Beyond the Monograph: Evidence, Safety, and Scope for Off-Label OMP Prescribing

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Session Objectives

Over the next 20 minutes or so we will:

- define off-label prescribing
- discuss why off-label prescribing matters
- review the label and off-label indications for oral micronized progesterone (OMP) and the evidence to support it
- Discuss the clinical implications for off-label use of OMP and how to minimize risk

Off-Label Prescribing: What It Is (and Is Not)

Definition of Off-Label Prescribing

Off-label prescribing uses authorized drugs beyond Health Canada/FDA-approved indications, doses, routes, or populations.

Regulatory and Ethical Considerations

Health Canada allows off-label use; prescribers are accountable and must ensure evidence-based, ethical practice.

Common Areas of Use

Off-label prescribing is common in pediatrics, oncology, geriatrics, and mental health and is guided by clinical evidence.

Importance of Professional Judgment

Legal off-label use depends on clinicians' judgment, documentation, and informed consent, not solely on monograph indications.

Wittich C, et al. Mayo Clin Proc. October 2012:87(10):982-990
Standing Senate Committee on Social Affairs, Science, and Technology, 2014

Why Prescribe Off-Label?

- To provide timely, evidence-informed care
- When clinical needs exceed narrow monograph indications
- When updated research or guidelines support newer uses

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Why This Matters

Off-label Prescribing Context

Off-label prescribing addresses gaps between approved uses and real clinical needs, common in Canadian healthcare.

Safety and Regulation

Off-label use requires evidence-informed decisions, patient consent, and careful monitoring to ensure safety.

Clinical and Policy Importance

Balancing clinical benefits and patient safety is key to policy decisions on expanding prescribing authority.

Canadian Context

Regulatory Framework

Off-label prescribing in Canada is governed federally by Health Canada and provincially by the professional colleges that oversee prescribers.

Prevalence of Off-label Use

Studies show that off-label prescriptions range from 11% to 50%, varying across therapeutic areas in Canadian healthcare.

Ethical and Safety Considerations

Ethical duties include providing valid evidence, documenting the rationale, obtaining informed consent, and addressing challenges in monitoring off-label use.

Standing Senate Committee on Social Affairs, Science, and Technology, 2014

Why Labels Don’t Keep Pace with Practice

- Regulatory updates are slow and costly; companies must invest in trials and submission fees.
- Off-label uses often become standard of care based on emerging evidence, but manufacturers may not pursue label expansion if:
  - Market size is small
  - No commercial incentive
  - Trials would be expensive

From Off-Label to On-Label: The Case of Lamotrigine

Initial Approval and Off-Label Use

Lamotrigine was first approved for epilepsy but widely used off-label for bipolar disorder (acute depression and maintenance therapy.)

Clinical Trials and Regulatory Approval

Clinical trials showed efficacy in delaying mood episode recurrence, leading to regulatory approval for bipolar I maintenance.

Regulatory Lag and Off-Label Challenges

Despite evidence, lamotrigine is unapproved for acute bipolar depression, showing regulatory delays behind clinical practice.

Maximizing Safety

What makes off-label use clinically safe?

- A clear, evidence-informed rationale
- Patient selection
- Monitoring and follow-up
- Documentation of risk–benefit assessment
- Informed consent

OMP Basics

Approved Indication (Canada)

OMP is approved for the prevention of endometrial hyperplasia in post menopausal women taking estrogen.

Contraindications

Contraindications include undiagnosed vaginal bleeding, active liver disease, hormone-dependent cancers, active or past history of arterial thromboembolic disease or history of VTE or PE.

Off-label Use Awareness

Prescribing OMP outside approved uses, like for sleep or vasomotor symptoms, is off-label.

Kellar J. OMP Report for College of Naturopaths of Ontario: Drug List Review. 2025

Common Off-Label Uses

Management of Vasomotor Symptoms

OMP is used off-label to manage perimenopausal hot flashes and night sweats, improving patient comfort.

Improvement of Sleep and Mood

Progesterone's neurosteroid effects may enhance sleep quality and mood stability in patients.

Cycle Regulation Benefits

OMP helps stabilize the endometrium, offering potential benefits for abnormal uterine bleeding and cycle regulation.

Assisted Reproductive Technology (ART): Luteal Phase Support

Used vaginally to support pregnancy; higher doses

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Prior JC, et al. **Menopause.** 2023;30(1):45-54.
Seifert-Klauss V, et al. **Maturitas.** 2000;37(3):161–169
Nolan, B et al. 2021. The Journal of Clinical Endocrinology & Metabolism:106(4);e942–e951

VMS Evidence

Canadian Phase III Trial

- 189 perimenopausal women tested 300 mg OMP versus placebo for 12 weeks with no significant primary VMS score difference.
- Participants reported perceived reductions in night sweats and improved sleep quality without serious adverse effects during the trial.

German Multi-center Trial

- tested 200-400 mg OMP daily in postmenopausal women, showing dose-dependent symptom improvement trends but not statistically significant.

