically offered a screening mammography every

2–3 years. While the CTFPC recommends against routine screening for those aged 40–49, this stance has long been subject to debate. The CTFPC's position recognizes that routine mammography in this age group has a probable benefit for breast cancer mortality, with screening of this population estimated to prevent 0.27 deaths from breast cancer per 1,000 screens. However, the CTFPC suggests that this mortality benefit is perceived to be outweighed by the burden of false positive results.[4]

Critics note limitations of the randomized control trials that serve as the foundation of the CTFPC's position, including relatively small patient sample sizes and long inter-mammographic intervals, and point instead to observational studies of modern screening protocols that demonstrate a relative reduction in breast cancer mortality of up to 40%.[5,6] Further, a 2023 review of national breast cancer survival data found that women diagnosed with breast cancer in their 40s had a 10-year net-survival that was 1.9% higher in Canadian jurisdictions that offered organized screening programs for those aged 40–49 (84.8%) compared to those lacking such programs for this demographic (82.9%), with provincial screening rates significantly correlating with 10-year net-survival.[7] This debate is further highlighted by the recent inclusion of individuals aged 40–49 in the US Preventive Services Task Force's biennial mammographic screening recommendations.[8]

Although the directionalities of the CTFPC's recommendations have remained unchanged since 2011, there has been greater emphasis on patient values and individual risk-benefit discussion. The 2024 draft guidelines highlight that breast cancer screening is a personal choice, and all individuals aged 40–74 years should be provided with information on the potential benefits and harms of screening, with mammography offered every 2 to 3 years if desired. As summarized in **Table 1**, the application of the CTFPC's recommendations varies between Canadian jurisdictions. In line with the breadth of emerging evidence demonstrating survival benefits with early screening, within the last year, five Canadian jurisdictions have committed to reducing the age of eligibility for screening mammography self-referral to age 40 years. In the current screening landscape, Manitoba and Québec are the only Canadian jurisdictions with organized screening programs that have not extended eligibility to those under the age of 50 years.

With the advent of more sensitive imaging technologies, certain populations may benefit from supplemental breast cancer screening. Breast density refers to the proportion of fibroglandular tissue relative to fat in the breast and is divided from least (A) to most (D) dense using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS).[9] Breast density is subjectively assessed on mammography and can change over time. Categories C and D are regarded as dense, with sensitivity of traditional mammography falling to as low as 50% in these cases.[10] In addition, increased breast density is associated with higher breast cancer risk, with the risk being 1.2 times higher in those with heterogeneously dense breasts (BI-RADS C), and 2.1 times higher in those with extremely dense breasts (BI-RADS D), relative to those with average breast density.[11] In this cohort, ultrasound, contrast-enhanced mammography (CEM), and/or magnetic resonance imaging (MRI) can be used as supplemental imaging and improve the sensitivity of screening by up to 21%, with CEM nearing the sensitivity of breast MRI at a fraction of the cost.[12,13] Nevertheless, while awaiting compelling survival data, recommendations for and access to supplemental imaging in patients with dense breasts vary across jurisdictions.

While the age of screening onset and recommended supplemental screening modalities continue to evolve, it is critical that primary care providers in Canada evaluate a patient's breast cancer risk at no later than 30 years of age,[14] discuss the benefits and harms associated with mammographic screening with all patients at average risk of breast cancer aged 40–74 years, and facilitate access to mammography for those who make an individualized decision to pursue screening.

Considerations in Breast Cancer Referral

In many urban centers, there is automatic integration of a patient into local multidisciplinary breast cancer treatment infrastructure at the time of diagnosis. In jurisdictions that lack such systems, it is critical that primary care providers recognize patients with early-stage disease who may benefit from a medical oncology consultation prior to surgical intervention.

While surgical resection is the foundation of treatment in early-stage breast cancer, pre-operative systemic therapy, also known as neoadjuvant therapy (NAT), is employed in select circumstances. NAT may render inoperable cancers operable or facilitate breast-conserving surgery, while offering prognostic information based on both clinical and pathologic response.[15] Recently, patients with stage II and III triple-negative breast cancer (TNBC) have been demonstrated to benefit from neoadjuvant chemoimmunotherapy and, as such, patients with a primary tumour measuring >2 cm or with nodal involvement should be referred to medical oncology in parallel to the surgical referral.[16] Similarly, neoadjuvant anti-HER2 therapy is utilized in patients with HER2-positive tumours measuring >2 cm or with nodal involvement, warranting presurgical medical oncology assessment.[17] In the case of hormone (estrogen) receptor-positive HER2-negative cancer, NAT is most often employed to downstage disease and facilitate surgical intervention in select cases. Thus, referral

Jurisdiction	Ages 40–44	Ages 45–49	Ages 50–74	Ages 75+
British Columbia	Available every 2 years	Available every 2 years	Recommended every 2 years	Available every 2 years
Alberta	Not recommended, available every year (referral required)	Recommended every 2 years	Recommended every 2 years	Available every 2 years (referral required)
Saskatchewan	Available (referral required)[1]	Available (referral required)[1]	Recommended every 2 years	Available every 2 years
Manitoba	Not recommended, available (referral required)	Not recommended, available (referral required)	Recommended every 2 years	Available every 2 years
Ontario	Available (referral required)[2]	Available (referral required)[2]	Recommended every 2 years	Available every 2 years (referral required)
Québec	Not recommended, available every 2 years (referral required)	Not recommended, available every 2 years (referral required)	Recommended every 2 years	Available every 2 years (referral required)
Newfoundland and Labrador	Recommended every 2 years	Recommended every 2 years	Recommended every 2 years	Available every 2 years
Nova Scotia	Recommended every year	Recommended every year	Recommended every 2 years	Available every 2 years
New Brunswick	Recommended every 1–2 years	Recommended every 1–2 years	Recommended every 2–3 years	Available every 2 years (referral required)
Prince Edward Island	Available every year	Available every year	Recommended every 2 years	Available every 2 years (referral required)
Yukon Territory	Available every year	Available every year	Recommended every 2–3 years	Available every 2 years
Northwest Territories	Not recommended, available every 2 years (referral required)	Recommended every 2 years	Recommended every 2 years	Available every 2 years
Nunavut[3]	Available every year	Available every year	Available every year	Available every year

Table 1. Varying Canadian breast cancer screening recommendations by jurisdiction; *courtesy of Greydon Arthur, MD, Charlotte J. Yong-Hing, MD, FRCPC, and Nathalie LeVasseur, MD, FRCPC.*

Self-referral available unless otherwise indicated.

[1]Beginning January 2025, individuals living in Saskatchewan can self-refer for screening mammography starting at age 40.

[2]Beginning October 2024, individuals living in Ontario can self-refer for screening mammography starting at age 40.

[3]Nunavut currently has no organized breast cancer screening program.

often originates from surgeons at the time of surgical candidacy assessment.

Beyond facilitating early medical oncology referral, primary care providers play a critical role in assessing a patient's familial risk and, in certain circumstances, helping patients navigate hereditary breast cancer testing. As a patient's longitudinal, often multigenerational provider, primary care physicians may have unique insight into a patient's family history and can help identify individuals at potential risk of genetic cancer predisposition. While there are subtle interprovincial differences in hereditary breast cancer testing eligibility criteria, the following should prompt consideration of referral for genetic testing:

Patient History

- Age at diagnosis
  - *Breast cancer at a young age (typically below ages 35–45 years)*
- Multiple primary breast cancers
  - *Often with one diagnosed before age 50*
- Disease pathology
  - *TNBC at age ≤60*
- Ancestry
  - *Ashkenazi Jewish heritage*
- Male breast cancer
- Ovarian cancer

Family History

- Family history of cancers affecting close relatives with any of the aforementioned characteristics
  - *Close relatives are defined as first- or second-degree relatives.*
- Multiple affected family members
  - *2–3 close relatives with breast cancer*
- Known mutations
  - *Family member with BRCA1, BRCA2, or other high-risk gene mutations*
- Multiple different malignancies
  - *Breast and ovarian cancer in close relatives*

Facilitating patient access to NAT in early-stage disease and recognizing patient and family history suggestive of possible hereditary breast cancer predisposition ensures opportunities for early intervention, screening intensification, and genetic counselling are not missed.

Evolving Treatment Modalities, Implications for Follow-up and Monitoring

The breast cancer therapeutic landscape is rapidly expanding, with recognition of the utility of immunotherapy in this setting and an ever-growing selection of targeted agents. While the diversification of this therapeutic arsenal has led to improved disease-specific outcomes and more favourable toxicity profiles, these novel agents often confer unique toxicities that merit discussion.

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block immune-inhibitory signalling in the tumour microenvironment. This blockade can enhance the native immune system's ability to recognize cancer antigens as foreign and induce T cell-mediated cytotoxicity. The ICI pembrolizumab has established an increasingly prominent role in the realm of breast cancer treatment over the last five years. Pembrolizumab was first approved by Health Canada in 2021 for use in combination with chemotherapy in the treatment of unresectable or metastatic TNBC in patients whose tumours express the immune checkpoint protein programmed cell death ligand 1 (PD-L1).[18] Health Canada expanded approval of pembrolizumab in 2022 to include use in combination with chemotherapy in the NAT setting, followed by adjuvant pembrolizumab monotherapy in patients with high-risk early-stage TNBC, irrespective of PD-L1 status.[16]

As ICIs block inhibitory immune signalling in an indiscriminate fashion, many of the toxicities associated with immunotherapy result from iatrogenic autoimmunity, termed immune-related adverse events (irAEs). In the clinical trials cited above, irAEs of any grade were reported in up to 26.5% of patients, manifesting most commonly as thyroid dysfunction (hypothyroidism 15.8%, hyperthyroidism 4.3%), pneumonitis (2.5%), and colitis (1.8%), though irAEs can affect any non-immune privileged tissue and, in rare circumstances, can be fatal if left unrecognized.[16,18] To identify these toxicities, one must first recognize that while many occur within 3 months of ICI initiation, irAEs can present at any point during treatment and delayed-onset irAEs may arise many months after treatment completion.[19] Once identified, despite variability in symptomatology and impacted tissue, treatment generally consists of some combination of ICI discontinuation, steroid-based therapy, hormone replacement in the case of some autoimmune endocrinopathies, and rarely, intensive immunosuppression.[20] Patients presenting to primary care with new unexplained symptoms or flare of existing autoimmune disease should be carefully considered for possible irAEs and warrant prompt discussion with the patient's medical oncologist.

Drug Class and Mechanism of Action	Approved Agent(s)	Approved Indication(s)	Toxicities of Interest
CDK4/6 inhibitors – Block proliferative cell cycle signalling	Palbociclib, ribociclib, abemaciclib	**1)** First-line treatment (or following progression on endocrine therapy) of HR^+, $HER2^-$ locally advanced or metastatic breast cancer in combination with an aromatase inhibitor (palbociclib, ribociclib, abemaciclib) **2)** Adjuvant therapy in early, node-positive HR^+, $HER2^-$ breast cancer with high disease recurrence risk (abemaciclib)	• Pancytopenia and risk of febrile neutropenia (<1% with all listed agents) • Nausea/vomiting and diarrhea (abemaciclib) • QT prolongation and associated risk of arrhythmia, including Torsades (ribociclib)
Immune checkpoint inhibitors – Block immunosuppressive signalling in tumour microenvironment	Pembrolizumab, atezolizumab	**1)** First-line treatment of locally advanced or metastatic TNBC in combination with chemotherapy (pembrolizumab) **2)** Neoadjuvant/adjuvant therapy for >T2N0 TNBC in combination with chemotherapy (pembrolizumab)	• Cutaneous: rash (often eczematous), rare risk of severe cutaneous a diverse reactions • Gastrointestinal: colitis, hepatitis • Endocrine: hyper/hypothyroidism, hypophysitis, diabetes mellitus (risk of DKA), adrenal insufficiency • Respiratory: pneumonitis • Renal: nephritis (AIN, glomerulonephritis) • Cardiac: autoimmune myocarditis • Neurologic: NMJ disorders, aseptic meningitis, peripheral neuropathy
Antibody-drug conjugates – Deliver cytotoxic payload to a tumour using antibodies	Trastuzumab deruxtecan, trastuzumab emtansine, sacituzumab govitecan	**1)** Treatment of $HER2^+$ metastatic breast cancer with prior exposure to trastuzumab and taxane (trastuzumab emtansine) **2)** Treatment of $HER2^+$ metastatic breast cancer with prior exposure to dual anti-HER2 therapy or HER2-low disease with at least 1 prior line of chemotherapy (trastuzumab deruxtecan) **3)** $2^{nd}/3^{rd}$ line treatment of metastatic TNBC or HR^+ $HER2^-$ breast cancer after 2–4 lines of prior chemotherapy (sacituzumab govitecan)	• Reversible myocardial dysfunction with reduction in LVEF (trastuzumab-based antibody-drug conjugates) • Pneumonitis (trastuzumab deruxtecan) • Neutropenia • Nausea/vomiting and diarrhea
PARP inhibitors – Prevent repair of DNA double-strand breaks in BRCA-deficient cancers	Olaparib	**1)** Adjuvant treatment for $HER2^-$ breast cancer treated with neoadjuvant or adjuvant chemotherapy in patients with germline BRCA1/2 mutation **2)** Treatment of metastatic breast cancer in patients with germline BRCA1/2 mutation	• Secondary neoplasms (myelodysplastic syndrome, acute myeloid leukemia; <1%) • Pneumonitis (<1%)
Anti-HER2 tyrosine kinase inhibitors – block growth signalling originating from the HER2 receptor	Tucatinib, lapatinib, neratinib (non-specific inhibitor)	**1)** Treatment of locally advanced or metastatic $HER2^+$ breast cancer, in combination with trastuzumab and capecitabine (tucatinib) **2)** Treatment of HR^+, $HER2^+$ metastatic breast cancer not suitable for trastuzumab, in combination with aromatase inhibitor (lapatinib) **3)** Extended adjuvant treatment of HR^+, $HER2^+$ breast cancer after completing trastuzumab-based regimen, used in combination with aromatase inhibitor (neratinib)	• Hepatotoxicity • Hand-foot syndrome • Reversible myocardial dysfunction with reduction in LVEF • QT prolongation and associated risk of arrhythmia, including Torsades • Diarrhea
PI3K/AKT inhibitors – block PI3K growth and proliferation pathway	Alpelisib, Capivasertib	**1)** Second-line treatment of HR^+, $HER2^-$, PI3K-mutated (alpelisib) or PTEN, PI3K, AKT-mutated (capivasertib) advanced or metastatic breast cancer	• Severe hyperglycemia and risk of DKA and HHS • Rash • Mucositis, diarrhea

Table 2. Indications for novel therapeutic agents approved by Health Canada since 2015 for the treatment of breast cancer and unique toxicities relevant in the primary care setting: *courtesy of Greydon Arthur, MD, Charlotte J. Yong-Hing, MD, FRCPC, and Nathalie LeVasseur, MD, FRCPC.*

Abbreviations: AIN: acute interstitial nephritis, **AKT:** protein kinase B, **BRCA:** breast cancer gene, **CDK:** cyclin-dependent kinase, **DKA:** diabetic ketoacidosis, **HER2:** human epidermal growth factor receptor 2, **HHS:** hyperosmolar hyperglycemic syndrome, **HR:** hormone receptor, **LVEF:** left ventricular ejection fraction, **NMJ:** neuromuscular junction, **PARP:** poly(ADP-ribose) polymerase, **PI3K:** phosphoinositide 3-kinase, **PTEN:** phosphatase and tensin homolo, **TNBC:** triple-negative breast cancer

Emerging treatments in breast cancer extend beyond immunotherapy and vary substantially in their mechanisms of action and molecular targets, offering exciting new therapeutic opportunities. Trastuzumab is an antibody that targets the cell surface marker HER2 that is expressed on 1 in 5 breast cancers. While this technology has been approved and widely utilized in Canada for some time, the ability of such antibodies to target breast cancer surface proteins has recently been leveraged to deliver a cytotoxic payload directly to the tumour, joining a class of drugs known as antibody-drug conjugates (ADCs). To date, three such ADCs have been approved for the treatment of metastatic breast cancer: trastuzumab-deruxtecan, trastuzumab-emtansine, and sacituzumab-govitecan. Beyond antibody-based therapies, several small molecule inhibitors have recently received Health Canada approval. These agents often either target common mechanisms of cell proliferation and survival, as in the case of cyclin-dependent kinase (CDK)4/6 inhibitors, or target-specific genetic susceptibilities unique to an individual patient's disease, as with olaparib in BRCA-mutated breast cancer.

As highlighted in **Table 2**, many of these novel agents are associated with unique, clinically relevant toxicities. In the primary care setting, an awareness of said toxicities is prudent to facilitate prompt treatment reassessment with medical oncology and, if required, further expert referral.

Take Home Message for Primary Care Providers

The current landscape of oncologic care is dependent on well-connected, multidisciplinary teams, with primary care providers being critical members of this infrastructure, from screening to survivorship and occasionally palliation. Together, as a patient's longitudinal care provider, primary care physicians are uniquely positioned to help patients contextualize their breast cancer among multi morbidities, share insights into the prognosis of competing comorbidities, and leverage preexisting knowledge of a patient's values and motivations to guide discussion of a patient's goals of care.

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Financial Disclosures

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C.Y-H.: None declared.
N.L.: None declared.

References

1. Brenner DR, Poirier A, Woods RR, et al. Projected estimates of cancer in Canada in 2022. CMAJ 2022;194:601-7.
2. Caswell-Jin JL, Sun LP, Munoz D, et al. Analysis of Breast Cancer Mortality in the US – 1975 to 2019. JAMA 2024;331:233-41.
3. Kantarjian HM, Wolff RA, Rieber AG. The MD Anderson Manual of Medical Oncology. Fourth Edition. New York City: McGraw Hill; 2022.
4. Thériault G, Slavtcheva N, Flemming J, et al. Breast Cancer (2024 Update) – Draft Recommendations. Canadian Task Force on Preventative Health Care; May 30, 2024 [September 22, 2024]. Available from: https://canadiantaskforce.ca/breast-cancer-update-draft-recommendations
5. Hellquist BN, Duffy SW, Abdsaleh S, et al. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. Cancer 2011;117:714-22.
6. Coldman A, Phillips N, Wilson C, et al. Pan-Canadian study of mammography screening and mortality from breast cancer. J Natl Cancer Inst 2014;106:dju261.
7. Wilkinson AN, Ellison LF, Billette JM, et al. Impact of Breast Cancer Screening on 10-Year Net Survival in Canadian Women Age 40-49 Years. J Clin Oncol 2023;41:4669-77.
8. Nicholson WK, Silverstein M, Wong JB, et al. Breast Cancer: Screening – Final Recommendation Statement. U.S. Preventative Services Task Force; April 30, 2024 [September 22, 2024]. Available from: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-screening#bootstrap-panel--12
9. D'Orsi C, Sickles E, Mendelson E, et al. Breast Imaging Reporting and Data System. ACR BI-RADS® Atlas, American College of Radiology; 2013 [September 22, 2024]. Available from: https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Bi-Rads
10. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology 2002;225:165-75.
11. Butler RS, Hooley RJ. Screening breast ultrasound: update after 10 years of breast density notification laws. AJR AM J of Roentgenol. 2020;214(6):1424-35.
12. Ohuchi N, Suzuki A, Sobue T, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan strategic anti-cancer randomized trial (J-START): A randomised controlled trial. Lancet 2016; 387:341-8.
13. Cheung Y, Lin Y, Wan Y, et al. Diagnostic performance of dual-energy contrast-enhanced subtracted mammography in dense breasts compared to mammography alone: Interobserver blind-reading analysis. Eur Radiol 2014;24:2394-403.
14. Lee C, Monticciolo D, Moy L. Screening Guidelines Update for Average-Risk and High-Risk Women. AJR AM J of Roentgenol. 2020;214(2):316-323.
15. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72.
16. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020;382:810-21.
17. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.
18. Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. N Engl J Med 2022;387:317-26.
19. Nakai Y, Otsuka T, Inoue T, et al. Two cases of delayed onset of immune-related adverse events after discontinuation of nivolumab in patients with metastatic renal cell cancer. IJU Cas Rep 2021;4:326-9.
20. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. J Clin Oncol 2021;39:4073-126.

