Thames Valley
Family Health Team

THE DOSE

Winter Edition

In this issue:

In case you are asked about Colchicine for the out-patient treatment of COVID-19:

Bottom line: At this point, there is not enough evidence to routinely recommend the use of colchicine for the treatment of COVID-19 in the outpatient setting.

Efficacy of Colchicine in Non-Hospitalized Patients with COVID-19 (ColCORONA)

- Not currently published in a peer reviewed journal
- Trial was ended at 75% recruitment due to "logistics of operating the central study call centre 24hrs per day for prolonged period of time" and the "need to disseminate the study results rapidly". This introduces an opportunity for bias in the results.
- In the Intention-to-treat population, the composite endpoint of hospitalizations or death was not significant nor were individual endpoints.
- In patients that had a proven COVID-19 infection confirmed by PCR: Primary composite outcome (death or hospitalization) was 4.6% in colchicine arm vs 6% for placebo, odds ratio 0.75 (95% CI 0.57-0.99 P value 0.049)
    - Reduction in death was not significant
- There was a **higher incidence of pulmonary embolism** in the colchicine group compared to placebo (11 vs 2 patients).

Colchicine: Adverse Effects and Drug Interactions

- Most common side effect is diarrhea, nausea and vomiting
- There is potential for drug interactions as colchicine is metabolized by CYP 3A4 and P-gp
    - Combining statins and colchicine may increase risk of rhabdomyolysis.
    - Avoid combination of CYP 3A4 or P-gp inhibitors
        - CYP 3A4 inhibitors can include clarithromycin, diltiazem, verapamil, azoles, and grapefruit etc.
        - P-gp inhibitors include amiodarone, azithromycin, carvedilol, azoles, verapamil etc.
- Patients with renal impairment or hepatic impairment are at higher risk of drug interactions and potential side effects including death

Up to date resources on COVID-19 management and vaccines

D. Angevine, T. Kontio, P. Patel, K. Koroluk RPh

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Hot off the press: Injectable once weekly semaglutide for the treatment of obesity

- In patients with a reduced caloric diet and increased activity, adding semaglutide 2.4mg sc weekly compared to placebo after 68 weeks achieved:

	Semaglutide	Placebo
Average percent body weight change	**-14.9 %**	**-2.9%**
Number of participants that achieved ≥5% weight loss	**86.4%**	**31.5%**
Number of participants that achieved ≥10% weight loss	69.1%	12%
Number of participants that achieved ≥15% weight loss	50.5%	4.9%
Number of participants that achieved ≥20% weight loss	32%	1.7%
Mean change in body weight	-15.3kg	-2.6kg
Any GI side effect	75%	48%
Discontinued trial due to side effects	7%	3.1%

- To **achieve ≥5% weight loss** with semaglutide compared to placebo over 68 weeks had a **number needed to treat of 2**.
- Weight loss with semaglutide plateaued at ~ 60 weeks.
- The most common side effects were transient GI side effects (nausea, vomiting, dyspepsia, constipation).
- Gallbladder disorders had a number needed to harm ~71 over 68 weeks (2.6% Semaglutide vs 1.2% placebo)
- Pancreatitis 0.2% in patients treated with semaglutide vs 0% in the placebo
- At present, the 2.4mg dose is not available in Canada, but the 0.5 mg and 1 mg doses are available for diabetes.
- Cost will likely be barrier to treatment.
- More information about the trial can be found here

Virtual groups for healthy eating

Healthy Lifestyle: focus on the ways in which your nutrition, activity level and lifestyle affect your health and how they can play a role in reducing your risk for chronic disease.

Heart Health: learn about lifestyle changes that can help you better manage your cholesterol levels and reduce your overall cardiovascular disease risk.

What's for dinner? Our dietitians will teach meal planning skills that work for you and teach you how to build healthy, nutritious meals one week at a time.

FHT patients can self- register at https://thamesvalleyfht.ca/programregistration/

Did you know?

On average, the A1C lowering effect and reduction in CV events between 10 and 25mg of empagliflozin was not statistically different in the EMPA-REG trial. It may be an option to split a 25mg tablet to **reduce the drug cost by ~50%** to help with affordability. (Note this would be off-label use)

We are currently offering the academic detailing session on Non-insulin pharmacotherapy in type 2 diabetes. Please contact your team pharmacist to arrange a session!

