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CANADIAN PRIMARY CARE TODAY

Clinical Insights, Perspectives and Disease Management

TABLE OF CONTENTS

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UPDATE IN THE MANAGEMENT AND TREATMENT OF ADULT ASTHMA FOR PRIMARY CARE PHYSICIANS

Asthma is a common illness; estimates are that it affects up to 18% of the global population, with rates increasing every year.[1,2] Approximately 3.8 million Canadians have asthma,[3] and these patients continue to suffer from inadequately controlled disease as well as exacerbations. Although we have more medication choice than ever, mortality rates in Canada have not declined. Our current pharmacologic strategy has been mostly unchanged for years; it starts with an anti-inflammatory medication, usually an inhaled corticosteroid (ICS) to treat the type 2 (T2) inflammation that is most common. When an ICS provides inadequate control, therapy is often stepped up to include an ICS/long-acting beta-agonist (LABA) combination and even additional therapies like leukotriene receptor antagonists or long-acting muscarinic agents (LAMAs). As patients with uncontrolled asthma are at risk for deleterious outcomes, controlling the disease and preventing exacerbations should be the goal for all patients.[4]

Asthma Control

Our approach to asthma management should begin with assessing asthma control on every visit. The most recent Canadian Asthma guidelines recommend assessing asthma control based on the criteria identified in **Table 1**.[5]

There are validated tools for measuring asthma control, but the key is to ask questions about symptoms and limitations. Lung function should be optimized. Measurements of inflammation are not routinely done in most clinical practices.

When a patient's asthma is not controlled, the basics of asthma management should be reviewed prior to

Daytime symptoms	two or fewer occurrences per week
Nighttime symptoms	preferably none
Physical activity	not limited
Exacerbations	none
Absenteeism	none (due to asthma)
Need for a reliever	two or fewer per week, whether SABA or budesonide/formoterol
FEV1 or PEF	≥ 90% of personal best
PEF diurnal variation	≤ 10–15%
Sputum eosinophils	≤ 2–3%

Table 1: Criteria for defining asthma control; adapted from Yang et al, 2021
FEV: Forced expiratory volume; PEF: Peak expiratory flow; SABA: short-acting beta-agonist

stepping up therapy.[6] The diagnosis of asthma should be confirmed, as often it is assumed and not objectively worked up. Lack of adherence to medication is a common issue affecting asthma control, as often patients discontinue their controller medications when they feel better. Even when patients do take their medication, they need to take it properly, or the active ingredients will not reach the site of action in the lung. Avoidable triggers of inflammation must be identified, and comorbidities that can affect control should be dealt with. Overall, it is best to take a structured approach in addressing these patients (**Table 2**).

Approach to the non-controlled asthmatic
1. Confirm the diagnosis
2. Assess medication adherence
3. Review and refine device technique
4. Avoid triggers
5. Manage comorbidities
6. Step up therapy

Table 2: Approach to the non-controlled asthmatic; adapted from Haughney et al, 2008

The diagnosis of asthma is based on a history of characteristic symptom patterns and evidence of variable expiratory airflow limitation obtained from bronchodilator reversibility testing. As asthma is a variable condition, often responsive to triggers that may not be consistent, other tests may be necessary such as a positive bronchial provocation test, excessive variability during PEF monitoring, excessive variation in FEV1 between visits, fractionated exhaled nitric oxide (FENO),[7] or a significant increase in FEV1 after ICS treatment. It is preferable to confirm the diagnosis prior to starting controller therapy to avoid inappropriate treatment or missing other important diagnoses,[8] and because diagnosis is often more difficult later. The results from a clinical examination, including chest auscultation, may be completely normal, but can be useful to rule out other conditions.

There are significant barriers to obtaining spirometry results in a primary care practice.[9] These barriers include lack of access, lack of expertise in performance of spirometry, patient reluctance or delay in attending a referral centre for spirometry, lack of time during clinician appointment to perform the test and then wait for repeat spirometry after bronchodilation, low confidence in the ability to interpret spirometry results, lack of remuneration for doing the test, and more recently, infectious concerns associated with aerosol generation during the COVID-19 pandemic. Solutions to these barriers could include providing compensation for doing proper quality-controlled spirometry in primary care,[10,11] rapid interpretative support for spirometry, centralized spirometry intake programs, and same-day spirometry in the hospital setting.

Non-adherence is recognized as one of the main reasons for suboptimal asthma management and poor clinical outcomes.[12] Adherence issues can be divided between intentional and unintentional. A non-confrontational approach is more effective for those with intentional non-adherence. It can be helpful to frame comments with remarks such as "Many people find it difficult to take all of their medications all of the time."[13] Symptom-driven treatment strategies can also help correct intentional non-adherence. Unintentional non-adherence includes forgetting medications or taking them incorrectly.[14] Setting reminders, placing medication near the site of a common activity, using phone apps, or simplifying a complex therapy regimen and not mixing devices can help unintentional non-adherence.[15,16]

If the inhaled medication does not reach the lungs, it will not work. Critical errors in inhaler technique in which no medication will reach the lungs include failure to take of a device's cap or loading it properly. Other errors can include not coordinating inhalation and device triggering or even exhaling into the device. Accurate inhaler technique is essential to asthma control, even when

adherence is otherwise perfect. As a rule, a metered dose inhaler (MDI) requires slow deep inhalations to prevent medication impacting the back of the throat, while a dry powder inhaler requires forceful inhalation for the medication to reach the lungs; yet another reason to not mix devices. The use of a valved holding chamber with an MDI can minimize upper airway side effects and improve lung deposition.[17]

Asthma triggers include cigarette smoking, both first- and second-hand, other inhalational activities such as vaping, cannabis and hookah use, indoor allergens such as dust mites or pet dander, and medications that increase the risk for bronchospasm, such as NSAIDs or beta-blockers.[5] Viral infections cannot be completely avoided but vaccination for influenza, COVID-19, and pneumonia can be of value.

Key co-morbidities, including chronic rhinosinusitis with nasal polyps, allergic rhinitis, obesity,[18,19] gastro-esophageal reflux disease (GERD), paradoxical vocal fold motion, anxiety, and depression, can contribute to or mimic the burden of lower respiratory symptoms. Clinicians may have to probe for these issues in patients who are not controlled, to provide optimal management.

Asthma Exacerbations

Exacerbations are important and occur across all levels of severity of asthma. Each episode increases the risk of unscheduled visits, hospitalizations, and mortality, as well as the loss of lung function.[20] As such, identification of those at high risk and the creation of preventative strategies are key. There are several factors that are clearly associated with an increased risk of asthma exacerbations (**Table 3**).[21]

- Uncontrolled asthma
- Lack of ICS due to poor adherence or poor technique
- SABA overuse
  - » Using more than two SABA cannisters per year has been associated with increased risk of exacerbations and mortality.[21]
- Comorbidities such as obesity, rhinosinusitis, GERD, food allergy and pregnancy, psychologic or socioeconomic issues, older age
- Exposures such as allergens, smoking and even air pollution
- Low lung function, especially if FEV1 < 60% predicted
- Having had a severe exacerbation in last month and last year
- History of ever needing intubation or intensive care unit admission for asthma

Table 3: Potentially modifiable risk factors for exacerbations; adapted from Reddell et al, 2021

Non-Pharmacologic Asthma Management

Asthma education should include details about asthma pathophysiology, stressing the inflammation component of the illness, defining expectations of good asthma control with recurrent assessment of such, and ensuring proper inhaler technique. Environmental assessment entails trigger identification and avoidance, which includes cessation of cigarette smoking, cannabis smoking, and inhalation of substances via other methods such as vaping and hookah, as well as identification and avoidance of allergens and irritants including potential occupational exposure. Outcomes are improved when education includes the patient's family.[22] Asthma action plans have been shown to decrease exacerbations.[23] An example of an adult asthma action plan can be found at fpagc.com/tools-resources. In addition, regular exercise, nutritional optimization, social support, and vaccination to prevent respiratory infections all are key components of non-pharmacologic asthma management.

Pharmacologic Asthma Management

The key class of therapy to treat asthma inflammation is ICS. The goal of ICS therapy is to use the lowest effective dose to achieve control while preventing exacerbations; this provides the optimal balance between efficacy and safety. When ICS are initiated, symptoms will start to improve in two weeks,[25] but it can often take months to achieve the full effect.[26] If the response is suboptimal, and all non-pharmacologic asthma management approaches have been attempted, additional therapy with a LABA is recommended rather than dose titration of the ICS, due to the plateau in the dose response curve that is seen at a daily dose equivalent to 200–250 µg of fluticasone propionate.[5]

Stepping up low-dose ICS therapy with the adjunctive use of a LABA works best in a combination inhaler to prevent the isolated use of a LABA without ICS, which has been associated with deleterious outcomes (**Figure 1**).[27] Further step-up therapy should be individualized to patient comorbidities and phenotypes,[28] and can include leukotriene receptor antagonists (LTRAs), LAMAs, and then strategies for patients with severe asthma. Immunotherapy can reduce asthma symptoms and the need for asthma medications and improve bronchial hyper-reactivity.[29] This can be especially useful in patients with concomitant allergic rhinitis, but the possibility of local or systemic adverse effects, such as anaphylaxis, must be considered, although they are much less likely in sublingual immunotherapy vs subcutaneous immunotherapy. LTRAs also play a role in allergic rhinitis and may have some extra benefit in obese asthmatics.[17] LAMA therapy has been shown to benefit patients with respect to exacerbations and lung function and is not

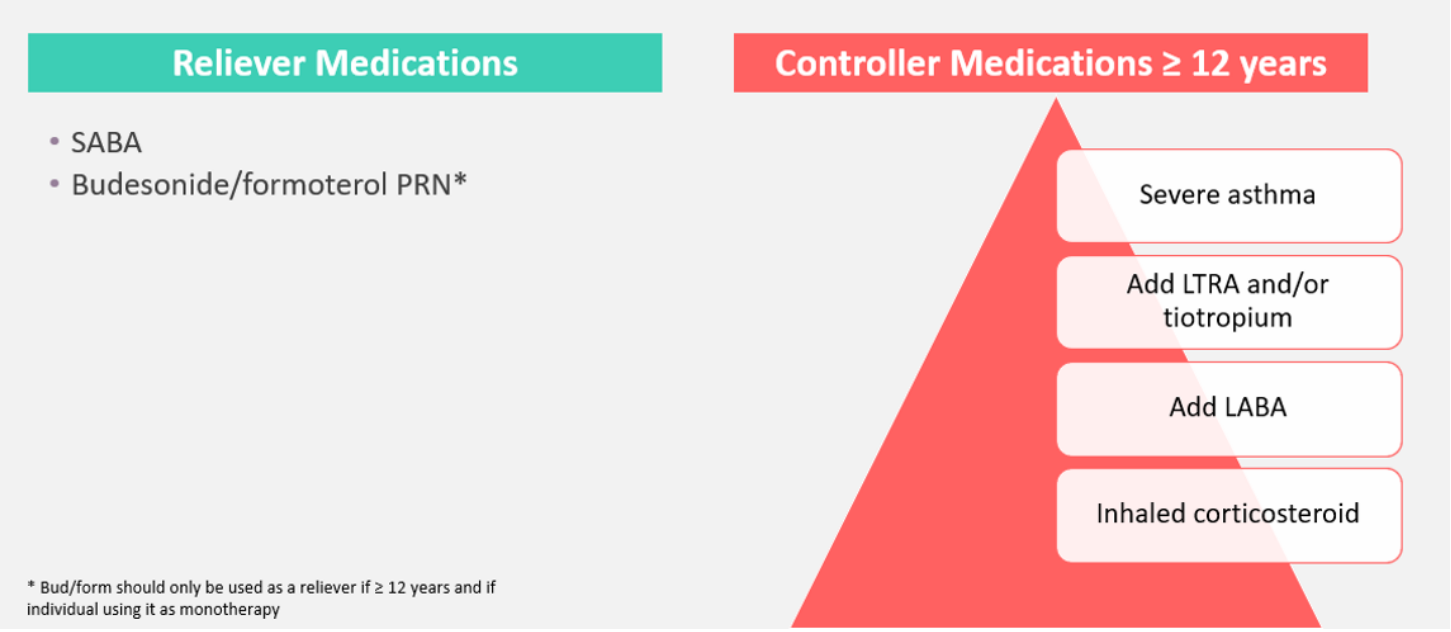

Figure 1: Recommended pharmacologic therapy adjustment steps to achieve asthma control

dependent on T2 inflammation markers.[30] The Canadian Thoracic Society's (CTS) asthma continuum depicts the recommended step-up algorithm for therapies.

