Agents Used to Treat Opioid Use Disorder

A. FDA Approved Indications in Substance Use Treatment (Documentation Required)

1. Buprenorphine
    i. Buprenorphine sublingual tablets (Subutex)
    ii. Generic buprenorphine/naloxone sublingual tablets
    iii. Buprenorphine/naloxone sublingual films (Suboxone)
    iv. Buprenorphine/naloxone sublingual tablets (Zubsolv)
    v. Buprenorphine extended-release injection (Sublocade)

2. Lofexidine oral tablets (Lucemyra)

3. Methadone
    i. Oral Concentrate (10mg/ml)
    ii. Oral Solution (5mg/5ml)
    iii. Oral Solution (10mg/5ml)

4. Naltrexone
    i. Generic naltrexone oral tablets
    ii. Naltrexone for depot injection (Vivitrol)

B. Commonly Prescribed Non-FDA approved Medications to Manage Opioid Withdrawal:

1. Clonidine
    i. Generic Clonidine oral tablets
    ii. Clonidine oral tablets (Catapres)
    iii. Clonidine patches (Catapres)

2. Ondansetron
    i. Generic ondansetron oral tablets
    ii. Generic ondansetron orally disintegrating tablets
    iii. Ondansetron oral tablets (Zofran)
    iv. Ondansetron orally disintegrating tablets (Zofran)

3. Hydroxyzine (Vistaril) oral capsules

4. Gabapentin oral tablets or capsules (Neurontin)

5. Naloxone
    i. Injectable and intranasal generic
    ii. Naloxone HCL (Narcan Nasal Spray)
    iii. Naloxone autoinjector (Evzio)

C. Emergency treatment of known or suspected opioid overdose:

Naloxone

iv. Injectable and intranasal generic
v. Naloxone HCL (Narcan Nasal Spray)
vi. Naloxone autoinjector (Evzio)

C. Minimal Documentation/Monitoring (Documentation Required)

1. All standard outpatient requirements (see section R for details).

2. Document rationale when making any medication changes.

3. CURES:

- Review of cures report is required prior to initiation of any controlled medication, and again at intervals no longer than 6 months throughout treatment or whenever misuse of the medication is suspected, including when it's used more frequently or at higher dose than prescribed without provider consultation or being prescribed by more than one provider at the same time. **DOCUMENT YOUR OBSERVATION IN THE PROGRESS NOTE.**

- In cases where there are discrepancies between CURES report and the urine toxicology report, diversion should be considered, and the following steps are recommended: (Note: There may be a delay of 1-2 weeks before recent dispensing data appears on the CURES report).

    1. Perform a thorough review of medication adherence by confirming the directions, the timing of the medications and compare them to appointments, pharmacy dispensing data, and the timing of the toxicology screen.

    2. Prescribe smaller quantities of the medications, order more frequent random toxicology screens, and schedule more frequent follow up appointments prior to refills.

4. NALOXONE: (Assembly Bill No. 2760)

A. When prescribing opioids, the prescriber shall offer a prescription for naloxone to a patient if:

    i. The prescription daily dose is >90 morphine mg equivalents
    ii. An opioid is prescribed with a benzodiazepine
    iii. The patient has an increased risk of overdose

B. When prescribing opioids, the prescriber shall provide education on overdose prevention and the use of naloxone to the following individuals:

    i. Patient
    ii. One or more persons designated by the patient (If available/applicable)

For more information, please use the following Link:
https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201720180AB2760

5. Sedation checks before dosing, BAL testing, observation 3 to 4 hours after dosing (at the time of the peak methadone level), etc. should be considered depending on the clinical situation and whenever there is a change in the patient's status.

6. Document coordination of care with other providers involved in the care of the patient, as clinically indicated.

7. When managing patients with OUD or AUD, document a plan to minimize the risk of overdose:

A. Educate patients about the risks of drinking alcohol while on medication assisted treatment with methadone or buprenorphine including sedation, overdose, and death.

B. Educate patients about the effect of alcohol use on methadone. Combining Alcohol with Methadone can lead to profound CNS depression and lead to increased risk of side effects and overdose which can increase the risk of death.

C. Based on the level of sedation and the clinical situation, following strategies should be considered:

- Serial breathalyzer testing
- Sedation checks before dosing
- Urine drug screening for alcohol or metabolites of alcohol (ethyl glucuronide & ethyl sulfate) and/or repeating labs i.e., LFTs and hemogram and alerting the patient's PCP.

D. Patients should be discouraged from illicit use of Suboxone, Methadone, Methamphetamine And Benzodiazepines (i.e., Illicit Methadone Supplementation).

9. When treating patients with concurrent use of BZDs, other CNS depressants and opioids document:

A. A plan to minimize the risk of overdose or other adverse events. Educate patients about the risks (including risk of death) inherent when BZDs, CNS depressants and opioid agonists are combined.

B. Diligently assess for BZD and other CNS depressant use, including asking about substances used, source, amount, and frequency of use. Add screening for specific substances to urine toxicology as indicated.

C. Educate patients about illicit pills that may be fentanyl or a potent designer benzodiazepine increasing the risk of sedation/overdose/death.

D. Advise the patient that BZDs should not be the treatment of choice for anxiety. Discuss with patient the increased risk of benzodiazepine use disorder in patients with OUD and request that the patient talks to the prescriber and transition to a non-BZD medication like an SSRI or SNRI in combination with CBT if available.

E. If the prescribing MD is unwilling to transition from BZDs to another medication, a "letter to

prescribing physician should be sent requesting that, quantity be limited and documentation regarding treatment failure provided. (See attached).

F. If there is evidence that the patient is not taking medication as prescribed, i.e., diverting or is unsafe to continue MAT; obtain a ROI to coordinate care with the prescribing physician and express the concerns. If the patient declines to allow coordination of care, advise that it may not be possible to continue medication assisted treatment for safety reasons.

