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THE DOSE

Thames Valley Family Health Team's Drug Information Newsletter

Thames Valley Family Health Team

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BEDMED: Does time of day matter for antihypertensives?

Bottom line: In primary care, there is **no major outcome difference** in taking antihypertensives in the morning or at bedtime. **Patients should choose a time of day that best suits their schedule**.[1]

New research study: A randomized, pragmatic trial of 3357 Canadian patients with hypertension tested whether morning or bedtime administration of antihypertensives had any difference on cardiovascular outcomes.[1]

Primary outcome: Time to occurrence of a composite of death and major cardiovascular (CV) events.

Findings align with newer trials.[2] The design and methods of older studies that recommended HS dosing (i.e. Hygia) are under scrutiny.[2]

Methods: Patients took all once-daily antihypertensives either in the morning or bedtime, including diuretics. Dosing of BID antihypertensives was unchanged.

Results: Participants were 56% female, median age 67, 18% with diabetes, 11% with coronary artery disease, 7% with chronic kidney disease. Most common antihypertensives: ACEI, ARB, CCB, and diuretics. Follow up time was 4.6 years. Overnight BP was lower in the bedtime group (117/63 mmHg vs. 124/66 mmHg).[1]

No significant differences were found in the primary endpoint (death or major CV events [adjusted hazard ratio, 0.96; 95% CI, 0.77-1.19]), nor in any safety outcomes.[1]

Check out The Dose August 2025, page 3 for an overview of new recommendations in the 2025 Hypertension Canada primary care.

Important update: RSV program now includes adults 75+

Ontario's public RSV immunization program[3] now includes:

- **NEW in fall 2025: All adults 75 years and older**
- High-risk adults 60 to 74 years old, such as LTC and retirement home residents
- Infants up to 8 months old during their first RSV season
- Pregnant people prior to childbirth if the infant cannot be vaccinated or under certain circumstances
- High-risk children up to 24 months old during their first RSV season

RSV trials were underpowered to detect efficacy in adults aged 75+, but most deaths from RSV in Ontario occur in those aged 60+.[4,5]

See The Dose Fall 2024, page 2 for a summary of efficacy and safety data for RSV vaccines.

Pharmacies CANNOT provide RSV vaccines under the publicly funded program. Only private paying patients with a prescription can be immunized at pharmacies.

Click here to see full eligibility details for high-risk adults and infants. The immunization program continues to use the Abrysvo and Arexvy products for the 2025-2026 season.

In this issue:

All bark and no bite: evidence for inhalers in acute cough

This applies to **patients without underlying respiratory conditions** (e.g. asthma, COPD, smoking history) recovering from an uncomplicated infectious cough. Cough caused by COVID-19 infection was not included in studies referenced below.

- Evidence and guidelines do not support routine use of inhalers or cough suppressants due to harms outweighing limited benefits.[6,7]
- **Best practice**: Educate patients on usual cough duration of 1-3 weeks and symptomatic management and provide a viral infection "prescription".

What is the evidence for inhalers in post-infectious cough?[6]

ICS shows no benefit on patient-reported outcomes[7,8]	No difference in patient outcomes (days off work, nocturnal awakenings) between placebo and beclomethasone. Placebo improved cough scores at two weeks by ~50%, and beclomethasone performed 5-10% more beyond placebo. No data on reduction of cough duration.
Ipratropium/albuterol not covered by ODB, evidence for reducing cough duration limited to nebulizer format only[9]	Nebulizer therapy is not often feasible or practical in primary care, and the evidence of benefit is limited to **nebulized** ipratropium/salbutamol: may resolve cough in more patients at day 10 than placebo (63% vs. 31%). The only ipratropium/albuterol inhaler (Combivent) costs $50 and is not covered by ODB.
Salbutamol does not reduce cough duration or severity in children or adults[10]	No different than placebo in reducing cough duration in children or adults at 7-day follow up and in reducing cough scores. Low quality evidence that adults with baseline wheezing or airflow obstruction may have reduced symptom severity, but not duration.

What is the evidence for cough suppressants in post-infectious cough?

While opioids and opioid derivatives may suppress cough frequency or severity, **there is no evidence for reduction in post-infectious cough duration**. Significant harms outweigh limited benefits.[11]

Evidence to support benefit	Potential harms
Dextromethorphan may reduce cough frequency and severity but **does not reduce duration** of acute cough.[12]	Do not use in children <6 years old due to risk of overdose.[13]
Codeine is **no better than placebo in reducing cough severity**. No evidence of reducing cough duration.[14]	CYP2D6 metabolite: Many interactions with common medications, increased risk of toxicity due to genetic differences in 2D6 metabolism.
Morphine **has not been studied** for acute cough.	See below
Hydrocodone **has no benefit** for acute cough.[15]	

Opioids can cause significant side effects even at low doses (constipation, GI upset, sedation, increased risk of falls in elderly, misuse, respiratory depression). Health Canada: Do not give opioid-containing cough and cold products to children <18 years old due to lack of efficacy and potential problematic use.[16]

Refresher on acute cough[17]

- The majority of acute bronchitis cases are viral, and antibiotics are therefore not recommended.
- >80% of patients **regardless of treatment** will have cough resolution by day 20.
- Acute uncomplicated bronchitis is self-limiting and usually persists for 1-3 weeks.
- Post-infectious or subacute cough lasts 3-8 weeks and occurs in 50% of viral cases.