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THE SPECTRUM OF MANAGEMENT FOR PSORIASIS: FROM THE KNOWN TO NEW ALTERNATIVES

Introduction

Psoriasis is a chronic, immune-mediated systemic condition characterized by inflammatory changes that may involve the skin and joints.[1] It is relatively common, with a prevalence rate of 2–4% in North America, and a global prevalence rate of up to 11.4%.[2-4] Years ago, affected patients may have ranged in age from 18–39 to 50–69 due to bimodal distribution.[5] While initially thought to be a dermatologic disease, it is now a recognized multisystem condition with a genetic predisposition.[5] The complex pathophysiology is thought to originate from dysregulation between the innate and adaptive immune systems.[2] T-lymphocytes, dendritic cells, cytokines such as interleukin (IL) 23, IL-17, and tumor necrosis factor (TNF) have all been implicated in and contribute to the inflammatory sequelae.[2,6] The chronicity and pathogenesis of disease may predispose patients to significant functional impairments, associated comorbidities such as metabolic syndrome and cardiovascular disease, and diminished quality of life.[2,7] This has prompted novel approaches to management with the introduction of biologics and small molecule therapies that address the underlying immune dysregulation.[8]

There are multiple clinical manifestations including plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis.[5,6] Among the most common is plaque psoriasis which typically presents as symmetrically distributed, well demarcated, erythematous, scaly plaques or patches that may be pruritic.[5,6] Common sites of involvement include the extensor surfaces of the elbows, knees, the trunk, gluteal cleft, and scalp. Guttate psoriasis is typically preceded by upper respiratory infections and represents approximately 2% of all cases of psoriasis. It involves several small (<1 cm) confetti-like papules

and plaques.[5] A severe, although uncommon form is erythrodermic psoriasis which results in widely distributed erythema, scales and exfoliation of a large surface area of the skin. Due to the widespread loss of the epidermal, dermal barrier and associated risk of fluid loss, electrolyte disturbances and infection, it is considered a dermatologic emergency. Pustular psoriasis is also an uncommon, potentially severe, clinical variant, with possible complications secondary to acute widespread erythema and development of multiple pustules.[5,6]

Psoriasis at other sites such as the intertriginous regions, nails, palms, and soles may present differently.[6] For example, intertriginous also known as inverse psoriasis, involves smooth, shiny plaques that generally lack scale and appear in skin folds such as the inguinal, genital, and inframammary regions. Nail psoriasis can present alone or concurrently with psoriasis or psoriatic arthritis. Features include pitting of the nail matrix, leukonychia, crumbling of the nail, and oil spots or tan brown discoloration of the nail bed.[5,6]

Differential Diagnosis

The differential diagnosis varies depending on the clinical presentation and variant of psoriasis. Given plaque psoriasis is the most common form, it is important to recognize other conditions such as, lichen simplex chronicus, seborrheic dermatitis, atopic dermatitis, nummular eczema, and superficial fungal infections which can present similarly.

Assessing Disease Severity

Clinical disease burden is generally quantified by extent of body surface involvement.[9] In terms of disease severity, several validated scoring scales have been used primarily in clinical trials. They may also serve a role in clinical practice. The Psoriasis Area and Severity Index (PASI) score is most often used. The Dermatology Life Quality Index (DLQI) may be used to assess impact on quality of life.[9,10]

There are several comorbidities associated with psoriasis, consideration of which may influence treatment choice.[1,9] The most implicated is psoriatic arthritis, affecting as many as one-third of patients with psoriasis.[2,5] Psoriatic arthritis can present as joint swelling, stiffness and pain of the small and large joints, or the axial skeleton.[5,11] Many of the current treatments for psoriasis, particularly biologics, can also effectively manage psoriatic arthritis.[11] Furthermore, cardiometabolic disease disproportionately affects patients with psoriasis compared to the general population. Psoriasis, in particular severe disease, is a risk factor for myocardial infarction, obesity, metabolic syndrome, and atherosclerosis.[2,5] However, the recent literature suggests that the risk of major adverse cardiovascular events such as myocardial infarction, stroke, heart failure, and cardiovascular death in fact decreases with ongoing treatment for psoriasis.[1] There is also an increased risk of inflammatory bowel disease such as Crohn's disease.[2,5] Lastly, the incidence of psychological illnesses such as depression and anxiety has been well documented and they play a role in overall quality of life for patients living with psoriasis. This highlights the importance of screening patients with concomitant mood symptoms while promptly and effectively managing the dermatologic manifestations, which has been shown to correlate with improvement in psychiatric symptoms.[1,5]

Indications for Referral

To prevent morbidity, primary care providers should consider early referral to dermatology for patients with extensive body surface area (BSA) involvement, disease refractory to first-line topical treatments, potentially severe variants including erythrodermic and pustular psoriasis, and if the diagnosis is uncertain. In addition, primary care providers play an important role in informing patients about the association between psoriasis and other conditions, and recognizing systemic findings, particularly musculoskeletal complaints, which necessitates prompt referral to rheumatology.

Management

Psoriasis is a chronic, relapsing condition which, while incurable, can be actively managed with an array of treatments. These include novel treatments such as biologics and small molecule therapies. Management is generally directed by the severity of disease activity and any associated comorbidities.[1,11]

In general, patients should be advised to maintain a healthy BMI and quit smoking due to the interplay between disease activity and cardiovascular risk. Additionally, for patients beginning systemic immunosuppressive therapy it is imperative to assess immunization history and update routine vaccinations prior to treatment. (**Box 1**)[12]

Baseline:
CBC with differential
Complete Metabolic Profile
TB test +/- Chest xray
Hep B and C serology
HIV serology based on risk factors
Ongoing:
Infectious work up, if indicated
Skin cancer screening
Case by case testing for latent TB
CBC with differential, CMP including liver function tests in patients on infliximab at the discretion of treating physician

Box 1. General monitoring parameters; *adapted from Menter, A et al., 2019.*

Mild Disease

Mild disease is classified as involving less than 3% of total BSA, where the size of the hand is approximately 1% BSA.[11] Topical corticosteroids play a critical role in management, particularly in patients with well localized disease.[9,11,13] Due to their anti-inflammatory, antiproliferative, vasoconstrictive, and immune suppressing mechanism of action, they serve as a cornerstone of therapy.[5] The vehicle used and potency of the corticosteroid in congruence with the disease location, severity, and patient preference are key considerations. Overall, potent and super potent corticosteroids have been shown to be the most effective agents compared to mild or moderately potent corticosteroids with efficacy rates ranging from 58–92%.[13] Intralesional corticosteroids such as triamcinolone may be utilized in regions with thick plaques or lesions.[13]

Ultimately, topical corticosteroids carry a risk of skin atrophy, folliculitis, telangiectasia, and striae, therefore combination therapy with steroid-sparing agents such as Vitamin D analogues (calcipotriol) or keratolytics (salicylic acid, tazarotene) may be used. Topical Vitamin D analogies block keratinocyte proliferation by binding to receptor sites on T cells with the potential to cause mild irritant dermatitis and rarely hypercalcemia.[5,11] Tazarotene is a topical retinoid that regulates keratinocyte proliferation, thus addressing hyperkeratosis. It has been shown to be more effective in combination with a topical corticosteroid compared to tazarotene monotherapy.[13] Side effects include pruritus, erythema, and burning. Calcineurin inhibitors such as pimecrolimus and tacrolimus block the activation of T cells and therefore propagation of proinflammatory cytokines, and have off-label use in psoriasis, with data derived from established efficacy in atopic dermatitis.[13] Coal tar is a traditional treatment option for psoriasis; however, the associated odour, staining, risk of local irritation, contact dermatitis, and phototoxicity limit its use in practice.[13] In 2023, roflumilast, a phosphodiesterase Type 4 inhibitor (PDE4), became approved in Canada as a topical alternative for plaque psoriasis. Through inhibition of PDE4 and thus cyclic adenosine monophosphate (cAMP), it results in downstream inhibition of proinflammatory cytokines which are propagated in patients with psoriasis.[14] Studies have demonstrated comparable side effects to placebo; commonly reported side effects include diarrhea, headache, and insomnia. While it offers a promising alternative to topical corticosteroids, as it was recently introduced to the market, it remains a costly alternative.

Phototherapy may be used for mild-to-severe psoriasis.[5,11,13] Among the various forms of phototherapy, narrowband UVB (NB-UVB) is typically used. A 2013 review found that a 75% improvement in PASI (PASI 75) was seen in an average of 62% of individuals after 14 to 34 treatments.[15] Although NB-UVB is less effective than psoralen and UVA (PUVA), its demonstrated efficacy combined with negligible risk of skin malignancy makes it a more favourable option.[5,11,13] It is usually administered 2–3 times per week, although it may be inaccessible for patients depending on their geographic location.

Moderate-to-Severe Disease

Approximately 20–30% of patients have moderate-to-severe psoriasis.[8] Moderate disease is classified as involving 3–10% BSA, while severe disease typically involves >10% BSA and is not expected to resolve with topical therapy, resulting in significant impact on quality of life.[9,11]

While biologic treatments have rapidly improved the management of moderate-to-severe psoriasis in the past decade, oral systemic therapies have long been used as treatment. These oral therapies are generally integrated as the first- or second-line treatments in stepwise reimbursement programs. As a result, the cost prohibitive nature of biologics means they are considered third-line therapies despite their superior efficacy compared to both conventional systemic therapies and small molecule agents.[8]

Methotrexate is considered a first-line systemic agent.[9] One RCT found that methotrexate's PASI 75 after 16 weeks was 35.5%.[16] Methotrexate exerts its action as an antimetabolite by inhibiting nucleic acid synthesis via folate antagonism. This decreases proliferation of lymphocytes, which drive the inflammatory process in psoriasis.[11,17,18] Methotrexate has been used in combination with etanercept and NB UVB phototherapy, and has shown benefit in psoriatic arthritis. Adverse effects include nausea, stomatitis and hepatotoxicity.[9,11,17]

Cyclosporine is a calcineurin inhibitor that blocks signalling of proinflammatory cytokines.[17] At a moderate dose it has been shown to achieve a PASI 75 in 50–70% of patients.[19] It can be utilized for its rapid onset of action which is particularly useful in an acute flare of disease; however, the cumulative risk of hypertension and nephrotoxicity preclude its long-term use.[17,18]

Acitretin is an oral retinoid, a derivative of Vitamin A that has increased benefit with combination phototherapy.[17] Acitretin exhibits immunomodulatory properties by affecting epidermal cell growth. Interestingly, it does not have immunosuppressive effects and thus may be used in patients with concurrent immunodeficiency states.[17] The efficacy ranges depending on the duration of therapy, although it is less efficacious overall in comparison with other systemic therapies. Due to its long half-life and risk of teratogenicity, there is a 3-year washout period required for patients intending to conceive.[12]

Class	Name of Biologic Generic (Brand Name)	Other Indications[13,19]	Relative Contraindications[19]	Dosing Frequency[13]	Adverse Events [13]	Efficacy in Clinical Trials[14,19]
TNFi	Adalimumab (Humira)	PsA, IBD	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection, NYHA class III or IV heart failure, MS	Every 2 weeks (SC)	Injection site reactions, serious infections, malignancies	PASI 75 at 16 weeks – 71%
TNFi	Certolizumab	PsA, Crohn's disease	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection, NYHA class III or IV heart failure, MS	Every 2 weeks (SC)	Headache, autoimmune phenomenon	PASI 75 at 12 weeks – 75–83%
TNFi	Etanercept (Enbrel, Brenzys, Erelzi)	PsA, RA, AS	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection, NYHA class III or IV heart failure, MS or demyelinating disease	Twice weekly x 3 months, then weekly thereafter (SC)	Injection site reactions, worsening heart failure, autoimmune phenomenon	PASI 75 at 12 weeks – 48%
TNFi	Infliximab (Remicade)	PsA, IBD	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection, NYHA class III or IV heart failure, MS or demyelinating disease	Dose at 0, 2, and 6 weeks then every 8 weeks thereafter (IV)	Infusion reactions, infections, allergic reactions, demyelinating disorders	PASI 75 at 10 weeks – 70–89%
IL-12/IL-23 inhibitor	Ustekinumab (Stelara)	PsA, Crohn's disease	Untreated hepatitis B infection, history of lymphoreticular malignancy, active infection	Dose at 0, and 4 weeks, then every 12 weeks thereafter (SC)	Nasopharyngitis, URTI, headache, infections, malignancy	PASI 75 at 12 weeks – 67%
IL-17 inhibitor	Brodalumab (Siliq)	PsA	History of IBD, recent suicidal behaviour or history of suicidal ideation	Weekly for 3 weeks then every 2 weeks thereafter (SC)	Injection site reactions, URTI	PASI 75 at 12 weeks – 67–-86%
IL-17 inhibitor	Bimekizumab (Bimzelx)	Undergoing investigation for PsA	Hypersensitivity to the medication or any of the excipients	Every 4 weeks for the first 16 weeks, then every 8 weeks thereafter (SC)	nasopharyngitis, oral candidiasis, URTI	PASI 90 at week 16 –85-86%
IL-17 inhibitor	Ixekizumab (Talz)	PsA	Hypersensitivity to the medication or any of the excipients	Dose at 0, 2, 4, 6, 8, 10 and 12 weeks then every 4 weeks thereafter (SC)	Injection site reactions, URTI	PASI 75 at 12 weeks – 81–84%
IL-17 inhibitor	Secukinumab (Cosentyx)	PsA, AS	History of IBD	Dose at 0,1, 2, 3 weeks then every 4 weeks thereafter (SC)	Nasopharyngitis, URTI, rhinitis, oral herpes, diarrhea	PASI 75 at 12 weeks – 81.6%
IL-23 inhibitor	Guselkumab (Tremfya)	PsA	Active infection, hypersensitivity to the medication or any of the excipients	Dose at 0, 4 weeks then every 8 weeks thereafter (SC)	Injection site reactions, URTI	PASI 90 at 16 weeks –70%
IL-23 inhibitor	Risankizumab (Skyrizi)	PsA, Crohn's disease	Active infection, Hypersensitivity to the medication or any of the excipients	Dose at 0, 4 weeks then every 12 weeks thereafter (SC)	URTI, headache	PASI 90 at 16 weeks – 70%
IL-23 inhibitor	Tildrakizumab (Ilumya)	/	Active infection, Hypersensitivity to the medication or any of the excipients	Dose at 0, 4 weeks then every 12 weeks thereafter (SC)	Nasopharyngitis, URTI, injection site reactions, headache	PASI 75 at 12 weeks – 64%

Table 1. Summary of biologic agents indicated for psoriasis; *courtesy of Jaggi Rao, MD, FRCPC.*

Abbreviations: PsA: psoriatic arthritis, **IBD:** inflammatory bowel disease (Crohn's and Ulcerative colitis), **NYHA:** New York Heart Association, **MS:** multiple sclerosis, **RA:** rheumatoid arthritis, **AS:** ankylosing spondylitis, **URTI:** upper respiratory tract infection, **IL:** interleukin, **TNFi:** tunour necrosis factor inhibitor, **SC:** subcutaneous, **IV:** intravenous

Small Molecules

Tofacitinib may be used off-label for psoriasis and has demonstrated utility in rheumatoid arthritis, ulcerative colitis and psoriatic arthritis (PsA). It is an oral Janus kinase inhibitor that interferes with signalling pathways of proinflammatory cytokines.[17] In clinical trials, at the low end of the dosing range, tofacitinib was more effective than placebo (PASI 75 of 46% vs 6.2%). Nevertheless, the FDA has issued black box warnings regarding the risk of thrombosis associated with tofacitinib. In 2022, Health Canada released a safety alert about the association between increased cardiovascular concerns and malignancy, in addition to the risk of thrombosis.[17,20]

Deucravacitinib is an oral tyrosine kinase 2 inhibitor. It exerts its mechanism of action through halting downstream proinflammatory cytokine signalling. In clinical trials the PASI 75 at 16 weeks ranged from 53–58%. Upper respiratory tract infections and nasopharyngitis were the most commonly observed side effects.

Apremilast is another non biologic therapy, specifically, an oral PDE4 inhibitor that is least frequently used.

Biologic agents have consistently shown to be significantly more efficacious in comparison to oral systemic agents and tofacitinib. **Table 1** provides a summary of the biologic agents.

A recent meta-analysis demonstrated that biologics, namely infliximab, ixekizumab, bimekizumab, and risankizumab resulted in a 90% improvement in PASI score and therefore were the most effective in treating psoriasis compared to non-biologics. Various combinations of biologics, topical therapies, such as topical corticosteroids, Vitamin D analogues, phototherapy, and oral systemic agents have also been studied in the literature.[9,19] The choice of initial biologic therapy requires consideration of a patient's psoriasis variant, their comorbidities, particularly PsA and other inflammatory conditions, desire to conceive, and access to insurance coverage, as well as response to previous treatment.

Conclusion

Psoriasis is a genetically linked, lifelong, widespread immune mediated condition with potentially severe medical and psychosocial implications.[11] The impact on a patient's quality of life can be detrimental, and patients are also at increased risk of several diseases including cardiac disease, metabolic syndrome, inflammatory bowel disease, and depression.[1,11,18] Due to the unremitting and relapsing nature of the condition, prompt and effective treatment is an essential aspect of management.

The immune activation and dysregulation via various cytokines play a central role in the pathogenesis of psoriasis, therefore novel biologic treatments aim to target the implicated mediators of disease. Biologics have revolutionized the landscape of moderate-severe psoriasis management and are highly effective at controlling and remitting disease. Despite this, cost and accessibility continue to be barriers to widespread use in clinical practice. Further insight into the disease process continues to shape the evolving treatment options and offers promising results for patients.