What is New in Asthma Management

Reliever therapy

SABAs have been entrenched as reliever therapy for many years and in older clinical practice guidelines were considered the first pharmacological step for asthma management. For many years, using ICS/LABA as a rescue approach in moderate- to-severe asthmatics was both an established and preferred reliever therapy vs SABA due to reductions in exacerbations. In mild asthma, however, this changed as a result of the Global Initiative in Asthma (GINA) recommendations in 2019,[31] which highlighted that:

a. SABA overreliance was dangerous and associated with exacerbations and mortality
b. SABA did not treat inflammation and therefore did not treat the underlying issue
c. Monotherapy with SABA was not recommended

GINA recommended use of a reliever that contained ICS to ensure that the inflammation treatment was escalated at the time of the worsening. The data at the time supported the use of ICS/formoterol as this reliever showed improved control vs SABA alone and reduced exacerbations.[32] Formoterol, despite being a long-acting beta agonist, is also a fast-acting beta agonist and therefore can be used as a reliever. In Canada, the only medication approved for this strategy is budesonide/formoterol. While regular ICS treatment and an asthma action plan would likely out-perform the p.r.n. use of ICS/formoterol in mild asthma, symptom-based therapy with ICS/formoterol is superior in patients with adherence issues as it addresses the patient's inclination to take medication when they need it. There are also combination therapies with ICS/SABA that are not available in Canada.[33,34]

The CTS guidelines continue to recommend SABA in addition to regular ICS therapy for mild asthma, but recognize that in those who are less adherent, ICS/formoterol would be preferable. In addition, the guidelines support the use of SABA monotherapy in very mild asthmatics, but only for those at low risk of exacerbations including:

a. Having good asthma control
b. No history of exacerbations, especially in the last year
c. Using two or less SABA per year
d. Not being a smoker

In summary, SABA therapy may be used adjunctively with ICS monotherapy, with ICS/LABA controller therapy other than budesonide/formoterol, or on top of triple therapy. However, monotherapy with SABA is not recommended.

Triple Therapy

Stepping up to triple therapy should be considered for those patients who are not controlled on dual therapy and have been shown to improve lung function and reduce exacerbations.[35] As discussed, ensure that the diagnosis has been properly made, review the basics such as adherence, technique, comorbidities, and triggers. This

is a step that can and should be done in primary care, but perhaps should get the clinician to consider that if they need such aggressive therapy, they are beginning to meet the criteria for severe asthma, and a biologic referral may be appropriate (see the severe asthma section below).

There are now two single inhaler triple therapies (SITT) for asthma available in Canada. Clinicians may also consider adding a LAMA to an ICS/LABA, which would be a multiple inhaler triple therapy (MITT). There is also good evidence that SITT outperforms MITT with respect to medication persistence rates, lung function,[36] and health status.[37] The two SITTs available in Canada are indacaterol (as acetate) / glycopyrronium (as bromide) / mometasone furoate inhalation powder hard capsules and fluticasone furoate, umeclidinium and vilanterol dry powder for oral inhalation.

Oral Corticosteroid (OCS) Dangers

While exacerbations are harmful, the impact of short courses of OCS for exacerbations is underestimated;[38] they are associated with adverse events such as psychiatric effects, osteoporosis, fracture, diabetes, glaucoma, cataracts, atypical infections and even mortality.[39] This risk is magnified in patients on long-term OCS, which have been used to achieve control in patients with more severe asthma. It is important to keep track of those short courses of OCS for exacerbations, as even two courses per year can lead to significant patient risk.

Severe Asthma

Severe asthma is defined as asthma requiring high-dose ICS plus a second controller medication.[40] The prevalence of persistent and severe asthma is between 5–10% of all patients with asthma, with these patients consuming a proportionally large amount of all asthma resources.[41]
In primary care, it is important to identify those patients who are at risk of poor outcomes (**Table 3**) and to identify those patients that require reassessment if not referral. The ReferID tool shown in **Figure 2** provides a quick method to assess patients in-office.[42] The criteria for reassessing patients with this tool to evaluate for severe asthma include having two or more exacerbations per year, use of OCS twice per year or in a maintenance fashion, a history of having been admitted to an ICU or intubated and using three or more SABA per year.
The primary care practitioner (PCP) is not expected to be involved in choosing or monitoring biologic therapy for asthma, but the PCP should identify those who would benefit from consideration of these therapies and make the appropriate referral. Biologics are currently divided into four classes: anti-IgE therapy, anti IL-5 therapy, anti-IL4/13 therapy, and anti-TSLP treatment. Treatments are chosen based on patient history, lung function, and biomarkers including allergy testing, serum IgE levels, blood eosinophil levels, and FENO levels. These biologic medications are very safe and do not affect immune function in the same way as biologics used for other conditions like colitis, rheumatoid arthritis, and psoriasis.

Conclusion

Most of the patients seen in primary care with asthma have mild disease. The basics of asthma care, include confirming a diagnosis, ensuring adherence to therapy and proper inhaler technique, avoidance of triggers, and the treatment of comorbidities, which will allow your patients to have good asthma control and prevent exacerbations. New relievers that also treat the inflammation, such as ICS/formoterol (currently indicated in Canada), can also help prevent exacerbations and avoid overreliance on SABA monotherapy, which does not treat the underlying condition. Stepping up therapy from ICS to ICS/LABA to triple therapy and referring patients for consideration for biologic therapy gives clinicians a tremendous array of therapeutic options to keep patients well-controlled in the primary care setting.

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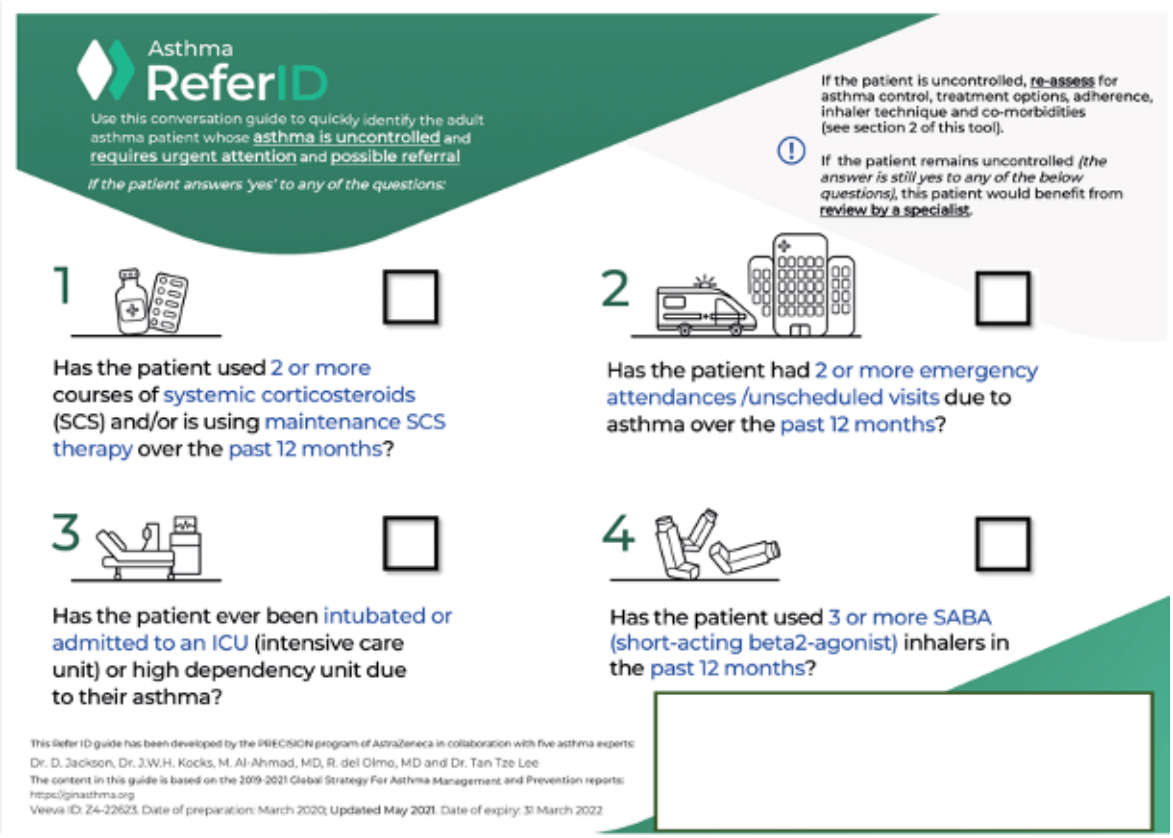