11. If a patient has a history of long-term BZD use:

A. Evaluate to determine the safest treatment plan.

B. As clinically indicated: taper/detox, monitoring at a higher level of care may be indicated prior to initiating OAT.

C. In others, gradually decreasing to the lowest effective dose is indicated. Clearly document risk vs. benefit of selected treatment course.

12. **If a patient on MAT is reported or directly observed by the provider to be altered or sedated, following steps need to be considered to ensure patient safety:**

A. Hold the daily dose of methadone/buprenorphine.
B. Assess, ensure patient has a safe ride home, and transport to ER for observation/intervention if clinically indicated.
C. Alert police if patient drives while appearing sedated/altered.
D. Meet with the patient (when not altered) to assess need for more intensive treatment or medical detoxification.
E. Alert any physicians prescribing sedatives.
F. Consider decreasing the methadone or buprenorphine dose.
G. Discontinue all take out doses.

D. Maximum Dosing:

1. Methadone:

A. Maximum dose varies for each patient and based on clinical efficacy and safety. Factors to be considered include observed response pre- and/or post- dosing, peak and trough methadone levels, signs/symptoms of over-medication, reported or observed side effects, urine toxicology results, EKG findings, co-occurring medical conditions and medications.

B. Consider ordering peak and trough methadone level when dose reaches 90mg to screen for rapid metabolism, high serum methadone level and as clinically indicated thereafter.

2. Buprenorphine

A**. Maximum Daily Dose (MDD)** for most patients is 24mg daily.

B. MDD up to 32mg for patients with co-occurring pain (generally divided BID to QID) or

for whom a lower dose has been determined to be insufficient (by observation of signs of persistent opioid withdrawal on a lower dose).

C. Confirmation that the patient is adhering to SL dosing is recommended.

3. Naltrexone:

A. Extended release (injectable): 380mg IM monthly

B. Oral: **Up to** 100mg **per day**.

4. Clonidine: Clonidine is an alpha-2 adrenergic agonist. It can provide relief to many of the physical symptoms of opioid withdrawal including sweating, diarrhea, vomiting, abdominal cramps, chills, anxiety, insomnia, and tremor. It can also cause drowsiness, dizziness, and low blood pressure. Blood pressure needs to be monitored at baseline and throughout the withdrawal management with Clonidine. Sudden cessation of clonidine treatment has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure. Such responses are dose depended.

Please see Table: 4 in the following reference for dosage information and more details.

❖ For more information on management of opioid withdrawal visit the following websites:
(Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence)

https://www.ncbi.nlm.nih.gov/books/NBK143167/
https://www.ncbi.nlm.nih.gov/books/NBK310652/

E. Duration of Treatment:

A. Varies depending on the treatment goal; for methadone, duration is defined in federal and state regulations and eligibility criteria are more stringent for maintenance treatment.

A. Long-term or extended detoxification (>30 days but not >180 days)

B. Maintenance treatment

B. Medication assisted treatment for OUD is considered long-term treatment for a chronic condition.

F. Standard laboratory, ECG monitoring and other screening as clinically indicated (Documentation Required)

1. Pre-admission screening:

A. Onsite urine drug screen with temperature testing
B. Breathalyzer testing
C. Clinical Opioid Withdrawal Score (COWS)
D. EKG if clinically indicated
E. Other medical clearance as indicated (i.e. if patient left the ER or hospital AMA or appears

unstable, infectious or in need of acute medical or mental health care)

2. Labs on Admission:

A. Blood work: Panel 7, LFTs, Hepatitis serology (B&C), RPR, HIV (with patient consent).
B. Urine: At Valley Medical Center the urine toxicology Panel includes Amphetamine, Barbiturates, BZDs, Cocaine, Fentanyl, opiates, PCP, and Oxycodone. THC, and other suspect drugs need to be added depending on history, medical U.A.
C. Provide HIV education and offer testing

3. Routine Labs: Per the practice of SCC OTPs; screen for medical concerns in a population that often does not receive regular medical care.

A. Annually: repeat the admission labs, except include hepatitis serologies only if clinically indicated.

B. Trough methadone level should be done when dose reaches 90-100mg. Repeat peak and/or trough levels as clinically indicated. Steady State Concentration is reached after 5-7 consecutive days at the same dose. The trough is drawn about 24 hours after the last dose and the peak can be drawn 3-4 hours after ingestion of the daily dose. The optical peak to trough is less than two and greater than two suggests a rapid rate of metabolism. A peak and trough level should be done if rapid metabolism is suspected and prior to initialing a split dosing.

4. Screening for Tuberculosis:

A. At admission and annually
B. PPD skin testing (if no history of prior positive), may be waived if documented test in the preceding 90 days.

C. Screening questionnaire + CXR if history of positive

5. ECG monitoring:

A. As clinically indicated before admission
B. During/after titration to a therapeutic dose
C. Follow up ECG as clinically indicated and specially under the following circumstances: (Table 2)

1. Pre-existing cardiovascular disease and/or family history of cardiovascular disease.

2. Drug-drug and drug-disease interaction with potential to increase risk of toxicity i.e., other drugs with the potential to increase the QTc interval.

*** Prolonged QTc interval has been defined as >450msec for men and >460-470msec for women.**

G. **Patient Education:**

A. Patient education prior to admission and routinely as needed. (Documentation Required)

1. Educate patients about the risks of drinking alcohol while on medication assisted treatment with methadone or buprenorphine including sedation, overdose and death.

2. Educate patients about the effect of alcohol use on methadone metabolism

B. Medical Counsel for women who are pregnant or post-partum (tailored to individual need and trimester of pregnancy).

1. Impact of specific substance use on patient, pregnancy, and baby
2. Importance of participation in prenatal, postpartum, and pediatric care
3. Impact of opioid withdrawal on patient, pregnancy, and baby
4. Neonatal abstinence syndrome – symptoms, factors affecting severity, treatment, impact of subtherapeutic methadone dose and use of cigarettes, alcohol, etc.
5. Post-partum depression – symptoms, treatment
6. Risk of relapse after delivery
7. Impact of pregnancy and delivery on methadone metabolism
8. Breastfeeding – factors to consider

H. Black Box Warning

A. The BBW for Methadone includes the following topics: appropriate use, addiction, abuse and misuse, respiratory depression, accidental ingestion, QT prolongation, neonatal opioid withdrawal syndrome, CYP450 interactions, risks from concomitant use with BZDs, CNS depressants, and opioid addiction treatment.

