



UNAPPROVED USES OF APPROVED MEDICATIONS

Exploring Off-Label Prescribing Practices

CE CREDIT INFORMATION

This speaker has no conflicts of interest associated with this presentation.

OBJECTIVES

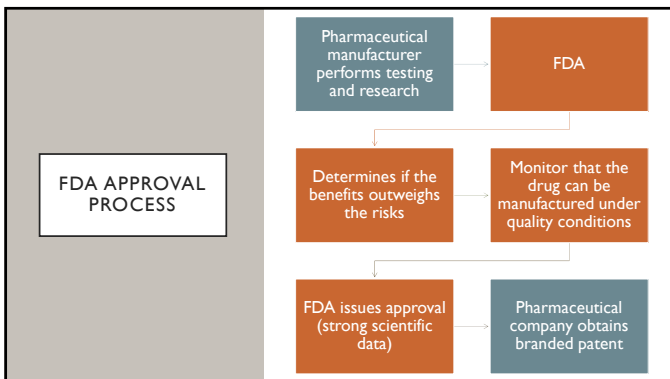
-  Review the role of the Food and Drug Administration in approving medications and the process for medication approval.
-  Evaluate the legalities associated with "off-label" prescribing and the evidence needed to justify off-label prescribing practices.
-  Examine common drugs that are prescribed in primary care and their unapproved uses

FDA APPROVAL

- Rigorous trials
- Pharmaceutical companies must follow a five-step approval process:
 - Step 1:** Discovery/concept
 - Step 2:** Preclinical research
 - Step 3:** Clinical research
 - Step 4:** FDA review
 - Step 5:** FDA post market safety monitoring

TOPIRAMATE

- **1979:** Created by scientist at Johnson & Johnson
 - Animal testing for various therapies
 - Emerged as an excellent anti-convulsant
- **1981:** data presented for pre-clinical development
- **1983:** placed on the pre-clinical development list (25th on a list of 25)
- **1986:** Investigational New Drug Application was filed with the FDA
- **1996:** Received marketing approval for the treatment of GTC seizures & partial-complex



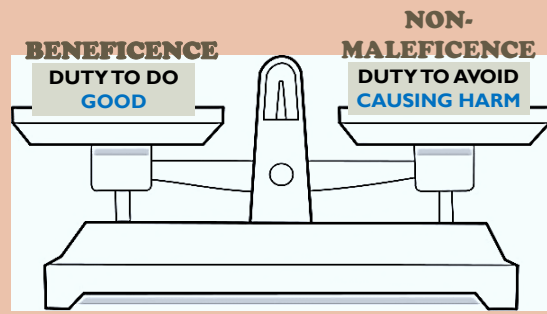
GENERIC MEDICATIONS:

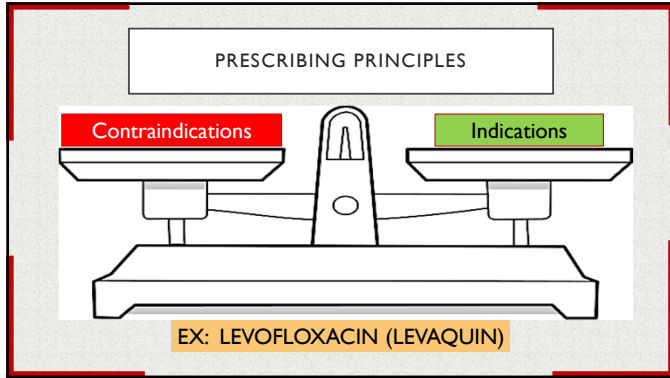
- Do not require same rigorous process
- Must prove that active ingredient is effective when used for the same condition

TOPIRAMATE

- **1996:** Received marketing approval for the treatment of GTC seizures & partial-complex
- **2009:** U.S. Patent expired
 - Anti-obesity activity had been noted as a "side-effect" of topiramate.
 - Vivus, Inc: Combined topiramate with phentermine
- **2012:** Qsymia was approved for the long-term treatment of obesity
- **2020:** Patent was expected to expire
- **2029:** Patent extended

LAW OF PRESCRIBING





OFF-LABEL PRESCRIBING

25% prescriptions in the U.S.