Guideline Recommendations (NAMS, NICE, BMS, SOCG, IMS)

- Estrogen plus OMP for VMS symptoms in perimenopause and menopause
- OMP alone noted as limited data, off label use.

Prior JC, et al. **Menopause.** 2023;30(1):45-54.
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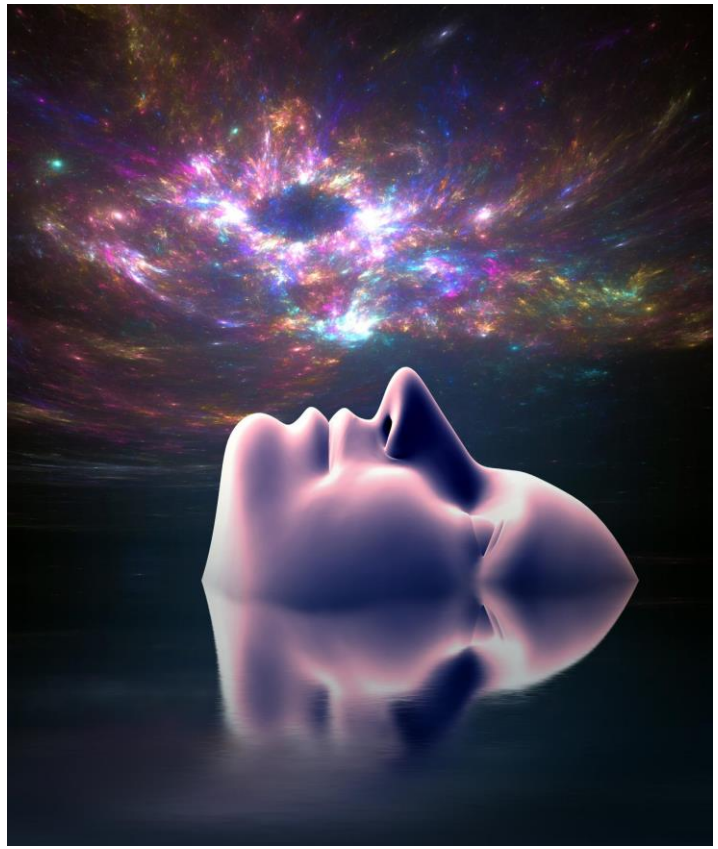
Sleep Evidence



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Sleep Onset Improvement

OMP reduces sleep onset latency by about 7 minutes compared to placebo in clinical studies.

Subjective Sleep Quality

Total sleep time improvements are varied, subjective sleep quality often shows positive changes with OMP.

Mechanism of Action

Progesterone metabolites modulate GABA-A receptors producing anxiolytic and sedative effects aiding sleep.

Study Population Considerations

Most studies involved postmenopausal women, some with estrogen therapy, limiting monotherapy conclusions.

Assisted Reproductive Technology (ART): Luteal Phase Support

- Progesterone replacement or supplementation as part of ART for infertile patients with progesterone deficiency is supported by evidence
- Multiple dosing regimens are available
  - Multiple studies have shown that vaginal administration of OMP capsules achieves luteal support comparable to dedicated vaginal progesterone products.
  - Pregnancy rates and endometrial support outcomes are similar between vaginal OMP and other vaginal progesterone formulations.
- Usual dosing: Vaginal administration of OMP 200 mg three times daily, starting on the day of oocyte retrieval and continuing for up to 12 weeks of gestation
- Guidelines endorse off-label use of OMP vaginally for this indication

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Safety Profile

- Overall safety profile of OMP is favourable for most individuals
- Many studies have found OMP to be safer than synthetic progestins (i.e. medroxyprogesterone acetate (MPA))
    - Less thromboembolic events (VTE)
- When used with estrogen, it seems to have a more favourable effect on invasive breast cancer compared to estrogen plus MPA or estrogen alone.

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Why Off Label Use Matters for OMP: Clinical Realities

- The approved monograph may not adequately reflect modern evidence
- OMP is used globally for multiple indications, beyond the Canadian label indication
- MDs, NPs, and midwives routinely prescribe it off-label
- Major menopause guidelines support the use of OMP plus estrogen for the treatment of perimenopausal and menopausal symptoms
- Reproductive/fertility guidelines support the use of OMP intravaginally for ART, luteal phase support.

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Who Prescribes OMP Off-Label?

Primary Prescribers of OMP

Family physicians, gynecologists, and nurse practitioners prescribe OMP off-label for symptoms like VMS and sleep problems.

Role of Pharmacists

Pharmacists can prescribe OMP with various levels of independence in Canada.

Dispense OMP – providing a therapeutic review/assessment of the patient before dispensing.

Safety Checklist for Off-Label Prescribing

Document Indication, Rationale, and Consent

Ensure clear documentation of the indication, supporting evidence for off-label OMP use, and informed consent.

