High-Yield Topics: Primary Care-Psychopharmacology

Information contained in these documents and subsequent implementation of therapy changes should be considered in combination with patients' relevant history and current clinical status. Specialty consultation should be utilized and may be necessary for complex cases or additional guidance.

CARDIOLOGY

1) Cardiac Effects of ADHD Medications
2) QTc Prolongation: Antidepressants & Antipsychotics
3) Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) & Blood Pressure

DRUG INTERACTIONS

4) Clopidogrel (Plavix) – Antidepressant Drug Interaction
5) Smoking & Drug Interactions
6) Opioid-Psychotropic Drug Interactions
7) Methadone-Psychotropic Drug Interactions
8) Oxycodone-Psychotropic Drug Interactions
9) Tramadol-Psychotropic Drug Interactions
10) Lithium: Therapy Management & Drug Interactions

ENDOCRINOLOGY

11) Strategies for Managing Metabolic Risks of Second Generation/Atypical Antipsychotics

GASTROENTEROLOGY/HEPATOLOGY

12) Liver Toxicity & Naltrexone
13) Alcohol Use Disorder Treatment in Liver Dysfunction
14) Psychotropics & Liver Impairment

HEMATOLOGY

15) Bleeding Risk & Antidepressants
16) Psychotropics & Blood Dyscrasias

NEPHROLOGY

17) Psychotropics & Renal Impairment

NEUROLOGY

18) Serotonin Syndrome Warnings
19) Psychotropics & Seizure Risk

ORTHOPEDICS

20) Bone Fracture Risk & Antidepressants

WOMEN'S HEALTH

21) Medication Use in Pregnancy & Breastfeeding
22) Anti-Epileptic Drugs/Mood Stabilizers & Hormonal Contraceptives

OTHER

21) Emerging Substance of Abuse: Kratom

Cardiac Effects of ADHD Medications

WHAT DO I NEED TO KNOW?

- Medications commonly used for treatment of ADHD include:
  - Stimulants – methylphenidate and amphetamine salts
  - Non-stimulants – atomoxetine, guanfacine, clonidine and bupropion (off-label)
- **Stimulants and atomoxetine may increase blood pressure and/or heart rate:**[1-5]

	↑ Systolic BP	↑ Diastolic BP	↑ HR
Methylphenidate	Incidence not defined; Average 2 – 4mmHg	Incidence not defined; Average 2 – 4mmHg	Incidence 5%; Average 3 – 6 bpm
Amphetamines	Incidence ≤ 35%	Incidence ≤ 22%	Incidence ≤ 6%
Atomoxetine	Incidence ≤ 12.5%	Incidence ≤ 21.5%	Incidence ≤ 23.4%

- Bupropion does not have significant effects on BP
- When used for ADHD, clonidine and guanfacine may have dose-dependent effects:
  - Clonidine: ↓ BP by 4 to 8.8mmHg and ↓ HR by 4 to 7.7bpm[6]
  - Guanfacine: mean ↓ in SBP of 5mmHg, ↓ DBP of 3mmHg and ↓ HR of 6bpm[7]
  - Monitor for rebound HTN when discontinuing
- **Though very rare (incidence <0.01%), stimulants and atomoxetine have been associated with cardiovascular (CV) disease/events and sudden cardiac death**
  - Highest risk in patients with congenital cardiac abnormalities
  - Patients with significant cardiac risk factors and/or family history are also at increased risk

FDA WARNINGS for Cardiac Risk with Stimulants and Atomoxetine:[3-5,8]

Atomoxetine is "associated with CV events in **patients with pre-existing** structural cardiac abnormalities or serious heart problems."

Methylphenidate is "associated with CV events in **patients with and without pre-existing** structural cardiac abnormalities or serious heart problems."

Amphetamine sulfate and mixed salts have a **BLACK BOX WARNING** and are "associated with CV events in **patients with and without pre-existing** structural cardiac abnormalities or serious heart problems."

- In 2011, two retrospective cohort studies evaluated CV risk[9,10]
  - Found no ↑ risk of serious adverse CV events in children and adults
  - One study notes that doubling of CV risk cannot be ruled out in children and young adults

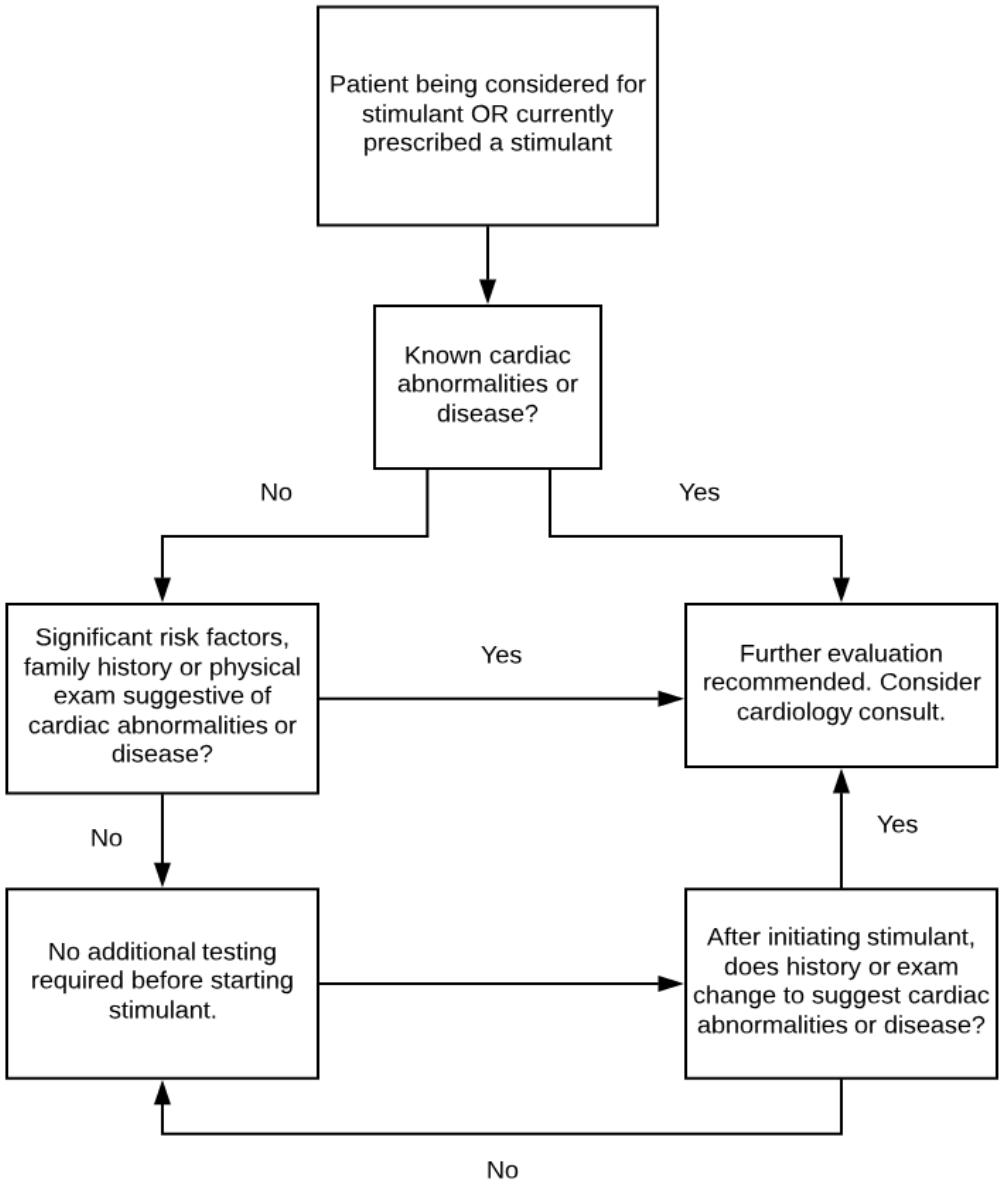
*FDA Drug Safety Communication issued in 2011 states that recommendations for use have not changed in response to study findings: "**Stimulants and atomoxetine should generally not be used in patients with serious heart problems or for whom an increase in blood pressure or heart rate would be problematic.**"*[8]

HOW DO I MANAGE STIMULANTS AND CARDIOVASCULAR RISK?

AHA & AAP Recommended Monitoring

- **Baseline:** review patient and family cardiac history, blood pressure, heart rate, EKG if history unclear or high risk
- **Each visit:** blood pressure, heart rate
- **Anytime:** EKG if cardiac concerns, consult cardiology

Treatment Algorithm for Stimulants and Atomoxetine[11-12]



As a general rule, stimulants should be avoided in patients with known structural cardiac abnormalities, cardiomyopathy, heart rhythm abnormalities or other cardiac problems

References: 1) Westover AN, Halm EA. Do prescription stimulants increase the risk of adverse cardiovascular events?: A systematic review. BMC Cardiovascular Disorders. 2012;12:41. 2) Hennissen L, et al. Cardiovascular Effects of Stimulant and Non-Stimulant Medication for Children and Adolescents with ADHD: A Systematic Review and Meta-Analysis of Trials of Methylphenidate, Amphetamines and Atomoxetine. CNS Drugs. 2017;31:199-215. 3) Ritalin LA (methylphenidate hydrochloride) package insert. Novartis. 4) Adderall XR (amphetamine mixed salts) package insert. Shire, Inc. Wayne, PA. Rev:11/2013. 5) Strattera (atomoxetine) package insert. Lilly, LLC. Indianapolis, IN. Rev: 05/2017. 6) Kapvay (clonidine hydrochloride) package insert. Shionogi Pharma, Inc. Atlanta, GA. Issued: 2010. 7) Intuniv (guanfacine extended release) package insert. Shire, Inc. Wane, PA. Rev: 02/2013. 8) FDA Drug Safety Communication: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in adults. Last Updated: 02/13/2018. Date Accessed: 03/04/2020. 9) Cooper WO, et al. ADHD Drugs and Serious Cardiovascular Events in Children and Young Adults. *N Engl J Med*. 2011;365:1896-1904. 10) Habel LA, et al. ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-Aged Adults. *JAMA*. 2011;306(24):2673-2683. 11) Perrin JM, et al. Cardiovascular Monitoring and Stimulant Drugs for Attention-Deficit/Hyperactivity Disorder. Pediatrics. 2008;122(2):451-453. 12) Graham L. AHA Releases Recommendations on Cardiovascular Monitoring and the Use of ADHD Medications in Children with Heart Disease. Am Fam Physician. 2009;79(10):905-910.

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QTc Prolongation: Antidepressants & Antipsychotics

WHAT DO I NEED TO KNOW?

- **Some antidepressants and antipsychotics can cause QTc prolongation, particularly at higher doses and in the presence of risk factors**

RISK FACTORS for Drug-Induced QTc Prolongation[1,2]

Sepsis	Female sex
Use of ≥1 QTc prolonging agent	Bradycardia
Heart failure	Loop diuretics
History of prolonged QTc	≥ 68 years old
Baseline prolonged QTc	Doses above recommended limits
Electrolyte abnormalities (i.e. K^+, Mg^{2+})	Other heart disease (e.g. MI)

QTc Interval Cut-Offs[3]

	Normal QTc	Borderline QTc	Prolonged QTc
Male	≤ 430ms	431 to 450	> 450ms
Female	≤ 450ms	451 to 470ms	> 470ms

Risk of Torsades de Pointes (TdP) Increases as the QTc Interval Increases[2,4]

Δ QTc interval < 5ms	Not associated with ↑ risk of TdP
Δ QTc interval < 20ms	*Potential* risk of TdP
Δ QTc interval ≥ 20ms	**Increased** risk of TdP, consider therapy intervention
QTc > 500ms or Δ QTc interval ≥ 60ms or abnormal QTc with symptoms	Clinically significant risk of TdP, intervention warranted

TdP = a serious, fatal ventricular arrhythmia that can lead to sudden cardiac death

HOW DO I MANAGE QTc PROLONGATION RISK WITH ANTIDEPRESSANTS AND ANTIPSYCHOTICS?[5,6]

- Antidepressant and antipsychotic induced QTc prolongation is:
  - Dose-dependent
  - Most likely to occur in the presence of risk factors or overdose
- Keep dose within recommended limits and adjust for reduced renal or hepatic function
- Avoid concomitant use of multiple QTc prolonging agents, when possible
- If risk factors present, consider using agents with lower QTc prolonging potential
- If using an antidepressant or antipsychotic with a high relative risk, follow FDA dose limit recommendations outlined in the manufacturer labeling. For example, citalopram max dose is 40mg/day (20 mg/day in patients > 60 years old).

Risk of QTc Prolongation with Antidepressants and Antipsychotics[2,5,6]

ANTIDEPRESSANTS					
Drug Name	Risk	Mean Δ QTc Interval	Drug Name	Risk	Mean Δ QTc Interval
Fluoxetine	Conditional	Insufficient data	Duloxetine	Unknown	Insufficient data
Paroxetine	Conditional	Insufficient data	Venlafaxine	Possible	10.6 ms
Sertraline	Conditional	3.0 ms	Bupropion	Unknown	Insufficient data
Escitalopram	High	7.27 ms	Amitriptyline	Conditional	Insufficient data
Citalopram	High	10.58 ms	Nortriptyline	Possible	Insufficient data
Mirtazapine	Possible	Insufficient data	Trazodone	Conditional	Insufficient data
ANTIPSYCHOTICS					
Drug Name	Risk	Mean Δ QTc Interval	Drug Name	Risk	Mean Δ QTc Interval
Chlorpromazine	High	Insufficient data	Asenapine	Possible	2 to 5 ms
Thioridazine	High	33 to 41 ms	Clozapine	Possible	10 ms
Haloperidol	High	7 to 15 ms	Olanzapine	Conditional	2 to 6.5 ms
Perphenazine	Possible	Insufficient data	Quetiapine	Conditional	6 to 15 ms
Pimozide	High	19 ms	Risperidone	Conditional	3.5 to 10 ms
Fluphenazine	Unknown	Insufficient data	Paliperidone	Possible	2 to 4 ms
Loxapine	Unknown	Insufficient data	Aripiprazole	Possible	-1 to -4 ms
Thiothixene	Unknown	Insufficient data	Lurasidone	Possible	4.6 to 7.5 ms
Iloperidone	Possible	9 ms	Ziprasidone	Conditional	16 to 21 ms

Conditional risk indicates the drug is associated with QTc prolongation or TdP only under certain conditions (i.e. presence of risk factors)
Possible risk indicates the drug can cause QTc prolongation but there is a lack of evidence for risk of TdP at recommended doses
High risk indicates the drug is known to prolong QTc and has been associated with risk of TdP, even at recommended doses
Unknown risk indicates insufficient evidence to classify risk

Risk of QTc Prolongation with Other Common Medications[2]

High Risk	Conditional Risk
Amiodarone	Diphenhydramine
Azithromycin	Furosemide
Donepezil	Hydrochlorothiazide
Fluconazole	Omeprazole, Pantoprazole, Lansoprazole
Levofloxacin	Loperamide
Methadone	Metoclopramide
Ondansetron	Metronidazole

EKG Monitoring[4,7]

- In general, antipsychotics and antidepressants can be started without EKG monitoring
- Routine monitoring of EKG recommended with use of a high-risk psychotropic agent, in individuals with additional risk factors or drugs with EKG monitoring requirements
- Obtain EKG anytime symptoms suggestive of QTc prolongation occur in individuals on medications with TdP risk

References: 1) Tisdale JE, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes.* 2013;6:479-487; 2) Woosley RL, Heise CW , Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, QTdrugs List, [Accession Date], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755; 3) Garson A Jr. How to measure the QT interval – what is normal? *Am J Cardiol.* 1993;72:14B–16B; 4) Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes. *Can Pharm J (Ott).* 2016;149(3): 139-152. 5) Beach SR, et al. QTc Prolongation, Torsades de Pointes, and Psychotropic Medications. *Psychosomatics*. 2018;*54*(1), 1–13; 6) Washington, N. B., Brahm, N.C., & Kissack, J. (2012). Which psychotropics carry the greatest risk of QTc prolongation? *Current Psychiatry, 11(10),* 36-39; 7) Shah, A. A., Aftab, A., & Coverdale, J. (2014). QTc Prolongation with Antipsychotics. *Journal of Psychiatric Practice, 20(3),* 196–206;