Figure 2: Refer ID asthma severity and control assessment tool

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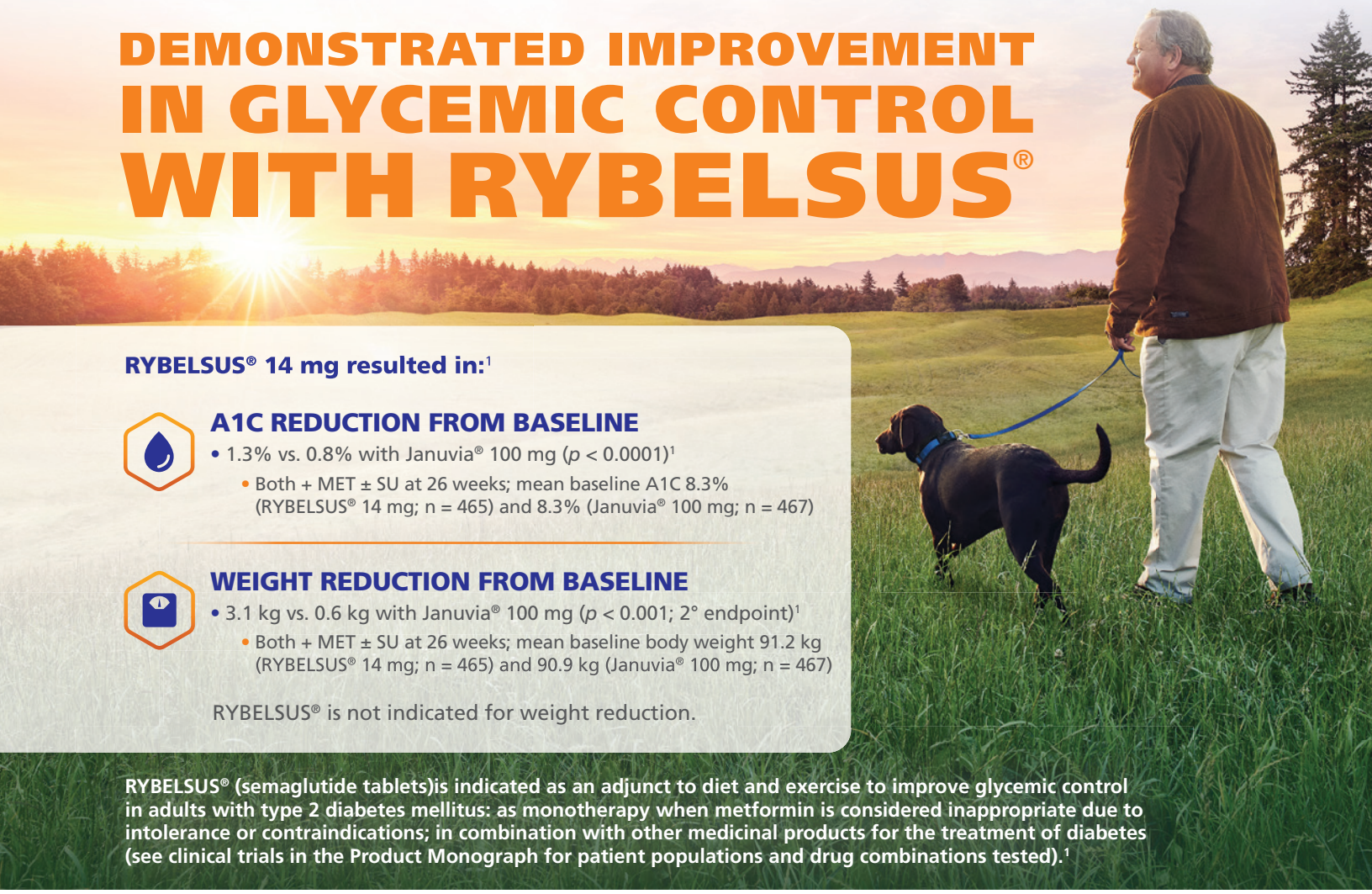

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- Pregnancy or breastfeeding

Most serious warnings and precautions:
Risk of thyroid C-cell tumours: In both genders of rats and mice, semaglutide caused treatment-dependent thyroid C-cell tumours at clinically relevant exposures. It is unknown whether semaglutide causes thyroid C-cell tumours in humans. Patients should be counselled regarding the risk and symptoms of thyroid tumours.

Relevant warnings and precautions:
- Hypoglycemia with concomitant use of insulin secretagogues or insulin
- Driving and operating machinery
- CV effects: increased heart rate; PR interval prolongation
- Pancreatitis
- Hypersensitivity
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- Renal insufficiency: Severe GI adverse reactions warrant monitoring of renal function; acute renal failure and worsening of chronic renal failure have been reported
- Fertility
- Hepatic impairment

For more information:
Please consult the Product Monograph at RYBELSUSPM-E.ca for more information relating to adverse reactions, drug interactions, and dosing information, which have not been discussed in this advertisement.

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* Comparative clinical significance has not been established. Adapted from the RYBELSUS® Product Monograph;[1] Rosenstock J, et al., 2019,[2] see below for study design (PIONEER 3).
CV, cardiovascular; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; SU, sulfonylurea.

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

A 78-week, double-blind trial to compare the efficacy and safety of RYBELSUS® vs. Januvia®. A total of 1864 patients with type 2 diabetes were randomized to RYBELSUS® 3 mg (n = 466), RYBELSUS® 7 mg (n = 465), RYBELSUS® 14 mg (n = 465), or sitagliptin 100 mg (n = 467) once daily, all in combination with metformin alone or metformin and sulfonylurea. The primary endpoint was change in A1C from baseline to week 26.

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MANAGEMENT AND TREATMENT OF ATOPIC DERMATITIS IN PRIMARY CARE

Atopic dermatitis (AD) is a chronic, relapsing, and remitting, inflammatory skin disease characterized by erythema, edema, xerosis, erosions/excoriations, oozing and crusting.[1] It typically begins in childhood and often in infancy. The disease can wax and wane and for many patients it becomes less severe or even remits over time. Seasonal variation is common, with most patients experiencing a worsening of symptoms in the wintertime, particularly in Canada.

AD is increasingly more common with both the incidence and prevalence increasing over the past several decades, particularly in industrialized countries.[2] The exact reason for the increase is unknown, but thought to be potentially related to environmental factors, and lack of exposure to certain pathogens.[3] AD is often associated with other "atopic" disorders, such as asthma, IgE mediated food allergy, and allergic rhinitis; but may also be associated with chronic rhinosinusitis with or without nasal polyps, eosinophilic esophagitis, and allergic conjunctivitis. The progression of atopic disorders from infancy to childhood to adulthood is known as the "atopic march".[4]

The clinical appearance and location of atopic dermatitis may vary depending on age of the patient, their ethnicity, and baseline disease severity. Infants typically present with AD on the face and extensor surfaces. Children and adolescents typically have flexural involvement, where the neck, antecubital fossae, and popliteal fossae are affected (**Figure 1**). Adults may have flexural disease, but isolated disease on the eyelids, nipples, and hands may also be seen (**Figure 2**).

Pruritus (itch) is a hallmark symptom of the disease. Historically, AD was referred to as the "itch that rashes". Itch is exacerbated by sweating, stress, heat, humidity, and woolen clothing. Sleep disruption is also a common sequelae of itch and in children, the sleep disruption often extends to the family, amplifying the burden of disease.

The pathophysiology of AD is complex and is thought to involve an interplay of genetic factors, cutaneous barrier abnormalities, and dysregulated immune pathways as shown in **Figure 3**.[5]

AD is diagnosed based on clinical features. There are numerous clinical criteria that can be employed, such as the Hanifin and Rajka criteria or several modifications of these criteria proposed subsequently, but these are more appropriately utilized in a research setting. The UK Working Party diagnostic schema or the American Academy of Dermatology (AAD) AD diagnostic guidelines are probably most easily used in clinical practice (**Table 1**).[6] Additional diagnostic tests such as fungal scraping and culture, skin biopsy, and blood tests are only required if there is diagnostic uncertainty or a lack of response to an adequate course of therapy.

While AD and food allergy are often seen in the same patient population, food allergy is rarely implicated in the pathophysiology of AD. Therefore, workup of AD patients for food allergy should not be undertaken as routine clinical practice. A double blind placebo controlled food challenge is the diagnostic test of choice in those rare cases where AD is thought to triggered by a food allergy.

Emollients are the cornerstone of AD treatment and maintenance as they restore and preserve skin barrier integrity. They are often used in conjunction with prescription treatments.[8] In infants, petrolatum can be used as it is inexpensive and not associated with a risk of cutaneous sensitization. Cosmetic acceptability limits its use in older children and adults. Any emollient is better than no emollient. A cream-based emollient is typically preferred over a lotion. Emollients containing ceramides or other barrier enhancing agents may provide additional efficacy over traditional emollient creams and lotions. The use of bland emollients in infants who are highly susceptible to developing AD may reduce the incidence of AD. Further studies in this realm are needed.

Topical treatments are appropriate for the majority of patients, particularly since most patients' AD is limited in extent and severity. Topical corticosteroids are the mainstay of therapy and the usage of topical steroids is supported by numerous clinical studies. Side effects of topical treatments are well known, but fortunately uncommon, particularly when topical agents are utilized appropriately. Topical steroids are grouped into "potency groups". The most commonly used scale has seven groups of topical steroid potencies, ranging from ultrapotent (class I) to low potency (class VII).[9] For most primary

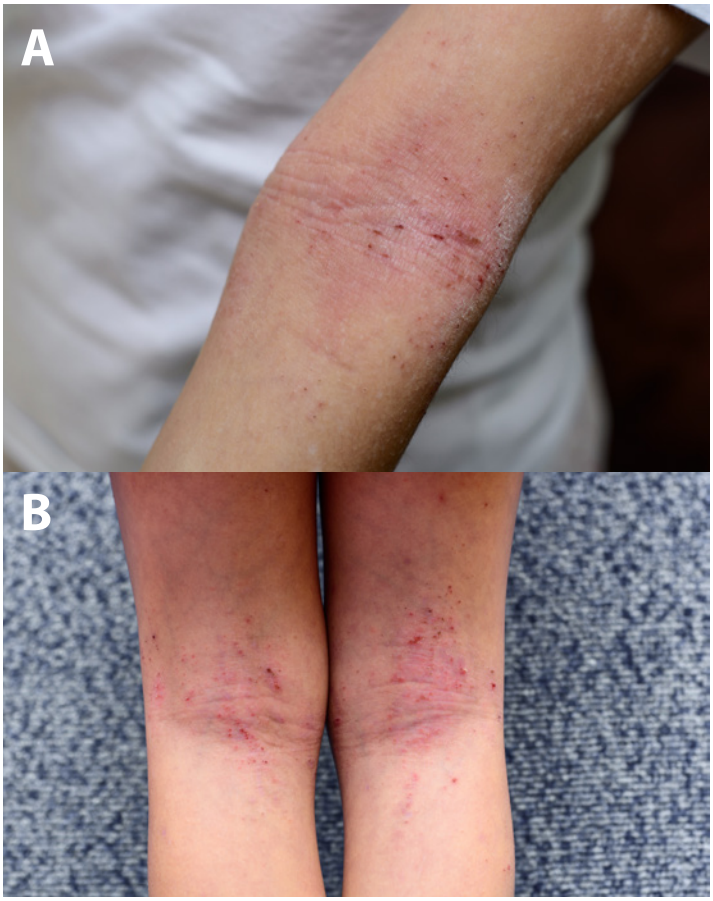

Figure 1. Examples of atopic dermatitis on a child's forearm (A) and the back of the knees (B); from shutterstock.com

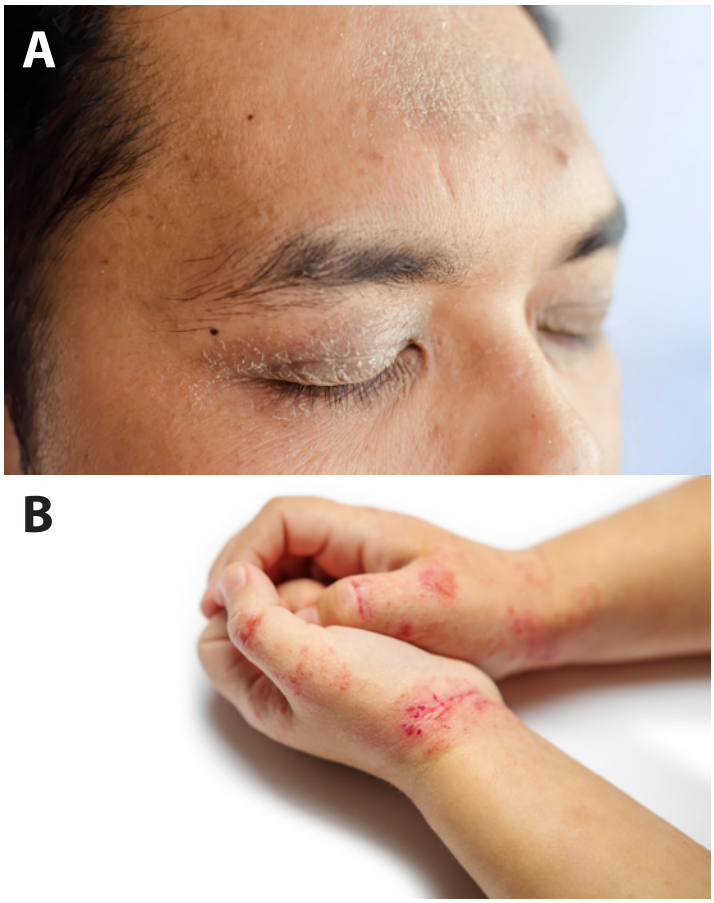

Figure 2. Atopic dermatitis on the eyelid of a male patient (A), and on the hands (B); from shutterstock.com