New Medications

Nexplanon (Etonogestrel) **Implant**

- Another option for a long-acting reversible contraceptive as it is effective up to 3 years
- Requires the insertion of a single progesterone based plastic rod into the upper inner arm
    - Note the rod does NOT have to be removed for a MRI
    - It contains a small amount of barium, so it is visible by X-ray
- Patients should be counselled on palpating the implant periodically to ensure it has not moved and to monitor for changes in bleeding patterns.
- Videos of insertion and removal can be found at: http://www.nexplanonvideos.com/ and a training course at https://www.etonogestrel-implant-training.ca/en.
- Click here for full details on Nexplanon

New ICS/LABA combination: Atectura Breezhaler (mometasone plus 150mcg indacaterol)

- Indication: treatment of asthma in individuals >12 years old that continue to have symptoms despite ICS therapy
- Dosing: 1 capsule by inhalation once daily. Recommended to take 2 breaths off each capsule to ensure full dose.
- Available in 3 strengths: 80/150mcg, 160/150mcg or 320/150mcg
- Currently, there is no ICS-only Breezhaler device. Patients would need inhaler education if stepping up from ICS alone or stepping down from Atectura to ICS only.
- Patient resource for how to use a Breezhaler: https://www.lung.ca/lung-health/get-help/how-use-your-inhaler/how-use-breezhaler
- Can be considered another option for ICS/LABA inhaler (No evidence for superiority compared to other ICS/LABA)
- Cost: ~60/month but is not currently covered by ODB or NIHB

Lunesta (eszopiclone)

- Indicated for the short -term treatment of insomnia
- Similar to other sleep aids, it has been shown to reduce sleep latency reduced by ~12mins, increase total sleep time by 28mins and reduce wake after sleep onset (WASO) by 17mins.
- It needs to be taken at least 8 hrs prior to waking to reduce next day sedation. This risk is increased in the elderly or patients on CYP 3A4 inhibitors
- It has a **black box warning** for being associated with complex sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have resulted in deaths.
- The risks of Z-drugs like eszopiclone are comparable to those of benzodiazepines in older adults (increased risk of falls, fractures, memory impairment, and motor vehicle accidents). Therefore, CBT-I is still the cornerstone recommendation for most patients with chronic insomnia (ACP recommendation)
- FHT patients can self- register for the Dream ON CBTi program https://thamesvalleyfht.ca/programregistration/
- Click here for full details on Lunesta

PRACTICE Resources

https://mysleepwell.ca/cbti/

https://www.npr.org/2019/03/20/705224359/do-this-today-to-sleep-well-tonight

https://cep.health/clinical-products/insomnia-management-of-chronic-insomnia-tool/

CBTi Coach- Free app

Combogesic (Acetaminophen 325mg/Ibuprofen 97.5mg)

- Now available over the counter
- Cost is ~$15 for 30 tablets
- Using 2 separate products gives more flexibility for dosing and is less expensive

Health Canada Updates:

Ondansetron (Zofran)

- The monograph has been updated that it is **not recommended** in pregnancy
- There is an association of 3 additional babies born with a cleft lip/palate per 10, 000 babes exposed to ondansetron in the first trimester.
    - (14 per 10, 000 pregnancies with ondansetron exposure vs background rate of 11 per 10, 000 pregnancies)
- There have been conflicting studies regarding cardiac malformations.

NSAIDs

- FDA has recommended to avoid the use of NSAIDS starting at 20 weeks of pregnancy due to potential of renal impairment/failure in the unborn baby and causing low levels of amniotic fluid. Complications of prolonged low levels of amniotic fluid can affect lung maturation and limb contractures
- Low dose ASA is not included in this warning.