- PRESCRIBING AN FDA APPROVED MEDICATION
- BUT NOT:
 - For the disease/symptom approved
 - At the dosage or dosage form approved
 - For the population approved

OCCURRENCES OF OFF-LABEL PRESCRIBING

30% have substantial research-based evidence

1. Ex: A drug is proven effective for an off-label condition of similar etiology, but the FDA doesn't have the research/resources from the pharmaceutical industry to relabel it with the new indication.
2. Ex: Limited options exist for on-label drugs for certain populations (i.e. children, older adults, pregnant women)
3. Ex: Prescribing the same drug, with a dosage approved for a different indication, will save the patient money

IS OFF LABEL PRESCRIBING LEGAL?

YES, but

- Based on sound medical evidence
- Have similar safety to on-label use
- Requires careful consideration

LAWS

- Controversial and vague
- Check state scope-of-practice
- Concerns of off-label prescribing
 - Unregulated research
 - Inadequate informed consent
 - Medical negligence
- Best practice is to prescribe legend drugs

RULES OF OFF LABEL PRESCRIBING

A comprehensive assessment and accurate diagnosis

Consider the evidence: Is it sufficient and justifiable?

- meta-analysis
- systematic reviews
- large randomized controlled trials


Discuss the use of the off-label medication with the patient and document their understanding and consent

YIELD

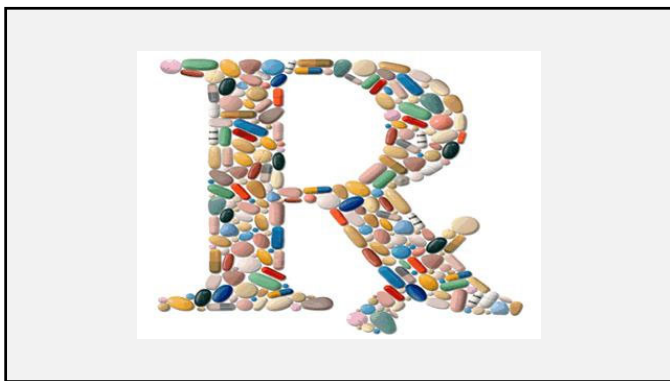
NEGLIGENCE

- The prescriber has an established duty to the patient
- This duty must be breached
- There must be some injury requiring compensation
- There must be a causal link between the breach and the injury

DO NOT



- Misrepresent/Falsify Diagnosis**
 - Diagnosis should reflect patient condition and be justifiable
- Break the trust of patient-provider relationship**
 - Disclose off-label use
 - Educate on the evidence
 - Shared-decision making
- Forget to document**
 - Ethical justification
 - Patient discussion
 - Patient consent



HOW DO YOU KNOW?

EBP	Reputable evidence-based and clinical practice guidelines
Epocrates	Free and paid versions; identifies off-label
Up-to-Date	Contains research and opinions

topiramate
generic

ADULT INDICATIONS & DOSING

sleep-related eating disorder (off-label)
25-100 mg PO qhs
Start: 25 mg PO qhs x1wk, then may incr. by 25 mg/day qwk; info: taper dose gradually to D/C

nightmares, post-traumatic stress disorder-assoc. (off-label)
75 mg PO qhs
Start: 25 mg PO qhs x1wk, then incr. by 25 mg/day qwk; info: taper dose gradually to D/C

alcohol dependence (off-label)
100-150 mg PO bid
Start: 25 mg PO qd x1wk, then incr. by 25 mg/day qwk; info: taper dose gradually to D/C

essential tremor (off-label)
150-300 mg/day PO divided qd-bid
Start: 25-50 mg PO qhs x1-2wk, incr. by 25 mg/day q1-2wk; Max: 400 mg/day; info: taper dose

TOPIRAMATE (TOPAMAX)

<p>APPROVED USES</p> <ul style="list-style-type: none"> • GTC Seizures • Complex Partial Seizures • Migraines 	<p>OFF-LABEL USES</p> <ul style="list-style-type: none"> • Neuropathic pain • Alcohol use disorder • Anti-psychotic induced weight gain • Binge-eating disorder • Cluster headache prevention • Eating disorders • Bipolar disorder • Obsessive-compulsive disorder (OCD) • Posttraumatic stress disorder (PTSD) • Obesity
---	---