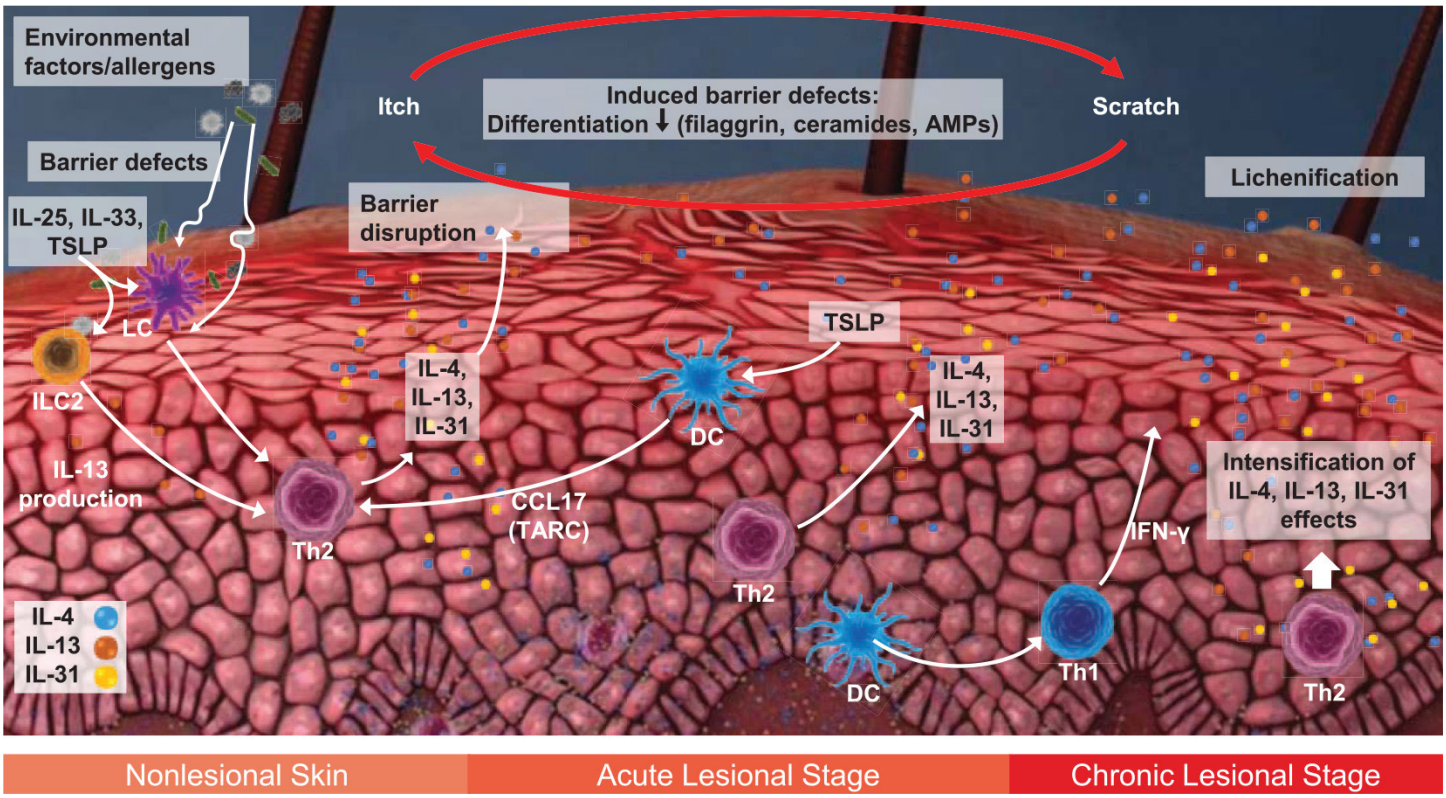

Figure 3. Pathophysiology of atopic dermatitis. (A) Nonlesional skin with underlying barrier defects is susceptible to immune activation in response to environmental factors/allergens. Immune activation by resident innate immune cells leads to type 2 inflammation, led by inflammatory cytokines IL-4, IL-13, and IL-31. (B) Type 2 inflammation mediates barrier disruption, promotes further inflammation, and increases itch, leading to acute skin lesions. (C) Chronic disease is characterized by intensification of the effect of type 2/Th2 cytokines as well as involvement of Th1 inflammation, resulting in lichenification of the skin; used with permission.
AMP, antimicrobial peptide; CCL17, chemokine ligand 17; DC, dendritic cell; IFN, interferon; IL, interleukin; ILC2, type 2 innate lymphoid cell; LC, Langerhans cell; TARC, thymus and activation regulated chemokine; Th, T helper cell; TSLP, thymic stromal lymphopoietin

care practitioners, having familiarity with a low potency steroid, such as hydrocortisone 2.5%, a mid potency steroid, such as betamethasone valeate 0.1%, and a high potency steroid, such as clobetasol propionate 0.05% will suffice. More importantly, is the prescribing of a sufficient enough quantity of medication. To estimate the appropriate quantity of medication to prescribe, it is easiest to do so based on the proportion of body surface area (BSA) affected. The patient's hand (palm and fingers) is approximately equal to 1% of their BSA. Every 1% of BSA that is affected, requires 0.5g to cover once. Therefore, a patient with 2% BSA of AD would need 2g per day if applying b.i.d. Lastly, topical steroids can be prescribed in different vehicles. All the listed topicals are available as a cream, ointment, or lotion. Ointments are typically more effective, but less cosmetically acceptable. Lotions are typically alcohol-based solutions designed for use in hair bearing sites like the scalp and do not have the consistency of emollient lotions.

As with any prescription medication, an appropriate discussion of benefits and risks of therapy is appropriate. Often, the discussion around topical steroids focuses solely on risks which both discourage compliance and adherence to therapy and also perpetuate the feeling that topical steroids are dangerous.

For "steroid phobic" patients or in those whom steroids have not been effective or in those who have had a side effect, there are non-steroidal options that can be considered. Currently there are two classes of non-steroidal medications that are currently approved in Canada and are useful for the treatment of AD. Topical calcineurin inhibitors (TCIs), including tacrolimus and pimecrolimus, are one such class of agent. Studies have shown that when used properly, these agents can be as effective as topical steroids in the treatment of AD. Patients will often experience stinging and burning with initial application, particularly if the skin is acutely inflamed. Another class of agents is the PDE4 inhibitor class. Currently, in Canada, crisaborole is approved for the treatment of mild-to-moderate AD. Again, stinging and burning can be a concern if applied to acutely inflamed skin. The tolerability of both TCIs and crisaborole may be improved if topical steroids are used for a short time to abruptly reduce acute inflammation before either TCIs or crisaborole are used.

ESSENTIAL FEATURES (must be present):
• Pruritus
• Eczema (acute, subacute, chronic)
✓ Typical morphology and age-specific patterns*
✓ Chronic or relapsing history
***Patterns include:**
1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions
IMPORTANT FEATURES (seen in most cases; adding support to the diagnosis):
• Early age of onset
• Atopy
✓ Personal and/or family history
✓ Immunoglobulin E reactivity
• Xerosis
ASSOCIATED FEATURES (these clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies):
• Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
• Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
• Ocular/periorbital changes
• Other regional findings (e.g., perioral changes/periauricular lesions)
• Perifollicular accentuation/lichenification/prurigo lesions
EXCLUSIONARY CONDITIONS (it should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as):
• Scabies
• Seborrheic dermatitis
• Contact dermatitis (irritant or allergic)
• Ichthyoses
• Cutaneous T-cell lymphoma
• Psoriasis
• Photosensitivity dermatoses
• Immune deficiency diseases
• Erythroderma of other causes

Table 1. Features to be considered in the diagnosis of patients with atopic dermatitis; adapted from Eichenfeld et al, 2003[7]

Data on the use of topical steroids and TCIs suggest that both classes of agents can be used as maintenance therapy in addition to being used for the acute management of AD flares. Twice weekly application of both topical steroid and non-steroidal medications has been shown to be effective as a maintenance strategy to reduce flares. In addition, using topical treatments proactively actually decreases the total amount of topical medication used over the long run.[10,11,12]

Newer topical non-steroidal agents are currently in development. In the US, topical ruxolitinib, a Janus Kinase inhibitor (JAKi), has been approved for treatment of mild-to-moderate AD. As well, two other topical agents have been approved in the US for the treatment of psoriasis. Topical roflumilast has posted positive phase 3 top line data[13] and topical tapinarof was shown to be efficacious in phase 2 studies for AD[14], with the phase 3 AD study currently just reporting positive top line data at the recent American Academy of Dermatology Meeting in 2023.

Equally important to prescribing the right emollient and topical treatment, delivery of clear (preferably written) instructions on how to apply these agents is helpful. An eczema care plan helps to reduce confusion. An easy-to-use eczema care plan can be found at www.eczemahelp.ca. Step 1 typically involves bathing with a gentle cleanser. Step 2 includes the application of prescription medications to the affected areas. If different agents are being used for different anatomic areas, it is clarified here in step 2. The third step incorporates application of the emollient to all areas.

Patients who are not adequately controlled with topicals, or who relapse quickly after acute treatment and cannot be managed with maintenance therapy, should be considered for referral to a dermatologist. Patients with high burden of disease as measured by BSA of involvement can also be considered for referral. Patients with 10% or more BSA should be referred for specialist care.

Patients with moderate-to-severe or extensive AD can be managed with additional treatment options. Phototherapy is a useful adjunct. Narrow band UVB is utilized most commonly in Canada for this purpose. However, access to phototherapy units can be an issue as these are conventionally found in dermatology offices which are most often located in urban or suburban areas in Canada. Convenience is another issue with the use of phototherapy as treatments, although quick, need to be done 2-3 times per week for optimal outcomes.

Systemic immunomodulatory agents, including methotrexate, cyclosporine, azathioprine, or mycophenolate mofetil/mycophenolic acid can be used for the treatment of AD; there are limited studies showing at least short term efficacy for each agent. Side effects may limit the long term use of these treatments.

Since 2017, new systemic agents have been available for the treatment of moderate-to-severe AD. Dupilumab, a biologic agent that blocks interleukin (IL) 4/13 signalling was approved for those ≥ 6 years of age for the treatment of AD and is also approved for the treatment of other atopic conditions including asthma, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyps. Another biologic agent, tralokinumab, which only blocks IL-13, is also approved for the treatment of adults with AD. One advantage in the use of biologic agents for AD is their relative ease of use as no biochemical laboratory monitoring is required.