PRACTICE Resources for medications during pregnancy:

Https://mothertobaby.org/fact-sheets/

Https://www.uktis.org/index.html

LHSC FRAME clinic: 519-685-8500 extension 58293, Fax: +1-519-685-8156, or email **FRAME@lhsc.on.ca**

Drug Shortages

Depo-Provera: This will potentially be a long-term back order with an **estimated end date of June 2022**. Please note some pharmacies are no longer able to order this product while others can get it from their wholesaler based on allocation. The estimated cross Canada shortage is June 2021. Please contact your family health team pharmacist or community pharmacist for other alternatives

What is new in community pharmacy:

- ✓ Community pharmacists are now able to administer the influenza vaccine to patients **2 years old and older**
- ✓ Community pharmacists are now able to renew prescriptions up to 12 months. They are required to notify the original prescriber that they have renewed the prescription.
- ✓ Forgery alert system is now active in Ontario. Community pharmacies are now notified electronically to check authenticity if a prescription has been reported as a forgery or if a prescriber's prescription pad has been stolen. Prescribers and pharmacists should contact ***drugprogramsdelivery@ontario.ca*** with the following information*:*
    - ➢ The prescriber details on the forged prescription including prescriber name, address, phone/fax number;
    - ➢ The name(s) of the drug(s) mentioned on the forgeries (if known); and
    - ➢ Attach a copy of the prescription and any additional forged prescription pages you may have.

Now covered in Ontario

Trintellix (vortioxetine) is now covered on Ontario Drug Benefits

Emerade (epinephrine Autoinjector)

- Now covered under the Allergen Program for patients eligible for Ontario Drug Benefits
    - Allerject and Epipen are covered as well under this program but are not interchangeable. A prescription would need to specify the product by brand name

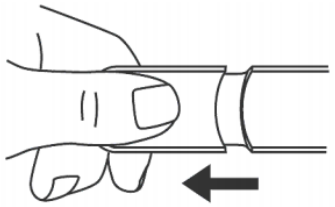
Available in 2 strengths:

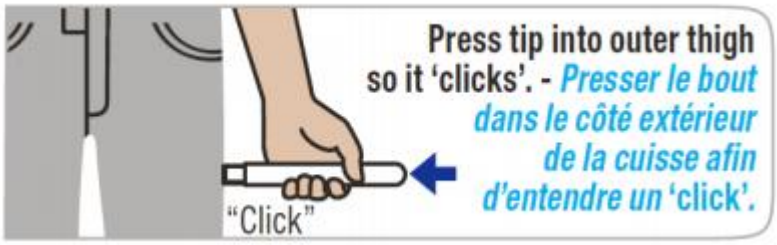
- 0.3mg for patients greater than 30kg (~66lbs)
- Patients that weigh greater than 60kg (132bs) could use either the 0.3mg or 0.5mg

Cost: $85 plus pharmacy fees (compared to $96 for the Epipen or Alleject)

How to use the auto injector

1. Pull off the protective cap at the needle end (there is only 1 removable cap)
2. Press the needle end into the outer thigh until it clicks
3. Hold for approx. 5 seconds. against the thigh before removing Emerade
4. Then gently massage the area.
5. Seek medical help





Admelog 100u/ml (insulin lispro)

- Biosimilar to Humalog
- Admelog has been shown to be non-inferior to Humalog for reduction in A1C and safety.
- It will be available in 100u/ml vial, cartridge or solostar pen.

How to prescribe Admelog?

- Prescriptions will need to specify Admelog as it is not interchangeable with Humalog. Prescriptions for insulin lispro will need to be clarified to either Admelog or Humalog
    - Note: Biosimilars are never deemed interchangeable even when demonstrating non- inferior status for efficacy and safety. Click here for more information on biosimilars.

How to convert from Humalog to Admelog

- They can be converted unit per unit and administered with the same timing as Humalog

What if my patient was previously on Humalog and doesn't want to change?

- Using the LU code 599, patients covered by Ontario Drug Benefits previously on Humalog may continue therapy with Humalog. However, new starts will be required to start on Admelog.

Note: Private plans will have their own coverage criteria and exceptions

Potential drug interactions with Cannabis

There are a lot of theoretical interactions with cannabis products. It is difficult to predict drug interactions due to the various compounds and products available. The risk and understanding of drug interactions will change as more research is available. Health Canada has recently published a product safety alert after reviewing recent case reports of **increased INR after initiation of CBD oil, THC oil, smoked or edible cannabis in patients previously stable on warfarin**.