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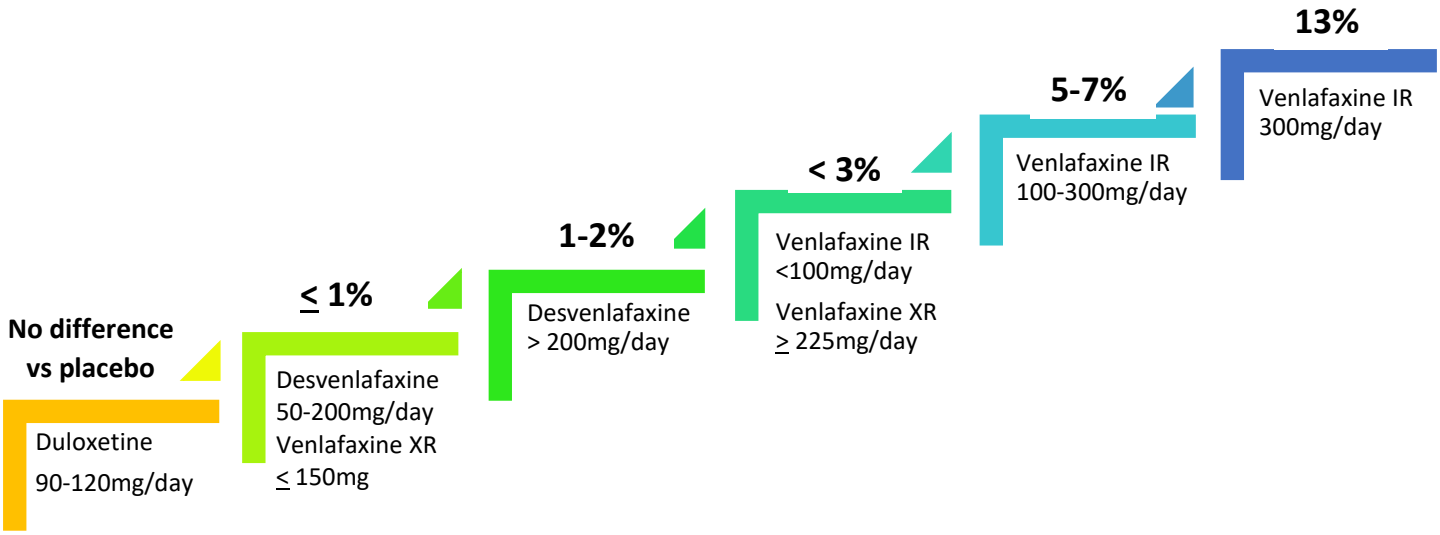
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) & Blood Pressure

WHAT DO I NEED TO KNOW?

- **SNRIs are associated with dose-dependent increase in blood pressure**[1]
- **More likely with venlafaxine (Effexor)** than other SNRIs
- Venlafaxine is predominately associated with increase in diastolic BP
  - Highly dose-dependent, incidence is statistically and clinically significant at dosages above 300 mg/day[2,3]
  - Majority of blood pressure increases are between 10 and 15 mmHg[2,3]
- Risk with duloxetine is low; usually only at higher than recommended doses[4]
- A pooled analysis found short-term desvenlafaxine treatment was associated with a small but statistically significant increase in supine systolic and diastolic BP[5]

Incidence of Sustained Elevations* in Blood Pressure[1-6]

**Sustained elevation defined as DBP ≥ 90mmHg or ≥ 10mmHg increase from baseline for 3 consecutive visits*

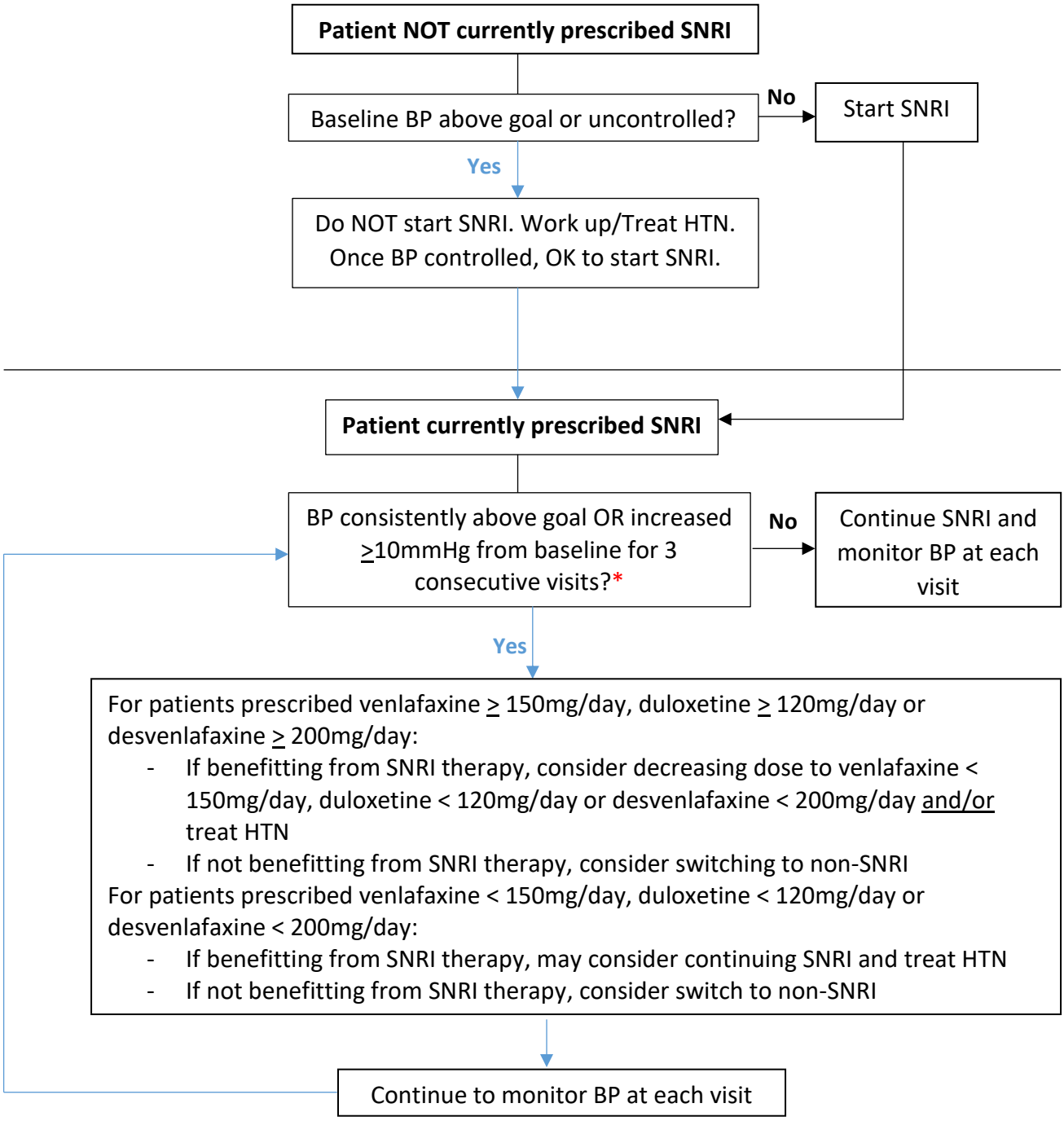


HOW DO I MANAGE SNRI USE AND HYPERTENSION RISK?

Recommended SNRI **Blood Pressure** Monitoring:

- Baseline, within 1st month and each subsequent visit
- Follow treatment algorithms for SNRI prescribing (see next page)

SNRI Treatment Algorithm^



*If severe HTN, sustained elevations ≥ 20mmHg, hypertensive urgency or emergency, SNRI should be discontinued or avoided. If hypertensive event determined to be SNRI-related, SNRI should not be restarted.

^Information herein and subsequent implementation of therapy changes should be considered in combination with patients' relevant history and current clinical status.

References: 1) Zhong Z, et al. A meta-analysis of effects of selective serotonin reuptake inhibitors on blood pressure in depression treatment: outcomes from placebo and serotonin and noradrenaline reuptake inhibitor controlled trials. *Neuropsychiatric Disease and Treatment*. 2017;13:2781-2796. 2) Effexor (venlafaxine hydrochloride) package insert. Wyeth Pharmaceuticals Inc, Philadelphia, PA. Rev 02/08. 3) Effexor XR (venlafaxine extended release) package insert. Wyeth Pharmaceuticals Inc, Philadelphia, PA. Rev 01/17. 4) Cymbalta (duloxetine hydrochloride) package insert. Eli Lilly and Company. Rev 04/08. 5) Thase ME, et al. Effects of desvenlafaxine on blood pressure in patients treated for major depressive disorder: a pooled analysis Curr Med Res Opin. 2015 Apr;31(4):809-20. 6) Pristiq (desvenlafaxine) package insert. Wyeth Pharmaceuticals Inc. Philadelphia, PA. Rev 10/11.

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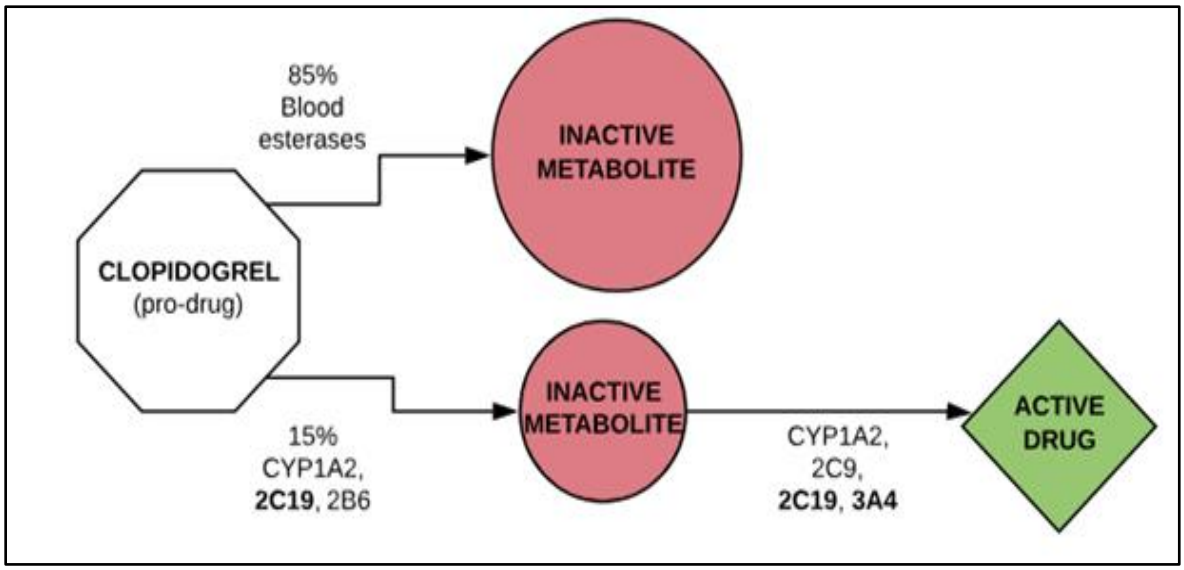
Clopidogrel (Plavix) - Antidepressant Drug Interaction

WHAT DO I NEED TO KNOW?

- **Clopidogrel is a "pro-drug" which means it requires activation by hepatic CYP enzymes before producing its intended therapeutic effects**



- Drugs that inhibit CYP2C19, CYP3A4, and CYP1A2 enzymes have been shown to:
  - Prevent conversion of clopidogrel to its active form
  - Decrease clopidogrel effectiveness
- Certain antidepressants inhibit CYP2C19, CYP3A4, and CYP1A2 enzymes

CYP2C19	CYP3A4	CYP1A2
Fluoxetine (moderate) Fluvoxamine (moderate)	Fluoxetine (weak) Fluvoxamine (weak)	Fluvoxamine (strong)

HOW DO I MANAGE THE INTERACTION BETWEEN CLOPIDOGREL AND ANTIDEPRESSANTS?

- **Avoid fluoxetine and fluvoxamine** in patients on clopidogrel
- If fluvoxamine or fluoxetine cannot be avoided, consider consultation with cardiology to switch clopidogrel to ticagrelor (Brilinta) or prasugrel (Effient)

References: 1) Wang ZY, et al. Pharmacokinetic drug interactions with clopidogrel: updated review and risk management in combination therapy. Therapeutics and Clinical Risk Management. 2015;11:449-467. 2) Bykov K, et al. Impact of an Interaction Between Clopidogrel and Selective Serotonin Reuptake Inhibitors. Am J Cardiol. 2017;119(4):651-657. 3) Bykov K, et al. Updating the Evidence of the Interaction Between Clopidogrel and CYP2C19-Inhibiting Selective Serotonin Reuptake Inhibitors: A Cohort Study and Meta-Analysis. Drug Saf. 2017;40(10):923-932. 4) Hirsh-Rokach B, et al. Differential impact of selective serotonin reuptake inhibitors on platelet response to clopidogrel: a randomized, double-blind, crossover trial. Pharmacotherapy. 2015;35(2):140-147. 5) College of Psychiatric and Neurologic Pharmacists. Psychiatric Pharmacotherapy Review 2018-2019.

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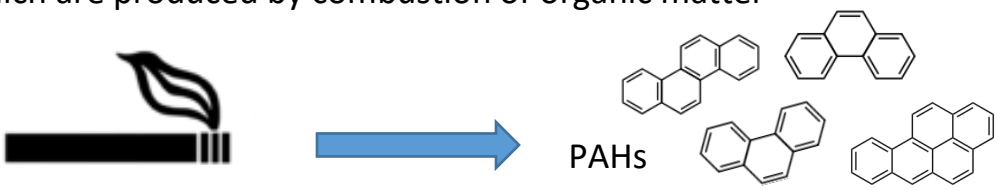
Smoking & Drug Interactions

WHAT DO I NEED TO KNOW?[1-4]

- Tobacco smoke contains 7000+ chemicals including **polycyclic aromatic hydrocarbons** (PAHs) which are produced by combustion of organic matter



- **PAHs increase activity of drug metabolizing enzymes CYP1A2 and 1A1 which may affect blood levels of certain medications**
- PAHs may also be produced from smoking cannabis, especially if mixed with tobacco
- Current research suggests nicotine exposure in the absence of smoke (e.g. nicotine patch, gum, lozenge) is not associated with significant drug interactions
- Research on effects of inhaled nicotine or cannabis via vape pens and e-cigarettes is still emerging
- **Current evidence suggests interaction may have greatest clinical significance at ≥ 10 cigarettes per day however any amount of tobacco smoke may have an effect**

HOW DO I MANAGE MEDICATIONS THAT INTERACT WITH SMOKING?[1,4]

- Routinely ask patients about their smoking status
- Patients who smoke or have recently quit should be screened for drug interactions **(See table on next page)**

Initiation of smoking:	Cessation of smoking:
• Induction of CYP1A2 and 1A1	• Reversal of CYP1A2 and 1A1 induction
• Will see ↑ drug metabolism and ↓ plasma levels of certain drugs	• Will see ↓ drug metabolism and ↑ plasma levels of certain drugs
➔ Consider ↑ dose	➔ Consider ↓ dose

- Empirical dose change may be necessary within 2-3 days after smoking initiation or cessation due to changes in enzyme inducers
- Impact on drug metabolism may continue for up to a month after smoking cessation warranting close monitoring during this time
- Offer evidence-based medication smoking cessation therapies when applicable:
  - Nicotine replacement therapy
  - Bupropion SR (Zyban or Wellbutrin)
  - Varenicline (Chantix)

Clinically Significant Drug Interactions with Smoking[1-10]

Drug Name	Effect of Smoking* (approx. % change in drug level)
Caffeine	↓ drug levels
Chlorpromazine	↓ drug levels (24%)
Clopidogrel	↑ active metabolite levels, ↑ anti-platelet effects
Clozapine	↓ drug levels (up to 50%)
Cyclobenzaprine	↓ drug levels
Duloxetine	↓ drug levels (38%)
Flecainide	↓ drug levels (25%)
Fluvoxamine	↓ drug levels (39%)
Haloperidol	↓ drug levels (up to 70%)
Hormonal contraceptives	↓ estradiol levels; ↑ risk of CV effects, women ≥ 35 y/o at highest risk
Melatonin	↓ drug levels; does not significantly alter endogenous melatonin
Methadone	↓ drug levels
Mexiletine	↓ drug levels
Mirtazapine	↓ drug levels (23-41%)
Olanzapine	↓ drug levels (12%)
Propranolol	↓ drug levels
Ramelteon	↓ drug levels
Riociguat	↓ drug levels (50-60%)
Ropinirole	↓ drug levels (30-38%)
Theophylline	↓ drug levels
Thiothixene	↓ drug levels
Tizanidine	↓ drug levels (30-40%)
*Smoking cessation or reduction in smoking may have opposite effects	

References: 1) Anderson GD and Chan LN. Pharmacokinetic Drug Interactions with Tobacco, Cannabinoids and Smoking Cessation Products. Clin Pharmacokinet. 2016;55:1353-1368. 2) Zevin S and Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet*. 1999;36:425-28. 3) Kroon LA. Drug interactions with smoking. *Am J Health-Syst Pharm*. 2007;64:1817-1921. 4) Fankhauser MP. Drug Interactions with tobacco smoke: Implications for patient care. *Current Psychiatry*. 2013;12(1):12-16. 5) Horn JR and Hansten PD. Get to Know an Enzyme: CYP1A2. Pharmacy Times. 2007. Accessed: November 29, 2018. 6) Lexi-Drugs. Hudson, OH: Lexicomp Inc. Date Accessed: 29 November 2018. 7) U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Last Updated: November 14, 2017. Accessed: 29 November 2018. 8) Preston CL. Stockley's Drug Interactions. Clozapine + Tobacco. London: Pharmaceutical Press. 9) Augustin M, et al. Differences in Duloxetine Dosing Strategies in Smoking and Nonsmoking Patients: Therapeutic Drug Monitoring Uncovers the Impact on Drug Metabolism. J Clin Psychiatry. 2018;79(5):e1-e5. 10) Al-Jaffar H. What are the clinically significant drug interactions with cigarette smoking? UK Medicines Information. 2017.