TOPIRAMATE RESEARCH EVIDENCE

- 7 cases of topiramate toxicity
- Symptoms of toxicity: sedation, speech disturbance, blurred vision, **metabolic acidosis**, agitation, ataxia, convulsions, and abdominal pain.
- List of absolute contraindications are minimal
- No reported fatalities or long-term consequence
- Relatively safe drug

METFORMIN

Marketed 1995

<p>INDICATIONS</p> <p>FIRST LINE FOR TYPE 2 DIABETES MELLITUS</p>	<p>OFF-LABEL USES</p> <ul style="list-style-type: none"> • Polycystic Ovarian Syndrome • Gestational Diabetes • Prevention of type 2 diabetes mellitus • Weight Reduction • Alzheimer's Disease
--	---

PRE-DIABETES & METFORMIN

Not FDA approved

Use clinical judgment

ADA

- BMI >35 kg/m2
- <65 years
- Hx of gestational diabetes

PCOS & METFORMIN

1. **Diagnosis:** PCOS is diagnosed based on the presence of two or more of the following criteria:

2. **Metformin Indications:** Metformin is used for PCOS to improve insulin sensitivity and reduce androgen levels.

3. **Contraindications:** Metformin is contraindicated in patients with renal impairment, liver disease, and heart failure.

4. **Side Effects:** Common side effects include gastrointestinal upset, weight loss, and vitamin B12 deficiency.

5. **Monitoring:** Regular monitoring of renal function and vitamin B12 levels is recommended.

INFERTILITY &
METFORMIN

NOT recommended for ovulation induction

- Live birth rates are higher with clomiphene (Clomid)

Correction of hyperinsulinemia may lead to menstrual cyclicity and enhanced spontaneous ovulation

May result in ovulation in some anovulatory women

- Discuss this implication with patients

OBESITY &
METFORMIN

Metformin produces approximately 5% weight loss

Does not qualify as a "weight loss drug"

Prevention of Type 2 Diabetes?

- Decreased new-onset diabetes compared with standard diet and exercise
- Intensive diet & exercise was more effective than Metformin in reducing the development of Type 2 DM
- Not enough data to show long-term prevention
- Evidence does show delayed onset

SPIRONOLACTONE

Marketed 1957

INDICATIONS	OFF-LABEL USES
<ul style="list-style-type: none"> Heart Failure HTN Edema Hyperaldosteronism, primary 	<ul style="list-style-type: none"> Hypokalemia, diuretic-induced Hirsutism Hair loss (female pattern) Acne Vulgaris Hormone therapy for transgender females

ANTI-ANDROGENIC EFFECTS

- Decreases 5-alpha reductase activity - weakly
 - Other 5-alpha reductase inhibitors:
Zinc, Finasteride, Saw Palmetto
- Increases steroid hormone binding globulin thus decreasing circulating free testosterone – increasing estrogenic state

HIRSUTISM & SPIRONOLACTONE (ALDACTONE)

History

- Treating hypertension in women with PCOS
- Discovered the antiandrogenic effects

Should only be used as an addition to CHC

Anti-androgen monotherapy should be avoided in child-bearing women

- Feminization of male fetus

Meta-analysis (7 trials analyzed) – Significantly more effective than placebo

- Spironolactone (2 trials)
- Finasteride (3 trials)
- Flutamide (2 trials)

ACNE VULGARIS & SPIRONOLACTONE

- Rationale is that it inhibits sebaceous gland activity
- Women with high androgenic states have increased sebum production

Systematic Review (2009) = insufficient evidence

Multiple studies have reported benefit

#1: Retrospective Study (N = 395; >21 years of age)

- ≥90% improvement = 66%
- 51-89% improvement = 19%
- <50% improvement = 6%
- 0% improvement = 9%
- Average 3-5 months

#2: Retrospective Study (N=80; 14-20 years)

- >90% improvement = 23%
- 51-89% improvement = 36%
- ≤ 50% improvement = 21%
- 0% response = 20%