B. See PI for Methadone for a complete discussion.

I. Warnings and Precautions (Documentation Required)

- For patients with substance use refer to Section P: medication guidelines for prescribing controlled psychotropic medications to patients with substance use.
- Respiratory Depression
- Cardiac Conduction Effects
- Incomplete Cross-tolerance between Methadone and other Opioids
- Misuse, Abuse, and Diversion of Opioids
- Physical Dependence
- Interactions with other CNS Depressants
- Interactions with Alcohol and Drugs of Abuse
- Head Injury and Increased Intracranial Pressure
- Acute Abdominal Conditions
- Hypotensive Effects
- Use with caution in elderly and debilitated patients
- Drug Interactions
- Potentially Arrhythmogenic Agents
- Withdrawal symptoms

- Anti-retroviral Agents
- Pregnancy, labor and Delivery and Breastfeeding
- Pediatric Use
- Caution if renal or hepatic impairment present
- Caution if sleep apnea present
- Caution if CNS depression present
- Caution if seizure hx present
- Caution if depression present

J. Drug-Drug Interactions – For more details refer to Table 3, PIs, and www.epocrates.com

For Patients being considered for MAT:

If the patient is taking/using a stimulant, benzodiazepine, or other CNS depressant(s) such as a muscle relaxant, sleeping pill, anti-convulsant, antihistamine, psychotropic, opioid, and/or alcohol:

A. document coordination of care with other providers who are or have been involved in the care of the patient.

B. Delay induction if patient appears is sedated or under the influence of a licit or illicit substance.

C. Extreme caution is warranted when patients are using sedatives, particularly if they have a history of overdose(s) accidental or intentional.

D. Methadone may interact with drugs that are metabolized by the CYP450 3A4 and potentially CYP2D6 and CYP2B6. (See Tables 1, 2 & 3)

E. Document drug-drug interactions particularly if the patient is on a medication that may prolong QTC interval.

K. Adverse Effects: (for a complete list of Adverse Effects please see PI for each drug i.e., METHADOSE Label (fda.gov)

Serious Adverse Effects:

- Dental problems associated with buprenorphine-containing drugs dissolved in the mouth
- Respiratory depression & failure
- Systemic hypotension
- Cardiac arrest
- Death
- Cardiac Arrhythmias (Torsade's de pointes)
- Hyperalgesia
- Overdose
- Withdrawal sxs if abrupt D/C
- Apnea
- Drug abuse & Dependence
- Cardiac Conduction Effects: Arrhythmias, Bigeminal rhythms, bradycardia, cardiomyopathy,

ECG abnormalities, extrasystoles, flushing, heart failure, Seizures
- Suicidality
- Hypotension
- Syncope

Common Adverse Effects:
- Constipation
- Mild Sedation
- Excess Sweating
- Dizziness/lightheadedness
- Asthenia
- Ataxia
- Headache
- Abdominal pain, anorexia, dry mouth, glossitis
- Agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizure
- Amenorrhea
- Disinhibition
- Irritability
- Libido changes
- Menstrual irregularities
- Diplopia
- Dysarthria
- Incontinence
- Urinary retention
- Dystonia
- ALT, AST elevation

L. Impacts of Pregnancy related to MAT: Refer to CSAM Chapter 4: Pregnancy and Neonatal Withdrawal

Comments related to Kratom:

Patients should be discouraged from using Kratom due to its safety concerns. The U.S. Food and Drug Administration (FDA) continues to warn people to avoid using products containing kratom or its ingredients. https://www.webmd.com/vitamins/ai/ingredientmono-1513/kratom

References:

1. CSAM
2. ASAM
3. SAMSHA
4. Epocrates
5. Micromedex
6. Physician's Package Inserts for various medications
7. UpToDate: Pharmacotherapy for opioid use disorder
8. Withdrawal Management, https://www.ncbi.nlm.nih.gov/books/NBK310652/
9. Keratom herbal supplement; https://www.nbcnews.com/health/health-news/what-kratom-popular-herbal-supplement-has-caught-flak-fda-n1066526
10. https://www.webmd.com/vitamins/ai/ingredientmono-1513/kratom
11. Benzodiazepines: How they work and how to withdraw. http://benzo.org.uk/manual/bzha01.htm
12. Opioid Therapies and Cytochrome P450 https://www.jpsmjournal.com/action/showPdf?pii=S0885-3924%2812%2900492-7
12. Clinical Factors Associated with Prolonged QTc and/or TdP https://www.crediblemeds.org/ndfa_list

Attachments:

Table 1: Common Cytochrome P450 3A/3A4 Inhibitors and Inducers
Table 2: Some reported causes and potentiators of the long QT Syndrome
Table 3: Pharmacokinetics & Drug-Drug Interactions

Table 1: Common Cytochrome P450 3A/3A4 Inhibitors and Inducers

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
Atazanavir	Amiodarone*	Apalutamide	Bexarotene
Clarithromycin	Aprepitant	Carbamazepine	Bosentan
Cobicistat and cobicistat-containing coformulations	Ceritinib	Enzalutamide	Dabrafenib
Darunavir	Cimetidine*	Fosphenytoin	Dexamethasone
Idelalisib	Conivaptan	Lumacaftor	Efavirenz
Indinavir	Crizotinib	Mitotane	Eslicarbazepine
Itraconazole	Cyclosporine*	Phenobarbital	Etravirine
Ketoconazole	Diltiazem	Phenytoin	Lorlatinib
Lopinavir	Duvelisib	Primidone	Modafinil
Mifepristone	Dronedarone	Rifampin (rifampin)	Nafcillin
Nefazodone	Erythromycin		Rifabutin
Nelfinavir	Fedratinib		Rifapentine
Ombitasvir-paritaprevir-ritonavir	Fluconazole		St. John's wort
Ombitasvir-paritaprevir-ritonavir plus dasabuvir	Fosamprenavir		
Posaconazole	Fosaprepitant*		
Ritonavir and ritonavir-containing coformulations	Grapefruit juice		
Saquinavir	Imatinib		
Telithromycin	Isavuconazole (isavuconazonium sulfate)		
Voriconazole	Lefamulin		
	Letermovir		
	Netupitant		
	Nilotinib		
	Ribociclib		
	Schisandra		
	Verapamil		

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism can alter the serum

concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.