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Opioid–Psychotropic Drug Interactions

WHAT DO I NEED TO KNOW?

- **Certain opioids have clinically significant drug interactions which have the potential to alter effectiveness of the opioid medication AND/OR increase risk of adverse events**

Drug-Drug Interactions Between Opioids and Psychotropic Agents or Substances

COMMON PSYCHOTROPICS		CODEINE	HYDROCODONE	METHADONE
Antidepressants	Bupropion	↓ opioid effect*	↓↑ opioid effect/AEs*	↑ opioid effect/AEs; EKG
	Citalopram	SS	SS	EKG changes possible; SS
	Duloxetine	↓ opioid effect*; SS	↓↑ opioid effect/AEs*; SS	↑ effect/AEs of both; EKG; SS
	Escitalopram	SS	SS	SS, EKG
	Fluoxetine	↓ opioid effect*; SS	↓↑ opioid effect/AEs*; SS	↑ opioid effect/AEs; EKG; SS
	Mirtazapine	CNS	CNS	CNS
	Paroxetine	↓ opioid effect*; SS; CNS	↓↑ opioid effect/AEs*; SS; CNS	↑ opioid effect/AEs; EKG; SS; CNS
	Sertraline	↓ opioid effect*; SS	SS	↑ opioid effect/AEs; EKG; SS
	TCAs	↓ opioid effect*; SS; CNS	↓↑ opioid effect/AEs*; SS; CNS	↑ effect/AEs of both; EKG; SS; CNS
	Venlafaxine	SS	SS	SS
Mood Stabilizers	Carbamazepine	↓ opioid effect*	↓ opioid effect*	↓ opioid effect*
	Lamotrigine			CNS
	Lithium	SS	SS	EKG, SS
	Valproic Acid			CNS
Antipsychotics	Aripiprazole			
	Fluphenazine			
	Haloperidol			EKG
	Olanzapine	CNS	CNS	CNS
	Paliperidone			
	Quetiapine	CNS	CNS	EKG, CNS
	Risperidone			
	Ziprasidone			EKG
Sedatives & Hypnotics	Benzodiazepines	**BBW**	**BBW**	**BBW**
	Diphenhydramine	CNS	CNS	EKG (HD); CNS
	Eszopiclone	**BBW**	**BBW**	**BBW**
	Hydroxyzine	CNS	CNS	EKG (HD); CNS
	Zolpidem	**BBW**	**BBW**	**BBW**
Other	Alcohol	**BBW**	**BBW**	**BBW**
	Buspirone	SS	SS	SS
	Cannabis	↓ opioid effect*; CNS	↓↑ opioid effect/AEs*; CNS	↑ opioid effect/AEs; CNS
	Gabapentin	CNS	CNS	CNS
	Trazodone	CNS; SS	CNS; SS	CNS; SS

GREEN=low risk of clinically significant interactions, generally considered safe to use with appropriate monitoring; YELLOW=potentially clinically significant interaction, monitor combination closely; ORANGE=clinically significant interaction, use alternative therapies for new starts, if possible; RED=potentially fatal interaction, recommend slow taper of opioid or interacting drug, avoid combination; **BBW**=FDA Black Box Warning: potentially fatal combination; SS = risk of serotonin syndrome is highest with tramadol but possible with all opioids especially at high doses and in combination with ≥ 2 serotonergic agents; AE=risk of adverse event; CNS = additive CNS depression, monitor sedation; EKG = possible EKG changes such as QTc prolongation; HD = at high doses; ^Although FDA warning exists, clinical risk with tramadol may be lower than with other, more potent opioids; *Potential for opioid withdrawal and reduced pain control

Common Psychotropics		Morphine	Oxycodone	Tramadol
Antidepressants	Bupropion		↑ opioid effect/AEs	↓ opioid effect*
	Citalopram	SS	SS	↓ opioid effect*; SS
	Duloxetine	SS	↑ opioid effect/AEs; SS	↓ opioid effect*; SS
	Escitalopram	SS	SS	↓ opioid effect*; SS
	Fluoxetine	SS	↑ opioid effect/AEs; SS	↓↑ opioid effect/AEs*; SS
	Mirtazapine	CNS	CNS	CNS
	Paroxetine	SS; CNS	↑ opioid effect/AEs; SS; CNS	↓ opioid effect*; SS; CNS
	Sertraline	SS	SS	↓ opioid effect*; SS
	TCAs	↑ opioid effect/AEs; SS; CNS	SS; CNS	↓ opioid effect*; SS; CNS
	Venlafaxine	SS	SS	SS
Mood Stabilizers	Carbamazepine	↓ opioid effect*	↓ opioid effect*	↓ opioid effect*
	Lamotrigine			
	Lithium	SS	SS	SS
	Valproic Acid			
Antipsychotics	Aripiprazole			
	Fluphenazine			
	Haloperidol			
	Olanzapine	CNS	CNS	CNS
	Paliperidone			
	Quetiapine	CNS	CNS	CNS
	Risperidone			
	Ziprasidone			
Sedatives & Hypnotics	Benzodiazepines	**BBW**	**BBW**	**BBW^**
	Diphenhydramine	CNS	CNS	CNS
	Eszopiclone	**BBW**	**BBW**	**BBW^**
	Hydroxyzine	CNS	CNS	CNS
	Zolpidem	**BBW**	**BBW**	**BBW^**
Other	Alcohol	**BBW**	**BBW**	**BBW**
	Buspirone	SS	SS	SS
	Cannabis	CNS	↑ opioid effect/AEs; CNS	↓↑ opioid effect/AEs*; CNS
	Gabapentin	CNS	CNS	CNS
	Trazodone	CNS; SS	CNS; SS	CNS; SS

GREEN=low risk of clinically significant interactions, generally considered safe to use with appropriate monitoring; YELLOW=potentially clinically significant interaction, monitor combination closely; ORANGE=clinically significant interaction, use alternative therapies for new starts, if possible; RED=potentially fatal interaction, recommend slow taper of opioid or interacting drug, avoid combination; **BBW**=FDA Black Box Warning: potentially fatal combination; SS = risk of serotonin syndrome is highest with tramadol but possible with all opioids especially at high doses and in combination with ≥ 2 serotonergic agents; AE=risk of adverse event; CNS = additive CNS depression, monitor sedation; EKG = possible EKG changes such as QTc prolongation; HD = at high doses; ^Although FDA warning exists, clinical risk with tramadol may be lower than with other, more potent opioids; *Potential for opioid withdrawal and reduced pain control

- Drug interactions with other psychotropic and non-psychotropic medications exist
- Consult with a drug information resource or pharmacist for drug interaction concerns
- **Discontinuation of an interacting drug may have the opposite effect as that listed and should be done slowly over several weeks**
- Drug interaction information herein and subsequent implementation of therapy changes should be considered in combination with patients' relevant history and current clinical status

References: 1) Smith HS. Opioid Metabolism. Mayo Clin Proc. 2009;84(7):613-624. 2) Feng X, Zhu L and Zhou Q. Opioid analgesics-related pharmacokinetic drug interactions: from the perspectives of evidence based on randomized controlled trials and clinical risk management. *Journal of Pain Research.* 2017;10:1225-1239. 3) McCance-Katz EF. Clinically Relevant Drug Interactions: Buprenorphine or Methadone with Other Frequently Prescribed Drugs. PCSS MAT Training. 2010. 4) U.S. Food and Drug Administration. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Drug Safety Communications. 2016. 5) U.S. Food and Drug Administration. Drug Development and Drug Interactions: Tablet of Substrates, Inhibitors and Inducers. Last Updated: September 2016. Date Accessed: November 27, 2018. 6) Indiana University School of Medicine, Department of Clinical Pharmacology. Drug Interactions Flockhart Table™. Date Accessed: 03/02/2020 < https://drug-interactions.medicine.iu.edu/MainTable.aspx >

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Methadone-Psychotropic Drug Interactions

WHAT DO I NEED TO KNOW?

- **Methadone is metabolized by liver enzymes, predominately CYP3A4 and 2B6**[1]
  - Others - CYP 2D6, 1A2, 2C9, 2C8, 2C19 - also play a smaller role
- **Drugs that affect CYP3A4 and 2B6 have potential drug interactions with methadone** (see table on next page)
- Potential for additive QTc prolongation with other pro-arrhythmic drugs
- The effects or extent of an interaction may vary. For example, the effects of an interaction can occur during treatment or when an interacting drug is stopped.
- Methadone has large inter-individual variability thus therapy must be individualized

HOW DO I MANAGE DRUG-DRUG INTERACTIONS IN PATIENTS ON METHADONE?

Minimizing Drug Interactions:

- Maintain an accurate and up-to-date drug profile (including herbal products, supplements, over-the-counter drugs and illicit substances)
- Regularly check Prescription Drug Monitoring Programs such as CURES
- Use alternative, non-interacting drugs when possible
  - If not possible, choose those with least interaction risk
- Avoid medications listed in methadone FDA Black Box Warning:
  - Benzodiazepines or other CNS depressants (including alcohol)
  - All CYP450 inhibitors and CYP 3A4, 2B6, 2C19 or 2C9 inducers
- Avoid use of medications with similar side effects as methadone
- When adding new, potentially interacting medications, start low and titrate slowly
- When stopping potentially interacting medications, titrate slowly and monitor closely
- Prescribe naloxone for emergency use to treat opioid overdose

Patient Counseling Points

- Consult with your doctor before taking any over-the-counter drugs, herbal products or supplements
- Educate patients about methadone's long half-life, potential cardiac effects and high risk of drug interactions
- Using alcohol or cannabis (particularly products with high CBD content) while taking methadone may result in over-sedation, dangerous breathing problems, coma and death
- Bring up-to-date list of medications to all appointments
- Ensure understanding of current medication regimen
- Review dangers of self-titrating or self-adjusting medications
- Report any sudden or unexplained signs or symptoms of overmedication or opioid withdrawal

Drug-Drug Interactions Between Methadone & Commonly Used Psychotropics[1-10]

Interacting Medication	Mechanism & Result of Interaction	Recommendations
Plain text = caution, monitor combination closely; **Bold black text = caution, use alternatives, if possible**; **Bold red text: AVOID** **Discontinuation of an interacting drug may have the *opposite* effect and may require slow taper with close monitoring		
ANTIDEPRESSANTS		
Fluvoxamine, Fluoxetine, Bupropion, Paroxetine	CYP inhibitors: ↑ opioid levels, risk of adverse effects	• If a new start, consider: sertraline, mirtazapine, venlafaxine • If on interacting drug: continue therapy and monitor**
Citalopram, Escitalopram	Additive pro-arrhythmic effects	
Duloxetine	Increased duloxetine and/or methadone levels; increased risk of side effects, adverse events	
TCAs (amitriptyline, desipramine, imipramine, nortriptyline)	CYP inhibitors: ↑ opioid levels, risk of adverse effects. Additive pro-arrhythmic effects and CNS depression.	
ANTIPSYCHOTICS		
Haloperidol, **Thioridazine**, **Ziprasidone, Quetiapine**	Additive pro-arrhythmic effects	• If new start, consider: aripiprazole, lurasidone, olanzapine, risperidone • If on interacting drug: continue therapy and monitor (except thioridazine and ziprasidone which should not be used with methadone)
MOOD STABILIZERS		
Carbamazepine	CYP3A4 inducer: ↓ opioid levels, ↑ risk of withdrawal or changes in pain control **FDA Black Box Warning**: stopping CYP3A4 inducer may ↑ opioid levels	• If a new start, consider: divalproex, lamotrigine, valproic acid • If on interacting drug: continue therapy and monitor**
SEDATIVES, HYPNOTICS AND ANXIOLYTICS		
Benzodiazepines **Zolpidem, Zaleplon, Eszopiclone**	**FDA Black Box Warning**: additive CNS depression, potentially fatal	• Discontinue benzo/hypnotic via slow taper. Consider non-pharmacologic interventions, low-dose hydroxyzine or diphenhydramine, gabapentin, clonidine (if opioid withdrawal-related), buspirone, trazodone
OTHER MEDICATIONS AND SUBTANCES		
Alcohol	**FDA Black Box Warning**: additive CNS depression, potentially fatal	• Discontinue alcohol while on methadone, offer alcohol-use disorder treatment, if applicable; AVOID naltrexone for AUD
Cannabis	CYP3A4 and 2D6 inhibitor: ↑ opioid levels and risk of adverse effects. Additive CNS depression.	• Discontinue cannabis while on methadone
Dextromethorphan (Robitussin, Delsym)	↑ dextromethorphan levels and risk of adverse effects	• Consider guaifenesin for cough
Danshen, Chamomile, Euchinacea, Goldenseal	Mixed CYP activity: may have unpredictable effects on opioid levels	• Avoid herbal supplements while on methadone
St John's Wort	CYP3A4 inducer: ↓ opioid levels, ↑ risk of withdrawal or changes in pain control **FDA Black Box Warning**: stopping CYP inducers may ↑ opioid levels	• Avoid St John's Wort while on methadone. Recommend FDA approved treatment for depression (see antidepressants above).

References: 1) Smith HS. Opioid Metabolism. Mayo Clin Proc. 2009;84(7):613-624. 2) McCance-Katz EF, et al. Drug Interactions of Clinical Importance among the Opioids, Methadone and Buprenorphine, and other Frequently Prescribed Medications: A Review. *Am J Addict*. 2010;19(1):4-16. 3) Chou R, et al. Methadone Safety: A Clinical Practice Guideline From the American Pain Society and College on Problems of Drug Dependence, in Collaboration With the Heart Rhythm Society. *The Journal of Pain.* 2014;15(4):321-337. 4) Methadone. In; Lexicomp. Hudson, OH: Lexicomp, Inc. Last Updated: 2/19/20. 5) Wanwimolruk S and Prachayasittikul V. Cytochrome P450 Enzyme Mediated Herbal Drug Interactions (Part 1). *EXCLI Journal*. 2014;13:347-391. 6) Wanwimolruk S, et al. Cytochrome P450 Enzyme Mediated Herbal Drug Interactions (Part 2). *EXCLI Journal.* 2014;13:869-896. 7) Ganzera M, et al. Inhibitory effects of the essential oil of chamomile (Matricaria Recutita L.) and its major constituents on human cytochrome P450 enzymes. *Life Sci.* 2006;78(8):856-61. 8) Leavitt SB. Methadone-Drug Interactions, 3rd Edition. Addiction Treatment Forum. 2005;1-31. 9) U.S. Food and Drug Administration. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Drug Safety Communications. 2016. 10) U.S. Food and Drug Administration. Drug Development and Drug Interactions: Tablet of Substrates, Inhibitors and Inducers. Last Updated: September 2016. Date Accessed: November 27, 2018.