New oral agents have also been approved. These extensively studied agents, upadacitinib and abrocitinib, are highly selective inhibitors of the JAK-1 pathway. JAK-1 is an important regulator of cytokine signalling for IL-4, IL-13, as well as other cytokines thought to drive inflammation in AD pathogenesis. Both of these agents have a rapid onset of action, with patients reporting relief from itch in as little as 1-2 days from the initiation of treatment. Appropriate workup and monitoring is required for these agents. Patients need to be screened for latent TB and monitored for potential transient disruptions to hematologic parameters as well as hepatic parameters. Reactivation of zoster is also more common in patients treated with systemic JAKi and appropriate vaccination with zoster vaccine is typically required as part of routine practice.

Systemic steroids should rarely be used in the management of atopic dermatitis, and should only be considered as rescue therapy, while the patient is bridged to a chronic therapy. Chronic oral steroid therapy is inappropriate for long term management of atopic dermatitis.[15]

AD remains a common presenting problem in primary care and in dermatology offices across the country. The treatment landscape has broadened significantly in the past few years and ongoing research into new and novel treatments continues so that patients can achieve superior outcomes and improved quality of life.

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BIPOLAR DISORDER IN PRIMARY CARE: DIAGNOSIS AND MANAGEMENT

Introduction

Primary care physicians play an important role in supporting and providing medical care for individuals with bipolar disorder. This includes correctly identifying bipolar disorder in those presenting with depressive symptoms to primary care settings or seeking psychiatric consultation and advise as needed; initiating treatment for depressive and hypomanic episodes; assessing risk for suicide or aggressive behaviour; referring to emergency services as needed; and providing maintenance care and monitoring for those with an established diagnosis with collaborative or as needed consultative support from psychiatric colleagues. The objective of this article is to provide up-to-date information to aid primary care physicians in achieving the above objectives related to diagnosing and managing patients with bipolar disorder.

What is bipolar disorder?

Bipolar disorder is a type of a mood disorder that includes various subtypes such as bipolar I disorder, bipolar 2 disorder, cyclothymic disorder and bipolar spectrum disorders (categorized in DSM-5 as "other specified or unspecified bipolar and related disorders)". Bipolar disorder affects approximately 2.4% of the population.[1]

Mania is the defining feature of bipolar I disorder. While major depressive episodes (MDE) are common and pose the greatest disease burden for individuals with bipolar I disorder, their occurrence is not required for diagnosis of this condition. Conversely, a diagnosis of bipolar 2 disorder requires occurrence of at least one major depressive episode, in addition to at least one hypomanic episode. Patients who present with hypomanic symptoms with or without depressive symptoms but do not meet the criteria for bipolar I or bipolar 2 disorder are assigned a diagnosis of cyclothymic disorder or other specified or unspecified bipolar disorder depending on the severity and duration of the symptoms. The clinical implications of the latter diagnoses remain uncertain at this point as few proven specific treatments exist for managing patients with these conditions.

Table 1 itemizes the DSM-5 criteria for a manic episode and a MDE.[2] In addition to experiencing a minimum number of symptoms most of the day and nearly every day for at least 1 week in case of a manic episode, and 2 weeks for a MDE, these symptoms must be associated with significant impairment in functioning, and unrelated to the effects of a substance or a medical condition. While the requirement of a minimum number of symptoms is the same for a hypomanic episode as the manic episode, these symptoms must be present for only 4 consecutive days for a hypomanic episode, while 7 days is required for a manic episode unless the patient was hospitalized for such symptoms. In addition, hypomanic episodes are never associated with psychosis nor marked impairment in functioning, although alteration in functioning is often present. Approximately one-third of hypo/manic and depressive episodes in patients with bipolar disorder present with a mixed features specifier.[3] Hypo/manic episodes with a mixed features specifier are less likely to respond to lithium, while depressive episodes with mixed features pose a greater risk of hypo/manic switch with antidepressant treatment.

Screening and diagnostic techniques for bipolar disorder

Patients presenting with depressive symptoms should be screened for previous hypo/manic episodes. A diagnosis of major depressive disorder (MDD) should only be made after excluding bipolar disorder. The rationale for this is that patients with bipolar disorder typically seek help for depressive symptoms and may not volunteer information concerning previous manic symptoms. Therefore, without systematic inquiry about previous manic symptoms, such patients can easily be misdiagnosed with MDD.

Asking patients who are seeking help for depressive symptoms to complete a mood disorders questionnaire (MDQ) may trigger their memory about previous manic symptoms; those who endorse any symptoms can be probed in greater detail to verify the occurrence of previous episodes. The MDQ is a screening tool and must not be used as an instrument to confirm diagnosis.

Family physicians may have limited time to screen patients; it is therefore important to ask screening questions that are sensitive in eliciting previous hypo/manic symptoms in those presenting with depressive symptoms. These include, "Has there been a period when you felt you had more energy than usual?" "Has there ever been a period when you had too many thoughts rapidly going through your head or when you had too many ideas that you thought were great?"; "Have you ever had a period when you felt you could function with less sleep than usual or you had a lot of energy even though

Criteria: Manic Episode	Criteria: Major Depressive Episode (MDE)
A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently goal-directed behavior or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary). B. During the period of modd disturbance and increased energy or activity, 3 or more of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent noticeable change from usual behaviour	A. Five (or more) of the following symptoms have been present during the same 2 week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or plesure A1 Depressed mood—indicated by subjective report or observation by others (in children and adolescents, can be irritable mood).
1. Inflated self-esteem or grandiosity	A2 Loss of interest or pleasure in almost all activities—indicated by subjective report or observation by others.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)	A3 Significant (more than 5% in a month) unintentional weight loss/gain or decrease/increase in appetite (in children, failure to make expected weight gains).
3. More talkative than usual or pressure to keep talking	A4 Sleep disturbance (insomnia or hypersomnia).
4. Flight of ideas or subjective experience that thoughts are racing	A5 Psychomotor changes (agitation or retardation) severe enough to be observable by others.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.	A6 Tiredness, fatigue, or low energy, or decreased efficiency with which routine tasks are completed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation	A7 A sense of worthlessness or excessive, inappropriate, or delusional guilt (not merely self-reproach or guilt about being sick).
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).	A8 Impaired ability to think, concentrate, or make decisions—indicated by subjective report or observation by others.
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.	A9 Recurrent thoughts of death (not just fear of dying), suicidal ideation, or suicide attempts.
D. The episode is not attributable to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or another medical condition. Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and therefore a bipolar I diagnosis.	B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; C. The episode is not due to the direct physiological effects of a substance or a medical condition

Table 1. DSM-5 criteria for a manic episode and MDE[2]

Bipolar Disorder and Substance Induced Bipolar symptoms		Bipolar Disorder and Borderline Personality		Bipolar Disorder and ADHD	
Bipolar Disorder	**Substance Induced Bipolar symptoms**	**Bipolar Disorder**	**Borderline Personality**	**Bipolar Disorder**	**ADHD**
• Cocaine and amphetamine use more common • Use of substances is episodic • Mood problems in the absence • of substance use • Hypomania/ mania symptoms present • Family history of bipolar or other • mood disorders	• Polysubstance use more common • Use of substances is continuous, dictated by access • Periods of substance use without any mood problems • Clear hypo/ manic symptoms usually absent • Family history of externalising and anxiety disorders	• Biphasic mood dysregulation • Mood symptoms meet threshold criteria for MDD • Reasonable functioning during euthymic periods • Family history of bipolar disorder	• Mood dysregulation in the • depressive spectrum • Mood symptoms often do not • reach threshold for MDD • Dysfunction persists even in euthymic periods • Family history of deprivation and abuse	• Onset of clear-cut symptoms • after age 12 years • Onset with dysthymia or depression • Symptoms are typically episodic • Family history of mood disorders • Variable or negative response to stimulants • Good Response to mood stabilizers	• Onset of clear-cut symptoms before age 12 years • Onset of hyper or disruptive behaviour • Symptoms are continuous • Family history of disruptive disorders • Good response to stimulants • Variable or no response to mood stabilizers

Table 2. Differential diagnosis of bipolar disorder, particularly in youth; courtesy of Lakshmi N. Yatham, MBBS, FRCPC, MRCPsych (UK), MBA (Exec)

you were sleeping fewer hours than usual?" If a patient endorses any of these, further probing questions should be asked about other symptoms to verify if the patient has had a discrete period of a minimum of 4 to 7 days when they had sufficient number of symptoms to meet the DSM-5 criteria for a hypomanic or manic episode.

It is important to consider substance induced bipolar disorder, borderline personality disorder, and attention deficit hyperactivity disorder (ADHD) in the differential diagnoses, especially in younger patients presenting with mood fluctuations, hyperactivity and erratic behavior. **Table 2** describes specific features that are helpful in differentiating between various conditions.

In a patient presenting with a depressive episode, does absence of a previous hypo/manic episode automatically exclude bipolar disorder?

It is important to bear in mind that if screening for previous history does not reveal hypo/manic episodes, does not necessarily mean that the patient has MDD. This is due to the fact that the majority (approximately 70%) of patients with bipolar disorder present with depression as the first mood episode[4] and may experience several depressive episodes as a part of the course of the illness before manifesting the first manic or hypomanic episode. In such patients, the presence of features such as family history of bipolar disorder; reverse vegetative symptoms such as sleeping too much or eating too much with carbohydrate craving; psychotic symptoms; post-partum onset or younger age at onset; episodic anxiety symptoms; or poor response or agitation with antidepressant medication, may suggest that the depressive episode is more likely part of a bipolar-related disorder than unipolar MDD.[5] This distinction has treatment implications as such patients may be at higher risk of hypo/manic switch with conventional antidepressant therapy. Therefore, if antidepressants are offered, patients should be counselled about these risks and advised to self-monitor for emergence of hypo/manic symptoms and seek help urgently. In addition, patients should be offered the choice of utilizing treatments with proven effectiveness for both bipolar depression and MDD, such as quetiapine.

Role of primary care physicians in the management of bipolar disorder

When to refer

Patients with bipolar disorder are at significantly increased risk of suicide, particularly during depressive episodes or when mood episodes are associated with mixed features.[6] Therefore, every patient with bipolar depression must be assessed for suicide risk and if there are concerns for patient safety, they should be referred to hospital emergency departments (EDs) for further evaluation and possible admission for in-patient care. Similarly, while patients with hypomanic or mild manic episode can be managed on an out-patient basis, the majority of patients with an acute manic episode, particularly those with psychotic symptoms or aggressive behaviour, will require in-patient care for stabilization. They may need to be referred to the hospital ED under the Mental Health Act if they refuse to seek help on a voluntary basis. If needed, atypical antipsychotics such as quetiapine (50 mg to 300 mg), olanzapine (5 to 10 mg), asenapine (10 to 15 mg sublingually) or risperidone (2 mg) can be administered in primary care offices to control agitation and calm the patient in order to facilitate assessment and referral to the ED for further evaluation and treatment.

Both psychiatric and substance use comorbidities are common in individuals with bipolar disorder. These frequently present diagnostic challenges which may warrant referral to a psychiatric consultation for diagnostic clarification. Other situations that might warrant referral include seeking advice on treatment options for: 1. Patients who are not responding to adequate trials with recommended first- and second-line agents; 2. Young women with bipolar disorder who are planning pregnancy; and 3. Patients who experience syndromal or sub-syndromal symptoms despite receiving maintenance therapy.

Treatment options for managing bipolar disorder

Several treatment strategies are available for managing patients with bipolar disorder.[7,8,9] These are described in **Table 3**. These recommendations are excerpted from the Canadian Network for Mood and Anxiety Treatments/ International Society for Bipolar Disorders Guidelines; the list has been modified to incorporate recent evidence that has emerged since the publication of these guidelines.