- These classifications are based upon US Food and Drug Administration (FDA) g Jidance,[1 2]l Other sources may use a different classification system resulting in some agents being classified differently.
- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (e.g., target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as Lexicomp interactions included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

* Classified as a weak inhibitor of CYP3A4 according to FDA system. [I]
Classified as a weak inducer of CYP3A4 according to FDA system, [I]

Reference:

UpToDate: Pharmacotherapy for Opioid Use disorder
https://www.uptodate.com/contents/pharmacotherapy-for-opioid-use-disorder

Table 2: Some reported causes and potentiators of the long QT syndrome*

Congenital

Jervell and Lange-Nielsen syndrome (including"channelopathies ")

Romano-Ward syndrome

Idiopathic

Acquired

Metabolic disorders

Hypokalemia

Hypomagnesemia

Hypocalcemia

Starvation Anorexia

nervosa

Liquid protein dietsHypothyroidism

Bradyarrhythmia's

Sinus node dysfunction

AV block: Second or third degree

Androgen deprivation therapy (GnRH agonist/antagonist therapy or bilateral surgical orchiectomy)

Antiarrhythmic drugs

Quinidine, procainamide, disopyramide

Flecainide, pilsicainide, propafenone

Amiodarone, dronedarone, vernakalant,Sotalol

Dofetilide, ibutilide

Antianginal drugs

Ranolazine, ivabradine

Anticholinergic drugs (antimuscarinics)

Solifenacin, tolterodine

Anti-infective drugs ◊

Antimalarial:

- High risk: Delamanid, quinidine, quinine

e risk: Chloroquine, halofantrine,piperaquine

Antituberculosis:

- High risk: Bedaquiline

Azole antifungals:

- Moderate risk: Fluconazole, voriconazole
- Low to moderate risk: Itraconazole

Clofazimine (moderate risk)

Fluoroquinolones (systemic):

Acquired (continued)

Antihistamines

Astemizole, bilastine hydroxyzine, terfenadine§

Antineoplastic drugs◊

- High risk: Arsenic trioxide, ivosidenib, lenvatinib, vandetanib
- Moderate risk: Ceritinib, crizotinib, dasatinib, encorafeni, gilteritinib , inotuzumab ozogamicin, midostauri, nilotinib, osimertinib, ribociclib, toremifene, vemurafenib

Analgesic, anesthetic, and sedative drugs

Anesthetic/sedative: Chloral hydrate, propofol

Opioids: Buprenorphine ·, hydrocodone,loperamide (in overdose), methadone

Bronchodilators (beta-2 agonists)

Arformoterol, 3lbuterol, formoterol, levalbuterol, indacaterol, oldaterol, salmeterol, terbutaline, vilanterol

Diuretics

Via electrolyte changes (especially hypokalemia or hypomagneser1ia)

Gastrointestinal drugs [0]

Antidiarrheal: loperamide* (in overdose)

Antiemetics:

- Moderate risk: Droperidol, ondansetron (risk with IV use greater than oral)
- Low to moderate risk: Granisetron, dolasetron, hydroxyzine, tropisetron

Promotility:

- High risk: Cisapride (restricted availability)
- Moderate risk: Domperidone
- Low to moderate risk (rare reports): Metoclopromide

Proton pump in1ibitors: Chronic use leading to hypomagnesemia (rare)

Neurologic drugs:

Apomorphine, deutetrabenazine, donepezil, ezogabine, fingolimod, pimavanserin, tetrabenazine

Psychotropic drugs

Antipsychotics: <>

- High risk: Chlorpromazine, IV haloperidol, ziprasidone
- Moderate **risk:** Anisulpride, clozapine, flupentixol, haloperidol (oral), olanzapine, quetiapine risperidone, thioridazine
- Low to moderate risk: Asenapine, iloperidone, paliperidone, pimavanserin

• Moderate risk: Gemifloxacin11, levofloxacin, moxofloxacin, sparfloxacin11 • Low to moderate risk: Ciprofloxacin, norfloxacin, ofloxacin Foscarnet (low to moderate risk) HIV antiretrovirals: • Moderate risk: Saquinavir • Low to moderate risk: Efavirenz, lopinavir-ritonavir, rilpivirine Macrolide antibiotics: • Moderate risk: Azithromycin, erythromycin, clarithromycin ▪ Low to moderate risk: Roxithromycin, telithromycin Pentamidine (IV), moderate risk Pentavalent antimonial (Anti parasitic/ antiprotozoal): ▪ Moderate risk: Meglumine antimoniate, sodium stibogluconate Telavancin (low to moderate risk)	Tricyclic and Tetracyclic antidepressants (TCAs; including doxepin) Selective serotonin reuptake inhibitors (lower risk tt1an TCAs): Citalopram, escitalopram, fluoxetine (Iless than citalopram) Others: ▪ Atomox11tine, trazodone, valbenazine **Vasodilator drugs:** Bepridil **Other drugs and herbs** Miscellaneous. Anagrelide, alfuzosin n, cocaine, eliglustat, gad) benate dimeglutnine, lofexidine, mifepristone, papaverlne (lntracoronary), pasireotlde, probucol, terlipressln Herb s: Cinchona (contains quinine), licorice extract (glycyrrhizin) i1 overuse leading to electrolyte changes **Other factors** Myocardial ischemia or infarction, especially with prominent T-wave inversions Intracranial disease, HIV infection Hypothermia Toxic exposure: Organophosphate insecticides

This is not a complete list of all corrected QT interval (QTc)-prolonging drugs and does not include drugs with either a minor degree or isolated association(s) with QTc prolongation that appear to be safe in most patients but may needto be avoided in patients with congenital long QT syndrome depending upon clinical circumstances. A more completelist of such drugs is available at the Credible Meds website.