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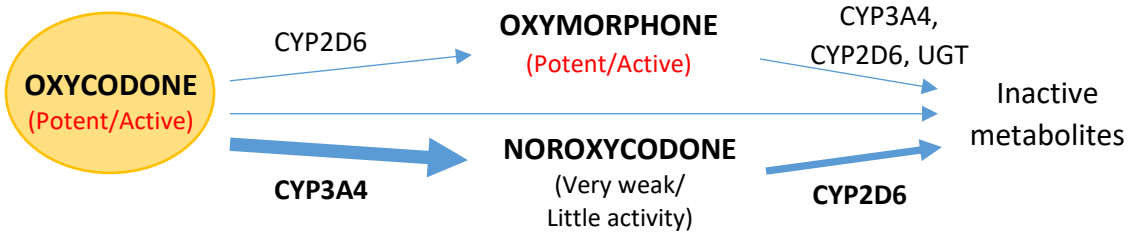
Oxycodone-Psychotropic Drug Interactions

WHAT DO I NEED TO KNOW?

- **Oxycodone is metabolized by liver enzymes into active and inactive metabolites**[1,2]



- **Drugs that affect CYP3A4 and possibly CYP2D6 have potential drug interactions with oxycodone** (see table)
- The effects or extent of an interaction may vary. For example, the effects of an interaction can occur during treatment or when an interacting drug is stopped.

Drug-Drug Interactions Between Oxycodone & Commonly Used Psychotropics[3-11]

Interacting Medication	Mechanism & Result of Interaction	Recommendations
Plain text = caution, monitor combination closely; **Bold black text = caution, use alternatives, if possible**; **Bold red text: AVOID** **Discontinuation of an interacting drug may have the *opposite* effect and may require slow taper with close monitoring		
Antidepressants		
Bupropion, Duloxetine, Paroxetine	CYP2D6 inhibitor: ↑ opioid levels and risk of adverse effects	• If new start, consider: citalopram, escitalopram, mirtazapine, sertraline, venlafaxine • If on interacting drug: continue therapy and monitor**
Fluvoxamine, Fluoxetine	CYP3A4 and 2D6 inhibitor: ↑ opioid levels and risk of adverse effects	
Mood Stabilizers		
Carbamazepine	CYP3A4 inducer: ↓ opioid levels, ↑ risk of withdrawal or changes in pain control **FDA Black Box Warning**: stopping CYP3A4 inducer may ↑ opioid levels	• If new start, consider: divalproex, lamotrigine, lithium, valproic acid • If on interacting drug: continue therapy and monitor**
Sedatives, Hypnotics and Anxiolytics		
Benzodiazepines **Zolpidem, Zaleplon, Eszopiclone**	**FDA Black Box Warning**: additive CNS depression, potentially fatal	• Discontinue benzo/hypnotic via slow taper. Consider non-pharmacologic interventions, low-dose hydroxyzine or diphenhydramine, gabapentin, clonidine (if opioid withdrawal-related), buspirone, trazodone
Other Medications and Substances		
Alcohol	**FDA Black Box Warning**: additive CNS depression, potentially fatal	• Discontinue alcohol while oxycodone, offer alcohol-use disorder treatment, if applicable; AVOID naltrexone for AUD
Cannabis	CYP3A4 and 2D6 inhibitor: ↑ opioid levels and risk of adverse effects. Additive CNS depression.	• Discontinue cannabis while on oxycodone
Danshen, Chamomile, Euchinacea, Goldenseal	Mixed CYP activity: may have unpredictable effects on opioid levels	• Avoid herbal supplements while on oxycodone
St John's Wort	CYP3A4 inducer: ↓ opioid levels, ↑ risk of withdrawal or changes in pain control **FDA Black Box Warning**: stopping CYP3A4 inducer may ↑ opioid levels	• Avoid St John's Wort while on oxycodone. Recommend FDA approved treatment for depression (see antidepressants above).

HOW DO I MANAGE DRUG-DRUG INTERACTIONS IN PATIENTS ON OXYCODONE?

Minimizing Drug Interactions:

- Maintain an accurate and up-to-date drug profile (including herbal products, supplements, over-the-counter drugs and illicit substances)
- Regularly check Prescription Drug Monitoring Programs such as CURES
- Use alternative, non-interacting drugs when possible
  - If not possible, choose those with least interaction risk
- Avoid medications listed in oxycodone FDA Black Box Warning:
  - Benzodiazepines or other CNS depressants (including alcohol)
  - CYP3A4 inhibitors and inducers
- Avoid use of medications with similar side effects as oxycodone
- When adding new, potentially interacting medications, start low and titrate slowly
- When stopping potentially interacting medications, titrate slowly and monitor closely
- **Prescribe naloxone for emergency use to treat opioid overdose**

Patient Counseling Points

- Consult with your doctor before using any over-the-counter drugs, herbal products or supplements
- Using alcohol or cannabis (particularly products with high CBD content) while taking oxycodone may result in over-sedation, dangerous breathing problems, coma and death
- Bring up-to-date list of medications to all appointments
- Ensure understanding of current medication regimen
- Review dangers of self-titrating or self-adjusting medications
- Report any sudden or unexplained signs or symptoms of overmedication or opioid withdrawal

References: 1) Smith HS. Opioid Metabolism. Mayo Clin Proc. 2009;84(7):613-624. 2) Oxycodone Pathway, Pharmacokinetics. PharmGKB. Last Updated: September 30, 2019. Date Accessed: February 24, 2020. < https://www.pharmgkb.org/pathway/PA166170927 > 3) Oxycodone. In; Lexicomp. Hudson, OH: Lexicomp, Inc. Last Updated: 19 February 2020. 4) U.S. Food and Drug Administration. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Drug Safety Communications. 2016. 5) U.S. Food and Drug Administration. Drug Development and Drug Interactions: Tablet of Substrates, Inhibitors and Inducers. Last Updated: September 2016. Date Accessed: November 27, 2018. 5) Wanwimolruk S and Prachayasittikul V. Cytochrome P450 Enzyme Mediated Herbal Drug Interactions (Part 1). *EXCLI Journal*. 2014;13:347-391. 6) Wanwimolruk S, et al. Cytochrome P450 Enzyme Mediated Herbal Drug Interactions (Part 2). *EXCLI Journal.* 2014;13:869-896. 7) Ganzera M, et al. Inhibitory effects of the essential oil of chamomile (Matricaria Recutita L.) and its major constituents on human cytochrome P450 enzymes. *Life Sci.* 2006;78(8):856-61. 8) Leavitt SB. Methadone-Drug Interactions, 3rd Edition. Addiction Treatment Forum. 2005;1-31. 9) U.S. Food and Drug Administration. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Drug Safety Communications. 2016. 10) U.S. Food and Drug Administration. Drug Development and Drug Interactions: Tablet of Substrates, Inhibitors and Inducers. Last Updated: September 2016. Date Accessed: November 27, 2018; 11) Feng X, Zhu L and Zhou Q. Opioid analgesics-related pharmacokinetic drug interactions: from the perspectives of evidence based on randomized controlled trials and clinical risk management. *Journal of Pain Research.* 2017;10:1225-1239

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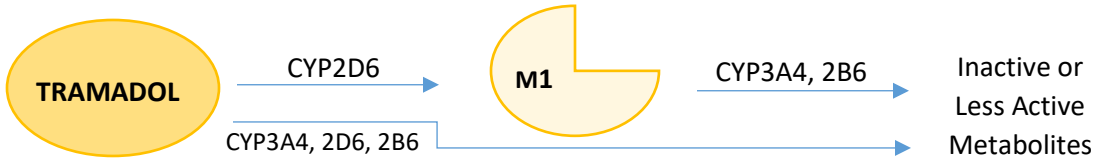
Tramadol-Psychotropic Drug Interactions

WHAT DO I NEED TO KNOW?[1-3]

- **Tramadol requires metabolism/activation by liver enzymes for full therapeutic effect**



- Tramadol and its major active metabolite, M1, have different pharmacologic effects

	Opioid Agonist Activity	Serotonin Reuptake Inhibition	Norepinephrine Reuptake Inhibition
Tramadol	Very Weak	Weak	Weak
M1	Weak (Potency: 1/10th of morphine)	None	None

- **Drugs that have serotonergic effects or those that affect CYP2D6 and/or CYP3A4 have potential drug interactions with tramadol** (see table on next page)
- The effects or extent of an interaction may vary. For example, the effects of an interaction can occur during treatment or when an interacting drug is stopped.

HOW DO I MANAGE DRUG-DRUG INTERACTIONS IN PATIENTS ON TRAMADOL?

Minimizing Drug Interactions:

- Maintain an accurate and up-to-date drug profile (including herbal products, supplements, over-the-counter drugs and illicit substances)
- Regularly check Prescription Drug Monitoring Programs such as CURES
- Use alternative, non-interacting drugs when possible
  - If not possible, choose those with least interaction risk
- Review medications listed in tramadol FDA Black Box Warning:
  - Avoid benzodiazepines or other CNS depressants (including alcohol)
  - Drug interactions possible with CYP3A4 inhibitors/inducers and CYP2D6 inhibitors
- Avoid use of medications with similar side effects as tramadol
- When adding new, potentially interacting medications, start low and titrate slowly
- When stopping potentially interacting medications, titrate slowly and monitor closely
- **Prescribe naloxone for emergency use to treat opioid overdose**

Patient Counseling Points
▪ Consult with your doctor before using any over-the-counter drugs, herbal products or supplements ▪ Using alcohol or cannabis (particularly products with high CBD content) while taking tramadol may alter tramadol effectiveness or cause serious side effects ▪ Bring up-to-date list of medications to all appointments ▪ Ensure understanding of current medication regimen ▪ Review dangers of self-titrating or self-adjusting medications ▪ Report any sudden or unexplained signs or symptoms of overmedication or opioid withdrawal

Drug-Drug Interactions Between Tramadol & Commonly Used Psychotropics[1-9]

Interacting Medication	Mechanism & Result of Interaction	Recommendations
Plain text = caution, monitor combination closely; **Bold black text = caution, use alternatives, if possible**; **Bold red text: AVOID** **Discontinuation of an interacting drug may have the *opposite* effect and may require slow taper with close monitoring		
Antidepressants		
Citalopram, Duloxetine, Escitalopram, **Paroxetine,** Sertraline, Venlafaxine	CYP2D6 inhibitors: ↓ opioid levels, ↑ risk of withdrawal symptoms or changes in pain control	• If new start, consider: mirtazapine • If on interacting drug: continue therapy and monitor**
Bupropion, TCAs	CYP2D6 inhibitors: ↓ opioid levels, ↑ risk of withdrawal symptoms or changes in pain control. Additive seizure risk.	
Fluoxetine	CYP3A4 and 2D6 inhibitor: May have unpredictable effects on opioid/tramadol levels	
SSRIs, SNRIs, TCAs and Buspirone	May increase risk of serotonin syndrome	
Mood Stabilizers		
Carbamazepine	CYP3A4 inducer: ↓ opioid levels, ↑ risk of withdrawal or changes in pain control	• If new start, consider: divalproex, lamotrigine, valproic acid • If on interacting drug: continue therapy and monitor**
Lithium	May increase risk of serotonin syndrome	
Sedatives, Hypnotics and Anxiolytics		
Benzodiazepines **Zolpidem, Zaleplon, Eszopiclone**	**FDA Black Box Warning**: additive CNS depression, potentially fatal	• Discontinue benzo/hypnotic via slow taper. Consider non-pharmacologic interventions, low-dose hydroxyzine or diphenhydramine, gabapentin, clonidine (if opioid withdrawal-related), buspirone, trazodone
Other Medications and Substances		
Alcohol	**FDA Black Box Warning**: additive CNS depression, potentially fatal	• Discontinue alcohol while on tramadol, offer alcohol-use disorder treatment, if applicable; AVOID naltrexone
Cannabis	CYP3A4 and 2D6 inhibitor: May have unpredictable effects on opioid/tramadol levels. Additive CNS depression.	• Discontinue cannabis while on tramadol
Danshen, Chamomile, Euchinacea, Goldenseal	Mixed CYP activity: may have unpredictable effects on opioid/tramadol levels	• Avoid herbal supplements while on tramadol
St John's Wort	CYP3A4 inducer: ↓ opioid levels, ↑ risk of withdrawal or changes in pain control. May increase risk of serotonin syndrome.	• Avoid St John's Wort while on tramadol. Recommend FDA approved treatment for depression (see antidepressants above)

References: 1) Smith HS. Opioid Metabolism. Mayo Clin Proc. 2009;84(7):613-624. 2) Feng X, Zhu L and Zhou Q. Opioid analgesics-related pharmacokinetic drug interactions: from the perspectives of evidence based on randomized controlled trials and clinical risk management. *Journal of Pain Research.* 2017;10:1225-1239. 3) Tramadol. DrugBank.ca. Updated: 10 March 2020. Date Accessed: 10 March 2020. 4) Tramadol. In; Lexicomp. Hudson, OH: Lexicomp, Inc. Last Updated: 03 March 2020. 5) U.S. Food and Drug Administration. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Drug Safety Communications. 2016. 6) U.S. Food and Drug Administration. Drug Development and Drug Interactions: Tablet of Substrates, Inhibitors and Inducers. Last Updated: September 2016. Date Accessed: November 27, 2018. 7) Wanwimolruk S and Prachayasittikul V. Cytochrome P450 Enzyme Mediated Herbal Drug Interactions (Part 1). *EXCLI Journal*. 2014;13:347-391. 8) Wanwimolruk S, et al. Cytochrome P450 Enzyme Mediated Herbal Drug Interactions (Part 2). *EXCLI Journal.* 2014;13:869-896. 9) Ganzera M, et al. Inhibitory effects of the essential oil of chamomile (Matricaria Recutita L.) and its major constituents on human cytochrome P450 enzymes. *Life Sci.* 2006;78(8):856-61.

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Lithium: Therapy Management & Drug Interactions

WHAT DO I NEED TO KNOW?

- Lithium is an effective therapy for bipolar disorder and treatment-resistant depression
- Lithium therapy requires careful monitoring and management due to:
  - Narrow therapeutic window
  - Drug interactions
  - Potential to cause problematic side effects and acute or long-term toxicity
- Extra care is required when prescribing lithium for:
  - Older adults and elderly
  - Patients with reduced renal function
  - Pregnant women and women of child-bearing age
  - Patients taking drugs that may affect lithium levels (see **Table 4**)
  - Patients with learning disabilities or cognitive impairment

HOW DO I SAFELY PRESCRIBE LITHIUM IN PRIMARY CARE?