POTENTIAL INDICATIONS

- Acne flares that cycle with menstruation
- On oral contraceptives with moderate-to-severe acne vulgaris (especially w/hormonal pattern)
- Not responding to conventional therapy and not wanting to use oral isotretinoin or who are not candidates for oral isotretinoin
- Late-onset AV, or persistent-recurrent AV past the teenage years (even without evidence of hyperandrogenism)
- Clinical signs of hyperandrogenism (i.e. hirsutism), androgenic alopecia, and/or increased sebum production

FINASTERIDE

Marketed 1992

Approved	Off-label
<ul style="list-style-type: none"> • Benign prostate hyperplasia • Androgenic alopecia (male pattern hair loss) 	<ul style="list-style-type: none"> • Hyperandrogenism (Hirsutism) • Endocrine Society practice guidelines recommend 2.5 mg or 5 mg once daily in premenopausal women.

Contraindicate: Women of childbearing age or pregnant

RISKS/SIDE EFFECTS

METFORMIN	SPIRONOLACTONE
<ul style="list-style-type: none"> • Lactic acidosis • Hypothermia • Hypotension • Resistant bradycardia 	<ul style="list-style-type: none"> • Dizziness • Fatigue • Irregular menses • Breast tenderness • Hyperkalemia • Gynecomastia • Nausea, vomiting, diarrhea

<p style="text-align: center; margin: 0;">GABAPENTIN</p> <p style="background-color: #f4a460; color: white; text-align: center; padding: 2px;">Marketed 1957</p> <p>Indications</p> <ul style="list-style-type: none"> Partial seizures Post-herpetic neuralgia Restless Leg Syndrome 	<p style="text-align: center; color: red; margin: 0;">Off-Label uses</p> <ul style="list-style-type: none"> • Neuropathic pain/Painful diabetic neuropathy • Fibromyalgia • Nausea and vomiting • Migraine prophylaxis • Postmenopausal hot flashes • Essential tremors • Interstitial cystitis • Pruritis • Irritable bowel syndrome (IBS) • Refractory chronic cough • Alcohol dependence • Insomnia • Bipolar Disorder • Anxiety • Social Phobia • Resistant depressant and mood disorders • Post-traumatic stress disorder (PTSD) • Attention Deficit Disorder
--	---

<p style="text-align: center; background-color: #f4a460; color: white; padding: 5px;">DIABETIC NEUROPATHY & GABAPENTIN</p> <p>FDA Approved:</p> <ul style="list-style-type: none"> • Duloxetine (Cymbalta) • Pregabalin (Lyrica) • Capsaicin Patch 	<ul style="list-style-type: none"> • Similar profile as Pregabalin (Lyrica) • Systemic Evaluation (1998) <ul style="list-style-type: none"> • N-165 • Pain reduction & Improved quality of life • Few high-quality comparative trials have been done
---	--

<p style="text-align: center; background-color: #f4a460; color: white; padding: 5px;">FIBROMYALGIA & GABAPENTIN</p> <p>FDA Approved:</p> <ul style="list-style-type: none"> • duloxetine (Cymbalta) • milnacipran (Savella) • pregabalin (Lyrica) 	<p>American College of Rheumatology (ACR) guideline-approved fibromyalgia medication:</p> <ul style="list-style-type: none"> • Amitriptyline (Elavil) <ul style="list-style-type: none"> • Meta-analyses support efficacy • Clinical improvement 25-45% • High frequency of side effects • Efficacy decreases over time • Cyclobenzaprine (Fexmid) <ul style="list-style-type: none"> • Similar structure to TCAs • Meta-analyses: 21% reported improvement • Gabapentin (Neurontin) <ul style="list-style-type: none"> • Single trial • 30% decrease in pain • Insufficient evidence
--	---

**MIGRAINES
&
GABAPENTIN**

- Endorsed by the Canadian Headache Society
- 11 prophylactic drugs rec'd strong recommendations including gabapentin
- Systematic review of 5 controlled trials
 - Gabapentin was **not efficacious**
- 20-week trial of 523 patients
 - Gabapentin was **not efficacious**
- Meta-analysis of 56 articles
 - 8 Randomized Controlled Clinical Trials
 - 7 showed statistically significant clinical benefit from GBP (though modest)