AV: atrioventricular; IV: intravenous.

* The list of medcations and other factors capable of prolonging the QTc represents an evolving area of clinical research. In some cases of longg QTc, two or more factors may be involved.

Not availablee in the United States.

t. In contrast with other class I antiarrhythmic drugs, amiodarone is rarely associated with torsade's de pointes (TdP); refer to accompanying text within UpToDate topic rreviews of acquired long QT syndrome.

o Classifications based upon US Food & Drug Administration guidance: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythrnic Drugs - Questions and Answers; Guidance: for Industry US Food and Drug Administration, June 2017 (revision 2) available at: https://www.fda.gov/ downloads/ Drugs/ Guidance/Compliance/Regulation/information/Guidance/ UCM07316l,Pdf. The use of other classification criteria may lead to some agents being classified differently by other sources.

§ Removed from market in most countries due to adverse cardiovascular effects.

¥ Although product labeling for buprenorphine analgesics warning of QTc prolongation at doses exceeding those recommended, data for buprenorphine ne in usual doses for treatment of opioid use disorder are reassuring, and it appears to be a suitable alternative for patients with significant QTc prolongation due to methadone. Refer to the UpToDate topic reviews of opioid intoxication and opioid use disorder for detail.

:t Over the counter; available without a prescription.

t Several of the cyclic antidepressants have not been adequately tested for QTc prolongation risk.

Reference: UpToDate: Pharmacotherapy for opioid use disorder. https://www.uptodate.com/contents/pharmacotherapy-for-opioid-use-disorder

Table 3: Pharmacokinetics & Drug-Drug Interactions[1-4]

Agent	Brand	Metabolism; CYP (Substrate)	$t_{1/2}$ (hr)	Comments
Agents Used for Treatment of Opioid Use Dependence				
Methadone	Methadose Oral Concentrate®, Oral Solution	3A4 (major), 2B6, 2C19, 2D6 (minor)	Methadone has a short analgesic half-life of 6 to 12 hours but has a variable elimination half-life of 12 to 150 hours due to its lipid solubility, redistribution into fat, and polymorphic variability by phenotype.	• A synthetic opioid with high oral bioavailability between 70-80% • Full agonist at Mu receptor • Long half live and high protein binding may lead to drug accumulation and potential overdose during induction • Has a number of DDIs with CYP4A4, 2D6 inducers, inhibitors and agents with potential to prolong QTC interval
Buprenorphine SL tablets	Subutex®	CYP3A4 and Glucuronidation	24 to 42 hours	• Low oral bioavailability but when given SL, it increases to 60-70% • Partial Mu agonist and Kappa receptor antagonist • Many DDIs with CYP3A4 inducers and inhibitors
Buprenorphine and Naloxone SL film	Suboxone	CYP3A4 and Glucuronidation for both Buprenorphine and Naloxone	Elimination $t_{1/2}$ is between 24 to 42 hours for buprenorphine and 2-12 hours for Naloxone	• Not indicated for use during pregnancy unless potential benefit justifies potential risk. • Breast-feeding is not advised while taking SUBOXONE SL film • Safety and effectiveness not studied in patients<16 y. o. • Administer with caution to elderly or debilitated patients • Administer with caution to patients with liver dysfunction • Many DDIs with CYP3A4 inducers and inhibitors
Buprenorphine Extended-Release injection for SQ Use	Sublocade®	CYP3A4	43 to 60 days	• CYP3A4 Inhibitors and Inducers: Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over- or under-dosing • Serotonergic Drugs: If concomitant use is warranted, monitor for serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug
Clonidine	Catapres	About 50% of dose hepatically metabolized (CYP450 unknown) and 50% excreted in the urine	6-20 hours	• Caution if: elderly, h/o depression, renal impairment, CVD, Cardiovascular dz, hypotension, alcohol use • Monitor for hypotension, sedation, bradycardia, depression, dizziness
Lofexidine	Lucemyra®	CYP2D6, CYP1A2, CYP2C19	12 hours	• Alpha2 Adrenergic agonist • Hepatic or Renal Impairment: Dosage adjustments are recommended based on degree of impairment • Risk of QTC Prolongation, monitor ECG and interacts with methadone to prolong the QTC • Increased risk of CNS depression with concomitant use of CNS depressant drugs • Increased Risk of Opioid Overdose after Opioid Discontinuation: Patients who complete opioid discontinuation are at an increased risk of fatal overdose should they resume opioid use • Risk of Discontinuation Symptoms: Instruct patients not to discontinue therapy without consulting their healthcare provider. When discontinuing therapy, reduce dose gradually • Oral Naltrexone: Concomitant use may reduce efficacy of oral naltrexone • CYP2D6 Inhibitors: Concomitant use of paroxetine resulted in increased plasma levels of LUCEMYRA. Monitor for symptoms of orthostasis and bradycardia with concomitant use of a CYP2D6 inhibitor

Table 3: Pharmacokinetics & Drug-Drug Interactions[1-4]