1. Monitor Lithium Levels and Manage Toxicity: [1-3]

- *When/how to draw levels?*
  - Advise patient to do labs roughly 12 hours from last dose to capture trough
  - For new starts, check level within 5 days of initiation and twice weekly until 2 consecutive stable levels
  - After dose increases or initiation of an interacting drug (see **Table 4**)
  - At least every 3-6 months when stable (more frequent in high risk patients)
  - Any time patient reports symptoms concerning for toxicity
- *What are therapeutic levels?*
  - Acute mania: 0.8-1.2 mEq/L
  - Maintenance: 0.6-1.0 mEq/L
- *What are toxic levels?*
  - Toxic effects may occur at any lithium level
  - Symptoms of toxicity are more likely to occur at lithium levels > 1.5 mEq/L
  - Lithium levels > 2.0 mEq/L are considered severe
- *What are signs of lithium intoxication or toxicity?*
  - Acute intoxication is usually associated with GI symptoms, possibly CV effects and later development of neurologic symptoms
  - Chronic intoxication usually associated with CNS symptoms

Table 1: Signs/Symptoms of Lithium Intoxication or Toxicity

Gastrointestinal	Anorexia, acute/severe nausea, vomiting, diarrhea
Renal	Polyuria, polydipsia, nephrogenic diabetes insipidus
Central Nervous System	Confusion, tremor, dysarthria, ataxia, nystagmus, extrapyramidal or neuromuscular symptoms, drowsiness, seizure; coma can occur in cases of severe toxicity
Cardiovascular	Arrhythmia, hypotension; cardiovascular collapse can occur in cases of severe toxicity

- *How do I manage lithium intoxication or toxicity?*
  - Lack of evidence-based consensus guidelines on management of toxicity
  - Understanding of lithium pharmacokinetics aids in management of toxicity
    - Peak plasma levels reached in 1 to 3 hours (IR) and 4 to 12 hours (ER)
    - Lithium is eliminated more quickly from serum (half-life ~ 8 hours) than from CNS (half-life ~ 24 hours) thus neurological symptoms may persist after serum levels return to non-toxic levels
    - Lithium is eliminated more slowly in those with reduced renal function, older age or on medications that increase lithium levels

Table 2: Management of Supratherapeutic Lithium Levels

Clinical Situation	Recommendations
Lithium level > 1.2 mEq/L WITH symptoms of toxicity	Send patient to ER
Lithium level ≥ 1.5 mEq/L without symptoms of toxicity	Send patient to ER
Lithium level 1.2 to 1.49 mEq/L without symptoms of toxicity	1. Repeat lithium level ASAP 2. Hold lithium dose(s) until repeat level obtained and no longer elevated 3. Instruct patient to go to ER if signs or symptoms of toxicity develop

2. Monitor Labs Potentially Affected by Lithium:[1,2,4]

Table 3: Recommended Lithium Monitoring

Parameter	Frequency	Rationale
BUN/SCr	Baseline, every 3 to 6 months*	Renal function is critical for drug clearance
Electrolytes	Baseline, every 3 to 6 months*	Electrolyte imbalance can affect lithium levels and lithium-induced EKG changes
T4/TSH	Baseline, within 6 months of initiation then annually*	Risk of hypothyroidism
Calcium	Baseline, within 6 months of initiation then annually*	Risk of hypercalcemia due to hyperparathyroidism
CBC with diff	Baseline and as clinically indicated	Risk of leukocytosis
EKG	At baseline for patients > 40 years old or with underlying cardiac risk factors and when clinically indicated	Risk of EKG changes or arrhythmias
Pregnancy Test	Baseline and as clinically indicated	Risk of congenital abnormalities or birth defects

*Unless clinically indicated sooner

3. Be Aware of Potential Drug Interactions:[2,5,6]

- Drug Interactions can alter lithium excretion resulting in either an increase or decrease in lithium level
- If possible, avoid drugs with potential drug interactions with lithium
- If interacting drugs cannot be avoided, monitor lithium levels more frequently and adjust lithium dose as appropriate

Table 4: Potential Drug Interactions with Lithium

Drug or Class	Potential Effect	Timescale	Other Considerations
ACE Inhibitors, ARBs	↑ in lithium levels (up to 4-fold)	Effects develop over several weeks, often delayed	Elderly at particularly high risk
Thiazide diuretics	↑ in lithium levels (up to 4-fold)	Effects usually apparent within 10 days	Loop diuretics may be safer but caution still advised Consider 50% lithium dose reduction
NSAIDs	↑ in lithium levels (25 to 50% or more)	Variable, effects may occur within a few days or after several months	As needed or PRN use generally more problematic than scheduled use Aspirin and sulindac have less evidence suggesting effects on lithium; caution is advised
Theophylline, Caffeine	↓ lithium levels (up to 50%)	Effects usually apparent within days to 1 week	

4. Educate Patients About Lifestyle or Dietary Changes That Can Affect Lithium Levels

- Increased salt intake may decrease lithium levels
- Decreased salt intake may increase lithium levels
- Dehydration may increase lithium levels
- Recommend avoiding major changes in dietary sodium, water intake, exercise habits and other activities that may affect hydration status

5. Monitor and Manage Lithium Side Effects[2,4-6]

- Overall strategies:
  - Watchful waiting
  - Decrease lithium dose
  - Change time of medication administration
  - Change formulation
  - Treat side effects
  - Consult with psychiatry about changing to alternative psychotropic agent

- Strategies for managing specific side effects:

Table 5: Lithium Side Effects and Management Strategies

Side Effect	Incidence and Risk Factors	Management Strategies
Nausea or diarrhea	35 to 45% More common during initiation or rapid titration (often transient)	Take with food Switch to ER formulation
Weight gain	Long-term lithium therapy	Encourage lifestyle and diet modifications
Hypothyroidism	8 to 19% More common in females	Thyroid replacement therapy
Polyuria or polydipsia	Up to 70%	Change to once daily dosing Decrease dose
Tremors (fine, symmetrical & intentional)	10 to 25% Can occur even if lithium levels are not high	Mild symptoms: keep levels at low end of range Persistent symptoms: consider β-blocker Minimize caffeine use
Dermatologic (i.e. acne or psoriasis)	Level-related; incidence not well defined	Consider lower lithium dose to target lower level

6. Regularly Review Important Counseling Points

- Emphasize importance of adherence with medication and lab monitoring.
- Maintain consistency in terms of salt and water intake. Notify provider if any major changes in diet or lifestyle (e.g. exercise).
- Notify provider of any prescription medication changes.
- Do not use over-the-counter NSAID pain medications such as ibuprofen or naproxen without first discussing with provider. If over-the-counter pain medication is needed, recommend acetaminophen.
- Review common side effects. Encourage patients to notify provider if bothersome or persistent symptoms develop.
- Review signs and symptoms of intoxication or toxicity. Instruct patients to notify provider right away if these develop.
- Instruct patients to seek medical care immediately if they develop signs or symptoms of severe toxicity such as confusion, altered mental status, ataxia, muscle weakness or seizures.

References: 1) Ng F, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. *Bipolar Disorder*. 2009;11:559-595. 2) Yatham LN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patient with bipolar disorder. *Bipolar Disorders*. 2018;20:97-170. 3) Haussmann R, et al. Treatment of lithium intoxication: facing the need for evidence. *Int J Bipolar Disord.* 2015;3: DOI 10.1186/s40345-015-0040-2. 4) Woo E and Kim YK. An Oldie but Goodie: Lithium in the Treatment of Bipolar Disorder through Neuroprotective and Neurotrophic Mechanisms. *Int J Mol Sci.* 2017;18: doi:10.3390/ijms18122679. 5) Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord*. 2016;4(1):27. doi:10.1186/s40345-016-0068-y. 6) Lithium. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed December 2, 2019.

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Strategies for Managing Metabolic Risks of Second Generation/Atypical Antipsychotics

WHAT DO I NEED TO KNOW?

- **Most second generation antipsychotics (SGAs) or atypical antipsychotics can have clinically significant effects on metabolic parameters, increasing risk for metabolic syndrome**
- Exact incidence is unclear and etiology is complex

Comparative Risk of Metabolic Effects Among SGAs[1]

Medication (Brand Name)	Weight Gain	Glucose	Triglycerides	HDL
Aripiprazole (Abilify)	+	+	+	+/-
Asenapine (Saphris)	++	+/-	Data unavailable	Data unavailable
Brexpiprazole (Rexulti)	++	+	+/-	+/-
Cariprazine (Vraylar)	+	++	+	++
Clozapine (Clozaril)	++++	++++	++++	Data unavailable
Iloperidone (Fanapt)	+++	++	++	Data unavailable
Lurasidone (Latuda)	+	+/-	+/-	++
Olanzapine (Zyprexa)	++++	+	++	++++
Paliperidone (Invega)	++	+	+	+++
Quetiapine (Seroquel)	+++	+	++	+++
Risperidone (Risperdal)	++	+	+	+++
Ziprasidone (Geodon)	+/-	+	+	+/-

Results displayed above represent change in parameter with antipsychotic vs placebo in individuals with schizophrenia[1]

- **Metabolic Syndrome Diagnostic Criteria:** Metabolic syndrome is diagnosed when at least **3 of the following 5 conditions** are present[2]

Parameter	Criteria for Men	Criteria for Women
Waist circumference	Greater than 40 inches	Greater than 35 inches
Fasting blood glucose	≥ 100 mg/dL or receiving drug therapy for hyperglycemia	
Blood pressure	≥ 130/85 mmHg or receiving drug therapy for hypertension	
Triglycerides	≥ 150 mg/dL or receiving drug therapy for hypertriglyceridemia	
HDL	< 40 mg/dL or receiving drug therapy for reduced HDL	< 50 mg/dL or receiving drug therapy for reduced HDL

HOW DO I MANAGE THE RISK OF METABOLIC SYNDROME AND ANTIPSYCHOTICS?

- **Monitoring:**
  American Diabetes Association and American Psychiatric Association Guidelines[3]

	Baseline	Week 4	Week 8	Week 12	Every 3 months thereafter	Annually
Medical history*	X			X		X
Weight (BMI)	X	X	X	X	X	X
Waist circumference	X			X		X
Blood pressure	X			X		X
Fasting glucose, HgbA1c	X			X		X
Fasting lipids	X			X		X
***Personal and family history of obesity, diabetes, hypertension and cardiovascular disease**						

- **Exercise, Diet and Lifestyle Modifications:** Recommended for all at-risk patients
- **Medication Options:**[4,5] If lifestyle and non-pharmacologic interventions fail
  - Switch to more weight-neutral agent, if clinically appropriate
  - Avoid concomitant use of medications with metabolic risk
  - **Metformin** adjunctive therapy (off-label use) most extensively studied
    - May help slow down weight gain or prevent future weight gain
    - May take 1 to 3 months for benefits to become apparent
    - Unlikely to see more than 10 to 15 lb weight loss
    - If no benefits after 6 months, metformin should be stopped
    - Most useful for:
      - Young patients who have significant weight gain within 1 year of starting antipsychotics
      - Patients prescribed SGAs/atypical antipsychotics with highest risk of weight gain (e.g. olanzapine, clozapine)
  - Other medications such as *aripiprazole* and *topiramate* have been used for weight loss effect, but studies suggest they produce less weight loss and carry greater risk of side effects than metformin

References: 1) Pillinger T, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry.* 2020;7:64-77. 2) Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640-1645. 3) American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care. 2004;27:596-601. 4) Newall H, Myles N, Ward PB, et al. Efficacy of metformin for prevention of weight gain in psychiatric populations: a review. *Int Clin Psychopharmacol*. 2012;27:69-75. 5) Dayabandara M, et al. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. *Neuropsychiatric Disease and Treatment.* 2017;13:2231-2241.

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Liver Toxicity & Naltrexone

WHAT DO I NEED TO KNOW?

- Early estimates of LFT elevations with naltrexone (incidence approx. 13 - 20%) were confounded by comorbid HCV, high doses and/or obesity[1,2]
- **Most LFT elevations are mild and resolve with discontinuation of naltrexone[3]**
- LFT elevations > 5x upper limit of normal (ULN) occur in approximately 2% of patients[4]
- **Hepatic toxicity is rare, occurring in < 1% of patients on naltrexone[3]**
  - **Usually on higher than recommended doses of > 100mg/day**
- Naltrexone is **not** considered hepatotoxic at recommended doses[5]
- LFT elevations may be confounded by active or recent alcohol use

HOW DO I MANAGE LIVER TOXICITY RISK WITH NALTREXONE USE?

Recommended Monitoring for Naltrexone (Oral and Injection)[5,6]

- Baseline: LFTS, GGT, Bilirubin, INR, Albumin, Serum Creatinine (injection)
- At 1 month: LFTs
- At 6 months: LFTs – sooner if clinically indicated
- Annually: LFTs, Serum Creatinine (injection) – sooner if clinically indicated

When to NOT USE Naltrexone	When to ADJUST Naltrexone	When to DISCONTINUE Naltrexone

• Baseline LFTs ≥ 5x ULN
• Acute hepatitis
• Hepatic failure
• Signs of cirrhosis or chronic hepatic impairment*
  ○ Normal AST/ALT
  ○ Elevated INR
  ○ Low albumin
• CrCl < 50ml/min (injection)
	• If LFTs increase but are still < 5x ULN:
	  ○ Continue naltrexone at ≤ 50mg/day
	  ○ Increase monitoring to every 2-4 weeks until LFTs < 3x ULN then every 3-6 months
		• LFTs increase to ≥ 5x ULN**
		• Acute hepatitis
		• Hepatic failure
		• CrCl < 50ml/min (injection)

*There are reports of safe use of naltrexone in patients with cirrhosis or chronic hepatic impairment. Consult with GI/liver specialist before initiating naltrexone in this patient population.
**May re-challenge cautiously once LFTs return to < 3x ULN.

References: 1) Brewer C and Wong VS. Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. *Addiction Biology*. 2004;9:81-87. 2) Mitchell MC, et al. Hepatic safety of injectable extended-release naltrexone in patients with chronic hepatitis C and HIV infection. *J Stud Alcohol Drugs.* 2012;73(6):991-997. 3) Liver Tox: Naltrexone. Clinical and Research Information on Drug-Induced Liver Injury. National Institutes of Health. 2014. Date Accessed: 8 Oct 2018. <https://livertox.nih.gov/Naltrexone.htm> 4) Anton RF, et al. Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence. The COMBINE Study: A Randomized Controlled Trial. *JAMA*. 2006;295(17):2003-2017. 5) VIVITROL package insert. Alkermes, Inc. 2010. 6) College of Psychiatric and Neurologic Pharmacists. Psychiatric Pharmacotherapy Review 2018-2019.

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Alcohol Use Disorder Treatment in Liver Dysfunction

WHAT DO I NEED TO KNOW?

- Total alcohol abstinence is ideal with alcohol use disorder (AUD) and liver dysfunction
- There is a lack of clinical trials evaluating use of AUD medications in liver dysfunction

Alcohol Use Disorder Pharmacotherapy

Medication	Target Symptoms	Considerations with Hepatic Impairment	Recommended Dose for AUD
Acamprosate (Campral®)	Maintaining abstinence after alcohol detox	No dose adjustments necessary **(preferred in hepatic impairment)**	Initial: 333mg TID Target: 666mg TID** ≥ 4 days of abstinence prior to initiation is ideal
Disulfiram (Antabuse®)	↑ abstinence in highly motivated individuals after ≥ 24 hours of abstinence	Use with caution	**Must wait ≥ 12 hours after last alcohol use** Initial: 125-500mg daily for 1-2 weeks Usual maintenance: 250mg daily Max: 500mg daily After discontinuation, effects may last 1 to 2 weeks
Naltrexone (Vivitrol®) PO or LAI	↓ heavy drinking ↓ alcohol cravings ↓ healthcare utilization, $$ ↑ abstinence	Not recommended but has been used **(See Naltrexone and Liver Toxicity reference sheet)**	**Must be opioid-free ≥ 7 to 10 days** Initial/Target: 50mg daily (PO) or 380mg IM every 4 weeks (LAI)
Topiramate (Topamax®)	↓ heavy drinking ↓ alcohol cravings ↑ abstinence	Use with caution; avoid in patients with hepatic encephalopathy	Initial: 25mg daily Max: 150mg BID
Gabapentin (Neurontin®)	↓ heavy drinking ↓ alcohol withdrawal ↑ abstinence ↑ sleep	No dose adjustments necessary	Initial: 300mg daily Target: 1800mg/day, divided TID
Baclofen (Lioresal®)*	↑ abstinence ↓ cravings and anxiety	No dose adjustments necessary	Initial: 5mg TID Usual maintenance: 10mg TID Max: 15mg TID
Ondansetron (Zofran®)*	↓ heavy drinking ↑ abstinence	Max 8mg/day in severe impairment	Usual maintenance: 1 to 16mcg/kg BID
Varenicline (Chantix®)*	In those with comorbid tobacco use disorder may: ↓ heavy drinking ↓ cravings ↑ abstinence	No dose adjustments necessary	Initial: 0.5mg daily x 1-3 days, then 0.5mg BID x 5-7 days, then 1mg BID Usual maintenance: 2mg daily

FDA-approved treatments for AUD; **Limited data/still under investigation, further studies needed to define role, recommend consultation with psychiatry prior to use*; PO=oral; LAI=long-acting injection; **Renal dose adjustments required; GREEN=generally considered safe to use; YELLOW=use with caution, may require dose adjustments; RED=not recommended

HOW DO I MANAGE AUD TREATMENT IN PATIENTS WITH LIVER DYSFUNCTION?