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References

1. Elmets CA, Leonardi CL, Davis DM, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol. 2019 Apr 1;80(4):1073-113.
2. W-H Boehncke, Schön MP. Psoriasis. Lancet. 2015;386:983-4.
3. Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013 Feb 1;133(2):377-85.
4. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017 Feb;31(2):205-12.
5. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. JAMA. 2020 May 19;323(19):1945-605.
6. Feldman SR. Psoriasis: epidemiology, clinical manifestations, and diagnosis. UpToDate. Waltham, MA: UpToDate Inc. Available from: https://www.uptodate.com
7. Kimball AB, Jacobson C, Weiss S, et al. The psychosocial burden of psoriasis. Am J Clin Dermatol 2005 Dec;6:383-92.
8. Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2023 Jul 12;7(7):CD011535
9. Samarasekera EJ, Smith CH. Psoriasis: guidance on assessment and referral. Clin Med. 2014 Apr;14(2):178.
10. Puzenat E, Bronsard V, Prey S, et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. J Eur Acad Dermatol Venereol. 2010 Apr;24:10-6.
11. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. Can Fam Physician. 2017 Apr 1;63(4):278-85.
12. CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2016. Available from: http://www.e-cps.ca
13. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD–NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. JAAD. 2021 Feb 1;84(2):432-70.
14. Feldman SR. Treatment of psoriasis in adults. UpToDate. Waltham, MA: UpToDate Inc. Available from: https://www.uptodate.com
15. Almutawa F, Alnomair N, Wang Y, et al. Systematic review of UV-based therapy for psoriasis. Am J Clin Dermatol. 2013 Apr;14:87-109.
16. Saurat JH, Stingl G, Dubertret L, et al, CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008 Mar 1;158(3):558-66.
17. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Am Acad Dermatol. 2020 Jun 1;82(6):1445-86.
18. Papp K, Gulliver W, Lynde C, et al. Canadian guidelines for the management of plaque psoriasis: overview. J Cutan Med Surg. 2011 Jul;15(4):210-9.
19. Menter A, Strober BE, Kaplan DH, et al Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019 Apr 1;80(4):1029-72.
20. Government of Canada. Public Advisory - Health Canada safety review finds link between the use of Xeljanz and Xeljanz XR (tofacitinib) and increased risk of serious heart-related issues and cancer. 2022 Jan 12. Available from: https://recalls-rappels.canada.ca/en/alert-recall/health-canada-safety-review-finds-link-between-use-xeljanz-and-xeljanz-xr-tofacitinib

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THE FAMILY PHYSICIAN'S UNIQUE ROLE IN HEART FAILURE MANAGEMENT

Introduction

Heart failure (HF) is an epidemic with a prognosis that is worse than some cancers. Prevention, early diagnosis, coordination, and implementation of guideline-directed medical therapy (GDMT) are imperative to stem this tsunami wave. The family physician stands in a unique, critical, and first-line position to be able to offer all 3. Their understanding and implementation of these roles are crucial for success in the battle against HF. This review offers a perspective on the role of family physicians in managing HF.

Definitions and Classifications

The universal definition of HF was recently established as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and is corroborated by elevated natriuretic peptide (NP) levels and/or objective evidence of pulmonary or systemic congestion. The stages of HF are as follows. **Stage A**, which describes patients at risk for HF but without current or prior signs of HF and without structural or biomarker evidence of heart disease. **Stage B**, or pre-HF, describes those with structural heart disease or abnormal cardiac function or elevated NP levels but without current or prior symptoms or signs of HF. **Stage C** describes patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality. **Stage D**, or advanced HF, describes patients with severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT, requiring advance therapies such as consideration for transplant, mechanical circulatory support, or palliative care. In addition, a revised classification of HF based on left ventricular ejection fractions (LVEF) was proposed. This includes HF with reduced ejection fraction (HFrEF), defined as HF with an LVEF of <= 40%; HF with mildly reduced ejection fraction (HFmrEF), defined as HF with an LVEF of 41–49%; HF with preserved ejection fraction (HFpEF), defined as HF with an LVEF of >= 50%; and HF with improved ejection fraction (HFimpEF), defined as HF with a baseline LVEF of <40% with a >=10% point increase from baseline LVEF, and a second measurement of LVEF of >40%[1] (**Figure 1**). The stages and classifications of HF emphasize that it is a dynamic condition that can cross a spectrum of stages and LVEF. The idea of a stable HF patient does not exist and should be avoided. Every effort should be made to ensure that patients receive the best possible therapy to improve symptoms, quality of life, prognosis, and to prevent worsening HF (WHF), even when symptoms are well controlled.

Risk Factors, Prognosis and Burden of Disease

As of 2019, it is estimated that 56.2 million people worldwide are living with HF. The prevalence ranges from 1–3% of the overall population, with a 29.4% increase observed from 2010 to 2019, varying by country. Incidence rates are 2–3 cases/1000 person years in Europe and North America.[2] In Canada, the 2021–2022 prevalence rate for patients aged 40 years or older was 3.9%, with the highest rate of 17.8% observed in

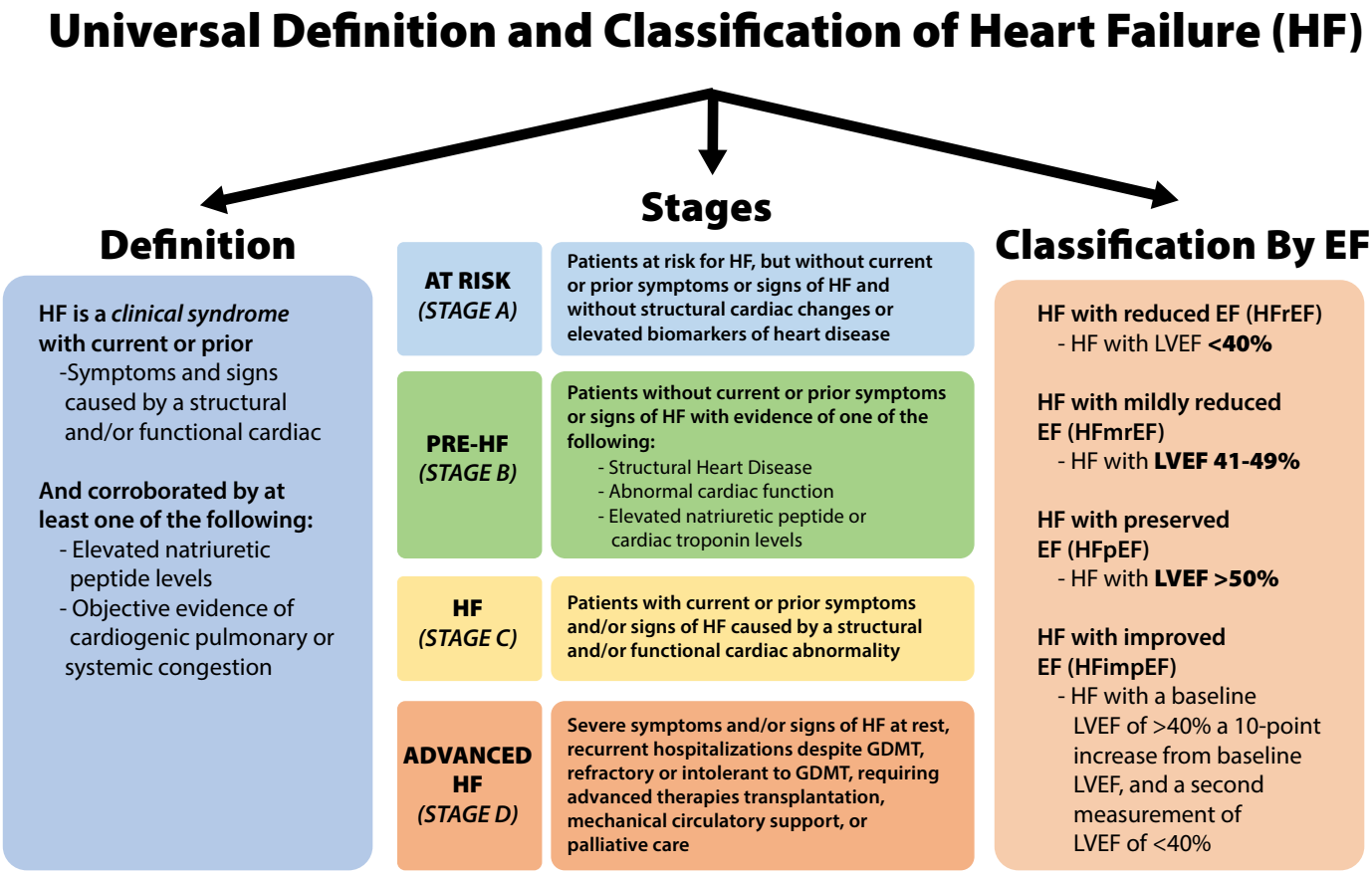

Figure 1. Universal Definition and Classification of HF. Definition, Stages and Classification by ejection fraction of HF allows for standardization in language and communication. It also emphasizes that HF is not a static disease but exists in a continuum. There is no such thing as a "stable" heart failure patient; *adapted from Gibson G, Blumer V, Mentz RJ, Lala A. Universal Definition and Classification of Heart Failure: A Step in the Right Direction from Failure to Function. American College of Cardiology July 13, 2021 https://www.acc.org/Latest-in-Cardiology/Articles/2021/07/12/12/31/Universal-Definition-and-Classification-of-Heart-Failure.*

patients aged 80 years or older. The incidence rate of HF is 511 per 100,000 persons, again differing by age. It is highest in patients over 80 years old, at 2,983 per 100,000 persons, and 799 per 100,000 in patients aged 65–79 years old.[3] Currently, more than 787,000 Canadians are living with HF, with >111,000 Canadians diagnosed annually. Despite improvements in evidence-based HF therapies, the 30-day readmission rate for HF remains at 21%, with a median hospital length of stay of 7 days. It is estimated that HF will cost Canada more than $2.8 billion a year by 2030.[4-6]

A 2019 meta-analysis looking at patients in Europe and North America report a 5-year survival rate of 57% for all types of HF. The survival rate was higher for those under 65 years, at 79%, while it was 50% for those over 75 years.[7] Hospitalization portends a poorer prognosis as evidenced by a study looking at a cohort of patients from 2005-2009, which showed a 5-year mortality rate of 75%, with no difference observed across both HFrEF and HFpEF patients.[8] Data from Ontario in 2007 showed that 10% of patients died within 30 days of hospitalization for HF.[9] Survival rates significantly decrease after each HF hospitalization, ranging from 2.4 years after the first hospitalization to 0.6 years after the fourth hospitalization. This data highlights the urgency to start patients on GDMT as quickly as possible to prevent hospitalizations and improve their prognosis.[10]

HF is the end-stage manifestation of many forms of heart disease. Thus, risk factors for HF involve traditional factors such as advancing age, hypertension, hyperlipidemia, smoking, excess alcohol intake, and a sedentary lifestyle. In addition, other disease processes such as ischemic heart disease, arrhythmia, obesity, diabetes, and chronic kidney disease (CKD) contribute to HF risk. Emerging mechanisms, owing to the discovery of new therapeutics, include inflammation and fibrosis, genetics (hypertrophic cardiomyopathy) and cardiac amyloidosis. With the increasing prevalence of obesity, diabetes, metabolic syndrome, and cardiovascular disease, HF cases continue to rise, reaching epidemic proportions.

Prevention and Diagnosis

Prevention and diagnosis of HF starts with a very high index of suspicion (**Figure 2**). Close attention should

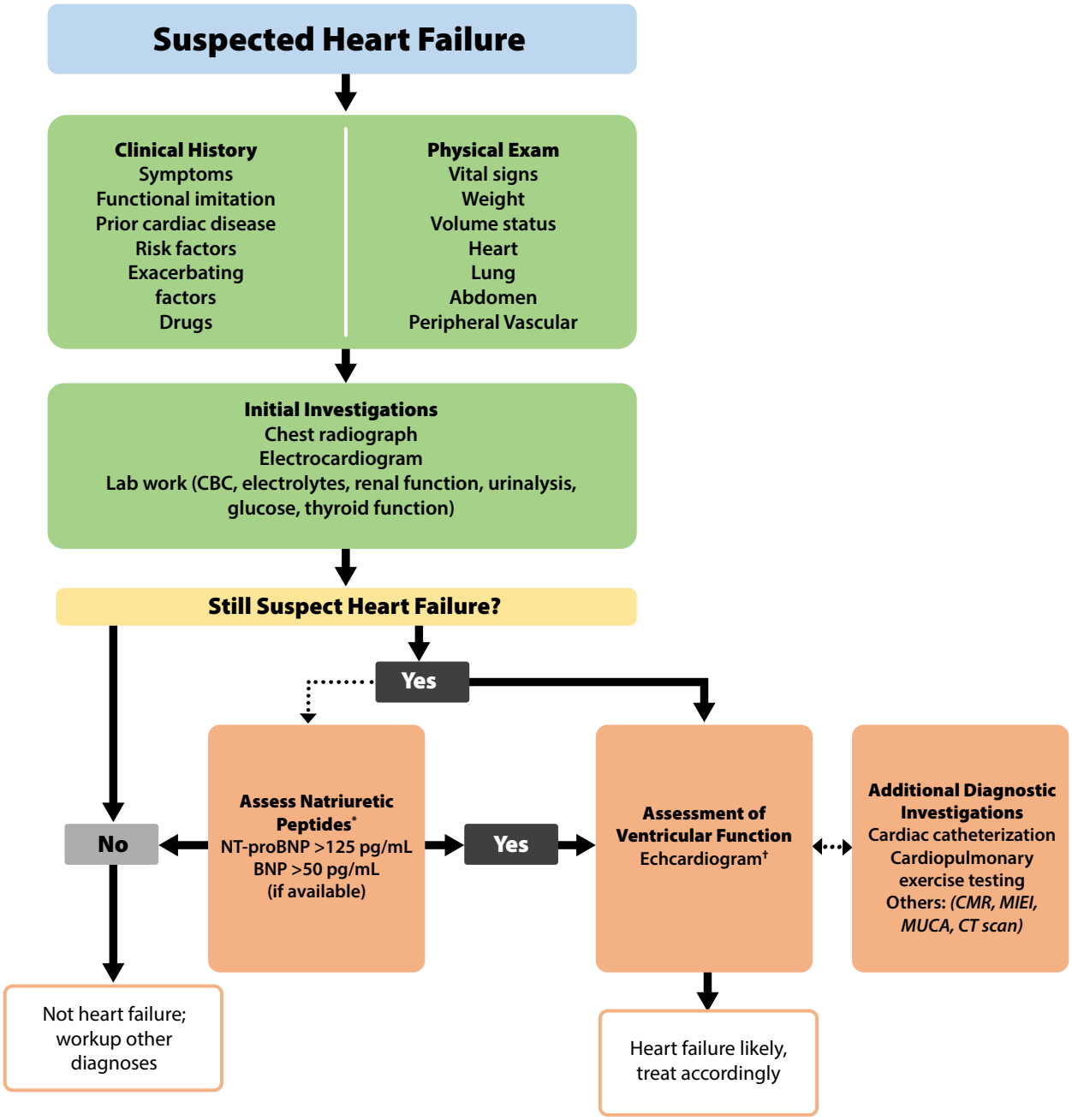

Figure 2. Suggested algorithm for diagnosis of HF in the ambulatory care setting; *as per Canadian Cardiovascular Society. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Mrioslaw R, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, Leblanc M-H, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can Journal of Cardiology 33 (2017):1342-1433.*

Algorithm for the diagnosis of the heart failure in the ambulatory care setting. For patients with heart failure, a history, physical exam, and initial investigations should be supplemented with natriuretic peptides and/or imaging tests.

*Natriuretic peptides are not available in all jurisdictions in Canada.

†Includes systolic as well as diastolic parameters (eg, numeric left ventricular ejection fraction, transmitral and pulmonary venous flow patterns, or mitral annulus velocities); a preserved ejection function on a routine echocardiogram does not rule out the clinical syndrome of heart failure and therefore clinical judgement is required if other indicators point to heart failure as a diagnosis. A lower BNP cutoff for suspecting heart failure in the ambulatory settings facilitates earlier implementation of guideline-directed care.

Abbreviations: BNP: B-type natriuretic peptide, **CBC:** complete blood count, **CMR:** cardiac magnetic resonance, **CT:** computed tomography, **MUGA:** multigated acquisition, **CMR:** cardiovascular magnetic resonance

be paid to high-risk patients who have a history of hypertension, longstanding diabetes, cardiometabolic syndrome, obesity, CKD, or a previous history of cardiovascular disease (coronary/peripheral artery disease, valvular heart disease, cardiac arrhythmias). A constellation of typical symptoms such as dyspnea, fatigue, weakness, functional limitation, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, along with less typical symptoms such as nocturnal cough, decreased appetite, palpitations, chest pain, nocturia/oliguria, dizziness, syncope, delirium, and confusion should trigger alarm bells to investigate further. When taking a patient's history, ask quantifying questions, such as (Do you get short of breath after walking from the parking lot to the office?) rather than questions that give a yes/no response (Are you short of breath?). A thorough physical examination should be conducted, which focuses on signs such as tachycardia, irregular pulse, tachypnea, an elevated jugular venous pressure (JVP) and hepatojugular reflux, a third heart sound, cardiac murmur, peripheral edema, rales, pleural effusion, hepatomegaly, and ascites. Weight can either increase acutely if there is edema, or decrease in advanced HF due to cachexia. Initial investigations should include an electrocardiogram (ECG), chest X-ray (CXR), and lab work including a complete blood count (CBC), electrolytes, estimated Glomerular Filtration Rate (eGFR), urinalysis, glucose levels, thyroid function, and urinary albumin-creatinine ratio. CKD, particularly albuminuria, is associated with incident HF and signals worse outcomes in patient with existing HF.[11-13]

Role of Natriuretic Peptides

Since an elevated NP level is included in the universal definition of HF, measuring and understanding the role of NP is crucial. NPs (B-type natriuretic peptide (BNP), N-terminal pro B-type natriuretic peptide (NT-proBNP), midregional pro A-type natriuretic peptide [MR-proANP]) are biomarkers triggered by end-diastolic wall stress, increased intracardiac filling pressures, and volumes. Elevated plasma concentrations of these biomarkers strongly correlate with the presence and severity of cardiac stress and HF. Physical findings such as rales, elevated JVP, and peripheral edema, as well as ECG and CXR have limited sensitivity of only 50–60%. NPs are highly accurate at differentiating HF from other causes of dyspnea. **NPs should be measured in all patients presenting with symptoms suggestive of new-onset or worsening HF, as their use facilitates both early diagnosis and the early exclusion of HF**.[14] However, due to confounding factors (**Table 1**), the diagnosis of HF cannot be made solely by elevated NP levels, and should be considered in conjunction with other clinical factors. Diagnostic levels of NPs vary depending on whether the patient has acute HF (with very high filling pressures) or chronic HF (with a mild increase in filling pressures at rest). NT-proBNP levels are more affected by increasing age, resulting in different cut-off levels by age compared to BNP (**Table 2**). In an ambulatory care setting, a BNP level <50 pg/mL and an NT-proBNP level < 125 pg/mL lowers the likelihood of HF, particularly in HFrEF where NP levels tend to be higher than in HFpEF. Obesity, which is often associated with HFpEF, falsely lowers NP levels, secondary to a decreased release of NP by adipose tissue. In these circumstances, NP levels below the cut-off do not definitively rule out HF. It has been suggested that cut-off levels should be lowered by up to 50% in obese patients, with a linear correlation indicating that a higher BMI corresponds to lower cut-off concentrations.[15] Results should always be interpreted with knowledge of renal function and BMI, which are the 2 most significant confounders of NP levels.