Naltrexone Oral Tablets	Revia®	Metabolized by liver cystolic dihydrodiol dehydrogenases and via Glucuronidation, eliminated renally	The mean elimination half-life (T-1/2) values for naltrexone and 6-ß-naltrexol are 4 hours and 13 hours, respectively,	• Pure Opioid antagonist • Since it's not metabolized by CYP450 enzymes, CYP450 inducers and inhibitors are unlikely to change the clearance of Naltrexone
Naltrexone IM Extended Release	Vivitrol®	Metabolized by liver cystolic dihydrodiol dehydrogenases and via Glucuronidation, eliminated renally	Elimination half-life is 5-10 days	• Mild renal insufficiency had little or no influence on Vivitrol and not studied in moderate to severe renal insufficiency • P'kinetic of Vivitrol not altered in mild to moderate hepatic insufficiency and not evaluated in severe hepatic impairment • Since it's not metabolized by CYP450enzyme, CYP450 inducers and inhibitors are unlikely to change the clearance of Vivitrol
Naloxone Nasal Spray	Narcan® Nasal Spray	Glucuronidation and eliminated renally	About 2 hours following a single nasal administration	• Opioid antagonist • Not metabolized by CYP450 enzymes, CYP450 inducers & inhibitors are unlikely to change the clearance of Naloxone
Ondansetron	Zofran	1A2, 2D6, 3A4	4-6 hours	• Caution if: QT prolongation, dysrhythmia, h/o torsade, hepatic impairment • Monitor for: HA, constipation, diarrhea, dizziness, bronchospasm
Trazodone	Desyrel	3A4	3-9 hours	• 150mg max for sleep • Caution with hepatic impairment • Monitor for hypotension, QT prolongation, priapism and anticholinergic SEs
First Generation Antipsychotics				
Chlorpromazine	Thorazine®	2D6 (major), 1A2/3A4	Biphasic – initial 2 hours; terminal 30 hours	• Use with caution in renal (not dialyzable) and hepatic impairment
Fluphenazine Fluphenazine decanoate	Prolixin®	2D6	4.4-16.4	• Contraindicated in hepatic impairment • Use with caution in renal impairment
Haloperidol Haloperidol decanoate	Haldol®	2D6/3A4 (major), 1A2, glucuronidation	14-37 21 (haloperidol decanoate)	
Loxapine	Loxitane®	1A2/2D6/3A4 (minor)	Biphasic – 5 hours; terminal 19 hours	• **Pgp inhibitor**
Molindone	Moban®	2D6	1.5	• Use with caution in hepatic impairment
Perphenazine	Trilafon®	2D6 (major), 1A2/3A4/2C9/2C19 (minor)	Perphenazine: 9-12 7-hydroxyperphenazine: 10-19	• Active metabolite (responsible for 70% of activity) • Contraindicated in liver damage • Use with caution in renal impairment
Pimozide	Orap®	1A2, 2D6, 3A4	55	• Use with caution in renal and hepatic impairment
Thioridazine	Mellaril®	2D6 (major), 2C19	21-24	• **Moderate 2D6 inhibitor** • Metabolite: mesoridazine (2x as potent as thioridazine) • Use with caution in hepatic impairment
Thiothixene	Navane®	1A2	34	
Trifluoperazine	Stelazine®	1A2	3-12	• Contraindicated in hepatic disease
Second Generation Antipsychotics				
Aripiprazole	Abilify® Aristada® Abilify Maintena®	2D6, 3A4	Aripiprazole: 75 Dehydro-aripiprazole: 94 2D6 poor metabolizers: 146	• Active metabolite: dehydro-aripiprazole • No dose adjustments for mild-to-severe renal impairment (GFR 15-90 mL/min) or mild-to-severe hepatic function (Child-Pugh score between 5-15)

Table 3: Pharmacokinetics & Drug-Drug Interactions[1-4]

			Maintena® 29.9 (300 mg) - 46.5 days (400 mg) - after q4 week gluteal administrations
			Aristada® 53.9-57.2 days – q monthly, q6 week, and q2 month injections

Factors	**Aripiprazole PO Dose Adjustments**
Known 2D6 Poor Metabolizers	Administer ½ of usual dose
Known 2D6 Poor Metabolizers & Strong 3A4 Inhibitors	Administer ¼ of usual dose
Strong 3A4 or 2D6 inhibitors	Administer ½ of usual dose
Strong 3A4 and 2D6 inhibitors	Administer ¼ of usual dose
Strong 3A4 inducers	Double usual dose over 1-2 weeks

Factors	**Maintena® Dose Adjustments if P450 modulators are added for > 14 days**
2D6 Poor Metabolizers	200 mg
Patients taking Abilify Maintena 400 mg	
Strong 3A4 or 2D6 Inhibitor	300 mg
3A4 and 2D6 Inhibitor	200 mg
3A4 Inducers	Avoid Use
Patients taking Abilify Maintena 300 mg	
Strong 3A4 or 2D6 Inhibitor	200 mg
3A4 and 2D6 Inhibitor	160 mg
3A4 Inducers	Avoid Use

Factors	**Aristada® Dose Adjustments if P450 modulators are added for > 14 days**
Strong 3A4 Inhibitor	Reduce Aristada dose to next lower strength (but no adjustments if taking 441 mg, if tolerated) Poor 2D6 metabolizers: Reduce dose to 441 mg from 662 mg, 882 mg, or 1064 mg (but no adjustments if taking 441 mg, if tolerated)
Strong 2D6 Inhibitor	Reduce Aristada dose to next lower strength (but no adjustments if taking 441 mg, if tolerated) Poor 2D6 metabolizers: No dose adjustment required
Strong 3A4 and 2D6 Inhibitor	Avoid use if patients taking 662 mg, 882 mg, or 1064 mg (but no adjustments if taking 441 mg, if tolerated)
3A4 Inducer	No dose adjustment for 662 mg, 882 mg, or 1064 mg dose; increase 441 mg dose to 662 mg.