- Of the FDA approved agents, **acamprosate** has not been associated with liver toxicity
- **Gabapentin** may be an option given its safety profile in liver impairment
- **Baclofen** is the only medication that has been formally tested for AUD with cirrhosis; however, evidence is limited
- AUD treatment in primary care:
  - Ongoing screening and, when needed, prompt intervention
  - Associated with greater engagement and reductions in heavy drinking
  - Should include both pharmacotherapy and addiction-focused medical management
- Components of **addiction-focused medical management** in primary care include:

Monitor	Educate	Encourage
• Self-reported use • Urine drug test • Medication adherence, response and adverse effects • Adverse health effects from alcohol	• Health consequences of alcohol • AUD treatment options (pharmacologic and non-pharmacologic)	• Abstinence from alcohol and other substances • Attendance at community support or recover groups • Lifestyle changes that support recovery

- Offer pharmacotherapy (see table on previous page) taking into consideration relevant patient-specific factors and current clinical status

References: 1) Leggio L and Lee MR. Treatment of Alcohol Use Disorder in Patients with Alcoholic Liver Disease. *The American Journal of Medicine.* 2017;130:124-134. 2) Addolorato G, et al. Treatment of alcohol use disorders in patients with alcoholic liver disease. *Journal of Hepatology.* 2016;65:618-630. 3) Mosoni C, et al. Baclofen for the Treatment of Alcohol Use Disorder in Patients With Liver Cirrhosis: 10 Years After the First Evidence. *Frontiers in Psychiatry*. 2018;9(474):1-5. 4) Lexi-Drugs. Lexicomp, Inc. Hudson, OH. Date Accessed: 09 March 2020. 5) Peng JL, et al. Management of alcohol misuse in patients with liver disease. *J Investig Med.* 2017;65(3):673-680.

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Psychotropics & Liver Impairment

WHAT DO I NEED TO KNOW?

- **The liver metabolizes many common psychotropic medications**
- In rare cases, drug-induced liver impairment may occur as a result of psychotropic medications, herbal agents, illicit substance use or exposure to environmental chemicals
  - Clinically significant hepatotoxicity = ALT > 3 times upper limit of normal (ULN)
  - Generally very low incidence (0.001 to 0.1%) when standard drug doses are used
  - May occur as a result of short or long-term use
  - Some psychotropic medications may carry greater risk than others (see **Table 1**)
  - Increased risk when combined with medication that are potentially hepatotoxic

Table 1: Psychotropics with Higher Incidence of Drug-Induced Liver Injury or Toxicity

Drug Category	Drugs with Highest Incidence within Drug Category (approx. incidence)
Antidepressants	• Overall incidence is rare • *Paroxetine* (<1%) and *Duloxetine* (ALT elevations 1%, hepatotoxicity < 1%) associated with higher, but still very low risk • *Nefazodone*, though rarely used, carries a **Black Box Warning** for hepatotoxicity (< 0.0004%).
Antipsychotics	• Benign increase in LFTs can occur during initiation but generally does not require discontinuation
Mood Stabilizers	• *Valproic acid* (**Black Box Warning** for hepatotoxicity; benign Liver Function Test elevations incidence up to 20%; hepatotoxicity/injury 0.03%) and *Carbamazepine* have the highest risk of hepatotoxicity compared to other mood stabilizers
LFTs=Liver Function Tests (e.g. AST, ALT)	

HOW DO I PRESCRIBE PSYCHOTROPIC MEDICATIONS IN PATIENTS WITH LIVER DYSFUNCTION?

- **Dose Adjustments**
  - If liver injury or hepatic impairment is present, adjust medications accordingly (see **Table 2**)
- **Monitoring**
  - Before prescribing medications that carry a risk of liver toxicity, obtain baseline LFTs
  - During therapy, periodic liver function monitoring is recommended
  - Indicators of liver injury:
    - AST and/or ALT > 3x ULN
    - Bilirubin > 2x ULN
    - Prolonged INR or prothrombin times
- **Avoid polypharmacy with multiple hepatotoxic agents including over-the-counter or herbal products, whenever possible**

Table 2: Hepatic Dose Adjustments for Common Psychotropic Agents

	Drug Name	Recommended Dose Adjustments in Liver Impairment
SSRIs/SNRIs	Citalopram	Do not exceed 20mg/day
	Duloxetine	Avoid use
	Escitalopram	Do not exceed 10mg/day
	Fluoxetine	Decrease dose or dosing frequency
	Paroxetine	Do not exceed 40mg/day
	Sertraline	Decrease dose or dosing frequency
	Venlafaxine	Decrease dose by at least 50% depending on degree of impairment
TCAs	Amitriptyline	Use with caution. Use lower starting and target doses and slower titration.
	Nortriptyline	Use with caution. Use lower starting and target doses and slower titration.
Antipsychotics	Aripiprazole	No adjustment necessary
	Clozapine	No guidelines available. Use with caution. Consider dose reduction.
	Fluphenazine	Avoid use
	Haloperidol	No guidelines available. Use with caution. Consider dose reduction.
	Olanzapine	No guidelines available. Use with caution. Consider dose reduction.
	Paliperidone	No adjustments necessary in mild-moderate impairment. Has not been studied in severe impairment.
	Quetiapine	Use lower starting doses and slower titration
	Risperidone	Use lower starting and target doses and slower titration
	Ziprasidone	No guidelines available. Use with caution.
Mood Stabilizers	Carbamazepine	Use with caution. Use lower starting and target doses and slower titration.
	Lamotrigine	Decrease starting, target and titration doses by 25% to 50% depending on degree of impairment
	Lithium	No dose adjustment necessary
	Topiramate	No guidelines available. Use with caution.
	Valproic Acid	Avoid use
Other	Bupropion	Decrease dose or dose frequency in mild-moderate impairment. Use with extreme caution in severe impairment.
	Mirtazapine	No guidelines available. Use with caution.
	Trazodone	No guidelines available. Use with caution.
Benzodiazepines	Alprazolam Clonazepam Diazepam	Use with caution
	Lorazepam Oxazepam Temazepam	Use with caution. However, if a benzodiazepine is necessary in a patient with liver impairment, these agents are preferred.

SSRIs=Selective Serotonin Reuptake Inhibitors; SNRIs=Serotonin Norepinephrine Reuptake Inhibitors; TCAs=Tricyclic Antidepressants

References: 1) Doroudgar S and Chou TI. How to modify psychotropic therapy for patients who have liver dysfunction. *Current Psychiatry.* 2014;13(12):46-49. 2) Telles-Correia D, et al. Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. *World J Gastrointest Pharmacol Therapy.* 2017;8(1):26-38. 3) Lexicomp Online, Lexi-Drugs. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc. Date Accessed: 09 March 2020.

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Bleeding Risk & Antidepressants

WHAT DO I NEED TO KNOW?

- Serotonin is involved in one of several mechanisms by which platelets form clots[1]
- Serotonin reuptake inhibition (i.e. SSRIs, SNRIs) may reduce platelet aggregation[1]
- **Although rare, SSRIs and SNRIs have been associated with ↑ risk of bleeding[2-6]**
  - Incidence of any bleeding < 0.1%
  - Incidence of GI bleed is < 0.01%
  - Risk may be increased in presence of risk factors (see table below)

HOW DO I MANAGE BLEED RISK IN PATIENTS ON ANTIDEPRESSANTS?

- Risk stratification and standardized management are not clearly defined in literature
- **For most patients, SSRIs/SNRIs can be used safely alone or in combination with drugs that increase bleeding risk or GI injury risk**
- May consider adjusting treatment based on additional risk factors

RISK FACTORS[7]
• Active Peptic Ulcer Disease
• Older Age
• History of GI Bleed
• Liver Disease/Cirrhosis
• Co-prescribed drug(s) that ↑bleeding risk: NSAIDs, ASA, anticoagulants, antiplatelet agents
• Co-prescribed drug(s) that ↑GI injury risk: NSAIDs, ASA, steroids

- "High Risk" not clearly defined in the literature. Decisions should be made on a case-by-case basis by assessing all risk factors, using clinical judgment and, when appropriate, specialty consultation.
- **Strategies to reduce bleeding risk in patients with additional risk factors:[1,4,7]**
  - Monitor for signs of bleeding and discuss risk with patient
  - Avoid or discontinue NSAIDs, ASA, steroids and blood thinners where appropriate
  - Add H2 receptor blocker or proton pump inhibitor for GI prophylaxis
  - Consider use of an antidepressant that does not affect the reuptake of serotonin
    - Bupropion (Wellbutrin), Mirtazapine (Remeron)
- **Insufficient evidence to support routine discontinuation of SSRI/SNRI therapy prior to surgical procedures**
  - Decision should be made in collaboration with surgical team on a case-by-case basis with careful consideration of risks vs benefits.

References: 1) PL Detail-Document, SSRI and SNRI and Bleeding Risk: Focus on Drug Interactions. Pharmacist's Letter/Prescriber's Letter. November 2014. 2) Carvajal A, et al. Selective Serotonin Reuptake Inhibitors and Gastrointestinal Bleeding: A Case-Control Study. *PLoS ONE*. 2011;6(5):e19819. 3) Cheng YL, et al. Use of SSRI, But Not SNRI, Increased Upper and Lower Gastrointestinal Bleeding. Medicine. 2015;94(46): 1-7. 4) Bixby AL, VandenBerg A, Bostwick JR. Clinical Management of Bleeding Risk with Antidepressants. *Ann Pharmacother*. 2018;doi: 10.1177/1060028018794005. 5) De Abajo FJ, Garcia-Rodriguez LA. Risk of upper gastrointestinal bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy. *Arch Gen Psychiatry.* 2008;65(7):795-803. 6) Dall M et al. There is an association between selective serotonin reuptake inhibitor use and upper gastrointestinal bleeding: a population-based case-control study. Aliment Pharmacol Ther. 2010;32:1383-1391. 7) Taylor D, Paton C, Kapur S. Maudsley Prescribing Guidelines. 12th ed. West Sussex, UK: Wiley & Sons, Ltd. 2015.

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Psychotropics & Blood Dyscrasias

WHAT DO I NEED TO KNOW?[1-4]

- Nearly all classes of psychotropic drugs have been associated with blood dyscrasias or hematologic adverse reactions
- **Exact incidence of drug-induced hematologic disorders is not well-defined**
  - Overall lack of epidemiologic studies
  - Current evidence mainly from case reports and post-marketing surveillance
  - Incidence varies depending on specific condition and drug
  - Generally considered to be extremely rare
  - **Risk is greater in women, those with genetic susceptibility and older age**
- The most common drug-induced blood dyscrasias include aplastic anemia, agranulocytosis and thrombocytopenia
- Potential mechanisms of drug-induced hematologic toxicity include:
  - Drug interacts with antibody and non-specifically targets cells
  - Drug binds to blood cell inducing cascade of cell toxicity and destruction
  - Drug interacts with plasma protein that stimulates antibody production

Psychotropic Drugs and Risk of Blood Dyscrasias

Hematologic Reaction Type	**Definition**	**Psychotropics Implicated** (% approximate incidence, if available)
Aplastic Anemia	ANC < 500/uL PLT < 20,000/uL Reticulocyte count < 20,000/uL	Carbamazepine (**BBW;** exact incidence not well defined)
Neutropenia or Agranulocytosis	Mild Neutropenia: ANC 1000/uL to 1499/uL Moderate Neutropenia: ANC 500/uL to 999/uL Agranulocytosis: ANC < 500/uL	Carbamazepine (**BBW**; neutropenia 0.5%) Chlorpromazine (agranulocytosis 0.13%; neutropenia 0.01%) Clozapine (**BBW**; agranulocytosis 0.8%; neutropenia 3%; risk is highest in 1st year of therapy) Mirtazapine (agranulocytosis 1.1 cases per 1,000 patients exposed) Quetiapine (0.3 to 1.5%) Olanzapine Valproic acid
Thrombocytopenia	Mild: PLTs 100,000 to 150,000/uL Moderate: PLTs 50,000 to 99,000/uL Severe: PLTS < 50,000/uL	Valproic acid (1 to 30%; dose-dependent)
ANC=Absolute Neutrophil Count; PLT=Platelets; **BBW**=FDA Black Box Warning		

HOW DO I MANAGE THE RISK OF BLOOD DYSCRASIAS AND PSYCHOTROPICS?[1,3,4]

Monitoring and Prevention

- Symptoms and presentation timeline depend on blood cell line affected
- Obtain baseline hematologic labs prior to starting a drug associated with hematologic toxicity, especially in patients with risk factors
- Follow drug-specific hematologic monitoring recommendations
- Avoid concomitant use of > 1 drug with known risk of hematologic toxicity (risk is considered additive)
- Avoid use of drugs with known risk of hematologic toxicity in high risk populations, when possible (i.e. women, older adults)

Management and Treatment

- Prompt recognition and removal of suspected drug are crucial for all types of drug-induced hematologic disorders
- Management varies depending on specific hematologic condition
- If hematologic adverse reaction is suspected:
    - Inpatient supportive care and treatment may be necessary
    - Consultation with hematologic specialist is recommended
    - Drug re-challenge is generally not recommended
- Most hematologic adverse effects resolve after discontinuation of offending agent
    - Except aplastic anemia which may be irreversible and has highest mortality rate

References: 1) Stubner S, et al. Blood Dyscrasias Induced by Psychotropic Drugs. *Pharmacopsychiatry*. 2004;37 Suppl 1:570-578. 2) Flanagan RJ and Dunk L. Haematological toxicity of drugs used in psychiatry. *Hum Psychopharmacol Clin Exp.* 2008;23:27-41. 3) Greene EM, Hagemann TM. Drug-Induced Hematologic Disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146079796. Accessed March 09, 2020. 4) Tisdale JE and Miller DA. Drug-Induced Diseases Prevention, Detection and Management, 2nd Ed. American Society of Health Systems Pharmacists, Inc; Bethesda, MD. 2010.

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Psychotropics & Renal Impairment

WHAT DO I NEED TO KNOW?

- The kidneys eliminate drugs and toxins circulating in the bloodstream
- Acute and chronic kidney dysfunction can affect the clearance of medications
  - Acute kidney injury (AKI) is generally defined as a 25 to 30% increase from baseline in serum creatinine
  - Other forms of kidney dysfunction include hemodynamic alterations, acute tubular necrosis, acute interstitial nephritis, nephrolithiasis and glomerulonephritis
- Kidney function and hemodynamics may be altered by drugs or toxins
  - The incidence of drug-induced AKI is not well defined and mechanisms may vary

Risk Factors for Drug-Induced Nephrotoxicity
• Intravascular volume depletion
• Age ≥ 60 years old
• Diabetes
• Exposure to multiple nephrotoxic agents
• Heart failure
• Sepsis
• Underlying renal insufficiency

TABLE 1: Psychotropic Agents Associated with Drug-Induced Kidney Injury or Toxicity

Drug Category	Incidence within Drug Category (approx. incidence)
Antidepressants (e.g. SSRIs, SNRIs, TCAs)	Post-marketing and/or case reports of SIADH (< 1%)
Antipsychotics	Generally not associated with nephrotoxicity.
Mood Stabilizers	**Lithium** (interstitial nephritis, glomerulonephritis, acute kidney injury, nephrogenic diabetes insipidus ≤ 12%); **Topiramate** (nephrolithiasis ≤ 3%)
SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; TCA=tricyclic antidepressant; SIADH=syndrome of inappropriate antidiuretic hormone	

HOW DO I PRESCRIBE PSYCHOTROPIC MEDICATIONS IN PATIENTS WITH RENAL IMPAIRMENT?