NP has also been found to be useful in screening for the prevention of incident HF (Stage B) in asymptomatic patients. NP levels may be elevated early in the disease process before the onset of symptoms. Several randomized controlled trials (RCTs) have shown the utility of using elevated NP levels to guide more intensified therapy, including increased use of cardiovascular investigations, renin angiotensin-aldosterone system inhibitors (RAASi), and beta-blockers. This approach has been shown to reduce outcomes such as new-onset HF, major adverse cardiovascular events, hospitalizations, and death in patients with cardiovascular risk factors.[16,17] Other uses of NP include assessing an increase of symptoms in established HF patients. To be effective, the NP level at a stable, dry state needs to be available. A clinically relevant change is suggested by an increase of at least 30% to 50%.[14,18] Another use is observing pre-discharge NP levels in acute HF patients. There should be a drop of at least 30% from the admission NP level.[18] The discharge NP level is the best predictor of prognosis in acute HF patients, including risks of death and re-hospitalization.[14] Persistently elevated NP levels that do not decrease with HF treatment indicate a high-risk patient with a poorer prognosis and a higher risk of WHF events that require closer monitoring and intensification of therapy. Therapies for HF such as RAASi, mineralocorticoid receptor antagonists (MRA), beta-blockers, diuretics, Sodium-Glucose Co-Transporter-2 inhibitors (SGLT2i), and cardiac resynchronization therapy (CRT), all chronically reduce NP levels, leading to left ventricular (LV) remodelling and better outcomes. Exceptions include the early titration of beta-blockers, which can transiently raise NP levels, as well as the use of sacubitril/valsartan, which increases BNP levels but lowers NT-proBNP levels. NT-proBNP is a more accurate reflection of clinical status and should be used in patients taking sacubitril/valsartan. The use of NP to guide HF therapy is controversial, with some studies showing benefit, and others not.[19,20] The difference lies in HF care. In studies with very aggressive usual care with intensive GDMT, NP-guided therapy may not be as effective in improving outcomes. (**Table 3**)

Causes of elevated NP levels other than primary HF
Non cardiac cause:
Advanced age (NTproBNP affected more than BNP)
Kidney disease
Severe anemia
Severe metabolic disease (thyrotoxicosis, DKA, severe burns)
Pulmonary disease (COPD, pneumonia, pulmonary embolism)
Critical illness (shock, sepsis)
Liver disease
Stroke
Medications (use of Sacubitril/Valsartan increases BNP but not NTproBNP)
Cardiac cause:
Acute coronary syndrome/myocardial infarction
Myocarditis
Valvular heart disease
Cardiac contusion/infiltration (malignancy, infiltrative disease such as amyloid)
Inherited disorders (congenital heart disease, hypertrophic cardiomyopathy)
Pericardial disease
Cardioversion/ICD shock
Atrial or ventricular arrhythmia (AF can increase levels by 3 fold)
Pulmonary hypertension, right heart failure
Invasive or surgical procedures on the heart
Causes of lower NP levels:
Obesity or elevated BMI (weight loss produces an increase in NP levels)
Certain pericardial disease (with pericardial effusion, NPs may rise after pericardiocentesis)

Table 1. Factors other than primary HF that can increase or lower NP levels. Attention should be paid to clinical factors when looking at NP levels; *adapted from reference 1, Bozkurt B, et al. European Journal of Heart Failure (2021) 23, 352-380.*

Role of Echocardiography

When HF is suspected, transthoracic two-dimensional and Doppler echocardiogram (TTE) is the first choice for initial imaging. TTE assesses chamber size, systolic and diastolic function of both the left and right ventricles, valvular status, wall thickness, LV mass, LVEF, and pericardial disease, which helps in diagnosis. If imaging is suboptimal, contrast echocardiography, or radionuclide angiography can be used. Other modalities, such as cardiac CT, MRI, and cardiac catheterization, can assist in diagnosis and in determining the etiology of HF. It is also important to classify patients into HFrEF, HFmrEF ,and HFpEF to start and prioritize therapy. The suggested timing of when to assess LVEF with TTE and other modalities is summarized in **Table 4**.

Once HF has been diagnosed and classified, its etiology should be determined. While the different etiologies are beyond the scope of this article, they are listed in **Figure 3**, and referring the patient to a cardiac specialist may be appropriate for further work-up and management.

Treatment of Heart Failure

Lifestyle, diet, exercise, self-care, and risk factor modification are important components of both prevention and treatment of HF, though these topics will not be discussed in this article. The treatment of HF is based on classification by LVEF. The evidence that forms the current treatment guidelines is discussed elsewhere and is beyond the scope of this review. For HFrEF, all societal guidelines uniformly recommend starting with the use of 4 pillars, including RAASi (ACEI/ARB/Angiotensin Receptor Neprilysin Inhibitor (ARNI), prioritizing ARNI), beta-blockers, mineralocorticoid receptor antagonist (MRA), and SGLT2i.[21-23] There are many suggested sequencing techniques for initiating the 4 pillars, although none have been proven to be superior.[24,25] High readmission and event rates in HFrEF patients, especially within 30 days post admission, and the efficacy of quadruple therapy (showing a 73% reduction of death over 2 years),[26] as well as large absolute reductions in mortality and hospitalization within days to weeks, emphasize the need to implement all 4 agents as quickly as possible (recommended range 4 weeks to 6 months). Some overarching principles include: **1)** Attempt to start low doses of as many pillars as possible (within the

	Natriuretic peptide cut points for the diagnosis of HF			
	Age, years	HF is unlikely	HF is possible but other diagnosis need to be considered	HF is very likely
Acute setting				
BNP	All	<100 pg/mL	100–400 pg/mL	>400 pg/mL
NT-proBNP	<50	<300 pg/mL	300–450 pg/mL	>450 pg/mL
	50–75	<300 pg/mL	450–900 pg/mL	>900 pg/mL
	>75	<300 pg/mL	900–1800 pg/mL	>1800 pg/mL
Ambulatory care setting				
BNP	All	<50 pg/mL		
NT-proBNP	All	<125 pg/mL		

Table 2. Cut off NP levels for the diagnosis of HF; *adapted from Ezekowtiz JA, et al., 2017. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Mrioslaw R, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, Leblanc M-H, Masoudi FA, Ross, HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can Journal of Cardiology 33 (2017):1342-1433.*

Abbreviations: BNP: B-type natriuretic peptide, **HF:** heart failure, **NT-proBNP:** N-terminal propeptide BNP

Uses of Natriuretic Peptides in Heart Failure:
1) Diagnosis of HF (acute and chronic, HFrEF and HFpEF, but does not diagnose etiology)
2) Prevention of new-onset HF symptoms in asymptomatic, high-risk patients or patients with asymptomatic LV dysfunction
3) Differentiating new symptoms in patients with established HF (cardiac or non-cardiac). Must compare with baseline NP levels when patient is euvolemic
4) Pre-discharge NP levels in acute HF patients to look at prognosis
5) Prognosis in high-risk patients, identifying those requiring more intense follow-up and therapy
6) Guiding HF therapy—controversial, usually in patients not receiving intensive follow-up and therapy

Table 3. Uses of natriuretic peptides in heart failure: *courtesy of Grace L. Chua, MD, FRCPC, FACC.*

limits of heart rate [HR], blood pressure [BP], volume status, renal function and potassium levels) before up-titrating doses, **2)** Some pillars can improve the tolerance, adherence, and persistence of other pillars. For example, SGLT2i can lower potassium levels, allowing the initiation of MRA. Compared to ACEI/ARB, ARNIs decrease hyperkalemia and improve renal function, SGLT2i and ARNIs may increase diuresis, allowing for the lowering or discontinuation of diuretics. **3)** When BP or renal function limits the adjustment of GDMT, look for potential therapies that do not confer prognostic benefits, such as diuretics, and calcium channel blockers to discontinue. **4)** Rapid sequencing is safe as long as there is early follow-up (within 1–2 weeks) of making a change. During follow-up, assess volume status, HR, BP, potassium levels, and renal function before making further changes. In fact, in-hospital initiation has been found to be safe and effective.[27-29] The STRONG-HF trial demonstrated the proof in concept for rapid up-titration of medications with close follow-up in acute HF. The high intensity care group showed an 8.1% reduction in 180-day HF readmission and all-cause death with a hazard ratio of 0.66 [95% CI 0.50–0.86, p=0.0021].[30] Once GDMT has been optimized, there should be an assessment of the need for second line therapies depending on clinical circumstances. An ECG and TTE should be obtained after 3 months to assess LVEF, the presence of significant functional mitral regurgitation, QRS duration, and rhythm to determine if device therapy is required. (**Figure 4**) This assessment should be conducted in conjunction with a cardiologist specializing in HF management.

The evidence for HFpEF is not as robust. The European Society of Cardiology (ESC) guidelines suggest using SGLT2i, diuretics for fluid retention, treatment of the etiology, and both CV and non-CV comorbidities such as hypertension, CAD, AF, diabetes, obesity, sleep apnea, CKD, anemia, and chronic obstructive pulmonary disease (COPD).[31] SGLT2is have irrefutable class 1 evidence for HF treatment across the spectrum of LVEF. Other therapies, such as MRA, ARB, and ARNI have less definitive data for treating HFpEF and carry a lower class 2b recommendation in the American guidelines.[23] LVEF exists

Suggested timing for measurement of LVEF, according to clinical scenario			
Clinical scenario	**Timing of measurement**	**Modality of measurement**	**Comments**
New-onset HF	Immediately or within 2 weeks for baseline assessment	ECHO (preferred when available); or CMRI	Report should include numeric EF or small range of EF and diastolic function evaluation
After titration of triple therapy for HFrEF, or consideration of ICD/CRT implantation	3 months after completion of titration	ECHO or CMRI (preferably the same, modality and laboratory test as initial test)	LVEF after medical therapy might increase, obviating device therapy
Stable HF	Approximately every 1–3 years, and possibly less frequently if EF is persistently >40%	ECHO or CMRI	Clinical rationale is to identify improving (better prognosis) or worsening ventricular function (worse prognosis, need for additional therapy such as ICD/CRT)
After significant clinical event (i.e., after some HF hospitalization)	Within 30 days, during hospitalization if possible; not necesary when repeated admissions occur without need to identify a cause	ECHO or CMRI	Frequently helpful information such as EF, degree of valvular dysfunction, and RSVP

Table 4. Suggested timing for measurement of LVEF; *adapted from Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Mrioslaw R, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, Leblanc M-H, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can Journal of Cardiology 33 (2017): 1342-1433 .*

Nuclear, computed tomography, or other measures are appropriate and acceptable in certain circumstances taking into account, radiation, cost, and information gained.

Abbreviations: CMRI: caridac magnetic resonance imaging, **CRT:** cardiac resynchronization therapy, **ECHO:** echocardiogram, **EF:** ejection fraction, **HF:** heart failure, **HFrEF:** heart failure with reduced EF, **ICD:** implantable cardioverter-defibrillator, **LVEF:** left ventricular EF, **RVSP:** night ventricular systolic pressure.

on a spectrum, and evidence for the 4 pillars of treatment becomes stronger with lower ejection fractions, making them recommended for HFmrEF. Patients with HFimpEF should still be considered at risk for WHF, and treatment should not be withdrawn unless the sole etiology for HF and LV dysfunction has been eliminated, with no residual cardiac fibrosis or risk of recurrence. Even then, withdrawal should be conducted after a full discussion with the patient regarding the risk of WHF, and should be gradual, with close monitoring of symptoms and LV function. An RCT showed HF relapse after withdrawal of HF therapy in dilated cardiomyopathy patients.[32]

Newer therapies for HFpEF are emerging and include the glucagon-like peptide-1 (GLP1) receptor agonist semaglutide, particularly for the obesity phenotype HFpEF, as well as the non-steroidal MRA finerenone.[33,34,36] In addition, the non-steroidal MRA finerenone and the interleukin-6 inhibitor ziltivekimab is currently under investigation in an ongoing phase 3 trial.[36]

The FINEARTS-HF and STEP-HFpEF trials offer new insights into heart failure with preserved ejection fraction (HFpEF). The FINEARTS-HF trial studied the effects of finerenone, a non-steroidal MRA in patients with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF). The trial demonstrated that finerenone significantly reduced total WHF events and cardiovascular death when compared to placebo. Over a median of 32 months, the drug reduced total WHF events by 18% and showed a consistent benefit across different subgroups of patients, including those already taking SGLT2i.The STEP-HFpEF and STEP-HFpEFDM trials investigated the use of semaglutide, a GLP-1 receptor agonist, in non-diabetic and diabetic patients with HFpEF and obesity. The studies demonstrate that weekly injections of semaglutide 2.4 mg led to significant improvements in quality of life, exercise capacity, and body weight in this population.

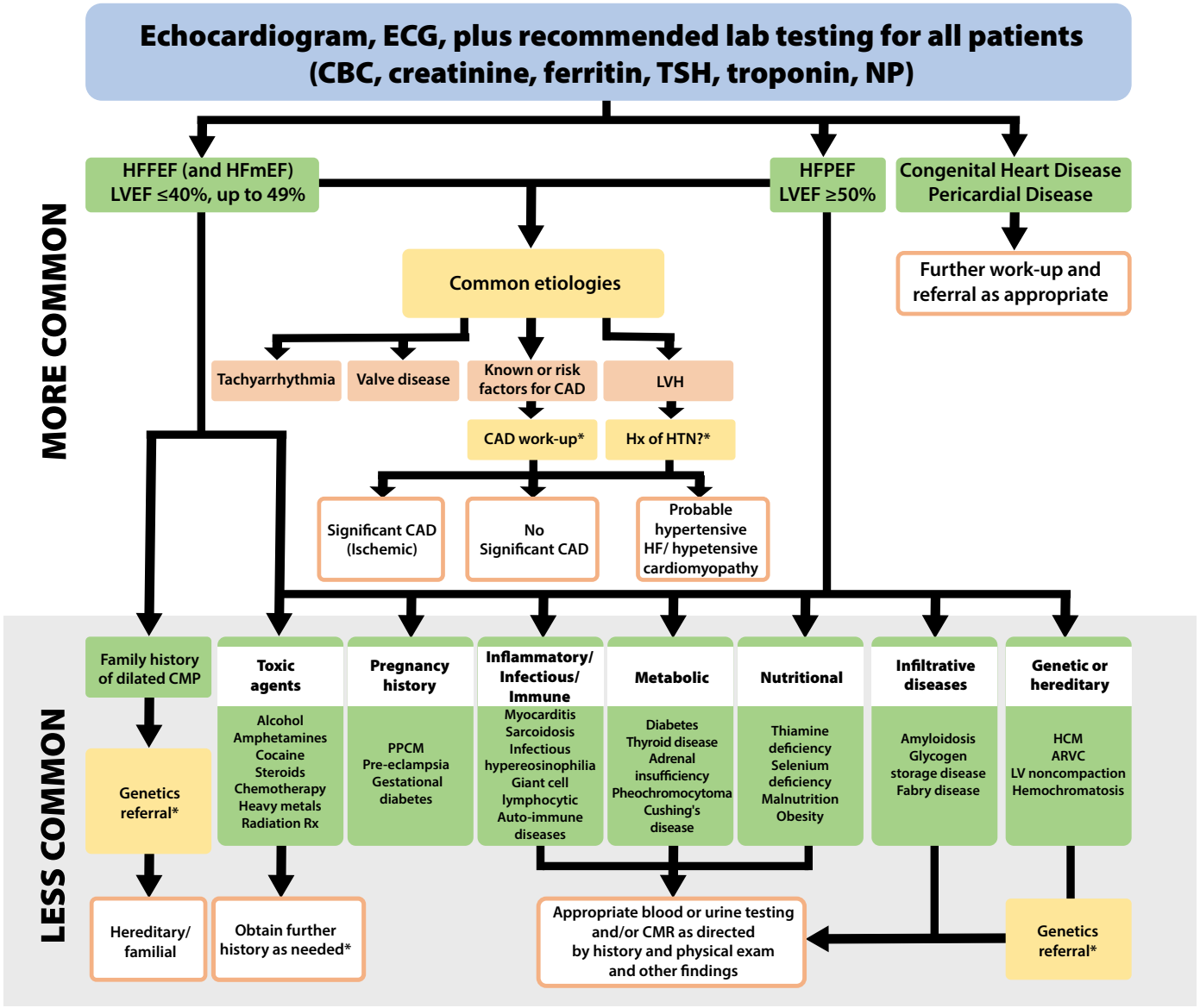

Figure 3. Classification and work-up of HF etiology; a*dapted from Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Mrioslaw R, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, Leblanc M-H, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can Journal of Cardiology 33 (2017):1342-1433.*

General guidance as to the workup to identify the most probable etiology for a patient's heart failure (HF). At all stages, a thorough clinical history and physical exam should aid in the selection of additional investigations. A detailed family history is invaluable, especially in patients who are younger or do not have an obvious etiology. Testing should be placed in context of the pretest probability, availability, and expertise of the test. More common etiologies (eg, coronary artery disease, hypertension) should be considered first, and further testing should be encouraged if another etiology is suspected in addition to a more common etiology (eg, hemachromatosis in a patient with known coronary artery disease).

*Patients might have mixed etiology of HF. A detailed medical and family history might guide investigations and should be completed in all patients. Direct testing on the basis of pretest probability, availability, and expertise.

Abbreviations: ARVC: arrhyth- mogenic right ventricular cardiomyopathy, **CAD:** coronary artery disease; **CBC:** complete blood count, **CMP:** cardiomyopathy, **CMR:** cardiac magnetic resonance, **ECG:** electrocardiogram, **HCM:** hypertrophic cardiomyopathy, **HFmEF:** heart failure with a midrange ejection fraction, **HFPEF:** heart failure with preserved ejection fraction, **HFrEF:** heart failure with reduced ejection fraction, **HTN:** hypertension, **Hx:** history; **LV:** left ventricle, **LVEF:** left ventricular ejection fraction, **LVH:** left ventricular hypertrophy, **NP:** natriuretic peptide, PPCM: peripartum cardiomyopathy, **Rx:** prescription; **TSH:** thyroid-stimulating hormone.