These recommendations are organized in a hierarchical fashion taking into account the evidence for the efficacy of an agent for the phase being treated; the efficacy of the agent for other phases of bipolar disorder; and the adverse event profile of agents.[7] The treatment algorithm for bipolar depression above indicates that quetiapine should be initiated prior to considering cariprazine. The rationale for this is that both quetiapine and cariprazine have demonstrated efficacy for the treatment of acute bipolar depression and acute mania; however, quetiapine has also demonstrated efficacy in preventing both mania and depression, but no data are available for cariprazine. Therefore, the management guidance is that treatment listed higher in the hierarchy for each phase should be initiated prior to progressing to the next treatment. The exceptions to this are: If specific clinical features of the mood episode; patient preference regarding the adverse event profile of a particular medication; or previous patient or family history of response or non-response to medications dictate alternative choices. Thus, if a patient is presenting for support with a bipolar depressive episode, quetiapine should be initiated prior to considering cariprazine or other treatment options listed in the hierarchy below.

The adverse events profile of psychotropic medications include: metabolic syndrome; effects on kidney, liver, thyroid and heart rhythm; hence, a medical review of systems, and laboratory evaluation that includes routine blood counts, liver function tests, thyroid-stimulating hormone, fasting blood sugar, lipid profile, blood urea nitrogen and estimated glomerular filtration rate should be performed before commencing treatment. Patients should be counselled regarding the adverse event profile of medications and the importance of treatment adherence prior to prescribing medications. Medical trials should be initiated utilizing adequate doses of each agent. In the absence of even a 20% improvement following a 2-week trial, the reasons for lack of response, which may include poor treatment adherence, ineffectiveness of the agent, comorbidities or contribution of other factors, must be explored. If a trial with a second agent also fails to elicit response, it might be reasonable to seek a second opinion from psychiatric consultation.

If lithium or divalproex is used for managing bipolar disorder, serum levels should be measured following approximately 5 days of reaching the target dose in order to monitor trough serum levels. Typically these are measured at approximately 12 hours following the last dose. Lithium levels should be maintained at between 0.6 and 1 mE/L, and valproate levels at between 350-700 mMol/L. If the levels fall outside this range, the doses should be adjusted accordingly. Valproate should be avoided in younger women because of the risk of polycystic ovary syndrome and higher teratogenic risk. If patients are receiving maintenance treatment with mood

Acute Bipolar Depression	Acute Manic Episode	Maintenance Treatment
First Line • Quetiapine • Cariprazine • Lurasidone + lithium or divalproex • Lithium • Lamotrigine • Lurasidone • Lumateperone • Lamotrigine adjunctive therapy	First Line • Lithium • Quetiapine with or without MS • Divalproex • Asenapine with or without MS • Aripiprazole with or without MS • Paliperidone (>6 mg) • Risperidone with or without MS • Cariprazine	First Line • Lithium • Quetiapine with or without MS • Divalproex • Lamotrigine • Asenapine • Aripiprazole with or without MS • Aripiprazole once- monthly
Second Line • Divalproex • SSRI/bupropion adjunctive therapy • ECT • Olanzapine + fluoxetine combination	Second Line • Olanzapine • Carbamazepine • Olanzapine with MS • Lithium plus divalproex • Ziprasidone • Haloperidol • ECT	Second Line • Olanzapine • Risperidone long-acting injectable with or without MS • Carbamazepine • Paliperidone (>6 mg) • Lurasidone with MS • Ziprasidone with MS

Table 3. First- and second-line treatments for mania, depression; maintenance treatment of bipolar disorders ; courtesy of Lakshmi N. Yatham, MBBS, FRCPC, MRCPsych (UK), MBA (Exec)

stabilizers, they should be asked routinely about adverse events including weight gain, polyuria and polydipsia, cold intolerance, and hair loss during follow-up visits. Serum levels should be monitored at approximately 6- 12–month intervals, along with additional laboratory assessments as appropriate. If lamotrigine is used, patients must be counselled on the risk of skin rash and Steven Johnson syndrome, and must be asked to routinely monitor for skin rash and report if they notice the occurrence of this. If atypical antipsychotics are used for acute or maintenance treatment of bipolar disorder, serum level monitoring is not required. However, patients must be monitored for the emergence of adverse events related to the specific tolerability profile of each of the agents. Psychoeducation is effective in reducing relapse in patients with bipolar disorder, and patients may be referred to psychoeducation groups if they are available.

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Dr. Stephen Glazer holds certification in Internal Medicine and Intensive Care Medicine from the University of Toronto in Ontario. He is also certified as a specialist in Sleep Medicine through the College of Physicians and Surgeons of Ontario. He has a strong interest in perioperative risk assessment.

Dr. Glazer is both a provincial and a national leader in Bariatric Medicine. In 2010, Dr. Glazer became the Medical Director for both the Bariatric Surgical and Medical Program at Humber River Hospital, a dedicated center of excellence for the management of Obesity in Ontario. He is an active board member of the Ontario Bariatric Network, sitting on numerous subcommittees, including being the Vice-Chair of the OBN Medical Program Task Force. He is involved in establishing the standards of care for patients in Ontario participating in both surgical and medical approaches for weight loss. In 2012, he was among one of the first Canadian physicians who successfully completed the American Board of Obesity Medicine (ABOM) Certification examination and is a diplomat of the ABOM.

In 2019, Dr Glazer became the President of the Canadian Association of Bariatric Physicians and Surgeons (CABPS), an national organization representing Canadian specialists interested in the treatment of obesity for the purposes of maintenance and improvement for the standards of Bariatric care in Canada, supporting both primary and continuing educational programs, knowledge, research and developing policies and new ideas in the areas of clinical care, education, and research in Bariatric Medicine and Surgery.

Dr Glazer participates in multiple clinical research projects and publications. He is the author of the Pre-Operative Management for Bariatric Surgery chapter for the 2020 Canadian Obesity Clinical Practice Guidelines. His greatest enjoyment is teaching and interreacting with other health care providers via lecturing at conferences or other educational venues. His enthusiasm and passion for the field of Obesity Medicine and the care of patients living with obesity is blatantly obvious and he hopes infectious to others.

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THE MANAGEMENT OF OBESITY IN 2023: AN UPDATE

Prevalence of obesity

In 2015, obesity was declared by the Canadian Medical Association (CMA) and other global health organizations (World Health Organization [WHO], World Obesity Federation and the American Medical Association [AMA]) to be a chronic, relapsing and remitting disease caused by the deposition of adipose tissue in organ systems within the body leading to dysfunction and adverse health outcomes. Obesity should be medically addressed no differently than other chronic illnesses such as diabetes, hypertension or coronary artery disease.

The incidence of obesity has risen dramatically over the past 30 years and it is currently estimated to affect 13% or 650 million individuals greater than 18 years of age worldwide.[1-3] In 2021, there were more than 8.2 million (29.2%) adult Canadians living with obesity (BMI >30), and more than 10 million (35.5%) of Canadians were classified as overweight (BMI >25).[4] In 2017, 30% of children between ages 5 and 17 were either overweight or obese.[5] The prevalence of obesity in 2015-2016 was highest in the Atlantic provinces and lowest in Quebec and British Columbia.[6] Data from the past 10 years indicates that the prevalence of obesity in adults and children may have stabilized.[7-9] Obesity is one of the largest contributors to adverse health outcomes; additionally, it is a global public health and financial challenge, accounting for approximately $7.1 billion annual direct and indirect costs in Canada.[10,11] The World Obesity Federation has predicted that by the year 2030, 1 in 5 women and 1 in 7 men, or 1 billion individuals globally, will be living with obesity.[12]

Risk factors

There are modifiable and nonmodifiable factors involved in body weight regulation. Genetic determinants play a significant role in determining body weight, especially at higher BMIs. Genetic abnormalities in the hypothalamus leptin-melanocortin pathway, as well as single genetic mutations, can occur, as well as variations in several genes which may predispose an individual to obesity. Physiologic pathways of the neuroendocrine system involved in hunger, satiety, reward and executive function also play a significant role in weight regulation. Behavioural, environmental and other factors including the microbiome and weight-promoting medications also play a role in increased weight.[13,14]

The presence of abnormal or excessive adiposity contributes to several diseases leading to increased morbidity and mortality. Obesity is a major contributor to cardiovascular disease (CVD),diabetes and metabolic syndrome. Sixty-six percent of hypertension is linked to excess body weight, and obesity accounts for 80%-85% of the overall risk of developing diabetes. Obstructive sleep apnea; musculoskeletal conditions such as osteoarthritis; venous stasis dermatitis; gout; recurrent skin infections; polycystic ovary syndrome (PCOS); menstrual irregularities; male and female infertility; and neurologic abnormalities including benign intracranial hypertension, stroke and dementia/ cognitive dysfunction are associated with obesity. In addition, depression, anxiety and eating disorders may be linked with obesity. Forty percent of all patients with nonalcoholic fatty liver disease (NAFLD) are obese, and there is a 3- to 7-fold increased risk of gallbladder disease in individuals with BMIs >32 kg/m^2 to 45 kg/m^2. Approximately 20% of all malignancies (esophageal, kidney, pancreas, colon, postmenopausal breast, endometrial) are linked to obesity unrelated to diet, and contribute to approximately 10% of all cancer deaths in non-smoking individuals.[15-22] Obesity may be responsible for decreasing life expectancy by as many as 14 years as a result of premature death from CVD or malignancy.[23,24] Minimal weight loss of 5%-10% may be associated with improvement of obesity-related comorbidities including diabetes; hypertension; hyperlipidemia; hepatic steatosis and inflammation; sleep apnea; arthritis; urinary stress incontinence; gastroesophageal reflux disease; and hormonal irregularities associated with PCOS.[25]

Pharmacologic Treatment Modalities

It is necessary for all individuals, regardless of their body size or weight, to adopt healthy eating patterns. The evidence-based approach of medical nutritional therapy should be utilized where nutritional requirements are determined which encourage overall health, promoting eating behaviours that are sustainable and realistic. This will enable the individual to achieve a risk reduction for chronic disease. Short-term weight loss over 12 months or less may be achieved through caloric restriction; however, long-term weight loss may not be sustainable due to the body's neurobiological compensatory mechanisms involved in the regulation of eating behaviours and body weight. A thorough evaluation for micronutrient deficiencies and nutritional status should be undertaken for each patient.[26] In conjunction with healthy eating, moderate to vigorous physical activity for at least 150 minutes per week is recommended. In addition, resistance training at least twice weekly

is encouraged for weight maintenance, along with a moderate increase in mobility to promote muscle mass.[27] Interventions including behaviour modification, cognitive therapy and valued-based strategies aimed at improving nutrition and activity are additional essential components for weight management.[28]

As part of a comprehensive, long-term approach to the treatment of obesity, four pharmacologic agents are approved in Canada for achieving weight loss and weight maintenance. The use of medication should be considered in conjunction with healthy behavioural changes and increased activity as described above. The use of pharmacotherapy may be indicated in individuals with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 in individuals with obesity-related complications. These include hypertension, type 2 diabetes (T2D), hyperlipidemia and obstructive sleep apnea. The use of obesity medications should be considered early in the course of management. Following three months of pharmacologic therapy, if a weight loss of ≥ 5% is not achieved, the medication should be discontinued.