Practice tool spotlight: Menopausal hormone therapy equivalency table, Canadian Menopause Society 2025[18]

While covering for a colleague, you receive a refill request for progesterone 200 mg HS for a 54-year-old female patient on an estradiol patch 75 mcg twice weekly. You are more familiar with micronized progesterone 100 mg HS dosing and are unsure why this patient is on a higher dose.

What is it? A dose equivalency resource based on expert consensus from members of the Canadian Menopause Society (CMS), evidence and guidelines where available.

What does it provide? Provides dose equivalencies for all systemic estrogen products and proportional progestogen doses needed for endometrial protection. Also includes helpful practice points including recommendations on estradiol levels (not needed) and monitoring on the document's second page.

When is it most helpful? To ensure that patients on systemic estrogen are on the appropriate progestogen dose, particularly useful with dose increases. Also helps in selecting a roughly equivalent product if patients must switch between dosage forms due to tolerability, cost or backorder.

How to access: **Freely available online, click here to access.**

Bottom line: Match a higher dose systemic estrogen with a proportionally higher dose progestogen to ensure adequate endometrial protection.

CANADIAN MENOPAUSE SOCIETY
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ODB coverage update: Slynd is covered

Slynd (drospirenone 4 mg tablets)[19,20]

A progestin-only contraceptive option that is **newly covered by ODB in 2024**, with a longer half-life than norethindrone (33 vs. 7.5 hours).[20]

Indication: Contraception in people with a possibility of pregnancy.

Dose: One tablet daily around the same time of day. Contains drospirenone 4 mg with a four-day hormone-free interval.

Missed doses: If **one pill is missed**, take two pills the next day at the regular time with **no need for back-up contraception**. If two or more pills are missed, take two pills the next day at the regular time with back-up contraception for the next 7 days.[19]

Vs. norethindrone missed dose protocol: If a pill is taken more than 3 hours late, take the next norethindrone pill immediately with back-up contraception for the next 48 hours.[21]

Contraindications: Pregnancy, renal impairment, adrenal insufficiency, personal history of cervical cancer or progestin sensitive cancers, liver tumours or hepatic impairment, and undiagnosed abnormal uterine bleeding.

Precautions: Potential for **hyperkalemia** in patients taking other drugs that may increase potassium (e.g. ACEI, ARB, spironolactone) – risk is comparable to a 25 mg dose of spironolactone. **Consider monitoring potassium in those at increased hyperkalemia risk.** Drug interactions with CYP3A4 inhibitors or inducers.[19]

Lactation: Suitable for lactation as negligible amounts are excreted in breast milk with no anticipated effects on infants.

Adverse effects: Hyperkalemia (see Precautions). Most common adverse reactions: acne (3.8%), abnormal bleeding (2.8%, 4.9% in adolescents), headache (2.7%) and breast pain (2.2%). Amenorrhea is possible within one year of starting. No major differences between BMI subgroups were observed.

Efficacy: Contraceptive efficacy rates of 97.5-99.3%. Effective in adolescents, patients with BMI <30 and with BMI ≥30 and patients >35 years old.[19]

Place in therapy: **More forgiving with missed or late doses** than norethindrone due to longer half-life. **Useful for patients with contraindications to estrogen therapy**, such as migraine with aura, VTE risk factors, postpartum or lactation.

Cost: $60-75/3 months supply. Covered by ODB with no LU code needed.

Rapid fire: quick updates for busy primary care providers

Diabetes Canada updated chronic kidney disease (CKD) guideline[22]

Link to guidelines. Highlights and practical tips:

Screening and diagnosis:

- Screen diabetic patients with no history of CKD **annually** with **BOTH** eGFR and random uACR (urinary albumin creatinine ratio)
- CKD is present if EITHER is true: **urinary ACR (uACR) is ≥2 mg/mmol** and/or eGFR <60 mL/min/1.73m^2 on repeat testing over 3 months.
- Assess eGFR and uACR in diabetic patients and CKD at least **annually**, and more frequently (every 3-6 months) if eGFR <60 mL/min/1.73m^2 or uACR >20 mg/mmol

Treatment – Four pillars of cardiorenal protection in diabetic kidney disease:

1. **Delay CKD progression**: Maximally tolerated **RAASi** (ACEI or ARB) for all adults with diabetes and CKD with hypertension or albuminuria.
2. **Delay CKD progression and ↓ CV events**: **SGLT2 inhibitor** for adults with type 2 diabetes and CKD.
3. **↓ renal events (driven by ↓ reduction in eGFR and ↓ CV death)**[23]: **GLP-1** (semaglutide) for adults with type 2 diabetic nephropathy and albuminuria.
4. **↓ composite renal and CV events**: **Non-steroidal mineralocorticoid antagonist** such as finerenone (LU 700) for adults with type 2 diabetic nephropathy.