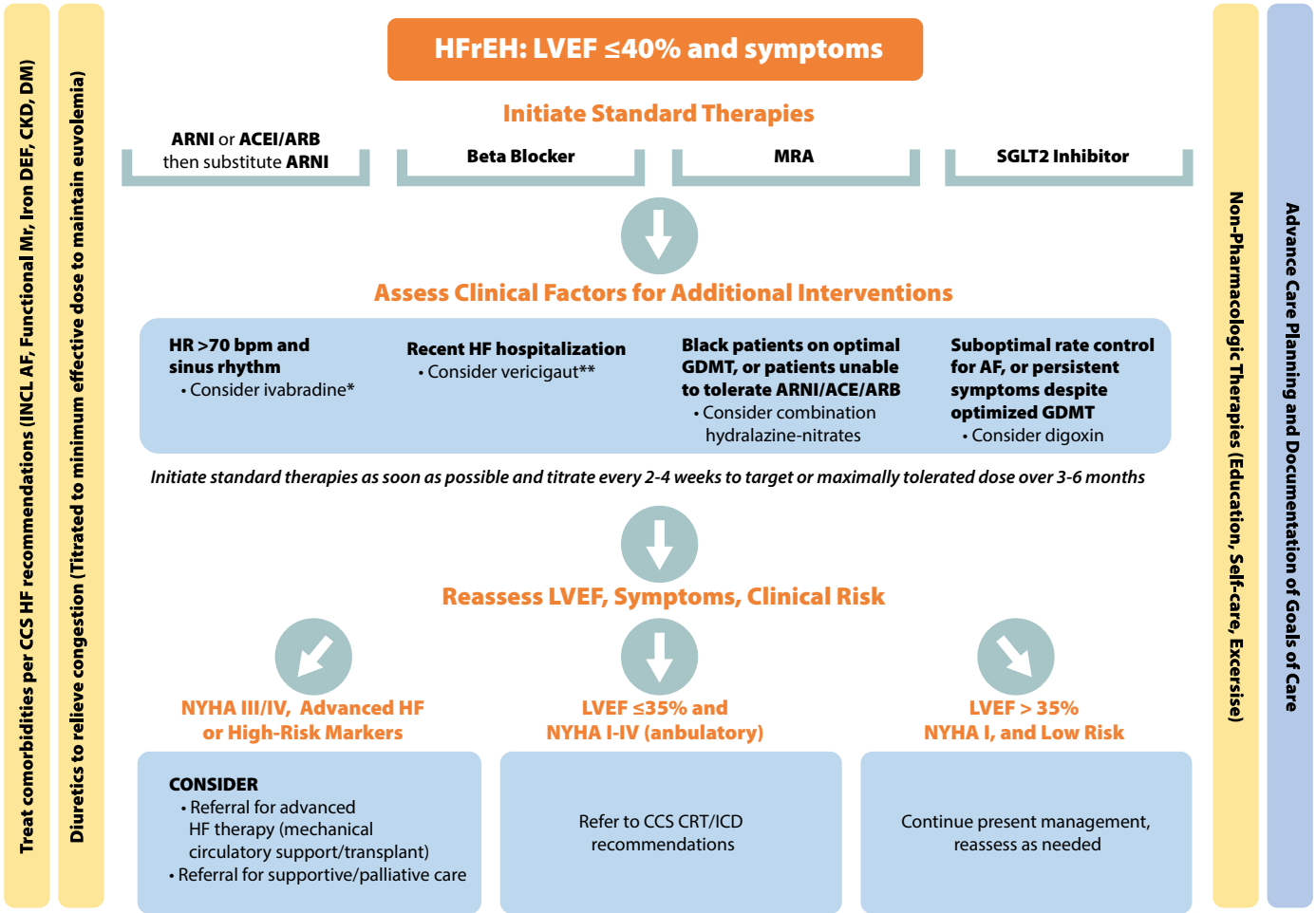

Figure 4. Canadian Cardiovascular Society/Canadian Heart Failure Society algorithm for management of HFrEF; a*dapted from McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz J, Giannetti N, Heckman GA, Howlett JG, Koshman SL, Lepage S, Mielniczuk L, Moe GW, O'Meara E, Swiggum E, Toma M, Zieroth S, Anderson K, Bray SA, Clarke B, Cohen-Solal A, D'Astous M, Davis, M, De S, Grant ADM, Grzeslo A, Heshka J, Keen S, Kouz S, Lee D, Masoudi, FA, McKelvie R, Parent M-C, Poon S, Rajda M, Sharma A, Siatecki K, Storm K, Sussex B, Van Spall H, Yip AMC, CCS/CHFS Heart Failure Guidelines Update: Defining a New, Pharmacologic Standard of Care of Heart Failure with Reduced Ejection Fraction, Canadian Journal of Cardiology 37(2021) 531-546.*

Simplified treatment algorithm for management of heart failure (HF) with reduced ejection fraction (HFrEF). Standard therapies are applicable to most patients with HFrEF for reducing cardiovascular mortality and hospitalization for HF. Additional, pharmacologic therapies should be individualized on the basis of clinical factors as outlined in the text. Every attempt should be made to initiate and titrate therapies with the goal of medication optimization by 3-6 months after a diagnosis of HFrEF. Throughout the patient journey, nonpharmacologic therapies should be prescribed, along with judicious use of diuretics to maintain euvolemia. Evidence also supports interventions to treat important comorbidities including iron deficiency, atrial fibrillation (AF), and functional mitral regurgitation (MR) in selected patients.

*Health Canada has approved ivabradine for patients with HFrEF and heart rate (HR) ≥77 bpm in sinus rhythm.

**Vericiguat is not yet approved for use in Canada.

Abbreviations: ACEI: angiotensin converting enzyme inhibitor, **ARB:** angiotensin receptor blocker; **ARNI:** angiotensin receptor-neprilysin inhibitor, **CCS:** Canadian Cardiovascular Society, **CKD:** chronic kidney disease; **CRT:** cardiac resynchronization therapy, **DM:** diabetes mellitus, **GDMT:** guideline-directed medical therapy, **ICD:** implantable cardioverter difibrillator, **LVEF:** left ventricular ejection fraction, **MRA:** mineralocorticoid receptor antagonist; **NYHA:** New York Heart Association; **SGLT:** sodium glucose transport

Key findings from the trials include:

- A substantial improvement in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), reflecting better symptoms and physical limitations.
- Greater weight loss compared to placebo, with a net 8.4% reduction in body weight at 52 weeks seen in the combined studies.
- Enhanced functional capacity, shown by an increase in 6-minute walk distance.
- Improvement in a hierarchical endpoint that includes death, HF events and KCCQ-CSS
- Reduction in inflammation markers such as C-reactive protein (CRP)

Together, these studies give promise for the use of non-steroidal MRAs (finerenone) and GLP1RA (semaglutide) in HFpEF, adding to the evidence already seen with SGLT2i. These agents share benefit in the treatment of the cardiovascular-kidney-metabolic syndrome, with inflammatory dysfunctional adipose tissue being the root cause.

Role of Family Physicians

Family physicians stand in a unique position in the spectrum of HF care. This starts with the prevention and management of HF risk factors, extends to maintaining a high index of suspicion, early diagnosis, starting treatment with GDMT, and referring patients to cardiologists. As HF progresses, coordination of care becomes crucial, with patients often requiring multiple services including cardiac rehabilitation, pharmacy reconciliation, diet intervention, home care, and palliative care. Collaborative care with the HF team is equally important, focusing on patient education, monitoring of clinical status, medication adjustments to avoid WHF events, particularly after HF hospitalization. Family physicians hold a critical position in defending against the HF tsunami wave.

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References:

1. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. Eur J Heart Fail. 2021; 23:352-380. doi:10.1016/j.cardfail.2021.01.022
2. Bozkurt, B, Ahmad T, Alexander KM, Baker WL, Bosak K, Breathett K, et al. Heart failure epidemiology and outcomes statistics: a report of the Heart Failure Society of America. J Card Fail. 2023; 29(1):1412-1451. doi:10.1016/j.cardfail.2023.07.006
3. Canadian Chronic Disease Surveillance System (CCDSS) [Date modified: 2024 March 20]. Public Health Agency of Canada, Health Infobase https://health-infobase.canada.ca.
4. Moghaddam N, Lindsay P, Hawkins NM, Anderson K, Ducharme A, Lee, DS, et al. Access to heart failure services in Canada: findings of the Heart and Stroke National Heart Failure Resources and Services Inventory. Can J Cardiol. 2023;39(10):1469-1479. doi:10.1016/j.cjca.2023.06.430
5. Poon S, Leis B, Lambert L, MacFarlane K, Anderson K, Blais C, et al. The state of heart failure care in Canada: minimal improvement in readmissions over time despite an increased number of evidence-based therapies. CJC Open. 2022;4: 667-675. doi:10.1016/j.cjco.2022.04.011
6. Heart and Stroke Foundation. Falling Short: How Canada is Failing People with Heart Failure—and How We Can Change That. https;//heartstroke.ca/-/media/pdf-files/canada/2022-heart-month/hs-heart-failure-report-2022-final.pdf.
7. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail. 2019; 21(11):1306-1325. doi:10.1002/ejhf.1594
8. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart failure with preserved, borderline and reduced ejection fraction 5-year outcomes. J Am Coll Cardiol. 2017;70:2476-2486. doi:10.1016/j.jacc.2017.08.074
9. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE, Tu JV. Trends in incidence of outcomes of heart failure in Ontario, Canada:1997 to 2007. CMAJ. 2012;184 (14):765-773. doi:10.1503/cmaj.111958
10. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J. 2007;154(2):260-266. doi:10.1016/j.ahj.2007.01.041
11. Blecker S, Kunihiro M, Kottgen A, Loehr LR, Bertoni AG, Boulware LE, et al. High-normal albuminuria and risk of heart failure in the community. Am J Kidney Dis. 2011; 58(1):47-55. doi:10.1053/j.ajkd.2011.02.391
12. Tao J, Sang D, Zhen L, Zhang X, Li Y, Wang G, et al. Elevated urine albumin-to-creatinine ration increases the risk of new-onset heart failure in patients with type 2 diabetes. Cardiovasc Diabetol. 2023;22(1):70. doi:10.1186/s12933-023-01796-6
13. Jackson CE, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, et al. Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet. 2009;374 9689):543-550. doi:10.1016/S0140-6736(09)61378-7
14. Mueller C, McDonald K, de Boer, RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019;21(6):715-731. doi:10.1002/ejhf.1494
15. Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RRJ, Lainchbury JG, Richards AM, Ordonez-Llanos J, et al. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Arch Intern Med. 2007;167(4):400-407. doi:10.1001/archinte.167.4.400
16. Tilson L, Tallon E, O'Connell E, Maurer B, Gallagher J, Murtagh G, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA. 2013;310(1):66-74. doi:10.1001/jama.2013.7588

17. Huelsmann, M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, et al. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol. 2013;62(15):1365-1372. doi:10.1016/j.jacc.2013.05.069
18. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Can J Cardiol. 2017;33(11):1342-1433. doi:10.1016/j.cjca.2017.08.022
19. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction (GUIDE-IT). JAMA. 2017;318(8):713-720. doi:10.1001/jama.2017.10565
20. McLellan J, Bankhead CR, Oke JL, Hobbs FDR, Taylor CJ, Perera R. Natriuretic peptide-guided treatment for heart failure: a systematic review and meta-analysis. BMJ Evid Based Med. 2020; 5(1):33-37. doi:10.1136/bmjebm-2019-111208
21. McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz J, Giannetti N, et al. CCS/CHFS Heart Failure Guidelines Update: defining a new pharmacologic standard of care of heart failure with reduced ejection fraction. Canadian J Cardiol. 2021;37(4):531-546. doi:10.1016/j.cjca.2021.01.017
22. McDonagh TA, Metra M, Adamo M, Gardner R, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36): 3599-3726. doi: 10.1093/eurheartj/ehab368. [published correction appears in Eur Heart J. 2021 Dec 21;42(48):4901. doi: 10.1093/eurheartj/ehab670]. Eur Heart J. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368
23. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022145:e895-e1032. doi: 10.1161/CIR.0000000000001073] [published correction appears in Circulation. 2022 Sep 27;146(13):e185. doi: 10.1161/CIR.0000000000001097] [published correction appears in Circulation. 2023 Apr 4;147(14):e674. doi: 10.1161/CIR.0000000000001142]. Circulation. 2022;145(18):e895-e1032. doi:10.1161/CIR.0000000000001063
24. McMurray JJV, Packer MP. How should we sequence the treatments for heart failure and a reduced ejection fraction? A redefinition of evidence-based medicine. Circulation. 2021;143(9):875-877. doi:10.1161/CIRCULATIONAHA.120.052926
25. Greene SJ, Bulter J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure—optimizing therapy with the need for speed. JAMA Cardiol. 2021;6(7):743-744. doi:10.1001/jamacardio.2021.0496
26. Bassi, NS, Ziaeian B, Yancy CW, Fonarow GC. Association of optimal implementation of sodium-glucose cotransporter 2 inhibitor therapy with outcome for patients with heart failure. JAMA Cardiol. 2020; 5(8): 948-951. doi:10.1001/jamacardio.2020.0898
27. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. [published correction appears in N Engl J Med. 2019 Mar 14;380(11):1090. doi: 10.1056/NEJMx190009]. N Engl J Med. 2019;380(6):539-548. doi:10.1056/NEJMoa1812851
28. DeVore AD, Braunwald E, Morrow DA, Duffy CI, Amrosy AP, Chakraborty H, et al. Initiation of angiotensin-neprilysin inhibition after acute decompensated heart failure; secondary analysis of the open-label extension of the PIONEER-HF trial. JAMA Cardiol. 2020;5(2):202-207. doi:10.1001/jamacardio.2019.4665
29. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patents hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022;28(3):568-574. doi:10.1038/s41591-021-01659-1
30. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies of acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet. 2022; 400(10367):1938-1952. doi:10.1016/S0140-6736(22)02076-1
31. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. [published correction appears in Eur Heart J. 2024 Jan 1;45(1):53. doi: 10.1093/eurheartj/ehad613]. Eur Heart J. 2023;44(37):3627-3639. doi:10.1093/eurheartj/ehad195
32. Halliday BP, Wassall R, Lata AS, Khalique Z, Gregson J, Newsome S, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open label, pilot, randomised trial. Lancet. 2019;393:61-73. doi:10.1016/S0140-6736(18)32484-X
33. Kosiborod MN, Abildstrom SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389(12):1069-1084. doi:10.1056/NEJMoa2306963
34. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med. 2024;390:1394-1407. doi:10.1056/NEJMoa2313917
35. Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Henderson AD, Lam CSP, Pitt B, Senni M, Shah SJ, Voors AA, Zannad F, Abidin IZ, Alcocer-Gamba MA, Atherton JJ, Bauersachs J, Chang-Sheng M, Chiang CE, Cioncel O, Chopra V, Comin-Colet J, Filippatos G, Fonseca C, Gajos G, Goland S, Goncalvesova E, Kang S, Katova T, Kosiborod MN, Latkovskis G, Lee APW, Linssen GCM, Llamas-Esperon G, Mareev V, Martinez FA, Melenovsky V, Merkely B, Nodari S, Petrie MC, Saldarriaga CI, Saraiva JFK, Sato N, Schou M, Sharma K, Troughton R, Udell JA, Ukkonen H, Vardeny O, Verma S, von Lewinski D, Voronkov L, Yilmaz MB, Zieroth S, Lay-Flurrie J, van Gameren I, Amarante F, Kolkhof P, Viswanathan P. NEJM September 1, 2024 DOI: 10.1056/NEJMoa2407107
36. Petrie M, Borlaug B, Buckholtz K, Ducharme A, Hvelplund A, Lam CSP, et al. HERMES: Effects of ziltivekimab versus placebo on morbidity and mortality in patients with heart failure with mildly reduced or preserved ejection fraction and systemic inflammation. Journal of Cardiac Failure. 2024;30(1) P126. https://doi.org/10.1016/j.cardfail.2023.10.024

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- Increased incidence of bleeding
- Increased risk of atrial fibrillation or flutter requiring hospitalization
- Potential for anaphylactic reaction to fish and/or shellfish
- Periodic monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in patients with hepatic impairment is recommended during therapy with Vascepa®
- Fertility
- Not recommended in pregnancy and nursing

For more information:

Please consult the Vascepa® Product Monograph at https://pdf.hres.ca/dpd_pm/00065525.PDF for important information relating to adverse reactions, drug interactions, and dosing/administration information which have not been discussed in this piece. The Product Monograph is also available by calling HLS Therapeutics Inc. at 1-833-266-3423.

*8,179 statin-treated adult patients with elevated serum triglyceride levels (≥1.5 mmol/L to <5.6 mmol/L) who were also at high risk for atherothrombotic events. Patients either had established CVD or were at high risk for CVD and were randomized to either Vascepa® or placebo. Patients with established cardiovascular disease were at least 45 years of age and had a documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease. Patients with other risk factors for cardiovascular disease were at least 50 years of age and had diabetes and at least one additional major cardiovascular risk factor. 5-point MACE was defined as time to first occurrence of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Most patients at baseline were taking at least one other cardiovascular medication including anti-hypertensives (95%), anti-platelet agents (79.4%), beta blockers (70.7%), angiotensin-converting enzyme (ACE) inhibitors (51.9%), and angiotensin receptor blockers (ARB) (27.0%), with 77.5% taking either an ACE inhibitor or ARB. At baseline, while on stable background lipid-lowering therapy, the median LDL-C was 1.9 mmol/L.
†Incidence rates of CV events per 100 patient years (Vascepa® vs. placebo): cardiovascular death, 1.0 vs. 1.2; non-fatal myocardial infarction, 1.4 vs. 2.0; non-fatal stroke, 0.5 vs. 0.7.
‡CV death includes adjudicated cardiovascular deaths and deaths of undetermined causality.
‖Comparative clinical significance has not been established.
CCS, Canadian Cardiovascular Society; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event.

References:

1. HLS Therapeutics Inc. Vascepa® Product Monograph. April 20, 2022.
2. Pearson GJ, *et al.* 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol*. 2021.
3. Gladstone DJ, *et al.* Canadian Stroke Best Practice Recommendations: Secondary Prevention of Stroke Update 2020. *Can J Neurol Sci*. 2022;49(3):315-337.
4. Data on File: Vascepa® Coverage. 2022. HLS Therapeutics, Inc.
5. Express Scripts. NIHB drug benefit list. Accessed August 22, 2022 at: https://nihb-ssna.express-scripts.ca/en/02051405060920l9/16/160407.
6. Ontario Exceptional Access Program. Accessed August 22, 2022 at: https://www.health.gov.on.ca/en/pro/programs/drugs/docs/eap_dins_list.xlsx.
7. Government of Saskatchewan. Exception Drug Status Program. Accessed August 22, 2022 at: https://formulary.drugplan.ehealthsask.ca/PDFs/APPENDIXA.pdf.
8. New Brunswick Drug Plans. NB drug plans formulary update. June 20, 2022. Accessed August 22, 2022 at: https://www2.gnb.ca/content/dam/gnb/Departments/h-s/pdf/en/NBDrugPlan/FormularyUpdates/NBDrugPlansBulletin-1080.pdf.
9. Government of Manitoba. Exception Drug Benefits. Accessed September 20, 2022 at: http://www.gov.mb.ca/health/mdbif/bulletin120.pdf.

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UPDATE ON INSOMNIA FOR PRIMARY CARE

Introduction

Insomnia is a common clinical issue with varying definitions depending on the source. The DSM-V defines insomnia disorder as one or more of: difficulty initiating sleep, maintaining sleep, or early morning wakening with an inability to fall back asleep.

These problems occur despite adequate time allowed for sleep (7 hours), cause dysfunction, and are not attributed to another disorder. The DSM-V then classifies insomnia as either episodic (at least 1 month but less than 3 months), persistent (lasting 3 months or more) and recurrent (2 or more episodes within a year), and considers potential contributing comorbidities.[1]

According to the International Classification of Sleep Disorders (ICSD-3) classification system, symptoms must occur at least 3 times per week, and insomnia is categorized as either short term or chronic. Short-term insomnia disorder in this paradigm (ICSD-3) occurs when the sleep problems have lasted more than 1 but less than 3 months, while chronic insomnia disorder occurs when symptoms persist for more than 3 months.[2]

Insomnia occurs more commonly in the female sex and in older adults aged >65. Additional risk factors for insomnia disorder include increased arousability, higher levels of body pain, comorbid medical or psychiatric conditions, previous episode(s) of insomnia, and a positive family history of insomnia.[3-5]

An estimated 40% of the Canadian population at some point in their lives has experienced 1 or more insomnia symptoms, with 13.4% of them meeting the criteria for

short-term or chronic insomnia disorder.[3] Once insomnia symptoms meet the criteria for insomnia disorder, chronicity is likely; 86% of patients with insomnia disorder continue to meet the criteria at 12 months, and 66% continue at 3 years. This calls for patient management within a chronic disease treatment model[3], with a focus on long term, sustainable strategies.

Despite being a well-known, pervasive, and ubiquitous disorder in medical practice, insomnia is often accompanied by mixed messages in standard education, and specialist support in Canada is limited. Hence, this article will focus on updated assessment and treatment strategies that primary care practitioners can implement, with a focus on chronic insomnia.