MIGRAINE PREVENTION

Approved	Off-label
<ul style="list-style-type: none"> • Beta Blockers <ul style="list-style-type: none"> • Propranolol • Timolol • AEDs <ul style="list-style-type: none"> • Divalproex • Topiramate • CGRP antagonists <ul style="list-style-type: none"> • Erenumab (Aimovig) • Atogepant (Qulipta) • Fremanezumab (Ajovy) • Galcanezumab (Emgality) • Eptinezumab (Vyepsti) • Rimegepant (Nurtec) 	<ul style="list-style-type: none"> • Beta Blockers <ul style="list-style-type: none"> • Metoprolol tartrate, succinate • Atenolol • Calcium Channel Blockers <ul style="list-style-type: none"> • Verapamil • ACEIs/ARBs <ul style="list-style-type: none"> • Lisinopril • Candesartan • Antidepressants <ul style="list-style-type: none"> • Amitriptyline • Venlafaxine

MIGRAINES PROPHYLAXIS PEDIATRICS

Triptans (Oral)
FDA >18 years

Triptans (Nasal)
FDA >12 years

Risks of Non-treatment

Improved QOL
School attendance

Risks of Treatment

Increased risk of medication errors
Lack of clear dosing guidelines
Unforeseen side effects

BUPROPION (WELLBUTRIN)

Marketed 1957

<p style="text-align: center; background-color: #808080; color: white; padding: 5px;">Approved</p> <ul style="list-style-type: none"> Major depressive disorder Seasonal affective disorder Smoking Cessation 	<p style="text-align: center; background-color: #804000; color: white; padding: 5px;">Off-label</p> <ul style="list-style-type: none"> ADHD Anti-depressant-induced sexual dysfunction Obesity Bipolar, depressive episode
---	---

BUPROPION (WELLBUTRIN)


In 2012, GlaxoSmithKline was charged a \$3 billion fine for marketing off-label uses for bupropion like sexual dysfunction and weight loss.

2012 → 2014

But in 2014, it was approved for weight loss in combination with the drug naltrexone under the brand name Contrave

<div style="border: 1px solid black; padding: 5px; text-align: center; background-color: white; margin-bottom: 10px;">OBESITY</div> <p style="color: red; font-weight: bold;">FDA Approved Medications</p>	<p>LONG-TERM TREATMENTS</p> <ul style="list-style-type: none"> Semaglutide (Wegovy): Weekly injections Tirzepatide (Zepbound): Weekly injection Liraglutide (Saxenda): Daily injections Orlistat (Xenical, Alli) Phentermine/Topiramate (Qsymia) – Schedule IV Bupropion-naltrexone (Contrave) <p>SHORT-TERM TREATMENTS</p> <ul style="list-style-type: none"> Appetite suppressants: <ul style="list-style-type: none"> Phentermine (Adipex-P, Lomaira) (Schedule IV) Benzphetamine (Schedule III) Phendimetrazine (Schedule III) Diethylpropion (Schedule IV)
---	--

FDA WARNING
COMPOUND DRUGS ARE NOT APPROVED BY FDA



Legal restrictions on making copies of FDA-approved drugs

Compounders: Section 503A of the FD&C Act

- Restricts compounding to certain amounts that is not done "regularly or in inordinate amounts."

• Section 503B of the FD&C Act states that compounded drugs:

- cannot be **a copy of one or more FDA-approved drugs.**
- may not be identical or nearly identical to an FDA-approved drug
 - unless the approved drug is on FDA's drug shortage list.

ONGOING WEIGHT LOSS RESEARCH

Novo Nordisk announced results for Amycretin

- a combination of GLP-1 and amylin that's being tested as a pill or injection

EHR data suggests that tirzepatide may be more effective for weight loss than semaglutide.