Hyperkalemia: dietary intervention if mild (K+ <5.4 mmol/L), potassium binder if moderate (K+ 5.4-5.9 mmol/L), and hold RAASi and nsMRA and refer to ER if severe (K+ >6 mmol/L).

2025 Obesity Canada guidelines[24]

Link to guidelines.

The first update since 2006 highlights advancements in epidemiology, pathophysiology, assessment, prevention and treatment of obesity.

Recommendations highlights:

- Acknowledgement of obesity as a **complex, progressive and relapsing chronic disease** where adiposity impairs health.
- Shifts focus of obesity management toward improved **patient-centred health outcomes**, rather than weight loss alone.
- Importance of **asking permission** before initiating a discussion on obesity management.
- Use of the **Edmonton Obesity Staging System** (EOSS) to determine treatment, beyond using BMI or waist circumference alone.
- Obtaining a **comprehensive history** to identify root causes of weight gain, including physical, mental and social barriers.
- Inclusion of newer therapeutic agents now indicated for obesity, some with evidence to reduce cardiovascular risk.
- Recommendations on lifestyle and behavioural interventions.

CEP academic detailing updates

New topic: Menopause

Do you know what the **MQ6** is? Learn how to use it to screen patients with menopausal symptoms and an evidence-based approach to choosing the best treatment. Link to tool.

Accredited detailing visits are open to physicians and nurse practitioners. Reach out to your TVFHT pharmacist or to CEP if you are not at a TVFHT site.

Did you know? There are **over 30 symptoms related to menopause**, including vasomotor, mood, fatigue, sexual and recurrent UTI symptoms.

Pharmacotherapy for obesity: Did you know that only five medications have an indication for weight loss in Canada? This topic covers the 4M framework for assessing, initiating, and managing treatment for patients with obesity. Link to tool.

Heart failure: Not sure if it's heart failure? NT-proBNP can be ordered as part of outpatient bloodwork and can help rule out heart failure with a high degree of confidence if <125 pg/mL. This topic covers the four standard therapies for patients with HFrEF. Link to tool.

Cover your bases: quadruple regimens for *H. pylori* eradication[25-27]

Bottom line: Due to increasing resistance and more frequent failures of triple therapies, first-line treatment for H. pylori eradication in Canada is **quadruple therapy for 14 days.**[25]

H. Pylori pearls and treatment recommendations

- **HP-PAC and generics are no longer recommended** due to 15-20% resistance rates to clarithromycin in Canada.
- Consider creating prescription favourites in the EMR to easily prescribe these regimens.
- Concerns about allergies or drug interactions? Consult a pharmacist.
- Provide all regimens in a **blister pack** to improve adherence. Each regimen is >10 pills per day!

1st line	**CLAMET Quad (or PAMC) x 14 days:** 1. PPI standard dose BID 2. Amoxicillin 1000 mg BID* 3. Metronidazole 500 mg BID 4. Clarithromycin 500 mg BID* **OR** **PBMT x 14 days:** 1. PPI standard dose BID 2. Bismuth subsalicylate 262 mg x 2 tabs QID 3. Metronidazole 500 mg QID 4. Tetracycline 500 mg QID*
2nd line	After 1st line treatment failure: ▪ If PAMC was used first → use PBMT for second treatment – see above ▪ If PBMT was used first → use PAMC or consider levo-amox (PAL) – see below
3rd line	After 1st line treatment failure. If PAMC was used first → use PBMT for second treatment If PBMT was used first → consider PAL Levo-amox (PAL) x 14 days: 1. PPI standard dose BID 2. Amoxicillin 1000 mg BID* 3. Levofloxacin 500 mg daily*
4th line	Referral or consultation with GI can be considered. Or if comfortable, Rif-amox (PAR) x 10 days: 1. PPI standard dose BID 2. Amoxicillin 1000 mg BID* 3. Rifabutin 150 mg BID†

*Requires renal dosage adjustment. **Consider using this BC resource for renal dosing of antibiotics**.[29]
†Rifabutin has rarely been associated with myelotoxicity (low white cell or platelet count).

Regimens for patients with penicillin or amoxicillin allergy

Consider referral for allergy testing if options are limited due to allergies and/or drug interactions.

1st line	**PBMT x 14 days:** 1. PPI standard dose BID 2. Bismuth subsalicylate 262 mg x 2 tabs QID 3. Metronidazole 500 mg QID 4. Tetracycline 500 mg QID*	**2nd line**	After 1st line treatment failure. Modified Triple Therapy (PCM) x 14 days: 1. Pantoprazole 40 mg BID 2. Clarithromycin 500 mg BID 3. Metronidazole 500 mg BID

Patient handouts for each regimen

- Pages 9-14 of Alberta Health Services *H. pylori* Primary Care Pathway
- Pages 4-7 of BC Divisions of Family Practice *Helicobacter Pylori* Enhanced Primary Care Pathway

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