Cannabis products that are smoked on a regular basis (>2 times per week) may cause an increase in metabolism by CYP 1A2 like patients that smoke cigarettes. A list of potential interactions can be found here. **The notable potential interactions with starting or stopping smoking are clozapine, olanzapine, fluvoxamine and theophylline.**

Practice Tools: Drugs that can affect THC and CBD levels

	THC Broken down by 3A4 and 2C9	CBD Broken down by 3A4 and 2C19
Drugs that can **increase** the levels of THC or CBD	**3A4 inhibitors:** Verapamil/diltiazem Azole Antifungals Clarithromycin, erythromycin **2C9 inhibitors** Septra metronidazole amiodarone	**3A4 inhibitors:** Verapamil/diltiazem Azole Antifungals Clarithromycin, erythromycin **2C19 inhibitors** (theoretical) but not shown with omeprazole - Monitor for CBD side effects
Drugs that can **decrease** the levels of THC or CBD	**3A4 inducers** Phenytoin Primidone St. John's wort **2C9 inducers** Rifampin carbamazepine	**3A4 inducers** Phenytoin Primidone St. John's wort **2C19 inducers** Rifampin carbamazepine

Practice Tool: THC and CBD potential effects on other medications

	THC Inhibits enzymes 2C9, 2B6	CBD Inhibits P-gp, 3A4, 2C19, 2B6
Potential to increase the levels of the following drugs	2C9 substrates Warfarin Phenytoin rosuvastatin 2B6 substrates methadone	3A4 substrates Zopiclone Diltiazem Simvastatin/atorvastatin Tacrolimus (case report of 3x increase in levels when combined with CBD) 2C19 substrate Clobazam (increased 3fold) Carbamazepine (2-6 fold increase) Clopidogrel (may reduce effectiveness of clopidogrel as it would needs to be metabolized to be active) citalopram 2B6 Substrates methadone P-gp substrates Digoxin dabigatran
Pharmacodynamic interactions	Additive cognitive and psychomotor impairment from CNS depressants Potential to cause tachycardia, hypertension and fluid retention	Additive cognitive and psychomotor impairment from CNS depressants

SADIE (Special Authorization Digital Information Exchange)

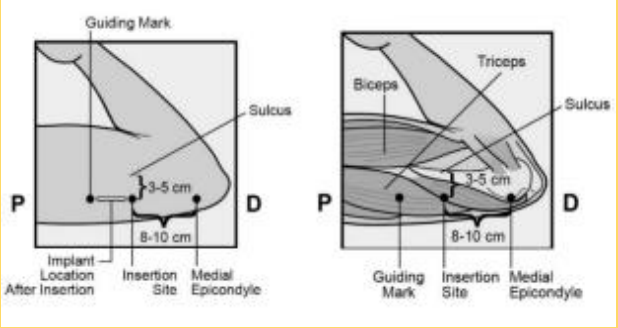
SADIE is an online portal for submitting Ontario Drug Benefit Exceptional Access Program requests. The benefits of using SADIE over the standard paper or PDF forms are:

- Can assign **designates** (i.e. clinic nurses or pharmacists) to complete or help complete the EAP request
- **Can search the reimbursement criteria for the requested drug**
- **Faster and a higher rate of approvals** – 75% reduction in rejections due to incomplete information
- **Easy to use** – SADIE only asks for required information with dynamic smart forms

Sign up for SADIE here: http://www.health.gov.on.ca/en/pro/programs/sadie/

Once weekly semaglutide in Adults with overweight or obesity

Patients	Included -18 years or older with one or more unsuccessful attempt at weight loss -BMI ≥30 or ≥27 plus one of the following HTN, dyslipidemia, sleep apnea, or CV disease Excluded -A1C≥ 6.5% or diagnosed with type 1 or type 2 diabetes - history of chronic pancreatitis or acute pancreatitis within 180 days of enrollment -previous surgical treatment for obesity - anti-obesity medication within 90days of enrollment Trial population was predominately white females (~70%) with an average weight of 105kg
Intervention	Semaglutide 2.4mg sc once weekly or highest tolerated dose **PLUS** Individualized dietary and activity counselling every 4 weeks to help them adhere to a reduce calorie diet (500kcal) and increased physical activity of 150mins per week. Dose titration was done every 4 weeks: 0.25mg then 0.5mg then 1mg then 1.7mg and 2.4mg
Comparison	Placebo injections Individualized dietary and activity counselling every 4 weeks to help them adhere to a reduce calorie diet (500kcal) and increased physical activity of 150mins per week
Outcome	Primary outcome - Percent body weight change: -14.9% with semaglutide vs -2.4% with placebo - The number of participants that achieved at least 5% weight loss: 86.4% with semaglutide vs 31.5% with placebo Other outcomes - ≥15% was achieved in 50.5% with semaglutide vs 4.9% with placebo - Mean Change in body weight was -15.3kg with semaglutide vs -2.6 kg with placebo - Reduction in waist circumference: -13.54cm with semaglutide vs -4.13cm with placebo Safety - Adverse events leading to discontinuation 7% vs 3.1% - Absolute incidence of GI side effects compared to placebo: ~26.3% - nausea (~27%), diarrhea (~15.6%), vomiting (~18.2%), constipation (~13.9%), dyspepsia (~7.2%), abdominal pain (~4.5%) - Gallbladder disorders (1.4% - NNH of 71 over 68 weeks) - Pancreatitis 0.2% in semaglutide group vs 0% in placebo