Mirabegron and gene expression of the adrenergic Beta-3 receptor (ADRB3) regulation in human subcutaneous adipose tissue

- Activates brown fat, which burns calories to produce heat
- May help with insulin resistance, glucose intolerance, and metabolic disorders

MENOPAUSAL SYMPTOMS

Approved	Off-label
<ul style="list-style-type: none"> • Brisdelle (Paroxetine) • Duavee (conjugated estrogen w/bazedoxifene (SERM)) • Ospemifene (ospemiferne) <ul style="list-style-type: none"> • Selective estrogen receptor modulator • Veozah (fezolinetant) neurokinin 3 (NK3) receptor antagonist 	<ul style="list-style-type: none"> • SSRIs <ul style="list-style-type: none"> • Paroxetine • Escitalopram • Fluoxetine • SNRIs <ul style="list-style-type: none"> • Venlafaxine • Gabapentin

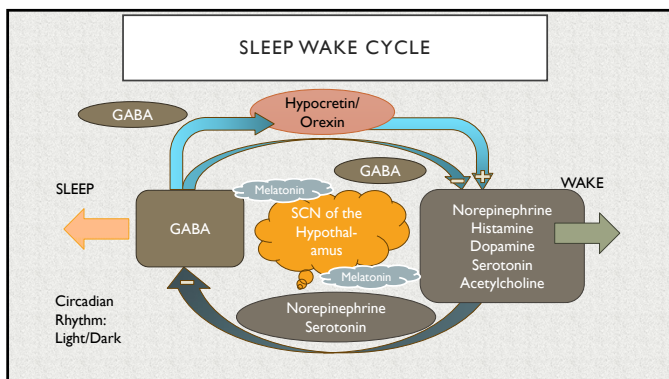
TAMSULOSIN

Off-Label Uses

- **Nephrolithiasis**
 - 2018 Cochrane Review
 - Efficacious
 - No increased side effects from tamsulosin
 - Alfuzosin, doxazosin, silodosin had statistically increased SE
- Double-blind, high-quality, placebo trial (n = 512)
 - No difference than placebo
- **LUTS (females)**
 - Meta-analysis
 - Effective
 - Safety remains unknown


OFF-LABEL MEDICATIONS FOR INSOMNIA

- Trazodone (Oleptro)
- Quetiapine (Seroquel)
- Melatonin
- Amitriptyline (Elavil)
- Imipramine (Tofranil)
- Gabapentin (Neurontin)



FDA APPROVED MEDICATIONS FOR INSOMNIA

- **Benzodiazepines**
 - Estazolam, Flurazepam, Temazepam, Triazolam, Quazepam
- **Nonbenzodiazepine benzodiazepine receptor agonists (BZRAs)**
 - Eszopiclone, Zaleplon, Zolpidem
- **Histamine H1 receptor antagonist:** Doxepin
- **Melatonin receptor agonist:** Ramelteon
- **Dual Orexin Receptor Antagonist:** Lemborexant



OTHER DRUGS WITH OFF-LABEL USES

Prazosin (Minipress) for Nightmares secondary to PTSD

Clomiphene (Clomid) for Male Infertility

Memantine (Namenda) for OCD

Clonidine (Catapres):


- Hot Flashes
- Migraine headaches
- Restless Leg Syndrome
- Sleep Apnea
- Smoking Cessation
- Tourette's Syndrome

BEFORE PRESCRIBING OFF LABEL, ASK YOURSELF?

- What is the drug approved for?
- Are there other drugs or therapies that are approved?
- What scientific studies are available to support the use of this drug?
- What are the potential benefits and risks?
- Will health insurance cover the treatment?

RULES OF OFF LABEL PRESCRIBING

- A comprehensive assessment and accurate diagnosis
- Shared decision making
- Document social determinants of health/health disparities