Prevention, Monitoring and Dose Adjustments

- Assess baseline renal function and follow renal monitoring guidelines
- Correct risk factors for nephrotoxicity before initiating drug therapy
- Ensure adequate hydration before and during therapy with potential nephrotoxins
- Use non-nephrotoxic options when possible and avoid nephrotoxic combinations
- Regardless of the cause of renal impairment, certain psychotropic medications may require dose adjustments in patients with renal dysfunction [See **Table 2**]

TABLE 2: Renal Dosage Modifications for Common Psychotropic Agents

	Drug Name	Dosage Modifications in Renal Impairment
SSRIs/SNRIs	Citalopram	Use with caution in CrCl<20mL/min
	Duloxetine	Avoid use in CrCl<30mL/min and ESRD
	Escitalopram	Use with caution in CrCl<20mL/min
	Fluoxetine	Accumulation may occur. Decrease dose or dosing frequency
	Paroxetine	Consider decreased dose in CrCl 30-60mL/min. Do not exceed 40mg/d in CrCl < 30mL/min.
	Sertraline	No dose adjustments necessary
	Venlafaxine IR	Reduce daily dose by 25% in GFR 10 to 70mL/min. Use with caution in GFR<10mL/min. Reduce daily dose by 50% in HD.
	Venlafaxine XR	Reduce daily dose by 25 to 50% in CrCl 30 to 89mL/min. Reduce daily dose by at least 50% in CrCl<30 mL/min. Reduce daily dose by at least 50% in HD.
TCAs	Amitriptyline	No guidelines available. Renally eliminated, use with caution.
	Nortriptyline	No guidelines available. Renally eliminated, use with caution.
Antipsychotics	Aripiprazole	No dose adjustment necessary
	Clozapine	No guidelines available. Consider decreased dose, especially in severe impairment.
	Fluphenazine	No guidelines available. Use with caution.
	Haloperidol	No guidelines available
	Olanzapine	No dose adjustment necessary. Not removed by dialysis.
	Paliperidone	Max 6mg/d PO or 78mg/mo IM in CrCl 50 to 79mL/min. Max 3mg/d PO in CrCl 10 to 49mL/min. Not recommended in CrCl<10mL/min (PO) or CrCl<50ml/min (IM).
	Quetiapine	No dose adjustments necessary
	Risperidone	PO and IM: lower dose and slower titrations recommended in CrCl<60mL/min
	Ziprasidone	No dose adjustments necessary
Mood Stabilizers	Carbamazepine	Decrease dose by 25% in GFR<10mL/min and HD
	Lamotrigine	No guidelines available. Use with caution. Consider decreased dose.
	Lithium	Start low dose, titrate slowly in CrCl 30-89 mL/min. Avoid in CrCl <30mL/min.
	Topiramate	Decrease dose by 50% and titrate slowly in CrCl<70mL/min. Do not exceed 50 to 100mg BID in HD; cleared by HD, consider 50 to 100mg post-dialysis dose.
	Valproic Acid	No dose adjustment necessary. Protein binding is decreased in renal impairment, recommend monitoring free instead of total valproate levels
Other	Bupropion	Use with caution. Consider decreased dose or dosing frequency. Use of 450mg XR tablet is not recommended.
	Mirtazapine	No guidelines available. Use with caution. Consider decreased dose.
	Trazodone	No guidelines available. Use with caution.
Benzodiazepines	Lorazepam	No dose adjustments necessary
	Alprazolam Clonazepam Diazepam Temazepam	No guidelines available. Use with caution. Some metabolites may accumulate.

ESRD=End Stage Renal Disease; HD=hemodialysis; GFR=glomerular filtration rate; SSRIs=Selective Serotonin Reuptake Inhibitors; SNRIs=Serotonin Norepinephrine Reuptake Inhibitors; TCAs=Tricyclic Antidepressants; XR=extended release; IR=immediate release; d=day; mo=month

References: 1) MacLaren, Robert. "Drug-Induced Diseases of the Kidney & Fluid & Electrolyte Disorders." *Drug-Induced Diseases: Prevention, Detection and Management.* 2nd Ed. James E. Tisdale and Robert A. Miller. ASHP Publications, 2010. 771 – 299. Print. 2) Lexi-Drugs. Lexicomp Inc. Hudson, OH. 3) Naughton CA. Drug-Induced Nephrotoxicity. *American Family Physician.* 2008;78(6):743-750. 4) Lederer E. Lithium Nephropathy. *Medscape: Drugs & Diseases.* Last Updated: 1/17/2018. Date accessed: 10/14/19.

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Serotonin Syndrome Warnings

WHAT DO I NEED TO KNOW? [1,2]

- Serotonin syndrome is a spectrum of neuromuscular, autonomic and neurologic symptoms that can occur in response to taking serotonergic medications
- Symptoms usually start within hours to 1 day of increasing dose or adding a drug
- **Most cases involve ≥ 2 serotonergic agents or an overdose of 1 serotonergic agent**
- Can look like other conditions (i.e. antidepressant discontinuation, anticholinergic toxicity) thus requires an accurate drug history
- Reported incidence is rare however believed to be under-reported, unrecognized and underdiagnosed

Mild Serotonin Toxicity
- Nervousness
- Insomnia
- Nausea
- Diarrhea
- Tremor
- Mydriasis

Moderate Serotonin Toxicity
- Hyperreflexia
- Sweating
- Agitation, restlessness
- Inducible clonus
- Ocular clonus
- Nystagmus

Severe Serotonin Toxicity
- Hyperthermia
- Confusion, delirium
- Sustained clonus, rigidity
- Rhabdomyolysis
- Death

Hunter Serotonin Toxicity Criteria: Decision Rules[3]

In the presence of a serotonergic agent:
1. IF (spontaneous clonus=yes) THEN serotonin toxicity=YES
2. ELSE IF (inducible clonus=yes) AND [(agitation=YES) OR (diaphoresis=yes)] THEN serotonin toxicity=YES
3. ELSE IF (ocular clonus=yes) AND [(agitation=yes) OR (diaphoresis=yes)] THEN serotonin toxicity=YES
4. ELSE IF (tremor=yes) AND (hyperreflexia=yes) THEN serotonin toxicity=YES
5. ELSE IF (hypertonic=yes) AND (temp>38°C) AND [(ocular clonus=yes) OR (inducible clonus=yes)] then serotonin toxicity=YES
6. ELSE serotonin toxicity=NO

Potential Sources of Serotoninergic Activity

Prescription Drugs (psychiatric and non-psychiatric)

Example(s): SSRIs, SNRIs, TCAs, MAOIs, Tramadol, Linezolid, Lithium

Herbal Supplements

St. John's Wort, L-Tryptophan

Over-the-Counter Drugs

Dextromethorphan, Chlorpheniramine

Illicit Drugs

Ecstasy, Cocaine, Amphetamine

Notes on Specific Psychotropic Medication Combinations:[1,2,4-7]

- **SSRIS/SNRIs/TCAs plus Triptans** → Evidence suggests that triptans are **unlikely to cause serotonin syndrome** even in combination with serotonergic drugs
  - Triptans act on different receptors than those thought to be involved in serotonin syndrome
- **SSRIs/SNRIs/TCAs plus Trazodone** → Start with low doses and increase cautiously
- **SSRIs/SNRIs plus TCAs** → Highly dependent on specific agents used and patient-specific factors; generally, use alternatives when possible or use low doses
  - Amitriptyline and Imipramine may ↓ metabolism of Citalopram and Escitalopram; additive pro-arrhythmic effects also possible → Consider alternatives or use low doses and monitor closely
  - Fluoxetine, Fluvoxamine and Paroxetine have greatest potential to ↓ metabolism of TCAs → Avoid when possible or use low doses and monitor
  - Clomipramine has highest serotonergic activity among TCAs
  - Amitriptyline and Imipramine have higher serotonergic activity than their metabolites, Nortriptyline and Desipramine
- **SSRIs/SNRIs/TCAs plus MAOIs → Avoid use of MAOIs with serotonergic drugs**
- **Mirtazapine** and **Bupropion** have **lowest serotonergic activity** among antidepressants and may be preferred in those on other serotonergic medications

HOW DO I MANAGE SEROTONIN SYNDROME RISK WHEN PRESCRIBING PSYCHOTROPIC MEDICATIONS?[1,2]

Prevention and Risk Mitigation:

- Assess all medications, supplements and substances
- Use lowest effective doses of all serotonergic medications
- Avoid using ≥ 2 high-dose serotonergic medications concomitantly, if possible
- Discuss risk of serotonin syndrome with patients on multiple serotonergic medications
  - Most cases occur when starting/adding serotonergic agents or increasing doses
  - Titrate doses slowly and consider more frequent follow-up

Treatment of Suspected Serotonin Syndrome:

- Most cases can be managed by stopping the drug or decreasing the dose
- For possible or mild symptoms → ↓ dose or, if possible, discontinue offending agent(s)
  - Consider psychiatric consultation for treatment planning
- For moderate or severe symptoms → refer patient to the ER/urgent care for evaluation, medication management and supportive care

References: 1) Foong AL, et al. Demystifying serotonin syndrome (or serotonin toxicity). Canadian Family Physician. 2018;64: 720-727. 2) Foong AL, et al. The scoop on serotonin syndrome. CPJ/RPC. 2018; 151(4): 233-239. 3) Dunkley EJC, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *Q J Med*. 2003;96:635-642. 4) Gillman, PK. Triptans, Serotonin Agents, and Serotonin Syndrome (Serotonin Toxicity): A Review. Headache. 2010;50:264-272. 5) Orlova Y, et al. Association of Coprescription of Triptan Antimigraine Drugs and Selective Serotonin Reuptake Inhibitor or Selective Norepinephrine Reuptake Inhibitor Antidepressants With Serotonin Syndrome. JAMA Neurology. 2018;75(5):566-575. 6) Lexi-Drugs. Lexicomp Inc. Hudson, OH. 7) Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *British Journal of Pharmacology.* 2007;151:737-748.

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Psychotropics & Seizure Risk

WHAT DO I NEED TO KNOW?

- There is a **bi-directional relationship** between mental illness and seizures
- **Psychiatric comorbidity with epilepsy is common**[1-3]
- Psychotropic-related seizures are generally **dose-dependent** and influenced by **patient-specific factors**[1]

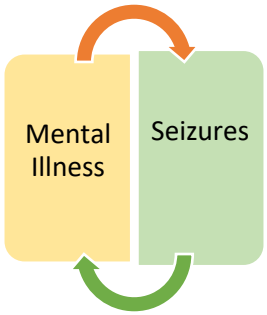

Table 1: Potential Predisposing Factors for Psychotropic-Related Seizures

- Personal history or family history of epilepsy
- Neurological abnormalities (e.g. brain injury)
- Cerebral atherosclerosis
- Older age
- Reduced drug clearance
- Pre-existing electroencephalogram alterations
- General physical illness

Table 2: Comparative Seizure Risk Among Psychotropic Drug Classes[1,2,4-7]

Drug Class	**Specific Agents or Factors Associated with Higher Risk** (approx. incidence)
Antidepressants	▪ Overall considered very rare, exact incidence not well defined ▪ Higher risk when > 1 antidepressant agent is used ▪ Lower risk in epileptic patients on anticonvulsants (vs no anticonvulsants) ▪ Specific agents associated with higher risk/incidence: ○ *Amoxapine* ○ *Bupropion* (0.4% at ≤ 450mg/day; 2.8% at ≥ 600mg/day; range 0.5 to 4.8%; generally lower risk with SR vs IR formulations) ○ *TCAs* (up to 0.6%; *Clomipramine* highest incidence at 1 to 12.2%)
Antipsychotics	▪ Rare, mostly limited to case reports with a few exceptions ▪ Dementia has been associated with higher risk of antipsychotic-related seizures ▪ Specific agents associated with higher risk/incidence: ○ *Chlorpromazine* (0.5% at < 1000mg/day; 9% at ≥ 1000mg/day) ○ *Clozapine* (**BBW**; 1% at < 300mg/day; 2.5% at 300 to 599mg/day; 4.4% at ≥ 600mg/day; risk is higher during initiation and/or fast titration)
Mood Stabilizers	▪ Carbamazepine, Valproic Acid and Lamotrigine have anti-epileptic effects and may be used to treat seizures ▪ *Lithium*, at toxic doses or levels, has been associated with seizures
Stimulants or Atomoxetine	▪ High comorbidity between epilepsy and ADHD ○ Children with epilepsy have 3 to 5-fold increased risk of ADHD ○ Children with ADHD have 4-fold increased risk of epilepsy ▪ Overall, data is mixed. Recent evidence suggests that use of stimulants or atomoxetine at recommended doses does not increase risk of acute seizures in those with and without epilepsy however caution is still advised.
BBW=FDA Black Box Warning for increased risk of seizures	

HOW DO I MANAGE SEIZURE RISK WITH PSYCHOTROPIC MEDICATIONS?[1,2,5,6,8,9]

- Appropriate psychotropic therapy may improve mental state in patients with epilepsy
- Seizure risk with most psychotropic agents is very low (see **Table 2** for exceptions) and should not interfere with appropriate psychiatric treatment
- Lack of formal consensus guidelines on management of psychotropic-related seizures
  - Reduction of dose or switch to alternative agent should be considered
  - Addition of an antiepileptic drug may also be reasonable
  - Neurology consult is recommended if psychotropic-related seizure is suspected

General Management and Risk Mitigation Strategies
▪ Discuss risks with patients, especially if they have other risk factors (see **Table 1**) ▪ Avoid high doses and psychotropic polypharmacy, when possible ▪ Regularly assess risks vs benefits of long-term psychotropic therapy, especially if seizure risk factors are present (see **Table 1**) ▪ Regularly assess for pharmacokinetic drug interactions that may alter drug metabolism, blood levels and, thus, seizure risk ▪ In patients with risk factors or known history of epilepsy: ○ Avoid psychotropics with documented high seizure potential (See **Table 2**) ○ Regularly assess for drug interactions that may alter blood levels of psychotropics or antiepileptics ○ Start with low doses and titrate slowly ○ Avoid complex multi-drug therapies, when possible ○ Monitor plasma drug concentrations of psychotropics and antiepileptics, when possible ○ Consider neurology consult, especially in patients with uncontrolled or difficult-to-control seizures

References: 1) Pisano F, et al. Effects of Psychotropic Drugs on Seizure Threshold. *Drug Safety.* 2002;25(2):91-110. 2) Kanner AM. Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: A review of the evidence. *Epilepsy & Behavior*. 2016;61:282-286. 3) Brikell I, Ghirardi L, D'Onofrio BM, Dunn DW, Almqvist C, Dalsgaard S, Kuja-Halkola R, Larsson H. Familial Liability to Epilepsy and Attention-Deficit/Hyperactivity Disorder: A Nationwide Cohort Study. Biol Psychiatry. 2018 Jan 15;83(2):173-180. doi:10.1016/j.biopsych.2017.08.006. 4) Williams AM, Park SH. Seizure associated with clozapine: incidence, etiology, and management. CNS Drugs. 2015 Feb;29(2):101-11. doi: 10.1007/s40263-014-0222-y. 5) Khoury R and Ghossoub E. Antipsychotics and seizures: What are the risks? *Current Psychiatry*. 2019;18(3):21-33. 6) Brikell I, Chen Q, Kuja-Halkola R, D'Onofrio BM, Wiggs KK, Lichtenstein P, Almqvist C, Quinn PD, Chang Z, Larsson H. Medication treatment for attention-deficit/hyperactivity disorder and the risk of acute seizures in individuals with epilepsy. Epilepsia. 2019 Feb;60(2):284-293. doi:10.1111/epi.14640. 7) Wiggs KK, et al. Attention-deficit/hyperactivity disorder medication and seizures. *Neurology*. 2018;90(13): DOI: https://doi.org/10.1212/WNL.0000000000005213. 8) Williams AE, Giust JM, Kronenberger WG, Dunn DW. Epilepsy and attention-deficit hyperactivity disorder: links, risks, and challenges. Neuropsychiatr Dis Treat. 2016 Feb 9;12:287-96. doi: 10.2147/NDT.S81549. 9) Landmark JC, et al. Proconvulsant effects of antidepressants – What is the current evidence? *Epilepsy Behav.* 2016;61:287-291.

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Bone Fracture Risk & Antidepressants

WHAT DO I NEED TO KNOW?

- There is **inconsistent data** linking antidepressant (mostly SSRI) use in patients > 65 years old to:
  - Decreased bone mineral density (BMD)
    - High variability and mostly clinically insignificant changes reported
  - Increased fracture risk
    - Odds ratios range from 1.01 to 2.4, higher within 1st year of treatment
- **Studies suggest depression is a risk factor for decreased BMD, increased fracture risk and osteoporosis**
  - *Risk of untreated depression may outweigh possible effects of antidepressants on BMD and fracture risk*

HOW DO I MANAGE CONCERNS ABOUT FRACTURE RISK IN PATIENTS ON ANTIDEPRESSANTS?