Table 3: Pharmacokinetics & Drug-Drug Interactions[1-4]

<table>
<tr>
<td>Asenapine</td>
<td>Saphris®</td>
<td>1A2 (major) and glucuronidation, 2D6/3A4 (minor)</td>
<td>24</td>
<td>

Weak 2D6 inhibitor
Intake of water ~2-5 minutes after asenapine administration caused decrease in asenapine exposure; Avoid drinking and eating 10 minutes after administration.
No dose adjustments for mild-to-severe renal impairment (GFR 15-90 mL/min) or mild-to-moderate hepatic impairment (Child-Pugh A and B)
Contraindicated in severe hepatic impairment (Child-Pugh C)
If taking paroxetine (2D6 substrate and inhibitor), reduce paroxetine dose by ½

</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Rexulti®</td>
<td>2D6, 3A4</td>
<td>91</td>
<td>

Moderate-to-severe hepatic impairment (Child-Pugh B or C) or CrCl <60 mL/min:

MDD max dose: 2 mg/day
Schizophrenia max dose: 3 mg/day

<table>
<tr><th>Factors</th><th>Brexipiprazole Dose Adjustments</th></tr>
<tr><td>Known 2D6 Poor Metabolizers & Strong/moderate 3A4 Inhibitors</td><td>Administer ¼ of usual dose</td></tr>
<tr><td>Strong 3A4 or 2D6 inhibitors</td><td>Administer ½ of usual dose</td></tr>
<tr><td>Strong/moderate 2D6 and 3A4 inhibitors</td><td>Administer ¼ of usual dose</td></tr>
<tr><td>Strong 3A4 inducers</td><td>Double usual dose and further adjust based on clinical response</td></tr>
</table>
</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Vraylar®</td>
<td>3A4 (major), 2D6</td>
<td>2-4 days</td>
<td>

CrCl <30 mL/min and severe hepatic impairment (Child-Pugh C): not recommended

<table>
<tr><th>Factors</th><th>Cariprazine Dose Adjustments</th></tr>
<tr><td>Strong 3A4 Inhibitors</td><td>Administer ½ of usual dose</td></tr>
<tr><td>3A4 Inducers</td><td>Not recommended</td></tr>
</table>
</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozaril®</td>
<td>1A2 (major), 2C19/2C9/2D6/3A4</td>
<td>4-66 (steady state 12 hours)</td>
<td>

Active metabolite: N-desmethyl-clozapine
Cigarette smoke can induce 1A2 (cannabis can induce 1A2; consider dose adjustment when patient stops or resumes smoking)

<table>
<tr><th>Factors</th><th>Clozapine Dose Adjustments</th></tr>
<tr><td>Strong 1A2 Inhibitors</td><td>Administer 1/3 of usual dose</td></tr>
<tr><td>Strong 3A4 Inducers</td><td>Not recommended</td></tr>
<tr><td>Discontinuation of 3A4 or 1A2 Inducers (e.g. tobacco smoke)</td><td>Consider reducing clozapine dose when 3A4 or 1A2 inducers are discontinued</td></tr>
</table>
</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt®</td>
<td>2D6 (major), 3A4</td>
<td><u>Extensive metabolizers</u>
Iloperidone: 18
P88: 26
P95: 23
<u>Poor metabolizers</u>
Iloperidone: 33
P88: 37
P95: 31</td>
<td>

Use with caution in moderate hepatic impairment
Not recommended in severe hepatic impairment

<table>
<tr><th>Factors</th><th>Iloperidone Dose Adjustments</th></tr>
<tr><td>Strong 2D6 or 3A4 Inhibitors</td><td>Reduce dose</td></tr>
</table>
</td>
</tr>
<tr>
<td>Lumateperone</td>
<td>Caplyta®</td>
<td>UGT1A1, 3A4, 2C8, 1A2</td>
<td>18 hours (IV administration)</td>
<td>

Administer without food (a high-fat meal with lumateperone can lower mean C_{max} by 33% and increases AUC by 9%)
Not recommended in moderate-to-severe hepatic impairment (Child-Pugh B or Child-Pugh C)

<table>
<tr><th>Factors</th><th>Lumateperone Dose Adjustments</th></tr>
<tr><td>3A4 Inducers</td><td>Avoid concomitant use</td></tr>
<tr><td>Moderate or strong 3A4 Inhibitor</td><td>Avoid concomitant use</td></tr>
</table>
</td>
</tr>
</table>

Table 3: Pharmacokinetics & Drug-Drug Interactions[1-4]

<table>
<tr>
<td>Lurasidone</td>
<td>Latuda®</td>
<td>3A4</td>
<td>Lurasidone: 18-40
ID-14283: 7.5-10</td>
<td>

Weak 3A4 inhibitor
Administer with food (≥350 calories) (administration with food increases AUC ~2x and C_{max} ~3x)
Active metabolite: ID-14283, ID-14326
CrCl < 50 mL/min: Initial dose 20 mg; max dose 80 mg
Moderate-to-severe hepatic impairment (Child-Pugh B or C):

Child-Pugh B: Initial dose 20 mg; max dose 80 mg
Child-Pugh C: Initial dose 20 mg; max dose 40 mg

<table>
<tr><th>Factors</th><th>Lurasidone Dose Adjustments</th></tr>
<tr><td>Strong 3A4 Inhibitors</td><td>Avoid concomitant use</td></tr>
<tr><td>Moderate 3A4 Inhibitors</td><td>Administer ½ of usual dose</td></tr>
<tr><td>Strong 3A4 Inducers</td><td>Avoid concomitant use</td></tr>
<tr><td>Moderate 3A4 Inducers</td><td>Increase dose</td></tr>
</table>
</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa®
Relprevv®</td>
<td>1A2 (major), 2D6, glucuronidation</td>
<td>PO: 30 hours
Relprevv: 30 days</td>
<td>

Use with caution in hepatic impairment
Not removed by dialysis
Cigarette smoke can induce 1A2 (cannabis can induce 1A2; consider dose adjustment when patient stops or resumes smoking)
See package insert for specific dose adjustments regarding drug-drug interactions

</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega®
Sustenna®
Trinza®</td>
<td>Pgp, ABCB1, 2D6, 3A4</td>
<td>Paliperidone: 23
Renal impairment (CrCl <80 mL/min): 24-51

Sustenna® 39-234 mg
25-49 days

Trinza® 273-819 mg
84-95 days (deltoid injection)
118-139 days (gluteal injection)</td>
<td>