Extended release Etonogestrel implant (Nexplanon)	
Indication	Prevention of pregnancy in Adults >18 years old
MOA	Etonogestrel is the active metabolite of desogestrel (progestin) that inhibits ovulation and cause changes in cervical mucus to impair passage of spermatozoa
Timing of insertion	**Not currently on any form of birth control:** Insert between Day 1 to Day 5 of the menstrual cycle. **Changing from COC**: Insert on the day after the last active pill up to 7 days post active pill **Progestin only tablet:** can be inserted on any day of the month if it is inserted within 24 hrs after taking the last tablet **Vaginal ring or patch:** Insert preferably on the day of removing the patch or vaginal ring up to the day the next dose would be due **IUD:** Insert on the same day as the removal **Depo:** Insert on the day that the next dose is due If inserted outside this window, pregnancy should be ruled out and it is recommended to use a barrier method for at least 7 days after insertion
Insertion details	**Insert 1 rod subdermally into the upper inner arm of the non-dominant hand up to 3 years.**  Videos of insertion and removal can be found at: http://www.nexplanonvideos.com/ and a training course at https://www.etonogestrel-implant-training.ca/en.
Efficacy	Less than 1 in 1000 females will get pregnant per year with typical use.
Drug Interactions	Drugs that induce 3A4 (HIV medications, carbamazepine etc.) could reduce etonogestrel levels leading to a reduction in effectiveness
Side effects	<u>Common side effects:</u> • Local injection site reaction (ie. Erythema 3%, hematoma 3%, bruising 2%, pain 1%, and swelling 1%) • Headache • Weight gain 2.8lbs after 1 year and 3.7 after 2 years • Acne 11.8% • Breast pain 10.2% • Emotional lability 5.8% <u>Serious side effects</u> Implant migration o Post-marketing reports of implants located within the vessels of the arm and the pulmonary artery o Patients should be encouraged to check from the rod periodically o If they cannot palpate the implant: two-dimensional X-ray, CT scan, ultrasound scanning (or magnetic resonance imaging (MRI) may be used
Changes in bleeding pattern	-Amenorrhea achieved in 1 in 5 patients -Frequent or prolonged bleeding in 1 in 5 patients **Note: Favorable bleeding pattern in the first 3 months is predictive of future bleeding pattern. Those without a favorable bleeding pattern have a 50% chance of improving over the course of treatment Depending on the trial 10-20% of participants discontinued drug therapy due to adverse reactions related to abnormal bleeding (CADTH review)**
Return to ovulation	There is a rapid return to fertility after removal. Etonogestrel levels are not detectable within 1 week of removal. There have been pregnancies observed as early as 7 days after removal.
Cost	$300 plus pharmacy fee Not currently covered by ODB or NIHB

Merck Medical Services line for questions about physicians who have consented to share their name as providers for insertion/referral: 1-800-567-2594

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ColCORNA: trial can be found here