Screen Contraindications

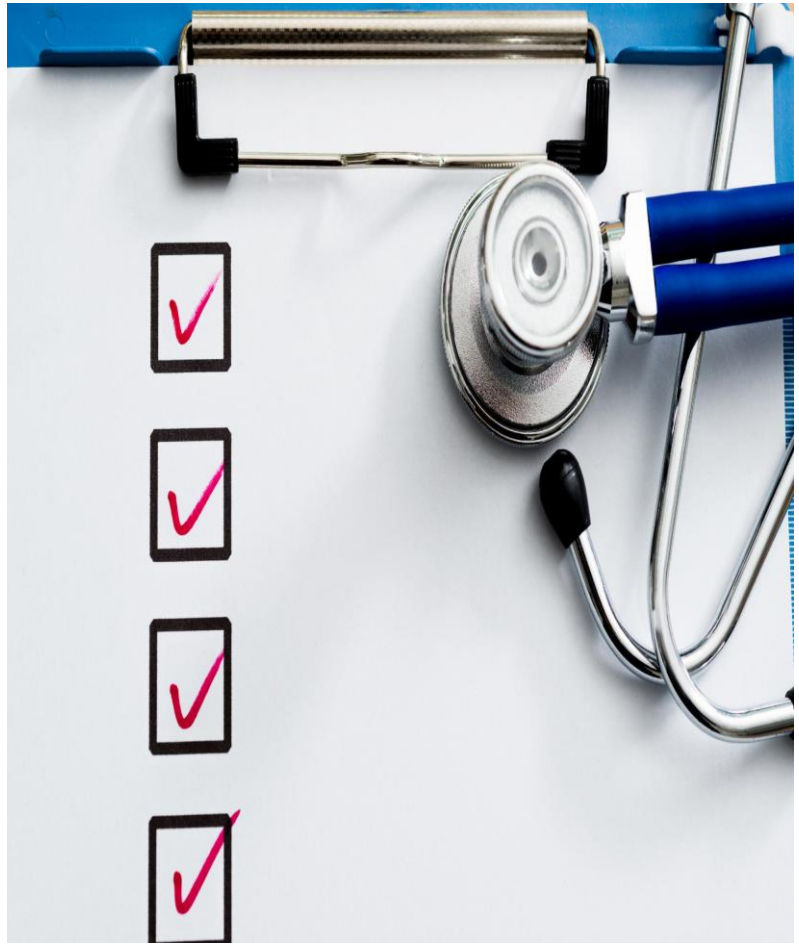
Screen patients for contraindications like breast cancer, thromboembolic risk, and liver disease before prescribing.

Evidence-Based Dosing

Use evidence-based dosing protocols

Monitor and Reassess

Monitor symptoms and adverse effects at baseline and follow-ups; periodically reassess risk versus benefit.



Bottom Line

Promising but Limited Evidence

Current research shows potential benefits of off-label OMP use for perimenopausal symptoms but lacks large-scale validation.

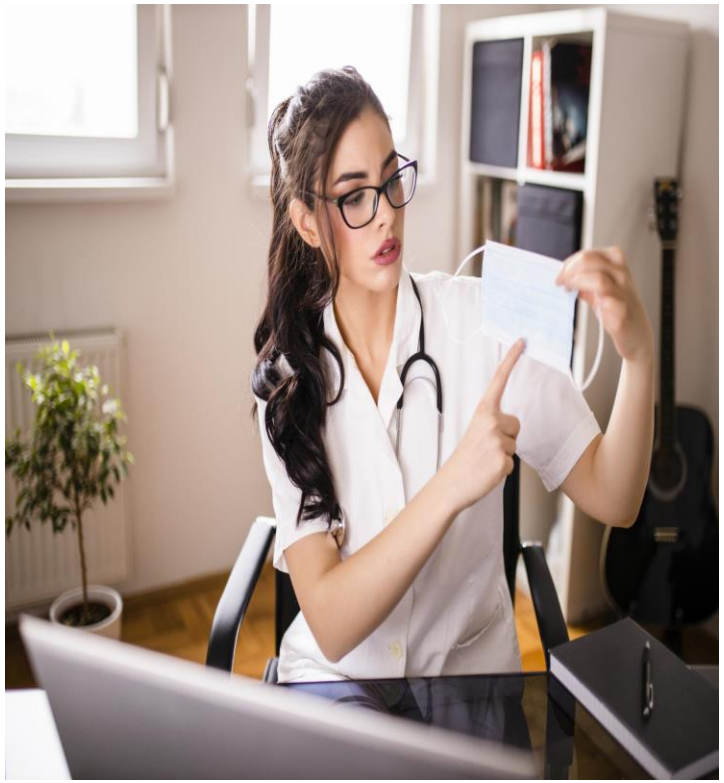
Need for Caution

Prescribers must use off-label OMPs cautiously due to limited definitive studies and ensure informed consent is obtained.

Monitoring is Key

Prescribers must monitor for effectiveness and safety. If it is not working – stop it. Reassess need to continue at each follow-up.

Refer When Necessary



Key Takeaways

Legal and Monitoring Requirements

- Off-label prescribing in Canada requires strong evidence, informed consent, and careful patient monitoring and documentation to ensure safety.

Collaboration and Best Practices

- Interprofessional collaboration and adherence to best practices protect patients and maintain public trust.
- When in doubt, refer

Questions?