- **Discuss with patients:**
  - **The inconsistent data linking antidepressant use to risk of fractures**
  - **The possibility that untreated depression is a risk factor for decreased BMD and increased fracture risk**
- Literature does NOT support use of bisphosphonates for prophylaxis against fracture risk associated with antidepressants
- Address other ongoing factors that might contribute to increased fracture risk:
  - Reduce number of prescribed CNS-active medications
  - Consider reducing dose or avoiding other medications that can increase fall risk
  - Ensure adequate vitamin D and calcium intake or supplementation
  - Patient counseling around preventable osteoporosis risk factors: poor diet, smoking, excessive caffeine, inactive lifestyle, weight extremes, excessive alcohol
  - Fracture risk analysis (DXA or FRAX) in patients with osteoporosis risk factors
  - Optimize therapy for other conditions that increase fracture risk (i.e. renal disease)

References: 1) Gebara MA, et al. Depression, Antidepressants and Bone Health in Older Adults: A Systematic Review. *J Am Geriatr Soc*. 2014;62(8):1434-1441. 2) Schweiger JU, et al. The Use of Antidepressive Agents and Bone Mineral Density in Women: A Meta-Analysis. *Int J Environ Res Public Health*. 2018;15;1373. 3) Rauma PH, et al. The association between major depressive disorder, use of antidepressants and bone mineral density (BMD) in men. *J Musculoskelet Neuronal Interact*. 2015;15(2):177-185. 4) Panday K, et al. Medication-induced osteoporosis: screening and treatment strategies. *Ther Adv Musculoskel Dis*. 2015;6(5):185-202. 5) Sansone RA and Sansone LA. SSRIs: Bad to the Bone? *Innov Clin Neurosci.* 2012;9(7-8):42-47.

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Medication Use in Pregnancy & Breastfeeding

WHAT DO I NEED TO KNOW?

- Medication use during pregnancy and breastfeeding is common
- In some cases, stopping or avoiding medications may pose greater risks
- Untreated mental health conditions during pregnancy and breastfeeding have been associated with adverse maternal and fetal outcomes

FDA Pregnancy and Lactation Labeling Rules: Old vs New

- Pregnancy risk letter categories criticized for being overly simplistic and misinterpreted
  - Medications with less safety research were given lower risk category
  - Thus older medications often categorized as riskier than newer medications
- In 2015, FDA restructured pregnancy and lactation warnings
- New labeling aims to summarize available, evidence-based, medication-specific data
- Prescription drugs approved on or after June 30, 2001 are gradually phased in
- Prescription drugs approved before June 30, 2001 are not required to adopt new labeling but must remove pregnancy risk letter category

Old Pregnancy Risk Categories	
Category	Risk
A	Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus in the 1st trimester of pregnancy
B	Animal studies have failed to show risk to the fetus, and there are no adequate, well-controlled studies in pregnant women, or animal studies have shown adverse effects, but well-controlled studies in pregnant women have shown no adverse effects
C	Animal studies have shown adverse effects on the fetus, or there are no animal reproduction studies and no well-controlled studies in humans
D	Evidence of fetal risk, benefits may be > risks
X	Evidence of fetal risk, risks > possible benefit

New Pregnancy and Lactation Labeling	
Labeling Category	Descriptive Subsections
Pregnancy (includes Labor and Delivery)	- Pregnancy Exposure Registry - Risk Summary - Clinical Considerations - Data
Lactation	- Risk Summary - Clinical Considerations - Data
Females and Males of Reproductive Potential (if relevant)	- Pregnancy Testing - Contraception - Infertility
New labeling will also note if/when no data is available	

HOW DO I MINIMIZE MEDICATION RISKS DURING PREGNANCY AND BREASTFEEDING?

ACOG Guidelines for Psychotropic Use During Pregnancy and Lactation (2008):

- Always discuss risks vs benefits of medication use with patients
- A single medication at a higher dose is preferred over multiple medications
- Medication selection should be based on history of response, prior use during pregnancy and reproductive safety information
- Medications with fewer metabolites, higher protein binding and fewer drug-drug interactions are preferred
- Patient enrollment in the FDA Pregnancy Registry can help improve safety information

Data on safety of medications during pregnancy & breastfeeding is constantly evolving

- Utilize available resources to assess current data

Resource	For Providers	For Patients	Languages Available
https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html • **Centers for Disease Control and Prevention** – *Treating for Two* is an ongoing program led by the CDC to improve health of women and babies by supporting research, providing guidance on safe medication use and providing up-to-date material to inform treatment decisions.	✓	✓	English Spanish
https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm • **National Institute of Health/Toxicology Data Network** - LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed.	✓		
https://mothertobaby.org/ • **MotherToBaby** - a service of the non-profit Organization of Teratology Information Specialists, is dedicated to providing evidence-based information to mothers, health care professionals, and the general public about medications and other exposures during pregnancy and while breastfeeding. • Includes Factsheets for patients and providers • Offers free phone, email, chat consultations for providers and patients	✓	✓	English Spanish
https://womensmentalhealth.org/ • **MGH Center for Women's Health/Reproductive Psychiatry Information Resource Center** - developed as a way of providing critical up-to-date information for patients in the rapidly changing field of women's mental health. This internet-based resource was designed in an effort to provide scientifically sound and clinically useful information to caregivers and patients. • Searchable summaries of data on topics • Frequent blog posts with answers to commonly asked questions	✓	✓	English
https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm • **FDA Pregnancy Registry Website** – List of studies (and associated contact information) that collect health data on drug or vaccine exposure during pregnancy.	✓	✓	15+ languages available
https://www.fda.gov/forconsumers/byaudience/forwomen/ucm118567.htm • **FDA Medicine and Pregnancy website** – General information for women regarding safe use of medications during pregnancy.		✓	

References: 1) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm, Accessed 11/ 27/2018, 2) Pernia S and DeMaagd G. The New Pregnancy and Lactation Labeling Rule. P&T. 2016;41(11):713-715. 3) Lim L and Thompson K. New prescription drug labeling for pregnant or nursing women. Pharmacy Today. 2016: 40-41. 4) Centers for Disease Control and Prevention National Center on Birth Defects and Developmental Disabilities. Treating for Two: A National Strategy for Safer Medication Use in Pregnancy. Accessed: November 27, 2018. <www.cdc.gov/treatingfortwo> 5) ACOG Guidelines on Psychiatric Medication Use During Pregnancy and Lactation. *Obstetrics & Gynecology.* 2008;111:1001-1020.

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Anti-Epileptic Drugs/Mood Stabilizers & Hormonal Contraceptives

WHAT DO I NEED TO KNOW?

- Many Anti-Epileptic Drugs (AEDs) are also used as Mood Stabilizers and can have significant drug interactions
- **Certain AEDs can decrease hormonal contraceptive effectiveness by ≥ 50%:**

Carbamazepine (Tegretol) | **Lamotrigine (Lamictal)** | **Oxcarbazepine (Trileptal)** | **Topiramate (Topamax) > 200mg/day**

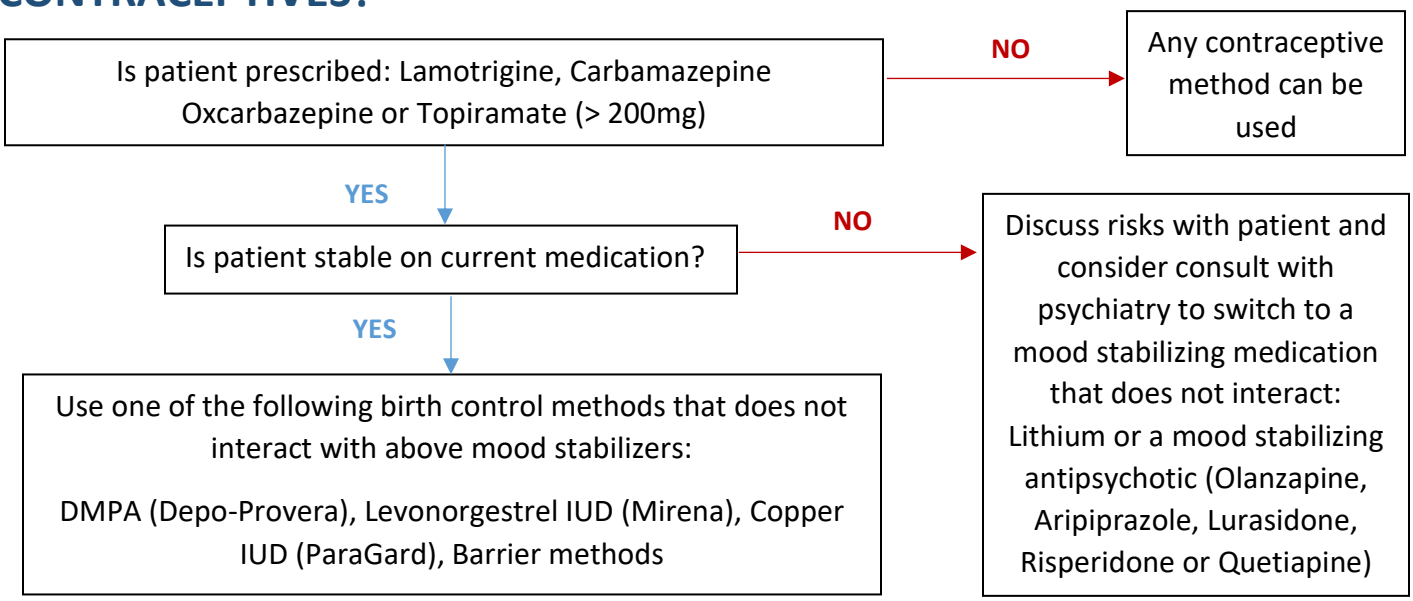
Effects may continue for up to 4 weeks after AED discontinuation

- **Ethinyl estradiol (EE) can ↓ serum levels of certain AEDs, reducing their mood stabilizing or anti-epileptic effects:**

Lamotrigine (Lamictal) | **Valproic Acid/Divalproex (Depakote)***

Generally, Valproic Acid/Divalproex should be avoided in all women of reproductive age due to risk of and FDA Black Box Warning for severe teratogenicity

HOW DO I MANAGE INTERACTIONS BETWEEN AEDS AND HORMONAL CONTRACEPTIVES?



References: 1) Williams D. Antiepileptic Drugs and Contraception. U.S. Pharm. 2014;39(1):39-42. 2) O'Brien MD and Guillebaud J. Contraception for women taking antiepileptic drugs. J Fam Plann Reprod Health Care. 2010;36(4):239-242. 3) Carl JS and Tweed E. Effect of Antiepileptic Drugs on Oral Contraceptives. Am Fam Physician. 2008;78(5):634-635. 4) Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. Expert Rev Clin Pharmacol. 2010;3(2):183-192.

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Emerging Substance of Abuse: Kratom

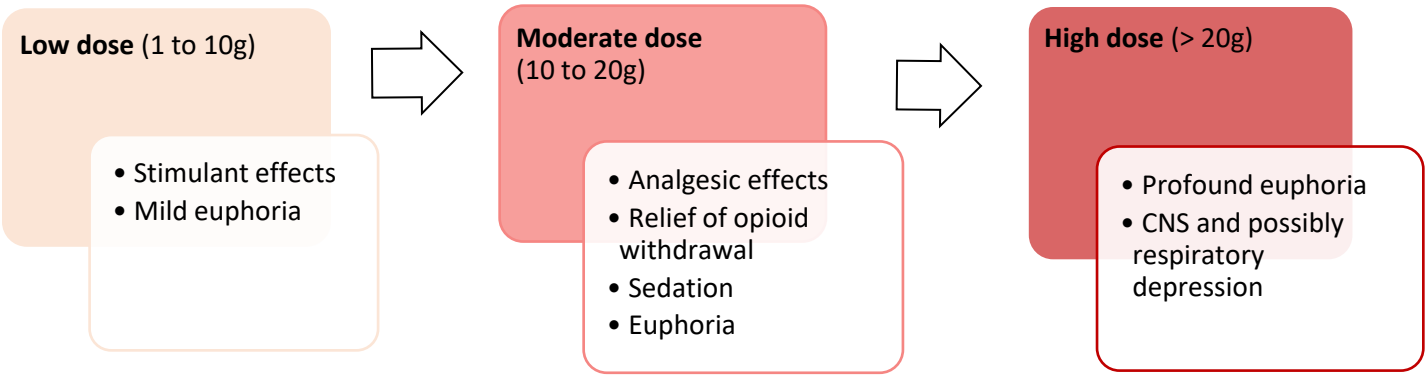
WHAT DO I NEED TO KNOW?

Facts About Kratom

- Kratom (*mitragyna speciosa*) is a plant indigenous to Southeast Asia
- Used for its stimulant effects, analgesia, opioid withdrawal and as an anti-diarrheal
- Other names: Biak-Biak, Ketum, Kakuam, Ithang, Thom
- Leaves are typically dried before consuming via chewing, swallowing, smoking, brewing as a tea or made into powders or extracts or pressed into tablets or capsules
- Currently unregulated in the U.S. and prohibited in some countries
- Can be obtained in stores or through online retailers

Kratom Pharmacology

- Contains numerous active compounds with various pharmacologic effects
  - Mitragynine has multimodal pain regulation including opioid receptor agonism
  - 7-OH-mitragynine is the active metabolite of mytraginine, has opioid agonist activity approximately 13-14x more potent than morphine
  - Other effects of kratom compounds include α2-adrenergic stimulation, anticholinergic, noradrenergic and serotonergic effects
- Potential for drug-drug interactions:
  - Hepatically metabolized primarily by CYP3A4, to a lesser extent 2D6 and 2C9
  - Also inhibits certain hepatic metabolism pathways
- **Kratom has dose-dependent narcotic effects:**



Current FDA Stance: No evidence that Kratom is effective or safe for any use

- Unrecognized as a controlled substance by Drug Enforcement Agency (DEA) thus not subject to regulation
- Listed on DEA's Drugs of Concern registry and has been criminalized in some states

Kratom Suppliers Use Unsubstantiated Medical Claims in their Marketing

- Promoting treatment of pain or opioid dependence and withdrawal
- Marketing Kratom as a "legal" high
- Claiming Kratom is safe because it is "natural"/derived from a plant

Current Understanding of Safety and Efficacy

- Largely based on anecdotal and case reports
- No controlled, clinical studies evaluating safety and efficacy of Kratom

Reported "Therapeutic"/Positive Effects	Documented Adverse Events/Negative Effects
• Stimulant • Analgesic • Sedative • Relief of opioid withdrawal • Enhance mood (euphoria) • Reduce anxiety • Improve PTSD symptoms • Anti-diarrheal	• Over-sedation • Weight loss • Psychosis • Irritability • Increased aggression • Seizures • Abuse, addiction and/or dependence • Opioid withdrawal symptoms with abrupt discontinuation (including newborns exposed in utero) • Respiratory depression • Multi-organ system dysfunction or toxicity, especially hepatic • Coma, death

HOW DO I MANAGE RISKS ASSOCIATED WITH USE OF KRATOM?

- Ask patients about use of Kratom
- Provide education regarding Kratom (See Patient Counseling Points below)
- Discuss reasonable treatment alternatives for pain or opioid use disorder such as FDA approved medications
- Currently, there is limited ability to detect on toxicology screens but specific urine testing is possible
- **Prescribe naloxone for emergency use to treat opioid overdose**
- Health care professionals and consumers should report Kratom-associated adverse events to the FDA online at www.fda.gov/medwatch/report.htm

Kratom - Patient Counseling Points

- Associated with significant adverse events such as anxiety, irritability, increased aggression, psychosis, physical dependence or addiction, seizures, liver damage, coma and death
- May have significant interactions with prescription and over-the-counter medications, herbal supplements or other substances
- Use of Kratom in combination with other sedating medications or substances (e.g. alcohol, cannabis) can have dangerous effects including death
- Suddenly stopping Kratom after regular use can lead to opioid withdrawal symptoms
- Use during pregnancy has produced opioid withdrawal symptoms in newborns
- **Without FDA regulatory oversight, cannot ensure authenticity, purity, quality, potency and safety of available kratom products and preparations, increasing the risk for contamination, inconsistencies and tampering**

References: 1) Eastlack SC, et al. Kratom-Pharmacology, Clinical Implications, and Outlook: A Comprehensive Review. *Pain Ther.* 2020; doi.org/10.6084/m9.figshare.11567916. 2) Singh D, et al. Traditional and non-traditional uses of Mitragynine (Kratom): A survey of the literature. Brain Research Bulletin. 2016;126:41-46. 3) Prozialeck WC, et al. Pharmacology of Kratom: An Emerging Botanical Agent with Stimulant, Analgesic and Opioid-Life Effects. J Am Osteopath Assoc. 2012;112(12):792-799. 4) SECON The Drug Screening Company. Drug Facts Sheet: Kratom. Date Accessed: November 26, 2018. < https://www.drugscreen.com/Docs/FactSheets/Kratom.pdf> 5) Drug Enforcement Administration, Office of Diversion Control. Kratom. Drug & Chemical Evaluation Section. Last updated: January 2013. Date Accessed: November 26, 2018. https://www.deadiversion.usdoj.gov/drug_chem_info/kratom.pdf

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