Orlistat 120 mg TID is a derivative of lipstatin. Its mechanism of action is inhibition of lipase, the enzyme that aids in the gastrointestinal (GI) absorption of fat contained in the human diet. This medication has no effect on appetite suppression or satiety. Published data from randomized, controlled trials has demonstrated a net weight loss (placebo subtracted) of 2.9% with orlistat vs low-fat and low-calorie control patients at one year.[29] Fifty-four percent of patients achieved ≥ 5% weight loss and 26% achieved ≥10% weight loss. Orlistat is associated with significant GI side effects including diarrhea, flatulence, and steatorrhea, and has had limited use as a therapeutic agent due to intolerance.

Liraglutide 3 mg injected subcutaneously once daily is a glucagon-like peptide-1 (GLP-1) receptor agonist. As an anti-obesity medication, its effects include central nervous system (CNS) actions resulting in increased satiety and decreased hunger while decreasing gastric emptying. In nondiabetic or prediabetic individuals, clinical trial results demonstrated that liraglutide achieved a net weight loss of 5.4% after one year with ≥ 5% net weight loss in 36.1% and ≥ 10% net weight loss in 22.5% of subjects.[30] Prediabetic patients followed for three years experienced net weight loss of 4.2% with liraglutide, and a 2.7-fold delay in the progression of prediabetes to diabetes.[31] Nausea is the most frequent side effect associated with this medication. In addition, constipation or diarrhea, vomiting, acid reflux and headache can occur. In addition, a slightly increased risk of cholelithiasis and pancreatitis may occur.[32] Liraglutide is contraindicated for patients with a history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type II.

Naltrexone/bupropion 16 mg/180 mg BID consists of an opioid receptor antagonist utilized to treat alcohol and opioid addiction, and a dopamine and norepinephrine reuptake inhibitor. Bupropion works centrally by increasing the production of alpha-melanocyte stimulating hormone (alpha-MSH) and beta endorphin in the hypothalamus. Naltrexone blocks the reuptake of alpha MSH. In addition, cravings are reduced through its influence on the mesolimbic reward system.[33] After one year, a randomized, controlled trial demonstrated a 4.8% net weight loss. Thirty two percent of patients had ≥5% net weight loss and 18% had ≥10% net weight loss.[34] Side effects include nausea, headache, constipation or diarrhea, sleep disturbances, and dizziness. Naltrexone/bupropion is contraindicated in patients with poorly controlled hypertension, opioid use, seizure disorders, and anorexia or bulimia. Caution should be used with any medications that lower seizure threshold or medications metabolized by the hepatic CYP2D6 enzyme system. Increased absorption of this medication occurs with high-fat meals; therefore, high-fat meals should be avoided while taking naltrexone/bupropion.[35]

Semaglutide 2.4 mg is administered weekly and is a newly- approved, centrally acting GLP-1 analog with similar activity as that of once-daily liraglutide: decreasing hunger and cravings, as well as promoting satiety.[36] In a clinical trial, semaglutide 2.4 mg demonstrated 12.5% net weight loss over 68 weeks of therapy. There was a ≥ 15% decrease in body weight in more than 50% of all study subjects vs 5.0 % with placebo.[37] The side effects and contraindications of semaglutide were similar to those of liraglutide. Trials demonstate that withdrawal of this or other anti-obesity medications is associated with significant weight regain, further emphasizing that obesity is a chronic and relapsing disease requiring long-term treatment.[38]

Therapeutic agents utilizing state-of-the-art knowledge of the control of weight and obesity are in development. Tirzepatide, a novel once weekly combined gastric inhibitory peptide (GIP) and GLP-1 receptor agonist, demonstrated in adults with obesity or overweight taking 5 mg, 10 mg, or 15 mg respectively, an average weight loss of 15.0%, 19.5%, and 20.9% compared to 3.1% in those taking placebo.[39] This medication presently is not available in Canada but will be an additional pharmacologic option.

Future potential therapeutic candidates may focus on targeted areas including leptin, ghrelin, mitochondrial uncouplers, and growth differentiation factor 15. A more advanced understanding of the incretin system, in particular GLP-1, gastric inhibitory peptide (GIP), and amylin activating the GLP-1 receptor and/or GIP receptor, is necessary. Leptin sensitizers and glucagon agonists also remain a focus in the development of anti-obesity medications.

Surgical treatment modalities

Bariatric/metabolic surgery remains an option for adult patients with a BMI of ≥35 kg/m^2 and obesity-related diseases (T2D; hypertension; cardiac disease; intractable gastroesophageal reflux disease; pseudotumour cerebri; and obstructive sleep apnea), or those with a BMI ≥40 kg/m2. Recent guidelines have recommended metabolic/bariatric surgery for individuals with a BMI ≥30 kg/m^2.[40] Contraindications to bariatric surgery include malignancy associated with a poor life expectancy; active and unstable psychiatric illness; alcohol and drug abuse; impaired cognitive function resulting in the inability to adhere to the behavioural changes necessary for optimization of bariatric surgery; and tobacco smoking. In the Asian population, bariatric/metabolic surgery should be considered for individuals with a BMI ≥27 kg/m^2 as diabetes and CVD occur at lower BMIs. While advanced age is not a contraindication to surgery, a thorough preoperative evaluation, including an assessment for frailty, which is independently associated with a higher occurrence of postoperative complications, should be undertaken.[41] The overall mortality rate from bariatric surgery is 0.01%.

In Canada, the most commonly performed bariatric surgery is Roux-en-Y gastric bypass (RYGB) where a small gastric pouch is created and the duodenum and proximal jejunum are bypassed. With this procedure, there is a decrease in the hunger-promoting hormone ghrelin and an increase in the satiety-promoting hormones PYY, GLP-1 and CCK. This procedure is associated with 65%-80% excess body weight reduction at 1-2 years. It is also associated with vitamin and mineral deficiencies requiring lifelong supplementation.

Vertical sleeve gastrectomy (SG) involves the removal of 75%-80% of the gastric fundus resulting in hormonal changes involving a reduction of ghrelin and leptin. It is associated with 55%-60% excess body weight reduction 1-2 years postoperatively. Vitamin and mineral absorption attributed to loss of a significant portion of the stomach may occur with this procedure, as well as reflux symptoms.

The most aggressive weight loss procedure is the biliopancreatic diversion with duodenal switch (BPD/DS) involving a sleeve gastrectomy along with a biliary pancreatic limb which joins the alimentary limb in a common channel approximately 75 -150 cm proximal to the ileocecal valve. The average weight loss with a BPD/DS is approximately 80% of excess body weight at 2 years and has a more sustained weight loss of 71% over 20 years. The 20-year rate of remission of diabetes after BPD/DS is 93.4%.[42] In diabetic patients specifically requiring insulin preoperatively, there is complete remission of diabetes 10 years postoperatively in 68.1% with 97% discontinuing insulin.[43] Another option for more aggressive weight loss is the single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) where the ileum is attached to the duodenum 250-300 cm proximal to the ileocecal valve. SADI-S is associated with less fat and nutrient deficiencies compared with BPD/DS. Weight loss and resolution of diabetes was superior with SADI-S compared with RYGB and SG.[44]

The adjustable gastric band has been associated with significant postoperative complications and has a high failure rate. Therefore, it is not recommended as a weight loss surgical intervention.[45]

Bariatric surgery is associated with improvement in quality of life; 40% decreased all-cause mortality; a 56% decrease in death rates from coronary artery disease (CAD); a 60% lower cancer mortality rate; and a 92% decrease in death rates associated with diabetes. In addition, obesity-related conditions such as hyperlipidemia; hypertension; adiposity-related liver disease; musculoskeletal pain; and sleep apnea significantly improve following bariatric surgery.[46] Remission of diabetes at 3 and 5 years respectively occurs in 75% and 37% following RYGB and 37% and 23% following SG.[47-48] In the prospective, controlled Swedish Obese Subjects study examining 4,000 patients who underwent bariatric surgery, weight loss after 10 years decreased by 25% following gastric bypass and 16% following SG vs their presurgical baseline weight.[49]

Conclusion

Obesity is a complex, chronic, relapsing disease. Many modifiable and nonmodifiable factors are involved in body weight regulation. The presence of abnormal or excessive adiposity contributes to organ dysfunction resulting in significant morbidity and mortality. In conjunction with assessment and modifications to nutrition and physical activity, behavioural interventions, pharmacotherapy and surgical interventions may be considered.

	Orlistat	Liraglutide	Naltrexone/Bupropion	Semaglutide
Mode of administration	Oral	Subcutaneous	Oral	Subcutaneous
Dose/frequency	120 mg TID	3.0 mg daily	16/180 mg BID	2.4 mg weekly
Effect on % weight loss at 1 year, placebo subtracted	-2.9%[28]	-5.4%[2]	-4.8%[5]	-12.5%[1]
Effect on weight over longer term, placebo subtracted	-2.8 kg at 4 years[8]	-4.2% at 3 years[3]	Not studied	Not available
% of patients achieving ≥ 5% weight loss at 1 year	54% (vs. 33% in placebo)[28]	63.2% (vs. 27.1% in placebo)[2]	48% (vs. 16% in placebo)[5]	86.4% (vs. 31.5% in placebo)[1]
% of patients achieving ≥ 10% weight loss at 1 year	26% (vs. 14% in placebo)[28]	33.1% (vs. 10.6% in placebo)[2]	25% (vs. 7% in placebo)[5]	69.1% (vs. 12% in placebo)[1]
% of patients achieving ≥ 15% weight loss at 1 year	Not studied	14.4% (vs. 3.5% with placebo)[3]	13.5% (vs. 2.4% with placebo)[36]	50.5% (vs. 4.9% with placebo)[1]
Effect on maintenance of previous lifestyle-induced weight loss	2.4 kg less weight regain vs. placebo over 3 years[7]	-6.0% additional placebo-subtracted weight loss at 1 year[4]	Not studied	Not studied
Contraindications	• Cholestasis • Chronic malabsorption syndrome • Pregnancy, attempting conception, breastfeeding	Personal or family history of medullary thyroid cancer Personal history of MEN2 syndrome Pregnancy, attempting conception, breastfeeding	Uncontrolled hypertension Any opioid use History of, or risk factors for, seizure Abrupt discontinuation of alcohol Concomitant administration of monoamine oxidase inhibitors Severe hepatic impairment End-stage renal failure Pregnancy, attempting conception, breastfeeding	Personal or family history of medullary thyroid cancer Personal history of MEN2 syndrome Pregnancy, attempting conception, breastfeeding
Common side effects	Loose, oily stools, flatus	Nausea, constipation, diarrhea, vomiting	Nausea, constipation, headache, dry mouth, dizziness, diarrhea	Nausea, diarrhea, constipation, vomiting
Medication interactions	• Fat-soluble vitamins • Levothyroxine • Cyclosporine • Oral anti-coagulants • Anti-convulsants	May affect absorption of medications due to slowing of gastric emptying	Yes: See chapter text	May affect absorption of medications due to possible slowing of gastric emptying

Table 1. Pharmacotherapy for Obesity; adapted from Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy for Obesity Management, 2022