ANY QUESTIONS



REFERENCES

- American Diabetes Association Professional Practice Committee (2025) 3. Prevention or Delay of Diabetes and Associated Comorbidities: Standards of Care in Diabetes—2025. *Diabetes Care* 1 January 2025; 48 (Supplement 1): S50–S58. <https://doi.org/10.2337/dc25-S003>
- Attia, G.M., Almoutery, M.M., Alnakhli, F.T. (2023) Role of metformin in polycystic ovary syndrome (PCOS)-related infertility. *Cureus*. 2023 Aug 31; 15(8). doi: 10.7759/cureus.44493. PMID: 37791160, PMCID: PMC10544455.
- Boomershine, C. (2023) Fibromyalgia treatment and management. *Medscape*. <https://emedicine.medscape.com/article/329838-treatment>
- Callaghan, B., Armon, C., Bril, V., Colbert, L., David, W.S., Del Toro, D.R., Frink, K., et al (2021) Polyneuropathy quality measurement set: quality improvement in Neurology. *Neurology*. 98(1) 22-30. <https://doi.org/10.1212/WNL.00000000000013037>
- Church, K. (2020) The possible benefits of metformin for type 2 diabetes and other health conditions. <https://www.evidencebasedhealth.com/type-2-diabetes/metformin-health-benefits-why-they-likely-go-beyond-type-2-diabetes/>
- Clark, A., Tate, B., Urban, B., et al. (2023) Bupropion mediated effects on depression, attention deficit hyperactivity disorder, and smoking cessation. *Health Psychology Research*. 2023;11. doi: [10.5964/hpr.v11i1.81043](https://doi.org/10.5964/hpr.v11i1.81043)
- Congressional Research Service (2021) Off-label use of prescription drugs. R45792. <https://crsreports.congress.gov/product/pdf/R/R45792/3>
- Doghramji, K., Doghramji, P.P. (2024) Insomnia clinical practice guidelines. July 22, 2024. Accessed February 01, 2025. <https://www.healio.com/clinical-guidance/insomnia/clinical-practice-guidelines-treatment-guidelines>
- Fariba, K., Saadabadi, A. (2021, August) Topiramate. *Stat Pearls*. Retrieved September 15, 2021 from <https://www.ncbi.nlm.nih.gov/books/NBK554530/>

REFERENCES

- Food and Drug Administration (2023) FDA approves novel drug to treat moderate to severe hot flashes caused by menopause. <https://www.fda.gov/news-events/press-announcements/fda-approves-novel-drug-treat-moderate-severe-hot-flashes-caused-menopause>
- Furey, K., & Wilkins, K. (2016). Prescribing "off-label": what should a physician disclose. *AMA Journal of Ethics*. <https://journalofethics.ama-assn.org/article/prescribing-label-what-should-physician-disclose/2016-06>
- Goodman CW, Brett AS. (2019) A Clinical Overview of Off-label Use of Gabapentinoid Drugs. *JAMA Intern Med*. 2019;179(5):695–701. doi:10.1001/jamainternmed.2019.0086
- Huecker, MR., Smiley, A., Saadabadi, A. (2021) Bupropion. *Stat Pearls*. Retrieved 9/2021 from <https://www.ncbi.nlm.nih.gov/books/NBK470212/>
- Long, T., Zhang, Y., Zeng, C., Zheng, S., Zhou, L., Liu, H. (2022) Effects of Low-Dose Spironolactone Combined with Metformin or Either Drug Alone on Insulin Resistance in Patients with Polycystic Ovary Syndrome: A Pilot Study. *Int J Endocrinol*. 2022 Mar 19;2022:9927240. doi: 10.1155/2022/9927240. PMID: 35345424; PMCID: PMC8957463.
- Magraith, K., Jang, C. (2023) Management of menopause. *Aust Prescr*. 2023 Oct; 46(3): 48-53. doi: 10.18773/austprescr.2023.014.
- Maryanoff, B. (2016, July) Phenotypic assessment and the discovery of topiramate. *ACS Med Chem Lett*. 2016 Jul 14; 7(7): 662–665. Published online 2016 Jun 13. doi: 10.1021/acsmchemlett.6b00176
- National Institute for Health and Care Excellence (2021) Headaches in over 12s: diagnosis and management. <https://www.nice.org.uk/guidance/cg150/resources/headaches-in-over-12s-diagnosis-and-management-pdf-35109624582853>
- O'Brien, P. (2019). Off-label considerations for mid-level practitioners. *American Med Spa Association*. <https://www.americanmedspa.org/blogpost/1633466/16454/Off-label-Considerations-for-Mid-level-Practitioners>