Consequences of Insomnia

While insomnia is frequently viewed as a nighttime sleep problem, 84% of people with insomnia report daytime symptoms such as irritability and increased daytime sleepiness.[6,7] Though often trivialized socially and by the medical system in general, insomnia is also associated with a decreased quality of life, academic difficulties, higher rates of absenteeism/presenteeism, motor vehicle accidents, and workplace disability. Moreover, insomnia is a risk factor for suicide, even in the absence of a mental health condition.[8]

Medically, chronic insomnia is strongly associated with an increased risk of many other chronic diseases, such as cardiovascular disease, chronic pain syndrome, depression, anxiety, diabetes, obesity, and asthma.[9]

Models of Insomnia

The sleep-wake-cycle is regulated by multiple neurotransmitter systems, some of which promote sleep and others that promote wakefulness.[10] Traditional sleep medications, such as benzodiazepines and z-drugs, enhance sleep by amplifying gamma-aminobutyric acid (GABA), a prominent inhibitory neurotransmitter. Wakefulness is thought to involve multiple neurotransmitter systems that are mediated by norepinephrine, serotonin, histamine, and more recently, primarily by the orexin system.[10,11]

It is now clear that a substantial portion of insomnia is not mediated simply by dysfunctional sleep promotion systems. The paradigm has shifted with evidence suggesting "hyperarousal" or "too much wakefulness," as a factor in many types of insomnia, with dysfunction of the orexin system as a key mediator.[11-13] Newly indicated agents are now available in Canada that specifically antagonize the orexin system, blocking central wakefulness-promoting activity.[14,15] These drugs facilitate sleep in a very different and more physiologically natural fashion.

Assessment of Insomnia

When a patient presents with insomnia, a history should be taken of insomnia symptoms including sleep latency, nighttime awakenings, wake time, and the regularity of their sleep pattern. Other associated sleep-related phenomena such as restless legs, snoring, or nighttime behaviours should be gathered. Short-term patient-recorded sleep logs can be very useful for assessing patterns.[9] Often, a comprehensive sleep history may not be realistic in primary care, thus, a summary questionnaire is provided for consideration.[16] As with any chronic disease, several visits may be required to fully assess and treat insomnia.

Objective measurements of sleep can include actigraphy, which measures sleep parameters via motor activity using a non-invasive accelerometer.[17] Actigraphy can supplement an insomnia workup; however, its accuracy may be compromised by medications, other sleep disorders, as well as commercial algorithms including other biological measures (i.e. Fitbit, Oura Ring, and smartphones). Some devices may also inaccurately exaggerate or extrapolate findings, leading to maladaptive cognitive beliefs about sleep. The ongoing use of sleep diaries or actigraphy outside of cognitive behavioural therapy is likely not necessary, may increase patient preoccupation with their sleep, and must always be taken into clinical context.

Another objective measurement is the sleep study. Referral for sleep testing may be necessary for insomnia patients with risk factors for, or symptoms of, other sleep disorders that may be contributing (e.g., sleep apnea, periodic limb movements). It also should be conducted in resistant or chronic cases and for patients on long-term hypnotic therapy.[7,9] In most areas of Canada, home sleep testing is the most accessible first option and is useful to confirm cases of moderate to severe obstructive sleep apnea. However, it cannot comprehensively assess all sleep problems, and milder cases of sleep apnea may be missed. Often, fully observed polysomnography is needed if home testing is negative, or if the patient has not responded to basic treatments.[16]

Comorbidities and Insomnia

Insomnia may occur as an independent disorder, a symptom/risk factor of comorbid sleep, psychiatric and/or medical conditions, or a combination of these. Approximately 75% of people with chronic insomnia have comorbid conditions[18] that must be reviewed and potentially treated. It is important to screen for comorbidities before, after, and during insomnia treatment, especially if the patient does not respond to therapy.[16] The comorbidity list is extensive (**Table 1**) and should be patient targeted (i.e. menopausal issues for women aged 40–60, or urinary issues for men over 60). However, each patient must be reviewed for the most common

Common Comorbidities and Medications Contributing to Insomnia		
Psychiatric Disorders	Mood disorders	Anxiety disorders
	ADHD, PTSD	Alcohol/substance use disorders
Other Medical Disorders	Neurologic (stroke, migraine)	Musculoskeletal (arthritis, fibromyalgia)
	Pulmonary (COPD, asthma)	Endocrine (hypothyroidism, hyperthyroidism, menopause)
	Digestive (GERD, colitis)	Cardiovascular (congestive heart failure)
	Chronic pain	
	Prostate and urinary	
Medications	Antidepressants	Decongestants and antihistamines
	Stimulants	Analgesics
	Antihypertensives	Herbal supplements
	Sedatives	Cannabis, Alcohol, Substances of abuse
	Anti-asthma drugs	

Table 1. Common Comorbidities and Medications Contributing to Insomnia; *courtesy of Atul Khullar, MD, MSc, FRCPC, DABPN (Cert sleep medicine), DABOM, FAASM, and Jennifer Swainson, MD, FRCPC, DABOM.*

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder, **COPD:** Chronic Obstructive Pulmonary Disease; **GERD:** Gastroesophageal reflux disease; **PTSD:** Post-Traumatic Stress Disorder

Assessment Pearls
Ask about next day functioning
Assess for contributing comorbidities
Establish a timeline and examine the interactions between comorbidities and insomnia
Understand the use of actigraphy and phone accelerometers
Consider sleep studies, being aware that home studies are only useful for confirming moderate to severe sleep apnea and full sleep studies are more definitive

Box 1. Assesment Strategies; *courtesy of Atul Khullar, MD, MSc, FRCPC, DABPN (Cert sleep medicine), DABOM, FAASM, and Jennifer Swainson, MD, FRCPC, DABOM.*

comorbidities, such as mood and anxiety disorders, sleep apnea, and chronic pain. In mental health populations, ADHD, trauma, and bipolar spectrum disorders may also need to be ruled out. Quick patient-rated scales, such as the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7) and the Snoring, Tiredness, Observed, Pressure, BMI, Age, Neck circumference and Gender questionnaire (STOP BANG), can be useful to efficiently assess comorbidities. The Insomnia Severity Index (ISI) can be used in conjunction with comorbidity scales to establish the severity of insomnia. Often, there is a bidirectional relationship between insomnia and many comorbidities, and treating one is likely to improve symptoms of the other.[19]

Clinically, it can often be difficult to decide whether to treat the insomnia or the comorbidity during a particular visit. Useful guides include establishing a timeline of how the insomnia relates to the comorbidity, whether it remains after treating the comorbidity, or assessing which treatment improves daytime functioning.[20] Often both the insomnia and the comorbidity are treated in parallel. (i.e. instituting Cognitive Behavioural Therapy for Insomnia [CBT-I] strategies while treating major depression and referring for a sleep study). **Box 1** reviews major assessment strategies.

Treatment

Goals of Therapy

The primary goal of any therapy for insomnia is to improve daytime functioning. Realistic treatment goals need to be set that aim to minimize daytime impairment, rather than focusing on sleep performance. A chronic poor sleeper will not become a good sleeper instantly.

Nonpharmacological Treatments

Sleep Hygiene and CBT-I

While good sleep hygiene is a cornerstone of any sleep intervention, it alone is not sufficient to treat chronic insomnia disorders. CBT-I is a first line insomnia treatment that incorporates sleep hygiene, along with stimulus control, cognitive restructuring, sleep restriction, and systemic relaxation.[7,9,21] It is highly effective in a wide variety of clinical settings,[22,23] with stimulus control and sleep restriction potentially being the most effective components.[24,25] CBT-I may be delivered in 2–8 sessions,

Advice for Cognitive Barrier	Elaboration
Keep realistic expectations	Even good sleepers do not always get 8 hours of quality sleep. There are individual differences in sleep requirements.
Do not blame insomnia for all daytime impairments	Consider alternative explanations that might contribute to those impairments.
Do not catastrophize after a poor night's sleep	Insomnia can be unpleasant, but it is not dangerous. The worst outcome: you will be sleepier the next day and sleep more soundly the next night.
Do not give too much importance to sleep	Even if sleep occupies one-third of your life, don't make it the sole focus of your existence.
Develop some tolerance to the effects of insomnia	Rearrange your schedule, but do not cancel planned activities.

Box 2 . Targeted cognitive barriers to sleep; *adapted from Driver H et al. Insomnia in adults and children. Available at: http://www.sleepontario.com/docs/INSOMNIA_BOOK_web.pdf.*

Clinical Tips – Selecting Pharmacotherapy
Consider medications that have demonstrated safety and efficacy for up to 12 months of use (i.e. eszopiclone, lemborexant, and daridorexant).
Tolerance/dependence risks of benzodiazepines and other z-drugs should be considered, but long-term use may be appropriate in some patients .
Risks of weight gain with sedating antidepressants and antipsychotics must be considered.
Fall risks associated with insomnia medications must be weighed; trazodone carries a similar fall risk to benzodiazepines and z-drugs.
For resistant insomnia, DORAs may be used off-label in combination with traditional hypnotics.
The monograph's recommended time-frame between hypnotic administration and driving or operating machinery should be adhered to with initial use. However, habituation to driving effects has been shown with regular use of hypnotics. Off-label sedatives have not been tested for driving safety and may be more deleterious. Substitutes such as alcohol, cannabis, OTC medications, and sleep deprivation itself can significantly impair driving.

Box 3. Clinical tips for selecting pharmacotherapy; *courtesy of Atul Khullar, MD, MSc, FRCPC, DABPN (Cert sleep medicine), DABOM, FAASM, and Jennifer Swainson, MD, FRCPC, DABOM.*

either individually, in groups, or through digital formats. The basic features of CBT-I should be included in any insomnia treatment plan. **Box 2**[26] outlines the major features that can be integrated within a family practice visit.

Unfortunately, even in well controlled clinical trials of CBT-I, 20–25% of patients do not respond,[27] and 30% drop out.[28] These rates may be even higher in primary care practice due to factors such as a lack of patient motivation, limited access to optimal types of CBT-I, unwillingness to change sleep and daytime behaviours, and patient selection. Patient selection errors can arise from both the type of patient, such as those lacking psychological mindedness and more commonly, the timing of the CBT-I treatment plan, particularly if it is initiated too early when the patient has an active comorbidity that precludes participation. Similar to other chronic diseases such as diabetes or hypertension, if patients do not adhere to recommendations for behavioural management and symptoms persist, pharmacotherapy should be introduced. Patients should not be stigmatized for using medication. Pharmacotherapy can work synergistically with CBT-I, often[29] offering immediate relief. This can enhance the therapeutic alliance and compliance to the CBT-I treatment plan. Similar to most behavioural therapies, CBT-I often shows a transient initial worsening of symptoms and may take 3–4 weeks to demonstrate improved sleep.[22,23,27]

Pharmacotherapy

There is a marked dichotomy between theory and practice regarding hypnotics. Many, but not all medications with a Health Canada–approved indication for the treatment of insomnia are potentially problematic when used long-term. Given the chronic nature of most insomnia cases, long-term medication use may be necessary, especially for patients with significant comorbidities, or a failure/inability to complete nonpharmacologic therapies. A clear rationale, ongoing assessment, and clinical awareness of the risks/benefits of long-term sedative use is essential.[16] Agents with evidence for safety and efficacy in long-term use should be strongly considered. Reluctance to provide patients access to long-term hypnotics may cause marked unnecessary suffering and often leads to unmonitored self-medication with more deleterious over the counter (OTC) medications or substances.

Pharmacotherapy Choices

In Canada, medications approved for insomnia include several benzodiazepines, z-drugs, a very low dose sedating antidepressant, and most recently, dual orexin receptor antagonists (DORAs) (**See Table 2**). Due to stringent exclusion criteria in clinical trials, older agents

Medications	Doses	Half-life (*hrs*)
Benzodiazepines		
Flurazepam (Dalmane)	15, 30 mg	40–250 (75 mean)
Nitrazepam (Mogadon)	5, 10 mg	16–38 (28.8 mean)
Temazepam (Restoril)	15, 30 mg	4–18 (8.8 mean)
Triazolam (Halcion)	0.125, 0.25 mg	1.5–2.5 (2 mean)
Z-drugs (Non-benzodiazepine sedative-hypnotics)		
Eszopiclone (Lunesta) (2020) *	1, 2, 3 mg	6 mean
Zopiclone (Imovane)	5, 7.5 mg	3.8–6.5 (6 mean)
Zolpidem (Sublinox) (2011)	SDT 5, 10 mg	2-3
Low dose antidepressant (wake blocker)		
Doxepin *	3, 6 mg	17 (51 metabolite)
Dual Orexin Receptor Agonist		
Lemborexant (Dayvigo) (2020) *	5, 10 mg	N/A**
Daridorexant (Quiviviq) (2023) *	50 mg	N/A**

Table 2. Medications Indicated for Insomnia in Canada; *courtesy of Atul Khullar, MD, MSc, FRCPC, DABPN (Cert sleep medicine), DABOM, FAASM, and Jennifer Swainson, MD, FRCPC, DABOM.*

*Designates data to support long term use

**Half life is not thought to correlate to clinical efficacy of the DORA

were also studied in insomnia populations without major comorbidities, making their efficacy less representative of most insomnia patients who have major comorbid conditions. Newer agents have long-term data that are more representative of the typical insomnia population.[30-32] Key points for using pharmacotherapy for insomnia are summarized in **Box 3**.

DORAs

The current evidence indicates that these drugs should be the first line of treatment for chronic insomnia due to their 1-year long-term efficacy data, and the lack of respiratory depression, tolerance, withdrawal, rebound insomnia, signal for falls, and abuse potential.[14,15] A recent meta-analysis of all insomnia pharmacotherapy options looked at their efficacy and safety. As a class, the DORAs were found to be the most preferable treatment in both areas, although this summary of evidence is limited by a lack of head-to-head comparison data.[33]

The major clinical differences between the 2 available DORAs are currently unclear. Lemborexant has been observed to increase rapid eye movement (REM) sleep, whereas daridorexant tends to increase sleep stages more evenly.[14,15] These features may be related to how they antagonize different types of orexin receptors, but the clinical significance remains unknown and requires further research. The clinical response to DORAs does not appear to be a class effect; therefore, if a patient does not respond to or tolerate one, the other should be considered.

These drugs should be considered as centralized sleep-wake stabilizing drugs rather than traditional sedatives. As such, DORAs work differently, possibly requiring 3–6 weeks of regular use to achieve their full effect.[30,32,33] The benefits often include more restorative sleep, the ability to return to sleep after awakening, and improved daytime functioning, rather than "a knock out pill". Patients must be counselled accordingly.

Benzodiazepines

All benzodiazepines, whether indicated for insomnia or not, have sedative and hypnotic properties but differ significantly in their onset, potency, and pharmacokinetics. Benzodiazepines are known to carry significant risks of adverse effects, such as delirium, falls, motor vehicle accidents, complex sleep behaviours, respiratory depression, cognitive impairment, memory issues, abuse, dependence, and withdrawal symptoms with long-term use.[34] These risks are of particular concern for the elderly or medically ill.[35] Although some studies have suggested benzodiazepines and z-drugs increase the risks of mortality and dementia, this has likely been overestimated due to study design; newer data suggest no clear association.[36,37] Risks may be attenuated by short duration and possibly intermittent use.[38]

Z-Drugs

The z-drugs, including zopiclone, eszopiclone, and zolpidem act on the same receptors as benzodiazepines and have similar therapeutic effects for overall sleep. However, they have more limited effects on sleep structure and somewhat fewer adverse effects, including cognitive impairment, dependence, tolerance, and rebound insomnia, especially with eszopiclone.[31,39-42] They have demonstrated 10–40 times less muscle relaxant effect than benzodiazepines,[43] and have not demonstrated any worsening of sleep apnea at recommended doses.[44]

The differences between benzodiazepines and z-drugs as well as among the z-drugs themselves, are related to their relative affinity for the various subunits of the GABA-A alpha receptor.[41] Zopiclone is the most similar to benzodiazepines among the z-drugs, while eszopiclone is the least similar.[41] Eszopiclone appears to have a safer long-term use profile and is likely less problematic than the other z-drugs.[31] It could be considered as a second- or third-line long-term strategy.

In Canada, the monographs for benzodiazepines and z-drugs typically indicate short prescriptions of 7–10 days and no more than 30 days. These guidelines are clearly for short-term insomnia, but they are arbitrarily determined, potentially damaging, and not always evidence-based. Nonetheless, frequent follow-up (3–6 weeks) and limited dispensing (14–60 days) is warranted, particularly at the beginning of insomnia treatment.

Similar to benzodiazepines, zolpidem and zopiclone are usually considered for short-term acute or intermittent use. Long-term use should be considered only for severe or comorbid insomnia cases that have failed other treatments or when these drugs have demonstrated a substantial improvement in daytime functioning.[16]

Low Dose Doxepin

Low dose doxepin (LDD) (3–6 mg) has a reasonable data set supporting its use for sleep maintenance and includes elderly specific data,[45] however, its effectiveness has not translated well to clinical populations. The absorption of LDD is quite variable and is significantly reduced if taken within 3 hours of food intake, and its effects on sleep onset are inconsistent.[45] LDD has limited public coverage in Canada. From a practical standpoint, a slightly higher dose of doxepin (10–40 mg) which is publicly reimbursed, is often used off-label, though it carries a higher potential for side effects.

Off-Label Insomnia Medications

Several medications are commonly used off-label for insomnia (See **Table 3** from[46]). These include sedating antidepressants, antipsychotics, alpha-2 delta ligands (anticonvulsants), and other benzodiazepines. As a rule, these medications have limited evidence supporting their use and have their own deleterious side effects. However, when insomnia is comorbid with another condition or resistant to standard treatments, rational use of off-label agents may be appropriate.[47,48] Public coverage in Canada for safer, approved agents with long-term efficacy is currently limited, which may also lead to the use of off-label agents.

Many off-label medications (tricyclic antidepressants [TCA's], mirtazapine, quetiapine, gabapentin/pregabalin) can cause significant weight gain, which can independently decrease sleep quality.[49] Low dose quetiapine (25–100 mg) is commonly used in clinical practice for insomnia, but the supporting data is of poor quality, and it may not help sleep architecture.[50] It should not be used for sleep except possibly in cases of significant comorbidities such as depression or severe generalized anxiety.

Data supporting the use of trazodone (50–200 mg) for insomnia without comorbidities is restricted to small studies.[51] Nevertheless, its widespread use is due to some clinical successes, and support from some experts in the field.[16,52] Though trazodone does not appear to have the memory, abuse, or rebound insomnia issues observed with benzodiazepines or z-drugs, it and other sedating antidepressants can have a similar fall risk.[53] Insomnia doses of trazodone and other sedating antidepressants usually do not have an appreciable antidepressant effect, however, trazodone has several theoretical receptor benefits that could independently promote sleep.[51] It could be considered a second- or third-line treatment option.

Over the Counter Medications

When assessing insomnia pharmacotherapy, a history of OTC medication use for sleep must be reviewed, as this is a common practice due to easy availability and misleading promotion.[54] Melatonin is frequently used by patients, and while it may help certain subgroups of patients with insomnia (i.e. elderly, neurodevelopmental disorders, children, and those with ADHD), it is not recommended overall due to a small and inconsistent overall effect size.[55] Although there is no consistent data indicating a lack of safety with melatonin, the lack of regulation on the purity and manufacturing of melatonin supplements in North America can lead to adverse outcomes, so caution is advised.[56] Magnesium supplementation is known to help overall sleep quality, but does not directly address insomnia.[57] As a rule, OTC sedating antihistamines should be avoided.[16]

Substances

Alcohol is well known as one of the most harmful substances for sleep, yet it remains commonly used, therefore, patients must be asked about their intake.