Patient	**Inclusion criteria** not currently hospitalized and not under immediate consideration for hospitalization Age > 40 plus one of the following high risk criteria • age of 70 years or older • obesity (body-mass index of 30 kg/m^2 or more) • diabetes • uncontrolled hypertension (systolic blood pressure ≥150 mm Hg) • known respiratory disease • known heart failure • known coronary disease • fever of at least 38.4°C within the last 48 hours • dyspnea at the time of presentation • bicytopenia, pancytopenia, or the combination of high neutrophil and low lymphocyte counts. **Exclusion** • inflammatory bowel disease • chronic diarrhea or malabsorption • pre-existent progressive neuromuscular disease • estimated glomerular filtration rate less than 30 ml/minute/1.73 m^2 • severe liver disease • current treatment with colchicine • current chemotherapy for cancer • a history of significant sensitivity to colchicine
Intervention	Colcichine 0.5mg bid x 3 days then colcichine 0.5mg po daily for 27 days
Comparator	Placebo
Outcome	

Clinical Outcome	Colchicine	Placebo	Odds Ratio (95% CI)	P Value
ITT population	N=2235	N=2253		
Primary composite endpoint - no. (%)	104 (4.7%)	131 (5.8%)	0.79 (0.61-1.03)	0.08
Components of primary endpoint:				
Death - no. (%)	5 (0.2%)	9 (0.4%)	0.56 (0.19-1.67)	
Hospitalization for COVID-19 no. (%)	101 (4.5%)	128 (5.7%)	0.79 (0.60-1.03)	
Secondary endpoint:				
Mechanical ventilation - no. (%)	11 (0.5%)	21 (0.9%)	0.53 (0.25-1.09)	
Patients with PCR-proven COVID-19	N=2075	N=2084		
Primary composite endpoint – no. (%)	96 (4.6%)	126 (6.0%)	0.75 (0.57-0.99)	0.04
Components of primary endpoint:				
Death – no. (%)	5 (0.2%)	9 (0.4%)	0.56 (0.19-1.66)	
Hospitalization for COVID-19 no. (%)	93 (4.5%)	123 (5.9%)	0.75 (0.57-0.99)	

Lunesta (eszopiclone)	
Class	Non- benzodiazepine GABA receptor agonist
Indication	Insomnia
Dosing	Use lowest possible dose Initial dose: 1mg qhs with at least 7-8 hours remaining before the planned time of awakening. Therapy should be reassessed after 7-10 days Max dose of 3mg qhs (NOTE: should avoid activities requiring concentration including driving the next morning
Dose adjustments	Geriatrics: maximum dose of 2mg qhs Renal impairment: no dose adjustment necessary Hepatic impairment: Max dose of 2mg in severe hepatic impairment
Contraindications	Hypersensitivity to eszopiclone
Precautions	• Impaired alertness and motor coordination, including risk of next morning impairment. Patient's taking 3mg should be advised to avoid driving the next morning • Increased effect seen in elderly patients • Abnormal thinking and behavior changes including bizarre behavior, agitation, hallucinations, and depersonalization have been reported • Worsening of depression including suicide thoughts and actions Black box warning from the FDA Eszopiclone has been associated with sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have resulted in deaths.
Special Populations	Pregnancy: risk observed in animal studies. Breast feeding: No human data- Not recommended Pediatrics: Not indicated in patients 18 and under Geriatrics: Consider avoiding use (BEERS 2019). Half-life increased to 9hrs. Max dose is 2mg qhs
Adverse Events	Common Side effects (>2%) • GI: unpleasant taste (up to 34%), dry mouth, vomiting • Neurologic: headache (up to 21%), dizziness, somnolence • Respiratory: respiratory infection, viral infections • Dermatologic: rash • Psychiatric: anxiety. hallucinations, abnormal dreams • Cardiac: >1% chest pain, peripheral edema • accidental injury ≤3% Serious Anaphylactoid reaction/angioedema Complex mannerisms including behavior and sleep
Drug interactions	CNS depressants: increased risk in next day impairment 3A4 inhibitors (clarithromycin) can increase the levels. Maximum dose is 2mg qhs Avoid taking after a high fat meal as this can delay absorption and increase next day impairment
Outcome data	Sleep latency reduced by ~12mins Total sleep time increased by 28mins Wake after Sleep onset (WASO) reduced by 17mins
Place in therapy	First line therapy remains CBTi Options for CBTi available in the community • Thames Valley Family Team patients can access Dream-On a 5-week virtual CBTi program • APP: CBT-I coach (free) • Book: Sink into sleep (cost ~$25)
Cost	~$1.60 per tablet plus pharmacy fees Not covered by ODB/NIHB

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