REFERENCES

- Patibandla, S., Heaton, J., Kyaw, H. (2023) Spironolactone. [Updated 2023 Jul 4]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554421/>
- Perloff, M.D., Berlin, R.K., Gillette, M., Petersile, M.J., Kurowski, D. (2016) Gabapentin in headache disorders: what is the evidence. *Pain Med*. 2016, Jan; 17(1): 162-71. doi: 10.1111/pme.12931
- *Pharmacy Times* (2016) 5 drug classes for sleep disorders. Retrieved 9/22/2019 from <https://www.pharmacytimes.com/view/5-drug-classes-for-sleep-disorders>
- Riemann, D., Espie, C.A., Akten, E., Arandottir, E.S., Baglioni, C., Bassetti, C.L.A., Bastien, C., Berzina, N., Bjorvatn, B., Dikous, D., Dolenc, G.L., Ellis, J.G., et al. (2023) The European insomnia guideline: an update on the diagnosis and treatment of insomnia 2023. *J. Sleep Res*. 2023 Dec; 32(6):e14035. doi: 10.1111/jsr.14035.
- Rotermund, C., Machetanz, G., Fitzgerald, J.C. (2018). The therapeutic potential of metformin in neurodegenerative diseases. *Front. Endocrinol.*, 19 July 2018. <https://doi.org/10.3389/fendo.2018.00400>
- Saleh, N. (2019). Do's and don'ts for off-label prescribing. *Infectious Diseases*. <https://www.mdlinx.com/article/do-s-and-don-ts-for-off-label-prescribing/lfc-3743/>
- Sanchez, C., Keri, J. (2022) Androgen receptor inhibitors in the treatment of acne vulgaris: efficacy and safety profiles of clascortene 1% cream. *Clinical Cosmetic and Investigational Dermatology*. 2022;15, pp. 1357-1366. <https://doi.org/10.2147/CICID.S289750>
- Sateia MJ, Buysse DJ, Krystal AD, et al. (2017) Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017; 13:307.
- Shridat, J., Lipoff, J. (2017). Prescribing to save patients money: ethical considerations. *Journal of the American Academy of Dermatology*. <https://doi.org/10.1016/j.jaad.2017.08.012>

REFERENCES

- Sprenger T, Viana M, Tassorelli C. Current Prophylactic Medications for Migraine and Their Potential Mechanisms of Action. *Neurotherapeutics*. 2018 Apr;15(2):313-323. doi: 10.1007/s13311-018-0621-8. PMID: 29671241; PMCID: PMC593650.
- Trivedi, A. (2024) Prescribing dilemma: balancing risk and benefits of off-label migraine treatment in a child. *Pharmaceutical Journal*.
- U.S. DEPT OF HEALTH & HUMAN SERVICES (2021). Prescription medications to treat overweight & obesity. *National Institute of Diabetes and Digestive and Kidney Diseases*. Retrieved 9/18/2021 from <https://www.niddk.nih.gov/health-information/weight-management/prescription-medications-treat-overweight-obesity>
- U.S. Food and Drug Administration. (2018). Understanding unapproved use of approved drugs "off label". <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label>
- Van Norman, G.A. (2023) Off-label use vs off-label marketing of drugs: Part 1: off-label use – patient harms and prescriber responsibilities. *J Am Coll Cardiol Basic Trans Science*. 2023, Feb 8 (2) 224-233
- Van Norman G.A. (2023) Off-label use vs off-label marketing: part 2: off-label marketing-consequences for patients, clinicians, and researchers. *JACC Basic Transl Sci*. 2023 Mar 27;8(3):359-370. doi: 10.1016/j.jacbts.2022.12.012. PMID: 37034284; PMCID: PMC10077121.
- Yasaei, R., Katta, S., Saadabadi, A. (2021, August) Gabapentin. *Stat Pearls*. Retrieved 9/16/2021 from <https://www.ncbi.nlm.nih.gov/books/NBK493228/>
- Zhang, H.L., Huang, Z.G., Qiu, Y., Cheng, X., Zou, X.Q., Liu, T.T. (2017) Tamsulosin for treatment of lower urinary tract symptoms in women: a systematic review and meta-analysis. *Int J Impot Res*. 2017 Jul;29(4):148-156. doi: 10.1038/ijir.2017.12. Epub 2017 Apr 20. PMID: 28424499.
- Zito, P.M., Bistas, K.G., Patel, P., et al. (2024) Finasteride. [Updated 2024 Feb 28]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. <https://www.ncbi.nlm.nih.gov/books/NBK513329/>