Drug Class	Reasons for Use	Considerations
Sedating antidepressants: • Mirtazapine (low-dose) • Tricyclic antidepressants (including doxepin >10 mg) • Trazodone	• Insomnia with mood disorder • Mirtazapine may be useful for low appetite or alcohol use issues • Comorbid migraine and other central sensitivity syndromes (TCAs only)	• Next-day sedation and motor restlessness can occur • TCAs also associated with anticholinergic adverse effects • Both TCAs and mirtazapine may be associated with weight gain • Trazodone may be better for sleep maintenance, not overall efficiency
Antihistamines: • Chlorpheniramine • Diphenhydramine • Hydrazine	• Insomnia associated with histamine-mediated sleep disturbance (e.g. allergies, atopic dermatitis) • Very short term • Rarely recommended due to side effect profile	• Excessive risk of daytime sedation, psychomotor/cognitive impairment and anticholinergic toxicity, especially in the elderly.
Anticonvulsants: • Gabapentin, low-dose • Pregabalin, low-dose	• Insomnia associated with centralized pain syndromes (e.g. fibromyalgia, neuropathic pain, restless legs syndrome)	• Weight gain and next-day sedation are common adverse effects • CNS depression and cognitive impairment may also occur
First-generation antipsychotics: • Chlorpromazine, low-dose • Methotrimeprazine • Loxapine	• Insomnia associated with very resistant bipolar disorder or schizophrenia	• Not recommended for insomnia in the absence of comorbidities, due to unacceptable risk of anticholinergic and neurological toxicity
Second-generation antipsychotics: • Olanzapine • Quetiapine • Paliperidone • Clozapine • Brexpiprazole • Risperidone • Lurasidone • Asenapine	• Insomnia with bipolar disorder or schizophrenia (olanzapine, quetiapine, clozapine, paliperidone, risperidone, asenapine, lurasidone) • Insomnia with major depressive disorder (augmentation with brexpiprazole) • Insomnia with generalized anxiety disorder (quetiapine)	• Not recommended for insomnia in the absence of comorbidities, due to unacceptable risk of metabolic syndrome • Metabolic issues and weight gain must be monitored
Other benzodiazepines: • Diazepam • Clonazepam • Lorazepam • Nitrazepam • Alprazolam • Oxazepam	• Insomnia with anxiety disorders or severe hyperarousal • Insomnia associated with restless legs syndrome (clinically done, minimal evidence to support)	

Table 3. Off-Label Agents Commonly Used for Comorbid Insomnia; *adapted from Khullar, A., 2021.*

Abbreviations: TCAs: tricyclic antidepressants

Strategies for Switching Insomnia Therapies
ADD, THEN TAPER
Use if the first drug is somewhat effective or has a risk of withdrawal. Add the new drug to help the patient sleep before taking away the old drug
Use this for initiating DORAs for someone taking other sleep medications
CROSS TAPER
Decrease the first drug and start the second
Use this when switching therapies to reduce side effects.
DIRECT SWITCH
Stop the first drug and immediately start the second
Consider this for same class switches (i.e. DORA to DORA, z-drug to z-drug)

Box 4. Strategies for switching insomnia therapies; *courtesy of Atul Khullar, MD, MSc, FRCPC, DABPN (Cert sleep medicine), DABOM, FAASM, and Jennifer Swainson, MD, FRCPC, DABOM.*

Abbreviations: DORAs: dual orexin receptor agonists

Cannabinoids are not prescribed for insomnia, but may improve sleep quality in those with comorbidities that have evidence supporting the benefits of cannabis, such as chronic pain.[58] The effects of various cannabinoids on sleep are complex, multidimensional, and dependent on the mixtures of the active ingredients, necessitating further study.[58] Self medication with alcohol and/or cannabinoids for sleep often strongly indicates not only insomnia, but also a major comorbidity that must be reviewed.

Switching and Deprescribing (Box 4)

Deprescribing or switching benzodiazepines and z-drugs should be considered for appropriate patients, especially those with advancing age, since side effects such as balance issues and memory complaints become increasingly prevalent.[46]

Plans to taper or switch medications require careful consideration of factors including the duration of medication use, relevant comorbidities, current efficacy, and the level of improved daytime function on the current medication.[59] Indiscriminately restricting, tapering, or stopping stable low doses of benzodiazepines or z-drugs may lead to more harmful behaviours such as increased unmonitored OTC medication or substance misuse.[60] A harm-reduction and cost-benefit approach is essential, as resources for tapering/discontinuation may be limited or the drug may clearly be improving daytime functioning and quality of life.[60]

Patient motivation and alliance is critical in this process. Strategies should include motivational interviewing rather than fear-based reasoning, along with understanding that a complete withdrawal may not be achievable, and that a lower dose can still yield significant benefits. Plan to taper and withdraw hypnotics during a low-stress period. For patients on long-term medications, the tapering schedule should be slow and gradual, often extending over many months.[46]

During the switching process, the patient may require more than one hypnotic, especially when switching from long-term z-drugs and benzodiazepines to DORAs. A common error is the premature withdrawal of the previous sleep medication before waiting 4–6 weeks for more robust efficacy of DORAs. Off-label, smaller doses of sleep medications from different classes may be necessary for patients with severe insomnia or multiple comorbidities and this is a common practice with the DORAs and z-drugs in Japan.[61]

Conclusions

It is important for primary care physicians to be mindful of the potential impacts of insomnia on both patient functioning, and comorbid chronic diseases. Insomnia is not simply an inconvenience; if left untreated, it may contribute to substantial morbidity and even mortality. While screening and taking a history for insomnia can be challenging during a short clinic visit, there are strategies to address this efficiently which can often help with the management of other chronic diseases. Moving beyond sleep hygiene and offering targeted achievable CBT-I strategies and informing patients about local resources is critical and can be accomplished during a short visit. Clinicians should consider the risks/benefits of both indicated and non-indicated pharmacotherapy and become familiar with newer treatment options such as the DORAs, which offer greater safety and efficacy and are designed with potential long-term use in mind.

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References

1. American Academy of Sleep Medicine. Internal Classification of Sleep Disorders,. 3rd ed. Darrien IL: American Academy of Sleep Medicine; 2014.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders,. 5th ed: American Psychiatric Publishing; 2013.
3. Morin CM, LeBlanc M, Bélanger L, Ivers H, Mérette C, Savard J. Prevalence of insomnia and its treatment in Canada. Can J Psychiatry. 2011;56(9):540-548. doi:10.1177/070674371105600905
4. Morin CM, Bélanger L, LeBlanc M, Ivers H, Savard J, Espie CA, et al. The natural history of insomnia: a population-based 3-year longitudinal study. Arch Intern Med. 2009;169(5):447-453. doi:10.1001/archinternmed.2008.610
5. LeBlanc M, Mérette C, Savard J, Ivers H, Baillargeon L, Morin CM. Incidence and risk factors of insomnia in a population-based sample. Sleep. 2009;32(8):1027-1037. doi:10.1093/sleep/32.8.1027
6. Ji X, Bastien CH, Ellis JG, Hale L, Grandner MA. Disassembling insomnia symptoms and their associations with depressive symptoms in a community sample: the differential role of sleep symptoms, daytime symptoms, and perception symptoms of insomnia. Sleep Health. 2019;5(4):376-381. doi:https://doi.org/10.1016/j.sleh.2018.12.009
7. Kaur H, Spurling BC, Bollu PC. Chronic Insomnia. StatPearls. Treasure Island (FL): StatPearls Publishing; 2020
8. Liu RT, Steele SJ, Hamilton JL, Do QBP, Furbish K, Burke TA, et al. Sleep and suicide: a systematic review and meta-analysis of longitudinal studies. Clin Psychol Rev. 2020;81:101895. doi:10.1016/j.cpr.2020.101895
9. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4(5):487-504.
10. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005;437(7063):1257-1263. doi:10.1038/nature04284
11. Muehlan C, Roch C, Vaillant C, Dingemanse J. The orexin story and orexin receptor antagonists for the treatment of insomnia. J Sleep Res. 2023;32(6):e13902. doi:10.1111/jsr.13902
12. Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev. 2010;14(1):19-31. doi:10.1016/j.smrv.2009.04.002
13. Kay DB, Buysse DJ. Hyperarousal and beyond: new insights to the pathophysiology of insomnia disorder through functional neuroimaging studies. Brain Sci. 2017;7(3). doi:10.3390/brainsci7030023
14. Sarathi Chakraborty D, Choudhury S, Lahiry S. Daridorexant, a recently approved dual orexin receptor antagonists (DORA) in treatment of insomnia. Sleep Sci. 2023;16(2):256-264. doi:10.1055/s-0043-1770805
15. Fuller MC, Carlson SF, Grant C, Berry V, Ivancich M, Cornett EM, et al. A comprehensive review of lemborexant to treat insomnia. Psychopharmacol Bull. 2024;54(1):43-64.
16. Alberta Guidelines. Towards Optimized Practice, Assessment to Management of Adult Insomnia - Clinical Practice Guidelines 2015 [updated December 2015]. Available from: https://www.albertadoctors.org/media/v51b22o2/adult-insomnia-guideline.pdf.
17. Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, et al. Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: an American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2018;14(7):1231-1237. doi:10.5664/jcsm.7230
18. Maire M, Linder S, Dvořák C, Merlo C, Essig S, Tal K, et al. Prevalence and management of chronic insomnia in Swiss primary care: cross-sectional data from the "Sentinella" practice-based research network. J Sleep Res. 2020;29(5):e13121. doi:10.1111/jsr.13121
19. Morin CM, Drake CL, Harvey AG, Krystal AD, Manber R, Riemann D, et al. Insomnia disorder. Nat Rev Dis Primers. 2015;1:15026. doi:10.1038/nrdp.2015.26
20. Khullar A. How to properly diagnose chronic insomnia with a view for successful treatment. Can J Diagnosis. 2020:9-10.
21. Pigeon WR. Treatment of adult insomnia with cognitive-behavioral therapy. J Clin Psychol. 2010;66(11):1148-1160. doi:10.1002/jclp.20737
22. van der Zweerde T, Bisdounis L, Kyle SD, Lancee J, van Straten A. Cognitive behavioral therapy for insomnia: a meta-analysis of long-term effects in controlled studies. Sleep Med Rev. 2019;48:101208. doi:10.1016/j.smrv.2019.08.002
23. Wu JQ, Appleman ER, Salazar RD, Ong JC. Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions: a meta-analysis. JAMA Intern Med. 2015;175(9):1461-1472. doi:10.1001/jamainternmed.2015.3006
24. Kyle SD, Siriwardena AN, Espie CA, Yang Y, Petrou S, Ogburn E, et al. Clinical and cost-effectiveness of nurse-delivered sleep restriction therapy for insomnia in primary care (HABIT): a pragmatic, superiority, open-label, randomised controlled trial. Lancet. 2023;402(10406):975-987. doi:10.1016/s0140-6736(23)00683-9
25. Falloon K, Elley CR, Fernando A, 3rd, Lee AC, Arroll B. Simplified sleep restriction for insomnia in general practice: a randomised controlled trial. Br J Gen Pract. 2015;65(637):e508-515. doi:10.3399/bjgp15X686137
26. Driver H, Gottschalk R, Hussain M, Morin CM, Shapiro C, van Zyl L. Insomnia in Adults and Children: Joli Joco Publications; 2012. Available from: http://www.sleepontario.com/docs/INSOMNIA_BOOK_web.pdf.
27. Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. Ann Intern Med. 2015;163(3):191-204. doi:10.7326/m14-2841
28. Harvey AG, Tang NK. Cognitive behaviour therapy for primary insomnia: can we rest yet? Sleep Med Rev. 2003;7(3):237-262. doi:10.1053/smrv.2002.0266
29. Riemann D, Espie CA, Altena E, Arnardottir ES, Baglioni C, Bassetti CLA, et al. The European Insomnia Guideline: an update on the diagnosis and treatment of insomnia 2023. J Sleep Res. 2023;32(6):e14035. doi:10.1111/jsr.14035
30. Kärppä M, Yardley J, Pinner K, Filippov G, Zammit G, Moline M, et al. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. Sleep. 2020;43(9). doi:10.1093/sleep/zsaa123
31. Rösner S, Englbrecht C, Wehrle R, Hajak G, Soyka M. Eszopiclone for insomnia. Cochrane Database Syst Rev. 2018;10(10):Cd010703. doi:10.1002/14651858.CD010703.pub2
32. Kunz D, Dauvilliers Y, Benes H, García-Borreguero D, Plazzi G, Seboek Kinter D, et al. Long-term safety and tolerability of daridorexant in patients with insomnia disorder. CNS Drugs. 2023;37(1):93-106. doi:10.1007/s40263-022-00980-8

33. Yue JL, Chang XW, Zheng JW, Shi L, Xiang YJ, Que JY, et al. Efficacy and tolerability of pharmacological treatments for insomnia in adults: a systematic review and network meta-analysis. Sleep Med Rev. 2023;68:101746. doi:10.1016/j.smrv.2023.101746
34. Brandt J, Leong C. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. Drugs R D. 2017;17(4):493-507. doi:10.1007/s40268-017-0207-7
35. Canadian Coalition for Senior's Mental Health. Canadian Guidelines on Benzodiazepine Receptor Agonist Use Disorder Amonth Older Adults. [PDF File]. Toronto, Canada; 2019. Available from: https://ccsmh.ca/wp-content/uploads/2019/11/Benzodiazepine_Receptor_Agonist_Use_Disorder_ENG.pdf.
36. Osler M, Jørgensen MB. Associations of benzodiazepines, z-drugs, and other anxiolytics with subsequent dementia in patients with affective disorders: a Nationwide Cohort and nested case-control study. Am J Psychiatry. 2020;177(6):497-505. doi:10.1176/appi.ajp.2019.19030315
37. Patorno E, Glynn RJ, Levin R, Lee MP, Huybrechts KF. Benzodiazepines and risk of all cause mortality in adults: cohort study. BMJ. 2017;358:j2941. doi:10.1136/bmj.j2941
38. Perlis M, Gehrman P, Riemann D. Intermittent and long-term use of sedative hypnotics. Curr Pharm Des. 2008;14(32):3456-3465. doi:10.2174/138161208786549290
39. Oswald I, French C, Adam K, Gilham J. Benzodiazepine hypnotics remain effective for 24 weeks. Br Med J (Clin Res Ed). 1982;284(6319):860-863. doi:10.1136/bmj.284.6319.860
40. Wilson S, Anderson K, Baldwin D, Dijk DJ, Espie A, Espie C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. J Psychopharmacol. 2019;33(8):923-947. doi:10.1177/0269881119855343
41. Nutt D. GABAA receptors: subtypes, regional distribution, and function. J Clin Sleep Med. 2006;2(2):S7-11.
42. Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to dose escalation: a prospective placebo-controlled study. Sleep. 2011;34(2):207-212. doi:10.1093/sleep/34.2.207
43. Montplaisir J, Hawa R, Moller H, Morin C, Fortin M, Matte J, et al. Zopiclone and zaleplon vs benzodiazepines in the treatment of insomnia: Canadian consensus statement. Hum Psychopharmacol. 2003;18(1):29-38. doi:10.1002/hup.445
44. Nigam G, Camacho M, Riaz M. The effect of nonbenzodiazepines sedative hypnotics on apnea-hypopnea index: A meta-analysis. Ann Thorac Med. 2019;14(1):49-55. doi:10.4103/atm.ATM_198_18
45. Yeung WF, Chung KF, Yung KP, Ng TH. Doxepin for insomnia: a systematic review of randomized placebo-controlled trials. Sleep Med Rev. 2015;19:75-83. doi:10.1016/j.smrv.2014.06.001
46. Khullar A. Insomnia Therapeutics. Compendium of Pharmaceuticals and Specialists. Ottawa, ON: Canadian Pharmacists Association; 2021. Available from: http://www.myrxtx.ca.
47. McCall C, McCall WV. What is the role of sedating antidepressants, antipsychotics, and anticonvulsants in the management of insomnia? Curr Psychiatry Rep. 2012;14(5):494-502. doi:10.1007/s11920-012-0302-y
48. Doghramji K, Jangro WC. Adverse Effects of psychotropic medications on sleep. Psychiatr Clin North Am. 2016;39(3):487-502. doi:10.1016/j.psc.2016.04.009
49. Beccuti G, Pannain S. Sleep and obesity. Curr Opin Clin Nutr Metab Care. 2011;14(4):402-412. doi:10.1097/MCO.0b013e3283479109
50. Anderson SL, Vande Griend JP. Quetiapine for insomnia: a review of the literature. Am J Health Syst Pharm. 2014;71(5):394-402. doi:10.2146/ajhp130221
51. Jaffer KY, Chang T, Vanle B, Dang J, Steiner AJ, Loera N, et al. Trazodone for insomnia: a systematic review. Innov Clin Neurosci. 2017;14(7-8):24-34.
52. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res. 2017;26(6):675-700. doi:10.1111/jsr.12594
53. Bronskill SE, Campitelli MA, Iaboni A, Herrmann N, Guan J, Maclagan LC, et al. Low-dose trazodone, benzodiazepines, and fall-related injuries in nursing homes: a matched-cohort study. J Am Geriatr Soc. 2018;66(10):1963-1971. doi:10.1111/jgs.15519
54. Cheung JMY, Jarrin DC, Beaulieu-Bonneau S, Ivers H, Morin G, Morin CM. Patterns of concomitant prescription, over-the-counter and natural sleep aid use over a 12-month period: a population based study. Sleep. 2021;44(11). doi:10.1093/sleep/zsab141
55. Salanitro M, Wrigley T, Ghabra H, de Haan E, Hill CM, Solmi M, et al. Efficacy on sleep parameters and tolerability of melatonin in individuals with sleep or mental disorders: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2022;139:104723. doi:10.1016/j.neubiorev.2022.104723
56. Grigg-Damberger MM, Ianakieva D. Poor quality control of over-the-counter melatonin: what they say is often not what you get. J Clin Sleep Med. 2017;13(2):163-165. doi:10.5664/jcsm.6434
57. Arab A, Rafie N, Amani R, Shirani F. The role of magnesium in sleep health: a systematic review of available literature. Biol Trace Elem Res. 2023;201(1):121-128. doi:10.1007/s12011-022-03162-1
58. Health Canada. Information for health care professionals: cannabis (marihuana, marijuana) and the cannabinoids. Ottawa ON: Health Canada; 2018. Available from: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html.
59. Watson NF, Benca RM, Krystal AD, McCall WV, Neubauer DN. Alliance for Sleep Clinical Practice Guideline on Switching or Deprescribing Hypnotic Medications for Insomnia. J Clin Med. 2023;12(7). doi:10.3390/jcm12072493
60. Fisher J, Sanyal C, Frail D, Sketris I. The intended and unintended consequences of benzodiazepine monitoring programmes: a review of the literature. J Clin Pharm Ther. 2012;37(1):7-21. doi:10.1111/j.1365-2710.2011.01245.x
61. Ozone M, Hirota S, Ariyoshi Y, Hayashida K, Ikegami A, Habukawa M, et al. Efficacy and safety of transitioning to lemborexant from z-drug, suvorexant, and ramelteon in Japanese insomnia patients: an open-label, multicenter study. Adv Ther. 2024;41(4):1728-1745. doi:10.1007/s12325-024-02811-2

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ADULT ADHD: WHAT IT IS AND HOW TO ASSESS AND TREAT IT

Introduction

Adult ADHD is a significant problem for an estimated 4.4% of the adult population, and is also prevalent in 10% of those with depressive or anxiety disorders and in 20% of those with chronic low mood.[1] Among patients referred for treatment-resistant depression, one in three may have undiagnosed ADHD.[2] Overall, ADHD is poorly understood, significantly undertreated, and a common reason for poor response to treatment in mood and anxiety disorders.