No dose adjustments in mild-to-moderate hepatic impairment, and not studied in severe hepatic impairment.
Renal impairment:

CrCl < 10 mL/min: Not recommended for use
CrCl 10-49 mL/min: max dose 3 mg/day
CrCl 50-79 mL/min: max dose 6 mg/day

<table>
<tr><th>Factors</th><th>Paliperidone Dose Adjustments</th></tr>
<tr><td>Strong 3A4 and Pgp Inducer</td><td>May consider increasing paliperidone PO dose (avoid concomitant use in Sustenna® and Trinza®)</td></tr>
<tr><td>Divalproex sodium</td><td>See package insert</td></tr>
</table>
</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel®
Seroquel XR®</td>
<td>3A4 (major), 2D6</td>
<td>Quetiapine: 6-7
Norquetiapine: 12</td>
<td>

Active metabolite: Norquetiapine
IR: Can be taken with or without food
XR: Administer without food or with a light meal (~300 calories), (a light meal had no significant effect on AUC or C_{max} of quetiapine)
Hepatic impairment:

IR: Initial dose 25 mg/day, increase by 25-50 mg/day to effective dose
ER: Initial dose 50 mg/day, increase by 50 mg/day to effective dose

<table>
<tr><th>Factors</th><th>Quetiapine Dose Adjustments</th></tr>
<tr><td>Strong 3A4 Inhibitors</td><td>Administer 1/6 of usual dose</td></tr>
<tr><td>Strong 3A4 Inducers</td><td>Administer ≤5x of usual dose with chronic treatment (>7-14 days) of strong 3A4 Inducers</td></tr>
<tr><td>Discontinuation of strong 3A4 Inducers</td><td>Reduce quetiapine dose by 5x within 7-14 days of 3A4 inducer discontinuation</td></tr>
</table>
</td>
</tr>
</table>

Table 3: Pharmacokinetics & Drug-Drug Interactions[1-4]

Risperidone	Risperdal® Perseris® Risperdal Consta®	2D6 (major), 3A4, Pgp, N-dealkylation	Risperidone: 3-20 9-hydroxyrisperidone: 21-30 Perseris®: 9-11 days Consta®: 3-6 days	• **Weak 2D6 inhibitor** • Active metabolite: 9-hydroxyrisperidone • Renal impairment: o CrCl ≥30 mL/min: Reduce dose o CrCl <30: Start at 0.5 mg BID, increase by ≤0.5 mg BID, may increase total dosage to >1.5 mg BID at 1 week or more • Hepatic impairment: o Child-Pugh A or Child-Pugh B: reduce dose o Child-Pugh C: Start at 0.5 mg BID, increase by ≤0.5 mg BID, may increase total dosage to >1.5 mg BID at 1 week or more • See package insert for specific dose adjustments regarding drug-drug interactions
Ziprasidone	Geodon®	1A2/3A4 (minor)	PO: 7 IM: 2-5	• Active metabolites: benzisothiazole sulfoxide and benzisothiazole sulfone • **Administer with food (≥500 calories without regard to fat content**, absorption is increased ≤2x with food)[3] • Ziprasidone not removed by dialysis • Use with caution in hepatic impairment. • IM ziprasidone contains cyclodextrin – use with caution in renal impairment • See package insert for specific dose adjustments regarding drug-drug

Table 3: Pharmacokinetics & Drug-Drug Interactions[1-4]

	Common DDI Offenders*					
	3A4		**2D6**	**1A2**		**Pgp**
	Inducers	Inhibitors	Inhibitors	Inducers	Inhibitors	Inhibitors
Weak Inhibitor: ↑ substrate† AUC ≥1.25 to <2x Inducer: ↓ substrate† AUC ≥20% to <50%	Armodafinil Modafinil 200 mg		Amiodarone Clobazam Escitalopram Fluvoxamine Labetalol Ritonavir Sertraline		Allopurinol	(↑ digoxin AUC ≥1.25x) Clarithromycin Verapamil
Moderate Inhibitor: ↑ substrate† AUC ≥2 to <5x Inducer: ↓ substrate† AUC ≥50% to <80%	Phenobarbital	Ciprofloxacin Diltiazem Fluconazole Fluvoxamine Verapamil	Duloxetine	Phenytoin Rifampin Ritonavir 800 mg Smoking	Oral contraceptives	(↑ digoxin AUC ≥2x with co-administration) Amiodarone Carvedilol Clarithromycin Ritonavir Some HIV medications & antifungals
Strong Inhibitor: ↑ substrate† AUC ≥5x Inducer: ↓ substrate† AUC ≥80%	Carbamazepine Phenytoin Rifampin St. John's wort	Clarithromycin Grapefruit juice Nefazodone Some HIV medications & antifungals	Bupropion Fluoxetine Paroxetine		Fluvoxamine Ciprofloxacin	

Not a comprehensive list of all potential drug-drug interactions, precautions and SEs; please refer to the desired drug's prescribing information for additional details and dosage adjustments, as necessary.

†According to the FDA, these area under the curve (AUC) changes are applicable to "sensitive" substrates; not all antipsychotics are "sensitive" substrates and yield the specific degree of AUC changes; please refer to the desired drug's prescribing information for additional details and dosage adjustments, as necessary.

1. Prescribing Information
2. Association, A. P. (2020). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. doi:10.1176/appi.books.9780890424841
3. Lincoln, J., Stewart, M. E., & Preskorn, S. H. (2010). How Sequential Studies Inform Drug Development: Evaluating the Effect of Food Intake on Optimal Bioavailability of Ziprasidone. Journal of Psychiatric Practice, 16(2), 103-114. doi:10.1097/01.pra.0000369971.64908.dc
4. Center for Drug Evaluation and Research. (n.d.). Table of Substrates, Inhibitors and Inducers. Retrieved December 01, 2020, from ***https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers***
5. ***https://www.practicalpainmanagement.com/resource-centers/quest-monitoring/scenario-metabolite-missing-screen-patient-medication-assisted-tre***