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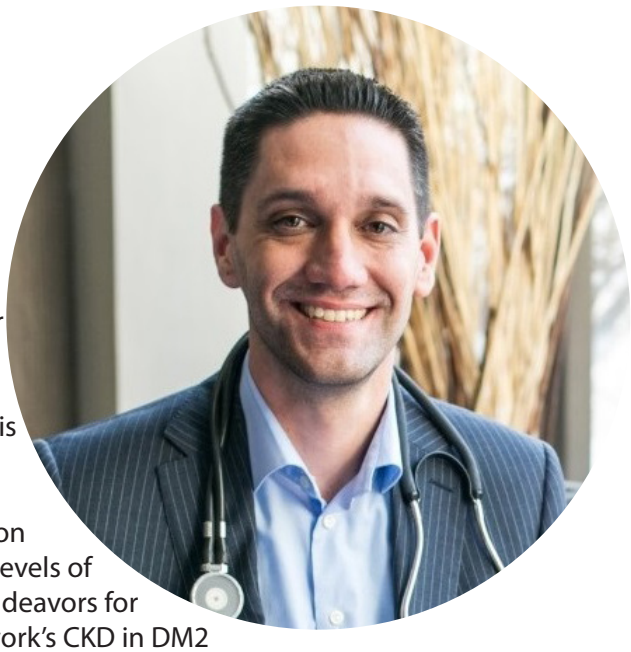

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MODERN MANAGEMENT OF CHRONIC KIDNEY DISEASE IN T2DM: A PRACTICAL OVERVIEW FOR PRIMARY CARE PROVIDERS

Introduction

The development of chronic kidney disease (CKD) in patients with T2DM (CKD in T2DM) is a common and major comorbidity. Not only is it associated with progressive kidney disease and end-stage kidney disease (ESKD), it is also associated with very high risk for major adverse cardiovascular events (MACE) and heart failure (HF) events.[1,2] CKD in T2DM is extremely costly from a health economic perspective; however, most importantly, it results in significant reductions in patient quality of life and survival.[3] For several decades, there has been a lack of new therapeutic options to address residual cardiorenal risk. The traditional pillars of therapy include glycemic control with a HbA1C target of 6.5%, blood pressure control with a blood pressure target of less than 130 mmHg, and the use of renin angiotensin aldosterone inhibitors (RAASi).[4] Recently, several options have emerged that can address residual kidney and cardiovascular risk in these patients, thereby providing organ protection. Importantly, these therapies are grounded in the foundation of solid randomized, controlled clinical trials and are now prevalent in the guidelines that inform the management of CKD in T2DM.[4,5] The novel pillars for kidney and cardiovascular protection include sodium glucose luminal transported 2 inhibitors (SGLT2i) and finerenone, a non-steroidal mineralocorticoid receptor antagonist (nsMRA).[4,5] This article highlights practical considerations of these pillars for primary care providers with a focus on kidney protection.

Glycemic Management

Tight glycemic control has been shown to reduce the progression of microvascular complications and, in particular, diabetic nephropathy (DN).[6] In certain long-term outcome studies of DN, tight glycemic control has also been shown to reduce ESKD.[6] Glycemic control targets, typically supporting a HbA1C target of 6.5% for reduction in the progression of nephropathy, continue to form a central pillar of the major diabetes guidelines.[4] It is important to note that in the earlier studies of tight glycemic control, the benefits were offset by the risk of hypoglycemia.[6] However, tight glycemic control may not carry the same risk with modern therapies, as many of these carry a much lower risk of hypoglycemia.[7]

SGLT2i's are effective agents in reducing blood glucose in patients with estimated glomerular filtration rates (eGFR) > 60 mL/min. Additional benefits include modest blood pressure reduction (3-4 mmHg) and modest weight loss (1.5-2.0 kg). It is important to note that the site of action of SGLT2i is in the proximal tubular lumen of the nephrons and delivery to this site is dependent on kidney filtration. As a practical consideration, because their mechanism of action is dependent on kidney filtration, the efficacy of SGLT2i blood glucose lowering diminishes with diminishing eGFR. In patients with an eGFR > 60 mL/min, an HbA1C reduction of approximately 0.8% is expected. When the eGFR declines below 45 mL/min, reductions of 0.25% or less have been demonstrated. Interestingly, the organ-protective properties of these agents remain, despite the loss of glycemic lowering efficacy.[8-10]

While glucagon like peptide 1 receptor agonists (GLP-1RA) are not thoroughly reviewed in this article, as they have not yet been shown to demonstrate hard kidney outcome reduction, they are agents to prioritize in this group of patients for several reasons.[5] GLP-1RA are extremely effective anti-hyperglycemic therapies. Additionally, they have a significant impact on weight loss (5%-10% of body weight), they do not require dose adjustment in patients with CKD, and they reduce MACE in this group of patients.[11]

Renin Angiotensin Aldosterone Inhibitor (RAASi) Agents for CKD in T2DM

To place the effect of SGLT2i's in context, reviewing the comparative effect of standard of care agents is a useful exercise. Prior to the emergence of SGLT2i's, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) represented the stand of care in CKD in T2DM and in non-diabetic albuminuric CKD.[4,5] Randomized trial data in these patient populations demonstrate an expected GFR protection of 0.75-1.0 mL/min/year. The outcome of reduction of progression of kidney function decline by 0.75 mL/min/year is a recognized benchmark that serves as a surrogate for predicting a reduction in ESKD.[12,13] ACEi's and ARBs remain a pillar of care in patients with albuminuric CKD.[4,5]

SGLT2i's: Kidney Outcomes for CKD in T2DM

Three landmark primary kidney outcome trials have been conducted on the SGLT2i's that are pertinent to medications that can be accessed in Canada. It is important to note that in these three trials, patients were required to be on an ACEi or ARB (unless intolerant or contraindicated) and this resulted in 97% or greater utilization of these medications. Ten additional randomized trials have been conducted in which kidney outcomes were reported as secondary outcomes. A meta-analysis of these trials reveals a relative risk reduction in the composite outcome of kidney disease progression (> 50% decline in eGFR, ESKD or renal death) of 38% (RR 0.62; 0.56-0.68) in favour of SGLT2i use for patients with T2DM.14 Due to their mechanism of action, an initial decline in eGFR of up to 30% is expected; this should not be a cause for concern.[15] From a safety perspective, the meta-analysis demonstrated a 21% (HR 0.79; 0.72-0.88) relative risk reduction in the incidence of acute kidney injury (AKI), demonstrating a protective effect of SGLT2i's for this outcome. Ketoacidosis was a rare event in patients with T2DM but does occur more frequently (HR 2.19; 1.49-3.04). In addition, lower limb amputation occurred more frequently in patients on an SGLT2i (HR 1.15; 1.02-1.30); however, this was driven by the results of one cardiovascular outcome trial (CVOT) and was not seen in the other trials.[14] There is an increased risk of genital mycotic infections (GMI) in patients with T2DM who receive treatment with an SGLT2i.[14]

GFR slope has become an important outcome in clinical trials. It is a measure of decline in GFR over the course of a year. It is assumed that by slowing the rate of decline in GFR, the hard outcome of ESKD will be delayed.[16] When examining the outcome of GFR slope, the CREDENCE trial, which included solely patients with T2DM, demonstrated a 2.74 mL/min/year benefit of canagliflozin vs ACEi or ARB alone.[8] Similarly, the DAPA-CKD trial, which included patients with and without T2DM, demonstrated a 1.92 mL/min/year protection in favour of dapagliflozin.[9] In the most recent primary kidney trial, EMPA-KIDNEY enrolled patients with and without T2DM. Patients with an eGFR of 20-45 mL/min did not require albuminuria to be enrolled in the trial, which was a requirement in the other two trials. In this trial, there was a 1.37 mL/min/year slope difference in favour of empagliflozin. Based on trial data, an SGLT2i can be initiated at an eGFR > 20 mL/min and continued until the patient develops ESKD or another contraindication.[10] The above data clearly establish SGLT2i's as a standard of care for kidney protection in patients with CKD in T2DM.[5]

SGLT2i's: Additional Outcomes for CKD in T2DM

Patients with CKD in T2DM are at high risk of MACE, HF events and mortality. In the meta-analysis discussed above, SGLT2i's were associated with a 23% reduction in the combined outcome of CV death or hospitalization for HF (HHF [hypertensive heart failure] HR 0.77; 0.73-0.81) and a reduction in CV death alone (HR 0.86; 0.80-0.92). Furthermore, a 12% reduction in all-cause mortality was reported (HR 0.88; 0.84-.93).[14] Although it is beyond the scope of this paper, significant benefits have also been shown in reductions in HF events in patients with and without established HF.

SGLT2i's: Non-diabetic CKD

Patients with non-diabetic CKD have been studied in some of the primary kidney trials and in other trials, such as those investigating HF. When comparing the sub-analysis from these trials of patients with and without T2DM, the beneficial kidney outcomes are seen in both groups and statistically, the positive outcome results are the same as positive outcome results of the overall trial. Meta-analysis demonstrates a 31% relative risk reduction in the primary kidney outcome (HR 0.69; 0.57-0.82) with a similar 34% reduction in AKI (HR 0.66; 0.54-0.61). From a CV perspective in patients without T2DM, similar benefits were seen in the reduction of the composite outcome of CV death or HHF and CV death alone, as in patients with T2DM. The safety profile is favourable for SGLT2i's in patients with T2DM and appears to be even more favourable in those without T2DM. There are no concerns over limb amputation, hypoglycemia, ketoacidosis, or GMI. This data establishes SGLT2i's as a new standard of care in patients without T2DM, particularly for those with albuminuria.[14,17] GFR slope analysis from the EMPA-KIDNEY trial also demonstrates benefit in patients with normoalbuminuria and an eGFR of 20-45 mL/min; however, this is a lower risk group with a higher number needed to treat (NNT).[10]

Finerenone: Outcomes for CKD in T2DM

The newest guideline-based pillar for kidney protection is finerenone.[5] It is important to understand that this is a novel class of medications known as nsMRA and should not be viewed as interchangeable with steroidal MRAs. Finerenone has been studied in two large randomized, controlled trials (FIGARO and FIDELIO) which were designed to be studied together. The pooled analysis of these two trials is FIDELITY which represents 13,026 patients with T2DM, a GFR > 25 mL/min and optimized RAASi. Patients with a potassium of 4.8 mEq/L or less were eligible, while on optimal RAASi therapy. When compared with placebo, finerenone demonstrated a 23% reduction (HR 0.77; 0.67-0.86) in the primary composite kidney outcome and a 20% reduction (HR 0.80; 0.64-0.99) in ESKD alone. Additionally, there was significant 14% reduction in MACE in favour of finerenone (HR 0.86; 0.78-0.95). There was also a reduction in HHF; however, formal phase 3 trials in patients with established HF have yet to be completed. Finerenone was also safe with the main consideration being a small, but higher rate of discontinuation due to hyperkalemia compared with placebo (1.7% vs 0.6%).[18] Therefore, this represents a novel, guideline-based organ protective therapy that primary care providers should add to their therapeutic armamentarium.[5]

Conclusion

SGLT2i's are a foundational therapy in the reduction and prevention of kidney disease, as well as CV outcomes in patients with and without T2DM.The medical community needs to broadly implement this class of medication at their organ-protective dose in patients with CKD, as has occurred with statins in the past. There is no other singular class of CKD medication that has been shown to have comparable efficacy in so many domains. Additionally, these medications are safe, with the adverse events in patients with T2DM being predictable, and almost non-existent in those without T2DM. Access to these medication remains disparate across Canada. It is incumbent on public payors to facilitate broad access to SGLT2i's. A recent Canadian study suggests that when accounting for kidney outcomes, SGLT2i's are also beneficial from a health economics perspective.[19] Finerenone has been approved in Canada. It has demonstrated extremely robust kidney and CV protection data in patients with CKD in T2DM. These classes of medications, including GLP-1RA, should be used systematically and in combination by primary care providers to optimally address residual organ risk in patients with CKD in T2DM.

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