ADHD is not a consequence of poor parenting, indulged laziness, or excessive consumption of sugar or food dyes. It is a neurodevelopmental disorder, a "hardwiring" problem, marked by delayed maturation of the Prefrontal Cortex and allied subcortical regions that constitute the "adult" brain.[3]

When we are young, we have limited self-control: we take what we want, say what we think, get excited, cry, and live in the moment. As our brains mature, we learn to control our behaviours, manage our emotional reactions, prioritize tasks, plan, and follow through on those plans. In individuals with ADHD, this maturation is delayed and too often remains incomplete.

Imaging studies on individuals not taking medication show that development of the prefrontal cortex in individuals with ADHD is approximately 3 years behind that of peers.[4] Thus, a 14-year-old with ADHD may have the self-regulation ability of an 11-year-old. This immature behaviour puts them out of step with their peers and often leads to difficulties fitting in, having few friends, and being bullied. This rejection can reinforce a negative self image due to poor school performance, poor motor control, and overall lack of success.

Most children with ADHD do not completely "grow out" of it. Most have lifelong difficulties with attention, impulsivity, or restlessness.[5] Adults with ADHD often will describe feeling as though they are stuck at the developmental stage of a 14-year-old.

ADHD is not a problem of being **unable** to pay attention, rather, it is a problem of being unable to **regulate** attention. If an activity is interesting/stimulating, those with ADHD have no problem paying attention, indeed they hyper-focus and cannot stop what they are doing. However, if the task is not of interest, then it is almost impossible for those with ADHD to focus on it. This phenomenon has been called "erectile dysfunction of the mind" (TE Brown) – without interest, nothing happens.

ADHD is also marked by poor control over impulses and emotional reactions. Everyone experiences urges to buy things, to say what we think, or to indulge in an extra piece of cake. However, we automatically and unconsciously anticipate the consequences - "what comes next," inhibit these impulses, and do not act on them. In individuals with ADHD, the first impulse too often goes unchecked and unregulated. The ADHD brain is stuck in the "now" and has difficulty anticipating "what comes next". As a result, adults with ADHD tend to make unfiltered comments, hasty decisions, and risk leading lives of regret. They not surprisingly have much higher rates of divorce, substance misuse, financial difficulties, and legal problems, including incarceration.[6]

Those with adult ADHD often experience more intense emotional reactivity. Emotional dysregulation is a core feature of ADHD,[7,8] experienced by 40–70% of patients and is marked by rapid and reactive shifts in mood. The adult brain, which normally buffers feelings, provides perspective, and maintains calmness, but in adult ADHD, these functions are often markedly underactive. This leads to anger outbursts, rapid emotional swings, and overall moodiness. The pattern of rapid triggered drops in mood and difficulty returning to normal seen in ADHD is the same pattern that is observed in borderline personality disorder (BPD).[9] Consequently, ADHD is easily misdiagnosed as BPD, particularly in young women. At least one-third of patients diagnosed with BPD have untreated ADHD.[10]

Restlessness, the third domain of ADHD, is a less problematic component of adult ADHD. In adults, inner restlessness manifests as a strong need to keep constantly busy, along with an inability to relax. Those with adult ADHD, similar to the activity of their minds, cannot rest. For example, at work, they may overcommit by volunteering for too many committees, become overextended, and have track records of not finishing or following through on commitments. Even on holiday, they do not rest, but instead explore.

Because of lifelong problems with follow-through, prioritizing, and overall self-control, those with ADHD have difficulty building a fulfilling adult life. Frequently, they are stuck in jobs that are below their potential. If they are fortunate enough to marry or hire "a prefrontal cortex" they can be very successful.

Who should be screened for adult ADHD?

If you suspect a patient may have ADHD, your intuition is likely correct.

In general, it is always beneficial to screen patients who are frequently and easily overwhelmed, present with constantly changing problems, or have longstanding patterns of impulsivity, conflict, or financial difficulties. Consider screening patients who are very talkative or very moody, as well as those who are always "a day late and a dollar short."

It is especially important to screen patients showing a poor response to standard treatment for mood or anxiety disorders. Notably, over 75% of adults with ADHD present with a comorbid psychiatric disorder.[11] Unfortunately, the comorbid illness usually becomes the focus of care, and the ADHD is missed, resulting in poor response to treatment.

Next steps if you suspect ADHD

When ADHD is suspected, provide the patient with the **Adult ADHD Self-Report Scale (ASRS)**, a validated 18 question screening tool for ADHD developed by the World Health Organization. If a patient answers positively to four of the first six questions, there is over a 90% likelihood they have ADHD.[12] Ask the patient to share the ASRS with people who know them well. Ask the patient to bring in old report cards and ideally have someone close to the patient come with them to the next meeting. You may also suggest that the patient conducts an online search of adult ADHD to see if the descriptions resonate with their experiences (**Table 2**). To increase confidence in the screening, add the **Weiss Functional Impairment Scale – Self Report (WFIRS-S)**, which is also self-rated.

At the next visit, review the screeners and report cards and ask the family member or friend about problems such as talking over others, impulsivity, disorganization, procrastination, and moodiness.

ADHD is a lifelong disorder, and a review of childhood behaviours will usually reveal problems with fitting in and longstanding problems with self-regulation.

Neuropsychiatric testing and psychiatry consults

ADHD is a clinical diagnosis that is based on presentation and history. Formal neuropsychiatric testing is rarely needed for the diagnosis and is financially out of reach for most. Unfortunately, seeking a consultation from a psychiatrist can be of limited value unless they have some

expertise in ADHD. Psychiatry training programs provide little or no attention to adult ADHD and supervisors, themselves untrained in assessing ADHD, may minimize or dismiss it. Consequently, it is advisable for family physicians to rely on their own assessments and proceed with treatment accordingly.

Treatment

When in doubt, treat. Treatment changes the trajectory of the lives of people with ADHD.

While full treatment involves patient education, skill development, and therapies such as cognitive behavioural therapy (CBT) or dialectical behaviour therapy (DBT), these are not typically provided by family physicians. The principal role for family physicians is to thoughtfully prescribe stimulants. Though non-stimulant treatments (i.e. atomoxetine, bupropion, guanfacine) can be beneficial, their effects are less pronounced, making stimulants the preferred first-line treatment for ADHD.

Stimulants increase activity in the "adult" regions of the brain and have an overall calming effect, rather than being experienced as excitatory or stimulating.[13] Improving activity in the "adult" regions increases the time between stimulus and response, reduces emotional lability, and improves focus. The key sign of stimulant effectiveness is that the patient feels calmer and more in control.

Some family physicians may feel uncomfortable prescribing stimulants, due to concerns such as abuse, divergence, or that prescribing stimulants may lead to substance abuse problems. However, the literature clearly supports that treating ADHD reduces rather than increases the risk of subsequent substance abuse.[14] While stimulant diversion is in fact a relatively minor problem, the highest risk is among college students, and even then, it involves a small minority who misuse or re-sell their medication. The benefits to the patient almost always outweigh the risk of misuse.

Stimulants can elevate blood pressure and should be treated if this becomes significant.[15] An electrocardiogram is not required as part of the standard workup and is recommended only if the patient or patient's family has a significant cardiac history.

Initiating stimulant treatment

Treatment can be started with either an amphetamine or a methylphenidate stimulant (**Table 1**). The key factor in selecting an agent is its duration of action. Longer-acting compounds are preferred because they provide more consistent benefits, improve adherence, and reduce the risks of diversion or misuse.

Stimulants should be started at the lowest dose for the specific compound and increased weekly to biweekly by one dosing increment. Most patients notice improvements by the second or third dose increase. They experience a less busy mind, feel calmer, and accomplish more with less effort. Family or friends notice that the patient is easier to live with, less interruptive, less moody, and is completing tasks.

With each dose increase, advise the patient to watch for any worsening of their condition. When the dose is too high, patients report feeling stimulated, "edgy", "sketchy", anxious, or in some cases tired, flat, or depressed. If this occurs, they should immediately lower their dose back to the previous level.[16]

It is of primary importance that the patient feel and be in control through the **entire** day. It is vital that parents with ADHD maintain control in the evening when they face the full demands of parenting. Treatment is not successful if they can function well at work but are irritable, moody, and unfocused with their children in the evening.

It is therefore essential to determine the duration of the stimulant's effect. Although longer-acting stimulants are reported to last 12 hours, this estimate is based on problem-solving tests administered in quiet settings, not on one's ability to self-regulate in a noisy and chaotic world.[17] Actually, most long-acting stimulants lose optimal effect after approximately 8 hours. Patients are usually good at identifying when the stimulant wears off – they again feel overwhelmed, scattered, moody, and unfocused.[18]

Patients often need a second dose of stimulant in the mid-afternoon. This dose is usually one-half to two-thirds of the morning dose, but sometimes it matches the full morning dose. Each patient is unique.

If the second dose worsens sleep, switch the second dose to a shorter-acting stimulant. Most patients with ADHD actually sleep better when using stimulants, because of their overall calming effect.

With a second dose, the patient may exceed the "maximum daily dose". This recommended maximum assumes that long-acting stimulants last the full day, which is often not the case. When exceeding the maximum dose, record that the stimulant appears to be metabolized rapidly, and that full coverage requires going above the recommended daily dose. Among the currently available stimulants, the most reliably long-acting agent is Foquest, which provides coverage for patients for a full 16 hours.

Medications & Illustrations			Delivery	Duration of Action[1]	Starting Dose[2]
Amphetamine-Based Psychostimulants					
First Line	Adderall XR®	Capsules 5, 10, 15, 20, 25, 30 mg 	Granules can be sprinkled	~12 h	5–10 mg q.d. a.m.
First Line	Vyvanse®	Capsules 10, 20, 30, 40, 50, 60, 70 mg 	Capsule content can be diluted in liquid or sprinkled	~13–14 h	20–30 mg q.d. a.m.
		Chewable Tablets 10, 20, 30, 40, 50, 60 mg 	Chewable tablets should be chewed thoroughly		
Methylphenidate-Based Psychostimulants					
First Line	Biphentin®	Capsules 10, 15, 20, 30, 40, 50, 60, 80 mg 	Granules can be sprinkled	~10–12 h	10-20 mg q.d. a.m.
First Line	Concerta®	Extended Release Tablets 18, 27, 36, 54 mg 	Osmotic-Controlled Release Oral Delivery System (OROS®)	~12 h	18 mg q.d. a.m.
First Line	Foquest®	Capsules 25, 35, 45, 55, 70, 85, 100 mg 	Granules can be sprinkled	~13–16 h	25 mg q.d. a.m.

Table 1. The Canadian ADHD Resource Alliance (CADDRA) Guide to Long-Acting Adult ADHD Pharmacological Treatments in Canada – July 2024 (Abridged Version); *original version of this sheet developed by Dr. Annick Vincent in collaboration with Direction des communications et de la philanthropie, Laval University.*

Up to one-third of patients may not achieve an optimal outcome with the first stimulant. If, after several dose increases, the patient does not feel any improvement, you can switch to the alternative stimulant category.[19] Simply stop the first and immediately start the alternative at lower doses. No washout period is needed.

Stimulants are usually well tolerated, however, if appetite decreases, encourage the patient to have a larger breakfast, consume protein-rich light snacks throughout the day, and eat a larger meal later in the day. If these problems persist, consider switching to a non-stimulant such as atomoxetine, which tends to have fewer effects on appetite.

A full review of strategies for treating disorders comorbid with ADHD is beyond the scope of this article. However, the basic principle is to "treat the worst first". If the patient has chronic low mood, treat the ADHD first; if the patient is severely depressed, treat the depression first. When managing ADHD-related depression, it is best to use a non-selective serotonin reuptake inhibitor (SSRI) antidepressant, because increases in serotonin reduce activity in dopamine circuits, which is already a problem in ADHD. Consider using antidepressants that do not have this inhibitory effect, such as bupropion (Wellbutrin), vortioxetine (Trintellix), or levomilnacipran (Fetzima). Once the mood has stabilized, the treatment can then focus on managing the ADHD by introducing a stimulant.

Websites/Youtube	Comments
CADDRA **https://www.caddra.ca**	Unquestionably the best website for information, tracking forms, screening tools and supports, including therapists and coaches
ADDitude Magazine **https://www.additudemag.com/**	Short, accurate articles about ADHD and helpful, practical strategies for those with ADHD
How to ADHD **https://howtoadhd.com/**	Somewhat dramatic, aimed at 15–25 year olds, however, it includes accurate information about the experience of having ADHD across the lifespan
r/ADHD and r/adhdwomen	reddit – A lot of real-world discussion about ADHD and various strategies
https://totallyadd.com/	A bit chaotic but many love its humour and friendly approach

Books	Comments
Driven to Distraction Ed Hallowel and John Ratey	A good overview of the condition and treatment and coping strategies
A Radical Guide for Women with ADHD Sari Solden and Michelle Frank	A self-guided workbook that helps women understand the unique problems ADHD presents for them
Order From Chaos Jaclyn Paul	Practical approaches to dealing with the daily chaos of ADHD
ADHD 2.0 Ed Hallowel and John Ratey	Practical coping strategies for patients trying to manage their ADHD
Taking Charge of Adult ADHD. Russell Barkley	Solid information and useful workbook from the leading expert on ADHD
You Mean I'm not Lazy, Stupid or Crazy Kate Kelley and Peggy Ramundo	Helpful for patients to understand the impact of ADHD and coping strategies
Change Your Brain, Change Your Life Daniel Amen	Controversial, but provides understandable explanations about regional brain functioning in ADHD

Table 2. Information Resources for Patients and Physicians; *courtesy of Lawrence Martin, MD.*

For most patients with ADHD, stimulants reduce anxiety. If the patient experiences general anxiety, it may be beneficial to treat the ADHD first to determine whether this provides adequate reduction of the persistent anxiety.

Conclusion

ADHD is a common problem that has a significant impact on a person's ability to function. It is a neurodevelopmental disorder often described as a "hardwiring" problem, which can be effectively treated in most patients. Treating ADHD is enormously satisfying because of the often-profound effect treatment has on a patient's life and trajectory. Instead of rapid, fragmented thoughts, strong emotional reactions, and difficulty staying on task, the patient can gain control and function more effectively, finally able to "adult", and simply be themselves.

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References

1. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163(4):716-723. doi:10.1176/ajp.2006.163.4.716
2. Sternat T. Abstract S2-10. Anxiety and Depression Association of America (AADA); 2016 March 31 to April 3; Philadelphia PA.
3. Shaw P, Malek M, Watson B, Greenstein D, de Rossi P, Sharp W. Trajectories of cerebral cortical development in childhood and adolescence and adult attention-deficit/hyperactivity disorder. Biol Psychiatry. 2013;74(8):599-606. doi:10.1016/j.biopsych.2013.04.007
4. Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. Jama. 2002;288(14):1740-1748. doi:10.1001/jama.288.14.1740
5. Di Lorenzo R, Balducci J, Poppi C, Arcolin E, Cutino A, Ferri P, et al. Children and adolescents with ADHD followed up to adulthood: a systematic review of long-term outcomes. Acta Neuropsychiatr. 2021;33(6):283-298. doi:10.1017/neu.2021.23
6. Steele M, Jensen PS, Quinn DM. Remission versus response as the goal of therapy in ADHD: a new standard for the field? Clin Ther. 2006;28(11):1892-1908. doi:10.1016/j.clinthera.2006.11.006
7. Retz W, Stieglitz RD, Corbisiero S, Retz-Junginger P, Rösler M. Emotional dysregulation in adult ADHD: what is the empirical evidence? Expert Rev Neurother. 2012;12(10):1241-1251. doi:10.1586/ern.12.109
8. Hirsch O, Chavanon M, Riechmann E, Christiansen H. Emotional dysregulation is a primary symptom in adult Attention-Deficit/Hyperactivity Disorder (ADHD). J Affect Disord. 2018;232:41-47. doi:10.1016/j.jad.2018.02.007
9. Moukhtarian TR, Reinhard I, Moran P, Ryckaert C, Skirrow C, Ebner-Priemer U, et al. Comparable emotional dynamics in women with ADHD and borderline personality disorder. Borderline Personal Disord Emot Dysregul. 2021;8(1):6. doi:10.1186/s40479-021-00144-y
10. Weibel S, Nicastro R, Prada P, Cole P, Rüfenacht E, Pham E, et al. Screening for attention-deficit/hyperactivity disorder in borderline personality disorder. J Affect Disord. 2018;226:85-91. doi:10.1016/j.jad.2017.09.027
11. Sobanski E, Brüggemann D, Alm B, Kern S, Deschner M, Schubert T, et al. Psychiatric comorbidity and functional impairment in a clinically referred sample of adults with attention-deficit/hyperactivity disorder (ADHD). Eur Arch Psychiatry Clin Neurosci. 2007;257(7):371-377. doi:10.1007/s00406-007-0712-8
12. Kessler RC, Adler L, Ames M, Demler O, Faraone S, Hiripi E, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. Psychol Med. 2005;35(2):245-256. doi:10.1017/s0033291704002892
13. Arnsten AF. The Emerging neurobiology of attention deficit hyperactivity disorder: the key role of the prefrontal association cortex. J Pediatr. 2009;154(5):I-s43. doi:10.1016/j.jpeds.2009.01.018
14. Boland H, DiSalvo M, Fried R, Woodworth KY, Wilens T, Faraone SV, et al. A literature review and meta-analysis on the effects of ADHD medications on functional outcomes. J Psychiatr Res. 2020;123:21-30. doi:10.1016/j.jpsychires.2020.01.006
15. Zhang L, Li L, Andell P, Garcia-Argibay M, Quinn PD, D'Onofrio BM, et al. Attention-deficit/hyperactivity disorder medications and long-term risk of cardiovascular diseases. JAMA Psychiatry. 2024;81(2):178-187. doi:10.1001/jamapsychiatry.2023.4294
16. Arnsten AF, Pliszka SR. Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. Pharmacol Biochem Behav. 2011;99(2):211-216. doi:10.1016/j.pbb.2011.01.020
17. McCabe SE, Dickinson K, West BT, Wilens TE. Age of onset, duration, and type of medication therapy for attention-deficit/hyperactivity disorder and substance use during adolescence: a multi-cohort National study. J Am Acad Child Adolesc Psychiatry. 2016;55(6):479-486. doi:10.1016/j.jaac.2016.03.011
18. Brams M, Moon E, Pucci M, López FA. Duration of effect of oral long-acting stimulant medications for ADHD throughout the day. Curr Med Res Opin. 2010;26(8):1809-1825. doi:10.1185/03007995.2010.488553
19. Hodgkins P, Shaw M, Coghill D, Hechtman L. Amfetamine and methylphenidate medications for attention-deficit/hyperactivity disorder: complementary treatment options. Eur Child Adolesc Psychiatry. 2012;21(9):477-492. doi:10.1007/s00787-012-0286-5

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References: 1. REXULTI. Data on File. Private coverage plan. **2.** Alberta Health. Drug benefit list. April 1, 2021. **3.** Manitoba Pharmacare. Formulary Search Results. December 1, 2021. **4.** Ontario Drug Benefit. Formulary. February 26, 2021. **5.** Data on File, Otsuka Pharmaceutical Co., Ltd. 2019. NIHB coverage. **6.** Newfoundland and Labrador. Benefit List update. May 12, 2022. **7.** Correctional Service Canada. Data on File. August 2019. **8.** Veterans Affairs Canada. Formulary Search Results. November 2, 2021. **9.** Northwest Territories. Data on File, NWT. November 17, 2020. **10.** New Brunswick Drug Plan Bulletin #1087. September 26, 2022. **11.** Nova Scotia Formulary Pharmacare News. September 2022. **12.** Health PEI. PEI Pharmacare Bulletin. November 16, 2022. **13.** REXULTI Product Monograph. Otsuka Pharmaceutical Co., Ltd.

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